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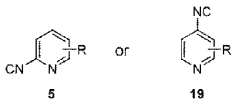
(54) **Pyridine-based isocyanides as novel reagents for multicomponent reactions.**

(57) The present invention provide novel substituted 2-isocyanopyridines and their use in methods comprising reacting substituted isocyanopyridines of the general formula



5 19

with a carbonyl-containing compound selected from the group consisting of an aldehyde and a ketone; in the presence of an acidic carbon compound selected from the group consisting of a carboxylic acid and a (thio)phenolic compound and/or a primary or secondary amine, including their use in Ugi, Passerini and Ugi-Smiles reactions, and conversion of the resulting secondary amide products to (thio)carboxylic acids, (thio)esters and amides.

Deze publicatie komt overeen met de oorspronkelijk ingediende stukken.

P32481NL00/RLA

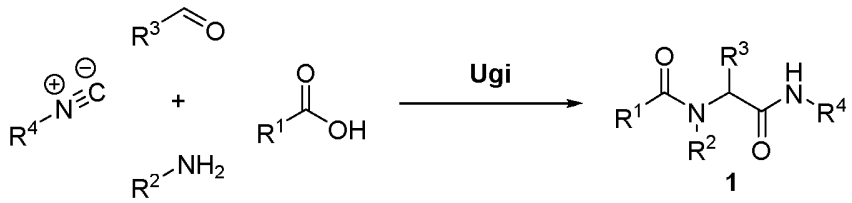
Title: Pyridine-based isocyanides as novel reagents for multicomponent reactions

Technical Field

[01] The present invention relates to substituted 2-isocyanopyridines, their preparation, the use of substituted 2-isocyanopyridines in various multicomponent reactions such as Ugi, Passerini and related reactions, and conversion of the resulting secondary amide products to (thio)carboxylic acids, (thio)esters and amides.

Background Art

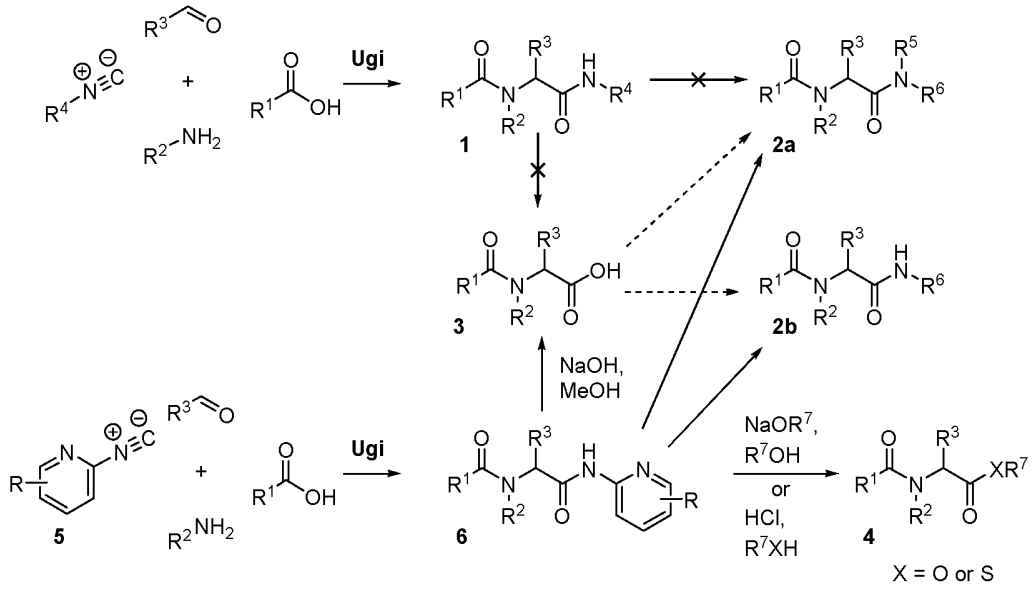
[02] Isocyanide-based multicomponent reactions (IMCRs) such as the Ugi reaction are of tremendous importance for the creation of compound libraries for *e.g.* drug discovery. Especially in this medicinal chemistry context, one of the most important limitations of this family of reactions is the lack of commercially available isocyanides (especially those with biologically relevant functionalities), and the lack of possibilities to diversify the functional group resulting from the isocyanide input (typically a secondary amide). For instance, the Ugi four-component reaction (Ugi, I; Meyr, R.; Fetzer, U.; Steinbrückner, C. (1959). "Versuche mit Isonitrilen". *Angew. Chem.* **71** (11): 386, U4CR, Scheme 1A) is a reaction between isocyanides, aldehydes (or ketones), primary amines, and carboxylic acids affording diamides **1.**



Scheme 1:

An Ugi four-component reaction

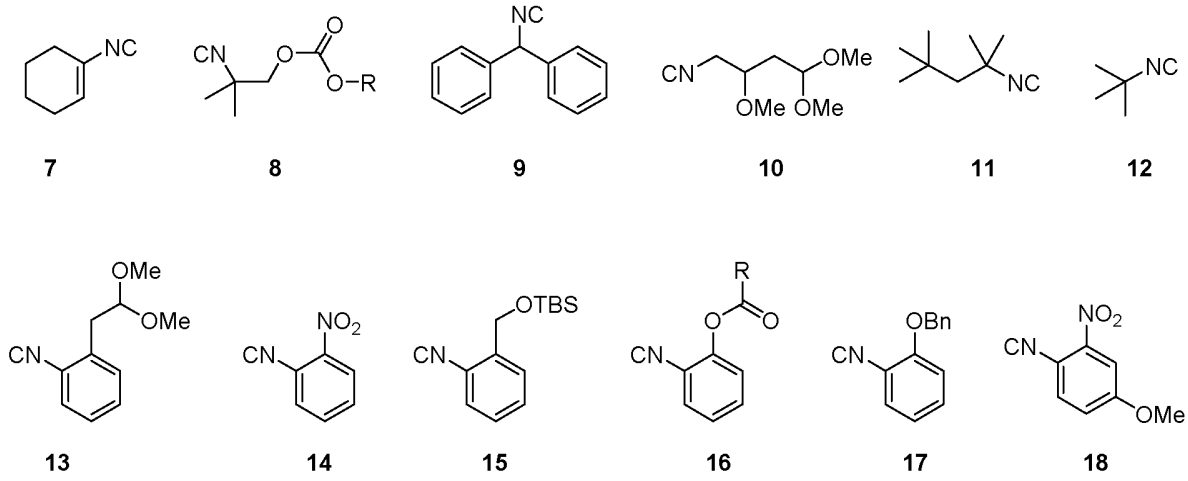
[03] One of the problems in the art is that only a limited number of R^1 groups is available due to the limited commercial availability of isocyanides. Furthermore, in order to fully exploit the synthetic potential of such reactions, it would be desirable to have the opportunity to convert the secondary amide in **1** to the corresponding tertiary amides (**2a**), other secondary amides (**2b**), carboxylic acids (**3**) and (thio)esters (**4**).



Scheme 2:

Ugi four-component reaction and desired conversion products

[04] In this regard, the carboxylic acids **3** are the most versatile intermediates, since standard methodologies allow their conversion to **2a**, **2b** and **4**. In this light, several attempts to create so-called convertible isocyanides, that allow the conversion of an Ugi product **1** to the corresponding secondary amide (**2**, $R^5 = R^6 = H$), or carboxylic acid (**3**) have appeared in literature. Scheme 3 presents an overview of the competing approaches to date. All these isocyanides suffer from one or more of the following severe limitations:



Scheme 3:

Previously reported convertible isocyanides.

[05] The isocyanides require lengthy, tedious synthetic routes and they are instable/difficult to handle. The deprotection conditions are incompatible with various

functional groups in the rest of the molecule. The functional groups in the isocyanide moiety are incompatible with various standard manipulations and cleavage of the convertible isocyanide require harsh reaction conditions or a multistep transformation.

Summary of Invention

[06] The present inventors have developed a range of 2- and 4-isocyanopyridines having unexpected properties and applications.

2-isocyanopyridines (**5**) 4-isocyanopyridines (**19**)

Scheme 4:

Substituted 2-isocyanopyridines and 4-isocyanopyridines

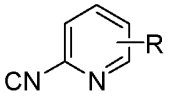
[07] The 2-isocyanopyridines **5** and the 4-isocyanopyridines **19** of the invention allow straightforward application in the Ugi reaction and other isocyanide-based multicomponent reaction (IMCRs). Furthermore, conversion of the resulting Ugi products **6** to **3** and **4**, as well as to **2a** and **2b**. The isocyanides of the present invention do not present any of the problems of currently used convertible isocyanides as mentioned herein before. They are stable solids when properly stored, for instance at −20°C, that are readily available in multigram quantities by standard transformation of (commercially available) 2- and 4-aminopyridines (**20** and **21**, respectively). The isocyanopyridines of the invention find application in multicomponent reactions such as Ugi and Passerini reactions. The products from these multicomponent reactions compound can, due to the advantageous characteristics of the isocyanopyridine-based moiety be further converted in good yields and under mild conditions. For instance, the conversion of the resulting Ugi products **6** to the corresponding carboxylic acids **3**, (thio)esters **4** or tertiary/secondary amides **2a/2b** proceeds under very mild conditions compatible with the presence of many common functional groups. In addition, and another aspect of the invention, is the demonstrated similar utility of convertible isocyanides **5** in other IMCRs such as the Passerini reaction. Among the investigated isocyanides, compound **5l** (R = 6-Br) seems to be the most preferred: It is a stable solid at −20°C (as determined by NMR over 7 months) that is readily accessible in multigram quantities from a relatively inexpensive amine precursor. In addition, the cleavage proceeds most efficiently with this particular substitution on the pyridine ring. Moreover, many of the isocyanopyridines **5** and **19** have not been described in the literature and are hence another aspect of the invention. Importantly, the use of the isocyanopyridines of the invention is conceptually significantly

different from existing approaches. Without being bound by theory, the present inventors believe that the design of the isocyanides of the present invention requires a delicate balance of electron-donating properties (ensuring sufficient nucleophilicity of the isocyanide in the IMCR) and electron-withdrawing properties of the substituent on the isocyanide (to allow mild cleavage of the amido moiety resulting from the isocyanide).

Description of the Invention

[08] Thus in a first aspect the invention pertains to a method for performing an isocyanide-based multicomponent reaction (IMCR) comprising a step of reacting

a substituted isocyanopyridine of the general formula **5** or **19,** preferably **5**,



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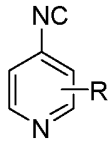


19

with a carbonyl-containing compound selected from the group consisting of an aldehyde and a ketone;

in the presence of an acidic carbon compound selected from the group consisting of (thio)carboxylic acids and (thio)phenolic compounds;

and/or a primary or secondary amine,

wherein R is selected from the group consisting of H, C_1-C_4-alkyl such as C_1-, C_2-, n-C_3-, i-C_3-alkyl,, halogenated C_1-C_4 alkyl, halogen (F, Cl, Br, I), (thio)ethers, sulfoxides, sulfones, esters, (substituted) (hetero)aryl, (substituted) cycloalkyl, alkoxy/(hetero)aryloxy, and mono-di-alkyl/(hetero)arylamino.

[09] Using the substituted isocyanopyridines of the invention results in good yields and clean reactions. The substituted isocyanopyridines can be readily synthesised in multigram quantities and are stable solids. The result application in IMCRs is straightforward under mild conditions and tolerates a wide range of substituents. The products of the IMCRs are readily deprotected to remove the pyridyl-amide moiety.

[10] In certain embodiments of the invention, the acidic carbon compound is a carboxylic acid. The IMCR is then also known as the Passerini reaction, see also reaction scheme 10.

[11] In certain other embodiments, the reaction is the Ugi 4-component reaction and is performed in the presence of an acidic carbon compound and a primary amine.

[12] In certain other embodiments, the reaction is an Ugi 3-component reaction in the absence of an acidic carbon compound and in the presence of a secondary amine.

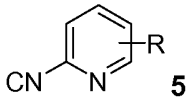
[13] In certain other embodiments, the reaction is the Ugi-Smiles reaction and the acidic carbon is a phenolic compound, i.e. an hydroxyl group directly attached to an aromatic ring.

[14] The substituent R used in the isocyanopyridines in the method of the invention can vary widely, but is preferably selected from the group consisting of H, C_1-, C_2-, n-C_3-, i-C_3-alkyl, halogen (F, Cl, Br, I), CF_3 ,(thio)ethers, sulfoxides, sulfones, esters, (substituted) (hetero)aryl, (substituted) cycloalkyl, alkoxy/(hetero)aryloxy, and mono-di-alkyl/(hetero)arylamino. In certain preferred embodiments R is selected from the group consisting of C_1-, C_2-, *n*-C_3-, *i*-C_3- alkyl, halogen (F, Cl, Br, I), CF_3 . A preferred substituted isocyanopyridine is a substituted 2-isocyanopyridine. In certain preferred embodiments for 2-isocyanopyridines, R is selected from the group consisting of 3-Me, 4-Me, 5-Me, 6-Me, 3-Br, 4-Br, 5-Br, 6-Br, 3-Cl, 4-Cl, 5-Cl, 6-Cl, 3-F, 4-F, 5-F, 6-F, 3-CF_3, 4-CF_3, 5-CF_3, 6-CF_3. In certain preferred embodiments for 2-isocyanopyridines R is selected from the group consisting of 3-Me, 4-Me, 5-Me, 6-Me, 3-Br, 4-Br, 5-Br, 6-Br, 3-Cl, 4-Cl, 5-Cl, 6-Cl 5-F, 5-CF_3. Good results have been obtained and hence preferred substituents are 2-isocyanopyridines wherein R is selected from the group consisting of 3-Me, 4-Me, 5-Me, 6-Me, 3-Br, 4-Br, 5-Br, 5-Cl, 5-CF_3, 6-Br, 6-Cl. The most preferred substituent for 2-isocyanopyridines R = Br. The most preferred position for 2-isocyanopyridines is the 6-position. The most preferred compound in the method of the invention is 6-bromo-2-isocyanopyridine.

[15] In certain preferred embodiments for 4-isocyanopyridines , R is selected from the group consisting of 2-Me, 3-Me, 5-Me, 6-Me, 2-Br, 3-Br, 5-Br, 6-Br, 2-Cl, 3-Cl, 5-Cl, 6-Cl, 2-F, 3-F, 5-F, 6-F, 2-CF_3, 3-CF_3, 5-CF_3, 6-CF_3, the 5 and 6 positions being equivalent with the 3 and 2 position, respectively. In certain preferred embodiments for 4-isocyanopyridines, R is selected from the group consisting of 2-Me, 2-Br, 2-CF_3, 2-Cl.

[16] The position of the substituent R on the pyridine ring in the method of the invention may vary. Substituent positions refer to the parent compound 2-isocyanopyridine or 4-isocyanipyridine compound, respectively, although the systematic IUPAC nomenclature for each of the compound may be different depending on the priority of the substituent relative to the isocyano group. For 2-isocyanopyridines, the substituent R can be at the 3-position; at the 4-position; at the 5-positon; at the 6-position. For 4-isocyanopyridines, the monosubstituent R can be at the 2-position; at the 3-position; the 5-position and 6-position being equivalent to the 3- and 2- position, respectively. Two or more substituents R are possible, independently selected.

[17] The substituted 2-isocyanopyridines or 4-isocyanopyridines are another aspect of the invention. The 2-isocyanopyridines or 4-isocyanopyridines are prepared using conventional methods as exemplified in the experimental section. The invention thus also relates to substituted 2-isocyanopyridines having the general formula



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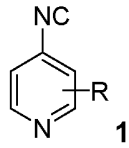
or substituted 4-isocyanopyridines having the general formula



19

wherein R is selected from the group consisting of H, C_1-C_4-alkyl such as C_1-, C_2-, n-C_3-, i-C_3- alkyl, halogenated C_1-C_4 alkyl, halogen (F, Cl, Br, I), (thio)ethers, sulfoxides, sulfones, esters, (substituted) (hetero)aryl, (substituted) cycloalkyl, alkoxy/(hetero)aryloxy, and mono-di-alkyl/(hetero)arylamino.

[18] For substituted 2-isocyanopyridines: In a preferred embodiment, R is selected from the group consisting of 3-Me, 4-Me, 5-Me, 6-Me, 3-Br, 4-Br, 5-Br, 6-Br, 3-Cl, 4-Cl, 5-Cl, 6-Cl, 3-F, 4-F, 5-F, 6-F, 3-CF_3, 4-CF_3, 5-CF_3, 6-CF_3. In a further preferred embodiment, R is selected from the group consisting of 3-Me, 4-Me, 5-Me, 6-Me, 3-Br, 4-Br, 5-CF_3, 6-Br, 6-Cl. In a more preferred embodiment R is Br and more preferably 6-Br, i.e. 6-bromo-2-isocyanopyridine.

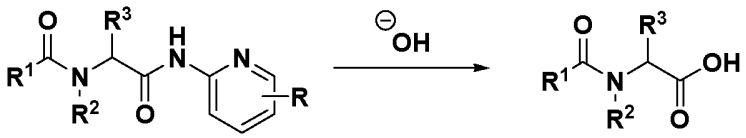
[19] For substituted 4-isocyanopyridines , R is selected from the group consisting of 2-Me, 3-Me, 2-Br, 3-Br, , 2-Cl, 3-Cl, , 2-F, 3-F, 2-CF_3, 3-CF_3. In certain preferred embodiments for 4-isocyanopyridines, R is selected from the group consisting of 2-Me, 2-Br, 2-CF_3, 2-Cl.

[20] Thus the invention also relates to, independently: 3-chloro-2-isocyanopyridine; 4-chloro-2-isocyanopyridine; 5-chloro-2-isocyanopyridine; 6-chloro-2-isocyanopyridine; 3-bromo-2-isocyanopyridine; 4-bromo-2-isocyanopyridine; 5-bromo-2-isocyanopyridine; 6-bromo-2-isocyanopyridine; 3-fluoro-2-isocyanopyridine; 4-fluoro-2-isocyanopyridine; 5-fluoro-2-isocyanopyridine; 6-fluoro-2-isocyanopyridine; 3-methyl-2-isocyanopyridine; 4-methyl-2-isocyanopyridine; 5-methyl-2-isocyanopyridine; 6-methyl-2-isocyanopyridine; 3-ethyl-2-isocyanopyridine; 4-ethyl-2-isocyanopyridine; 5-ethyl-2-isocyanopyridine; 6-ethyl-2-isocyanopyridine; 3-n-propyl-2-isocyanopyridine; 4-n-propyl-2-isocyanopyridine; 5-n-propyl-2-isocyanopyridine; 6-n-propyl-2-isocyanopyridine 3-i-propyl-2-isocyanopyridine; 4-i-propyl-2-isocyanopyridine; 5-i-propyl-2-isocyanopyridine; 6-i-propyl-2-isocyanopyridine; 3-trifluoromethyl-2-isocyanopyridine; 4-trifluoromethyl-2-isocyanopyridine; 5-trifluoromethyl-2-isocyanopyridine; 6-trifluoromethyl-2-isocyanopyridine; 2-chloro-4-isocyanopyridine;2 -bromo-4-isocyanopyridine. For these individual compounds, substituent positions refer to the parent compound 2-isocyanopyridine or 4-isocyanipyridine compound, respectively, although the systematic IUPAC nomenclature for each of the compound may be different depending on the priority of the substituent relative to the isocyano group.

[21] Methods for the synthesis of isocyanopyridines are known in the art, For instance for R = H: Bioorganic and Medicinal Chemistry, **2009** , vol. 17, # 1 p. 74 – 84; Russian Journal of Organic Chemistry, **1999** , vol. 35, # 5 p.693 – 697.

[22] In a further aspect the invention relates to follow up transformations, i.e. reactions that follow the multicomponent reactions with the isocyanopyridines of the invention. The products of the multicomponent reactions described herein readily undergo a set of further conversions to yield valuable synthetic products that can be used in further transformations.

[23] Specifically, the invention also pertains to the saponification, hydrolysis, solvolysis, alcoholysis and/or transamidation of the product of the isocyanide-based IMCRs. In more detail, the invention pertains in one embodiment to the conversion of the N-2-pyridylamide- (or N-4-pyridylamide-, not shown here) containing product of an Ugi reaction to the corresponding carboxylic acid under basic conditions as exemplified below.



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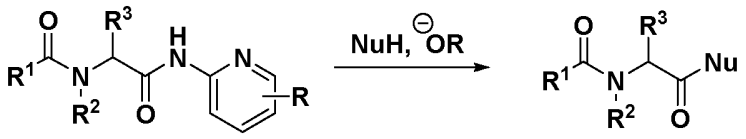
[24] The product compound from the multicomponent reaction using the substituted isocyanides of the present invention is converted under basic conditions, preferably in a solvent to a carboxylic acid by saponification of the N-2-pyrimidylamide or N-4-pyridylamide group. The basic conditions can be provided by the use of basic compounds such as LiOH, NaOH, KOH or sodium methoxide in aqueous and/or alcoholic solutions. Other solvents may be used.

[25] In another embodiment, the invention pertains to the nucleophilic substitution of the *N*-2-pyridylamide or *N*-4-pyridylamide-group of the *N*-2-pyridylamide- or *N*-4-pyridylamide-containing product of an Ugi reaction in the presence of a nucleophile under acidic or basic conditions, as exemplified below:



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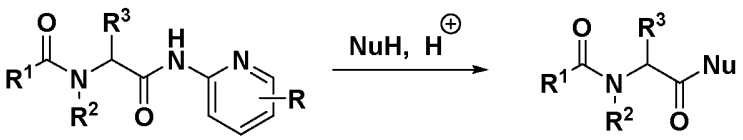
2a Nu = NR^5R^6
2b Nu = NHR^6
3 Nu = OH
4 Nu = OR^7, SR^7

or



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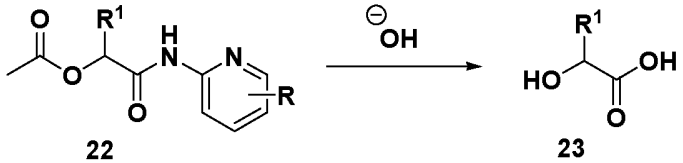
3 Nu = OH
4 Nu = OR^7, SR^7

[26] By contacting the product compound from the multicomponent reaction using the substituted isocyanides of the present invention with a nucleophile under acidic or basic conditions, the *N*-2-pyridylamide or *N*-4-pyridylamide group of the product compound is substituted with the nucleophile. The basic conditions are as outlined herein. The acidic conditions can be provided using mineral or organic acids such as HCl; or acetic acid. Solvents may be used. The resulting nucleophilic substitution products are obtained in good yields and purities. In preferred embodiments, the nucleophile is selected from the group consisting of water, alcohols, and thiols. More preferably, when the conditions are basic, the nucleophile is selected from the group consisting of water, primary C_1-C_8-alcohols, primary C_1-C_8 alkylamines, secondary C_2-C_8 alkylamines and C_4-C_8 cycloalkylamines.

[27] In another embodiment, the conditions are acidic and the nucleophile is selected from the group consisting of water, alcohols, thiols. More preferably, the nucleophile is selected from the group consisting of water, primary C_1-C_8-alcohols, primary C_1-C_8- thiols, benzylic thiols.

[28] Further embodiments of the invention relate to the conversion of the *N*-2-pyridylamide- (**22**) or *N*-4-pyridylamide- containing products of the Passerini reaction under basic conditions to provide the corresponding alpha-hydroxy carboxylic acids **23**, as exemplified below. The basic conditions may be as described herein elsewhere.



22 **23**

Brief Description of Drawings

[29] Figure 1. Yields of various substituted 2-isocyanopyridines **5a-l** from the corresponding amines (over two steps) for the various isocyanides.

[30] Figure 2. Yields of benchmark Ugi reactions with various substituted 2-isocyanopyridines with isobutyraldehyde, benzylamine and acetic acids to give **6a-l** (R^1 = CH_3, R^2 = Bn, R^3 = *i*Bu)

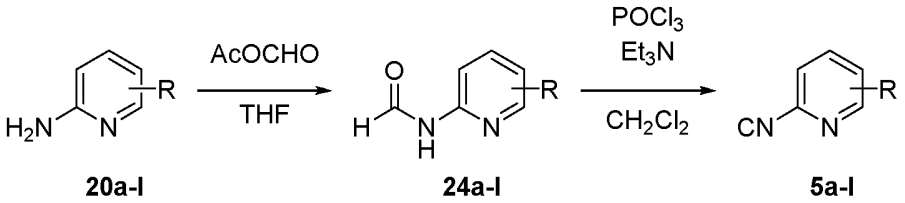
[31] Figure 3. Yields of hydrolysis of Ugi products **6a-l** using 2.5 equiv. (light grey bars) or 5.0 equiv. (dark grey bars) of NaOH in MeOH/H_2O.

Description of Embodiments

1. Synthesis of convertible isocyanides

[32] A range of substituted 2-aminopyridines **20a-l** were converted to the corresponding 2-isocyanopyridines **5a-l** *via* the formamides **24a-l** using the following procedure (Scheme 5,

General Procedures I and II). Figure 1 discloses yields of various substituted 2-isocyanopyridines **5a-l** from the corresponding amines over two steps.



20a-l **24a-l** **5a-l**

Scheme 5.

Synthesis of substituted 2-isocyanopyridines, (a: R = 3-Me, b: R = 3-Br, c: R = 4-Me, d: R = 4-Br, e: R = 5-Me, f: R = 5-F, g: R = 5-Cl, h: R = 5-Br, i: R = 5-CF_3. j: R = 6-Me, k: R = 6-Cl, l: R = 6-Br).

General procedure I: Synthesis of 2-formamidopyridines 24

[33] In a flame-fried roundbottom flask equipped with a reflux condenser formic acid (41 mmol, 2.05 eq.) was added dropwise to acetic anhydride (40 mmol, 2.0 eq.) and the resulting mixture refluxed at 65°C for 2-3 hours. The mixture was cooled to room temperature and slowly added to a cold solution of a 2-aminopyridine **20** (20 mmol, 1.0 eq.) in anhydrous THF (50 mL) at 0°C. After 1h, the reaction was allowed to warm up to RT and stirred for 2-3 more hours. The solvent and excess of acetic acid were evaporated and the residue was redissolved in EtOAc. The crude mixture was washed with a saturated $NaHCO_3$ and the water layer was extracted with EtOAc (2×). The organic layers were combined, washed with brine and dried over Na_2SO_4. The solvent was evaporated to furnish the corresponding formamide.

General procedure II: Synthesis of 2-isocyanopyridines 5

[34] Unless stated otherwise: To a flame dried 3-neck flask a 2-formamidopyridine **24** (10 mmol, 1.0 eq.) was added and dissolved in anhydrous CH_2Cl_2 (30 mL). Then, Et_3N (60 mmol, 6.0 eq.) was added and the solution was cooled to −78°C. $POCl_3$ (11.5 mmol, 1.15 eq.) in anhydrous CH_2Cl_2 (5 mL) was added dropwise to the mixture. After 1h, the mixture was warmed up to 0°C and stirred overnight. The crude reaction mixture was carefully quenched with saturated $NaHCO_3$ (25 mL). The layers were separated and the water layer was extracted with CH_2Cl_2 (2×). The organic layers were combined and washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (CH_2Cl_2) to afford the 2-isocyanopiridine. The product was stored in the freezer at −18°C.

[35] The yields (over two steps) for the various isocyanides are depicted in Figure 1. [As an example, isocyanide **5l** (R = 6-Br) was obtained in 71% yield over two steps after chromatography].

[36] The substituted 4-isocyanopyridines **19** were obtained analogously, starting from the corresponding substituted 4-aminopyridines **21**.

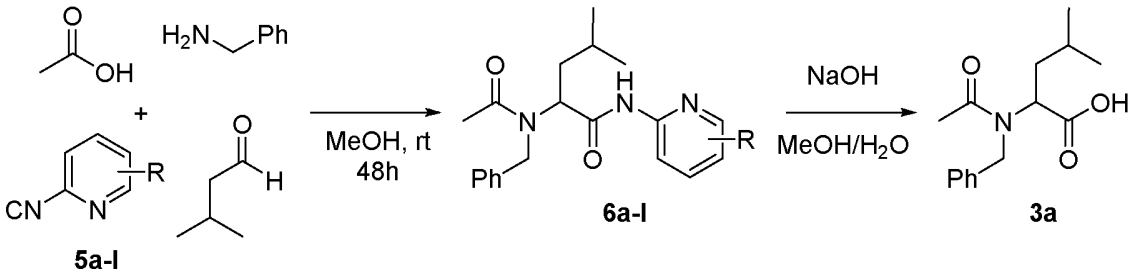
[37] Analytical data:

5a: 3-methyl-2-isocyanopyridine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.32 (d, J = 4.1 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.29 (dd, *J* = 7.5 Hz, 4.7 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2 (C_q), 147.0 (CH), 140.3 (C_q), 139.4 (CH), 130.3 (C_q), 124.6 (CH), 17.9 (CH_3). IR (neat): *v*max (cm^{-1}) = 3053 (w), 2122 (s), 1572 (s), 1115 (s), 804 (s), 633 (s), 534 (s), 498 (s), 413 (s), 401 (s). HRMS (ESI): *m/z* calculated for $C_7H_7N_2$ 119.0604 (M+H), found 119.0609.
5b: 3-bromo-2-isocyanopyridine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.43 (d, *J* = 4 Hz, 1H), 8.04 (d, *J* = 8.1 Hz), 7.29 (dd, *J* = 4.8 Hz, 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.2 (C_q), 147.9 (CH), 142.0 (CH), 139.7 (C_q), 125.6 (CH), 117.2 (C_q). IR (neat): *v*max (cm^{-1}) = 3043 (s), 2120 (s), 1564 (s), 1416 (s), 1030 (s), 804 (s), 497 (s), 411 (s), 401 (s). HRMS (ESI): *m/z* calculated for $C_6H_4BrN_2$ (M+H) 182.9552, found 182.9552.
5c: 4-methyl-2-isocyanopyridine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.33 (d, *J* = 4.7 Hz, 1H), 7.19-7.18 (m, 2H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.2 (C_q), 150.6 (C_q), 149.3 (CH), 140.4 (C_q), 125.7 (CH), 121.9 (CH), 20.8 (CH_3). IR (neat): *v*max (cm^{-1}) = 3053 (w), 2122 (s), 1603 (s), 1404 (s), 837 (s), 496 (s), 451 (s), 413 (s), 401 (s). HRMS (ESI): *m/z* calculated for $C_7H_7N_2$ (M+H) 119.0604, found 119.0613.
5d: 4-bromo-2-isocyanopyridine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.33 (d, *J* = 5.0 Hz, 1H), 7.56 (d, *J* = 6.6 Hz, 1H), 7.54 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.7 (C_q), 150.2 (CH), 140.6 (C_q), 134.5 (C_q), 128.2 (CH), 124.7 (CH). IR (neat): *v*max (cm^{-1}) = 3075 (w), 2133 (s), 1564 (s), 1381 (s), 837 (s), 633 (s), 498 (s), 451 (s), 418 (s), 401 (s). HRMS (ESI): *m/z* calculated for $C_6H_4BrN_2$ (M+H) 182.9552, found 182.9555.
5e: 5-methyl-2-isocyanopyridine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.29 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.0 (C_q), 149.9 (CH), 139.0 (CH), 138.1 (C_q), 135.0 (C_q), 120.7 (CH), 18.2 (CH_3). IR (neat): *v*max (cm^{-1}) = 3057 (w), 2127 (s), 1578 (s), 1474 (s), 1034 (s), 833 (s), 633 (s), 536 (s), 525 (s), 494 (s), 413 (s), 401 (s). HRMS (ESI): *m/z* calculated for $C_7H_7N_2$ 119.0604 (M+H), found 119.0609.
5f: 5-fluoro-2-isocyanopyridine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.35 (s, 1H), 7.55 - 7.51 (m, 1H), 7.41-7.36 (m, 1H).
5g: 5-chloro-2-isocyanopyridine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.45 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.5 (C_q), 148.8 (CH), 138.5 (CH), 138.1 (C_q), 133.1 (C_q), 122.1 (CH). IR (neat): *v*max (cm^{-1}) =3051 (w), 2125 (s), 1572 (s), 1452 (s), 1115 (s), 1014 (s), 842 (s), 496 (s), 401 (s). HRMS (ESI): *m/z* calculated for $C_6H_4ClN_2$ 139.0058 (M+H), found 139.0064.
5h: 5-bromo-2-isocyanopyridine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.56 (s, 1H), 7.96 (d, *J* = 8.4

Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.6 (C_q), 150.9 (CH), 141.3 (CH), 138.6 (C_q), 122.4 (CH), 121.5 (C_q). IR (neat): *v*max (cm^{-1}) = 3049 (w), 2125 (s), 1566 (s), 1456 (s), 1450 (s), 1365 (s), 1094 (s), 1011 (s), 841 (s), 494 (s). HRMS (ESI): *m/z* calculated for $C_6H_4BrN_2$ (M+H) 182.9552, found 182.9544.
5i: 5-trifluoromethyl-2-isocyanopyridine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.82 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H).
5j: 6-methyl-2-isocyanopyridine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (t, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H) 2.55 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.1 (C_q), 159.6 (C_q), 139.6 (C_q), 138.7 (CH), 124.4 (CH), 118.3 (CH), 18.3 (CH_3). IR (neat): *v*max (cm^{-1}) = 3078 (w), 2130 (s), 1595 (s), 1450 (s), 796 (s), 633 (s), 538 (s), 496 (s), 401 (s). HRMS (ESI): *m/z* calculated for $C_7H_7N_2$ 119.0604 (M+H), found 119.0609.
5k: 6-chloro-2-isocyanopyridine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.78 (t, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.9 (C_q), 151.1 (C_q), 141.0 (CH), 139.2 (C_q), 125.8 (CH), 119.8 (CH). IR (neat): *v*max (cm^{-1}) = 3082 (w), 2124 (s), 1574 (s), 1427 (s), 1163 (s), 989 (s), 864 (s), 802 (s), 532 (s), 498 (s), 413 (s), 401 (s). HRMS (ESI): *m/z* calculated for $C_6H_4ClN_2$ 139.0058 (M+H), found 139.0063.
5l: 6-bromo-2-isocyanopyridine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 (t, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1 (C_q), 141.2 (CH), 140.6 (C_q), 139.3 (C_q) 129.6 (CH), 120.1 (CH). IR (neat): *v*max (cm^{-1}) = 3056 (w), 2131 (s), 1570 (s), 1431 (s), 989 (s), 802 (s), 631 (s), 538 (s), 503 (s), 496 (s), 436 (s), 405 (s). HRMS (ESI): *m/z* calculated for $C_6H_4BrN_2$ (M+H) 182.9552, found 182.9546.
19a 2-Chloro-4-isocyanopyridine: Yield: (formamide: 94%, isocyanide: 40% = overall 38%) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.47 (d, *J* = 4.5 Hz, 1H), 7.33 (s, 1H), 7.22 (d, *J* = 4.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.7 (C_q), 152.8 (C_q), 151.1 (CH), 121.2 (CH), 119.2 (CH).
19b 2-Bromo-4-isocyanopyridine: Yield: (formamide: 96%, isocyanide: 41% = overall 39%) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.46 (d, *J* = 5.2 Hz, 1H), 7.49 (d, *J* = 1.2 Hz, 1H), 7.25 (dd, *J* = 5.2, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8 (C_q), 151.5 (CH), 143.0 (C_q), 124.8 (CH), 119.5 (CH).

2. Selection of the optimal convertible isocyanide

[38] The synthesized isocyanopyridines were then used in the benchmark Ugi reaction with isovaleraldehyde, benzylamine and acetic acid (MeOH, RT, 24 h) to give Ugi products **6a-l**, (scheme 6) which were then subjected to hydrolysis (2.5 or 5.0 eq. NaOH, MeOH/H_2O, 48h, rt) to give carboxylic acid **3**. The yields for the Ugi reaction and the subsequent hydrolysis for various convertible isocyanides **5a-l** are depicted in Figures 2 and 3, respectively. Reactions with 4-isocyanopyridnes give similar results.



Scheme 6.

Benchmark Ugi reaction with various substituted 2-isocyano pyridines and subsequent hydrolysis.

[39] The results in Figures 2 and 3 indicate that isocyanide **5l** (R = 6-Br) is very effective in both the Ugi reaction and subsequent hydrolysis, and can be produced in relatively high yield from the corresponding amine (Figure 1).

[40] Analytical data:

6a: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.92 (bs, 1H), 8.30 (d, *J* = 3.9 Hz, 1H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.37-7.20 (m, 5H), 7.06 (t, *J* = 6.0 Hz, 1H), 5.19 (t, *J* = 7.5 Hz, 1H), 4.65 (s, 2H), 2.29 (s, 3H), 2.21 (s, 3H), 1.97 (m, 1H), 1.58 (m, 1H), 1.46 (m, 1H), 0.88- 0.86 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6 (C_q), 169.0 (C_q), 149.3 (C_q), 146.0 (CH), 139.4 (CH), 137.1 (C_q), 128.8 (CH), 127.3 (CH), 126.8 (C_q), 126.0 (CH), 121.2 (CH), 57.1 (CH), 49.5 (CH_2), 36.9 (CH_2), 25.2 (CH), 22.9 (CH_3), 22.4 (CH_3), 22.2 (CH_3), 17.9 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1674 (m), 1448 (s), 1420 (s), 633 (s), 534 (s), 496 (s), 401 (s). HRMS (ESI): *m/z* calculated for $C_{21}H_{28}N_3O_2$ (M+H) 354.2176, found 354.2193.

6b: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.11 (broad s, 1H), 8.43 (d, *J* = 4.1 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.38-7.18 (m, 5H), 6.97 (dd, *J* = 7.6, 4.5 Hz, 1H), 5.22 (t, *J* = 6.5 Hz, 1H), 4.63 (s, 2H), 2.14 (s, 3H), 2.01 (m, 1H), 1.58 (m, 1H), 1.46 (m, 1H), 0.92 (d, *J* = 5.0 Hz, 3H), 0.88 (d, *J* = 5.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6 (C_q), 168.7 (C_q), 148.6 (C_q), 147.3 (CH), 141.3 (CH), 137.0 (C_q), 128.8 (CH), 127.4 (CH), 126.1 (CH), 121.2 (CH), 111.6 (C_q), 57.3 (CH), 49.5 (CH_2), 36.5 (CH_2), 25.2 (CH), 22.9 (CH_3), 22.4 (CH_3), 22.3 (CH_3). IR (neat): *v*max (cm^{-1}) = 2956 (w), 1628 (m), 1497 (s), 1431 (m), 633 (s), 534 (s), 498 (s), 405 (s). HRMS (ESI): *m/z* calculated for $C_{20}H_{25}BrN_3O_2$ (M+H) 418.1125, found 418.1130.

6c: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.03 (bs, 1H), 8.14 (d, *J* = 4.8 Hz, 1H), 7.82 (s, 1H), 7.28-7.17 (m, 5H), 6.84 (d, *J* = 4.6 Hz, 1H), 5.22 (t, *J* = 7.2 Hz, 1H), 4.66 (d, *J* = 17.5 Hz, 1H), 4.60 (d, *J* = 17.5 Hz, 1H), 2,31 (s, 3H), 2.14 (s, 3H), 1.95 (m, 1H), 1.56-1.45 (m, 2H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.2 (C_q), 169.5 (C_q), 151.2 (C_q), 149.5 (C_q), 147.6 (CH), 137.0 (C_q), 128.8 (CH), 127.3 (CH), 126.0 (CH), 120.9 (CH), 114.6 (CH), 56.8 (CH), 49.2 (CH_2), 36.8 (CH_2), 25.2 (CH), 22.8 (CH_3), 22.3 (CH_3), 22.3

(CH_3), 21.3 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1697 (s), 1630 (m), 1568 (s), 1414 (s), 633 (s), 523 (s), 498 (s), 407 (s). HRMS (ESI): *m/z* calculated for $C_{21}H_{28}N_3O_2$ (M+H) 354.2176, found 354.2185.

6d: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.21 (bs, 1H), 8.19 (s, 1H), 8.10 (d, *J* = 5.0 Hz , 1H), 7.27 – 7.22 (m, 5H), 7.17 (d, *J* = 6.6 Hz, 1H), 5.17 (t, *J* = 6.8 Hz, 1H), 4.66 (d, *J* = 17.5 Hz, 1H), 4.57 (d, *J* = 17.5 Hz, 1H), 2.18 (s, 3H), 1.94 (m, 1H), 1.52 (m, 2H), 0.88 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4 (C_q), 169.6 (C_q), 151.9 (C_q), 148.5 (CH), 136.6 (C_q), 134.1 (C_q), 128.8 (CH), 127.5 (CH), 126.2 (CH), 123.0 (CH), 117.1 (CH), 56.8 (CH), 49.4 (CH_2), 36.6 (CH_2), 25.1 (CH_3), 22.8 (CH_3), 22.4 (CH_3), 22.3 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1628 (s), 1560 (s), 1396 (s), 633 (s), 536 (s), 498 (s), 401 (s). HRMS (ESI): *m/z* calculated for $C_{20}H_{25}BrN_3O_2$ (M+H) 418.1125, found 418.1128.

6e: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.98 (bs, 1H), 8.10 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.26-7.16 (m, 5H), 5.22 (m, 1H), 4.65 (d, *J* = 17.5 Hz, 1H), 4.59 (d, *J* = 17.5 Hz, 1H), 2.27 (s, 3H), 2.13 (s, 3H), 1.92 (m, 1H), 1.55-1.48 (m, 2H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.2 (C_q), 169.2 (C_q) 149.0 (C_q), 147.8 (CH), 138.5 (CH), 137.0 (C_q), 129.0 (C_q), 128.7 (CH), 127.3 (CH), 126.0 (CH), 113.5 (CH), 56.7 (CH), 49.2 (CH_2), 36.8 (CH_2), 25.1 (CH), 22.7 (CH_3), 22.4 (CH_3), 22.4 (CH_3), 17.8 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1630 (m), 1522 (s), 1385 (s), 1298 (s), 633 (s), 534 (m), 498 (s). HRMS (ESI): *m/z* calculated for $C_{21}H_{28}N_3O_2$ (M+H) 354.2176, found 354.2193.

6f: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.17 (bs, 1H), 8.16 (s, 1H), 7.98 (dd, *J* = 9.1 Hz, 3.8 Hz, 1H), 7.37 (m, 1H), 7.28-7.17 (m, 5H), 5.21 (m, 1H), 4.67 (d, *J* = 17.5 Hz, 1H), 4.60 *J* = 17.5 Hz, 1H), 2.20 (3H), 1.96 (m, 1H), 1.56-1.53 (m, 2H), 0.91 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4 (C_q), 169.1 (C_q) 156.2 (d, *J* = 250 Hz, C_q), 147.4 (C_q), 136.7 (C_q) 135.5 (d, *J* = 25 Hz, CH), 128.8 (CH), 127.5 (CH), 126.1 (CH), 124.8 (d, J = 20 Hz, CH), 114.6 (CH), 56.7 (CH), 49.3 (CH_2), 36.6 (CH_2), 25.1 (CH), 22.7 (CH_3), 22.4 (CH_3), 22.4 (CH_3). IR (neat): *v*max (cm^{-1}) = 2959 (w), 1630 (s), 1526 (s), 1472 (s), 1391(s), 633 (s), 534 (s), 498 (s). HRMS (ESI): *m/z* calculated for $C_{20}H_{25}FN_3O_2$ (M+H) 358.1925, found 358.1932.

6g: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.16 (bs, 1H), 8.24 (s, 1H), 7.92 (d, *J* = 8.9 Hz, 1H), 7.58 (d, *J* = 8.8 Hz), 7.26-7.15 (m, 5H), 5.18 (m, 1H), 4.65 (d, *J* = 17.4 Hz, 1H), 4.57 (d, *J* = 17.4 Hz, 1H), 2.18 (s, 3H), 1.94 (m, 1H), 1.56-1.51 (m, 2H), 0.89-0.87 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4 (C_q), 169.4 (C_q) 149.5 (C_q), 146.6 (CH), 137.6 (CH) 136.6 (C_q), 128.8 (CH), 127.5 (CH), 126.6 (C_q), 126.1 (CH), 114.5 (CH), 56.8 (CH), 49.4 (CH_2), 36.5 (CH_2), 25.1 (CH), 22.7 (CH_3), 22.4 (CH_3), 22.4 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1628 (m), 1522 (m), 1375 (s), 1292 (s), 633 (s), 538 (s), 498 (s). HRMS (ESI): *m/z* calculated for $C_{20}H_{25}ClN_3O_2$ (M+H) 374.1630, found 374.1633.

6h: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.20 (bs, 1H), 8.34 (s, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.27-7.17 (m, 5H), 5.20 (t, *J* = 6.7 Hz, 1H), 4.67 (d, *J* = 17.4 Hz, 1H), 4.59 (d,

J = 17.4 Hz, 1H), 2.20 (s, 3H), 1.95 (m, 1H), 1.57-1.54 (m, 2H), 0.91-0.89 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4 (C_q), 169.4 (C_q), 149.9 (C_q), 148.9 (CH), 140.4 (CH), 136.6 (C_q), 128.8 (CH) 127.5 (CH), 126.1 (CH), 115.1 (CH), 114.5 (C_q), 56.8 (CH), 49.4 (CH_2), 36.5 (CH_2), 25.1 (CH), 22.7 (CH_3), 22.4 (CH_3), 22.4 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1626 (m), 1518 (m), 1367 (s), 1290 (s), 633 (s), 523 (m), 498 (s), 413 (s), 403 (s). HRMS (ESI): *m/z* calculated for $C_{20}H_{25}BrN_3O_2$ (M+H) 418.1125, found 418.1138.

6i: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.47 (bs, 1H), 8.56 (s, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 8.7 Hz, 1H), 7.28-7.17 (m, 5H), 5.21 (m, 1H), 4.68 (d, *J* = 17.4 Hz, 1H), 4.59 (d, *J* = 17.4 Hz, 1H), 2.23 (s, 3H), 1.97 (m, 1H), 1.60-1.55 (m, 2H), 0.92 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5 (C_q), 169.8 (C_q) 153.8 (C_q), 145.4 (q, *J* = 3.7 Hz, CH), 136.5 (C_q), 135.3 (q, *J* = 3.7 Hz, CH), 128.8 (CH), 127.6 (CH), 126.2 (CH), 123.5 (q, *J* = 270 Hz, C_q), 122.3 (q, *J* = 31 Hz, C_q), 113.2 (CH), 56.9 (CH), 49.5 (CH_2), 36.5 (CH_2), 25.1 (CH), 22.7 (CH_3), 22.4 (CH_3), 22.4 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1626 (m), 1520 (s), 1325 (s), 908 (s), 731 (s), 633 (s), 532 (s), 496 (s). HRMS (ESI): *m/z* calculated for $C_{21}H_{25}F_3N_3O_2$ (M+H) 408.1893, found 408.1909.

6j: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.84 (bs, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.30-7.18 (m, 5H), 6.88 (d, *J* = 7.5 Hz, 1H), 5.28 (m, 1H), 4.68 (d, *J* = 17.6 Hz, 1H), 4.62 (d, *J* = 17.6 Hz, 1H), 2.46 (s, 3H), 2.16 (s, 3H), 1.93 (m, 1H), 1.57-1.48 (m, 2H), 0.91-0.81 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.1 (C_q), 169.2 (C_q), 157.0 (C_q), 150.4 (C_q), 138.3 (CH), 137.1 (C_q), 128.8 (CH), 127.3 (CH), 126.0 (CH), 119.2 (CH), 110.7 (CH), 56.5 (CH), 49.0 (CH_2), 36.8 (CH_2), 25.1 (CH), 24.0 (CH_3), 22.8 (CH_3), 22.4 (CH_3), 22.3 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1630 (m), 1454 (s), 633 (s), 536 (s), 498 (s), 403 (s). HRMS (ESI): *m/z* calculated for $C_{21}H_{28}N_3O_2$ (M+H) 354.2176, found 354.2182.

6k: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.98 (bs, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.30-7.18 (m, 5H), 7.04 (d, *J* = 7.6 Hz, 1H), 5.23 (m, 1H), 4.67 (d, *J* = 17.4 Hz, 1H), 4.60 (d, *J* = 17.4 Hz, 1H), 2.20 (s, 3H), 1.94 (m, 1H), 1.57-1.52 (m, 2H), 0.91 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ173.2 (C_q), 169.5 (C_q) 151.0 (C_q), 149.0 (C_q), 140.5 (CH), 136.7 (C_q), 128.8 (CH), 127.5 (CH), 126.1 (CH), 119.7 (CH), 112.0 (CH), 56.5 (CH), 49.2 (CH_2), 36.7 (CH_2), 25.1 (CH), 22.7 (CH_3), 22.4 (CH_3), 22.3 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1628 (s), 1572 (s), 1435 (s), 1157 (s), 633 (s), 536 (s), 498 (s), 424 (s), 413 (s), 403 (s). HRMS (ESI): *m/z* calculated for $C_{20}H_{25}ClN_3O_2$ (M+H) 374.1630, found 374.1632.

6l: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.06 (bs, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.27-7.14 (m, 6H), 5.27 (m, 1H), 4.67 (d, *J* = 17.4 Hz, 1H), 4.60 (d, *J* = 17.4 Hz, 1H), 2.18 (s, 3H), 1.92 (m, 1H), 1.54-1.48 (m, 2H), 0.88 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.1 (C_q), 169.5 (C_q) 151.2 (C_q), 140.1 (CH), 139.3 (C_q), 136.8 (C_q), 128.8 (CH), 127.4 (CH), 126.1 (CH), 123.4 (CH), 112.3 (CH), 56.4 (CH), 49.1 (CH_2), 36.8 (CH_2), 25.1 (CH), 22.7 (CH_3), 22.3 (CH_3), 22.3 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1624 (s), 1566 (s), 1429 (s),

1388 (s), 1155 (s), 633 (s), 530 (s), 496 (s), 403 (s). HRMS (ESI): *m/z* calculated for $C_{20}H_{25}BrN_3O_2$ (M+H) 418.1125, found 418.1139.

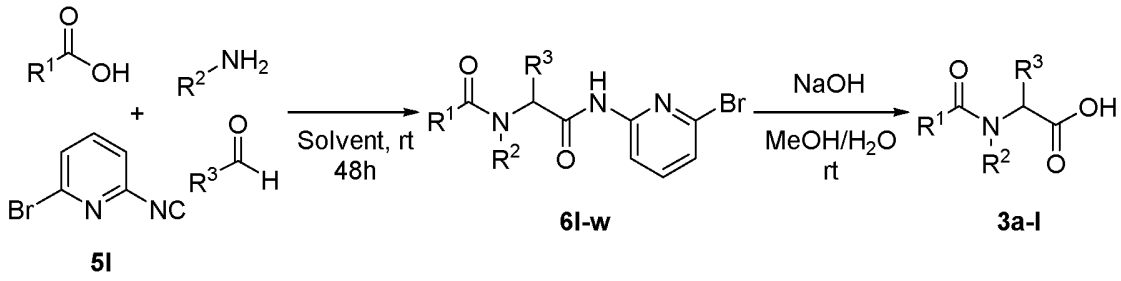
3a: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.3). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.40 (bs, 1.3H), 7.42-7.18 (m, 6.5H), 5.05 (d, *J* = 15.6 Hz, 0.3H), 4.75-4.70 (m, 2H), 4.51 (d, *J* = 17.3 Hz, 1H), 4.42 (m, 0.3H), 4.22 (d, *J* = 15.6 Hz, 0.3H), 2.30 (s, 0.9H), 2.17 (s, 3H), 1.92 (m, 1H), 1.73 (m, 0.3H), 1.65-1.49 (m, 2.3H), 1.36 (m, 0.3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 0.9H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.59 (d, *J* = 6.7 Hz, 0.9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.4 (C_q), 174.4 (C_q), 173.3 (C_q), 173.0 (C_q), 138.2 (C_q), 136.5 (C_q), 128.8 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 126.9 (CH), 126.6 (CH), 59.5 (CH), 57.2 (CH), 51.7 (CH_2), 47.5 (CH_2), 38.4 (CH_2), 38.1 (CH_2), 25.2 (CH), 24.4 (CH), 22.2 (CH_3), 22.2 (CH_3), 22.2 (CH_3), 22.0 (CH_3), 22.0 (CH_3), 21.7 (CH_3). IR (neat): *v*max (cm^{-1}) = 2955 (w), 1735 (s), 1718 (s), 729 (s), 632 (s), 546 (s), 501 (s). HRMS (ESI): *m/z* calculated for $C_{15}H_{22}NO_3$ (M+H) 264. 1594, found 264.1603.

3. Evaluation of 5l as a convertible isocyanide in various MCRs and follow-up transformations

[41] Next, we further evaluated the utility of isocyanide **5l** in isocyanide-based MCRs and subsequent hydrolysis, solvolysis, transamidation, and other transformation. Because of its broad scope of application and its importance to medicinal chemistry, we started with the application in the Ugi reaction. Given the ease of transformation of carboxylic acids to various derivatives (amides, esters, etc.) we focused primarily on hydrolysis as a follow-up transformation of MCR products derived from **5l**.

3.1 Ugi reactions with V-l

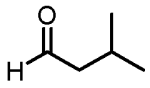
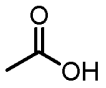
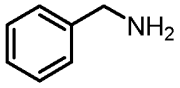
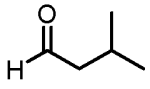
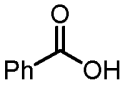
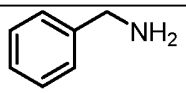
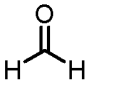
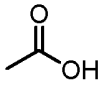
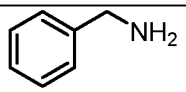
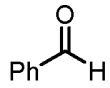
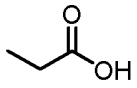
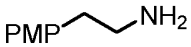
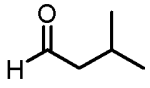
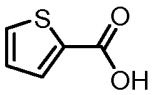
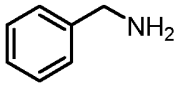
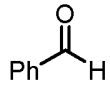
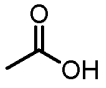
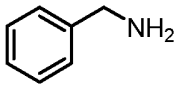
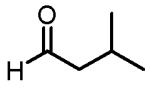
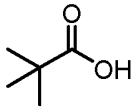
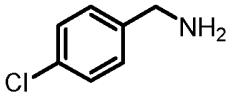
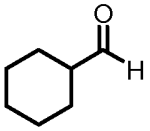
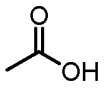
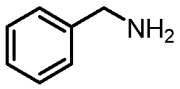
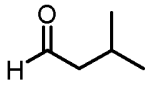
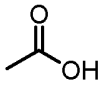
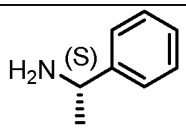
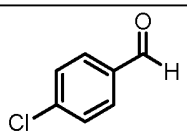
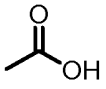
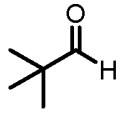
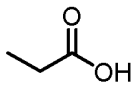
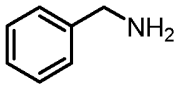
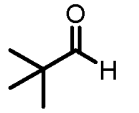
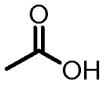
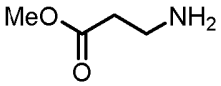
[42] Isocyanide **5l** was reacted with various aldehydes, amines, and carboxylic acids to give the corresponding Ugi products **25a-k** (Scheme 7, General Procure III). The resulting Ugi products **25a-k** were readily saponified to carboxylic acids **3a-k** under mildly basic conditions.



Scheme 7:

Various Ugi reactions with isocyanide **5l** and subsequent hydrolysis

Table 1. Yields of Ugi reactions with **5l** and saponification of the resulting Ugi products **6l-w**

Entry	Aldehyde R^1CHO	Acid R^3COOH	Amine R^2NH_2		Ugi 4CR		Hydrolysis	
				Solvent	Product	Yield	Product	Yield
1				MeOH	**6l**	70%	**3a**	99%
2				TFE	**6m**	80%	**3b**	99%
3				MeOH	**6n**	39%	**3c**	99%
4				TFE	**6o**	70%	**3d**	99%[a]
5				TFE	**6p**	82%	**3e**	99%
6				TFE	**6q**	73%	**3f**	99%[a]
7				MeOH	**6r**	58%	**3g**	99%
8				MeOH	**6s**	89%	**3h**	99%[a]
9				MeOH	**6t**	91%	**3i**	99%[a]
10				TFE	**6u**	77%	**3j**	99%[a]
11				MeOH	**6v**	92%	**3k**	99%[a]
12				MeOH	**6w**	73%	**3l**	99%[a]

a) The deprotection requires elevated temperatures or elongated reaction time.

General procedure III: Ugi reaction and subsequent hydrolysis

[43] The amine (1.0 mmol, 1.0 eq.) and the aldehyde (1.0 mmol, 1.0 eq.) were dissolved in the appropriate solvent (3 mL) and prestirred for 2 hours at room temperature. The carboxylic acid (1.5 mmol, 1.5 eq.) and 2-bromo-6-isocyanopyridine (220 mg, 1.2 mmol, 1.2 eq.) were added subsequently. Additional solvent (1 mL) was added and the reaction mixture stirred for 48 hours at room temperature. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (cyclohexane : EtOAc) to yield the dipeptide Ugi-products generally as a foamy solid.

[44] Unless stated otherwise: The Ugi product (0.1 mmol, 1.0 eq.) was dissolved in MeOH (0.75 mL) and 2M NaOH (0.25 mL, 5.0 eq.) was added. The resulting mixture stirred for 48 hours at room temperature. Conversion of the amide to the acid was monitored by TLC, indicated by formation of 6-bromopyridin-2-amine (a characteristic blue spot appears without stain). The crude mixture was acidified to pH=1 with 1M HCl and extracted with EtOAc. The organic layer was washed with 1M HCl and with brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield the corresponding carboxylic acid.

[45] Analytical data:

6l: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.06 (bs, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.27-7.14 (m, 6H), 5.27 (m, 1H), 4.67 (d, *J* = 17.4 Hz, 1H), 4.60 (d, *J* = 17.4 Hz, 1H), 2.18 (s, 3H), 1.92 (m, 1H), 1.54-1.48 (m, 2H), 0.88 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.1 (C_q), 169.5 (C_q) 151.2 (C_q), 140.1 (CH), 139.3 (C_q), 136.8 (C_q), 128.8 (CH), 127.4 (CH), 126.1 (CH), 123.4 (CH), 112.3 (CH), 56.4 (CH), 49.1 (CH_2), 36.8 (CH_2), 25.1 (CH), 22.7 (CH_3), 22.3 (CH_3), 22.3 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1624 (s), 1566 (s), 1429 (s), 1388 (s), 1155 (s), 633 (s), 530 (s), 496 (s), 403 (s). HRMS (ESI): *m/z* calculated for $C_{20}H_{25}BrN_3O_2$ (M+H) 418.1125, found 418.1139.

6m: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.38 (bs, 1H), 7.78-6.97 (m, 13H), 5.04 (m, 1H), 4.75 (d, *J* = 15.0 Hz, 1H), 4.47 (m, 1H), 1.96 (m, 2H), 1.72 (m, 1H), 0.99 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.1 (C_q), 169.4 (C_q), 151.1 (C_q), 139.9 (CH), 139.2 (C_q), 135.8 (C_q), 135.2 (C_q), 130.3 (CH), 128.6 (CH), 128.4 (CH), 127.6 (CH), 127.5 (CH), 123.2 (CH), 112.3 (CH), 57.5 (CH), 51.5 (CH_2), 36.3 (CH_2), 24.9 (CH), 22.9 (CH_3), 22.0 (CH_3). IR (neat): *v*max (cm^{-1}) = 3252 (w), 2955 (w), 1697 (s), 1564 (s), 1522 (m), 1431 (s), 1155 (s), 787 (s), 698 (m). HRMS (ESI): *m/z* calculated for $C_{25}H_{27}BrN_3O_2$ (M+H) 480.1281, found 480.1272.

6n: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.2). ^{1}H NMR ($CDCl_3$, 500 MHz) δ8.69 (bs, 1H), 8.22 (bs, 0.2H), 8.12 (d, *J* = 8.1 Hz, 0.2H), 8.08 (d, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1.2H), 7.38-7-26 (m, 3.6H), 7.20 (dd, *J* = 4.9, 2.7, 2.4H), 4.70 (s, 2.4H), 4.14 (s, 2H), 4.04 (s, 0.4H), 2.30 (s, 3H), 2.19 (s, 0.6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.4 (C_q), 167.4 (C_q), 151.0 (C_q), 140.4 (CH), 139.3 (C_q), 135.3 (C_q), 129.1 (CH), 128.9 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 126.6 (CH), 123.7 (CH), 112.4 (CH), 53.4 (CH_2), 51.6 (CH_2),

50.6 (CH_2), 49.9 (CH_2), 21.8 (CH_3) 21.4 (CH_3). IR (neat): *v*max (cm^{-1}) = 3227 (w), 3040 (w), 1701 (s), 1623 (m), 1568 (s), 1431 (s), 1155 (s), 1128 (s), 789 (s), 729 (s). HRMS (ESI): *m/z* calculated for $C_{16}H_{17}BrN_3O_2$ (M+H) 362.0499, found 362.0485.

6o: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.23 (bs, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.50-7.41 (m, 5H), 7.17 (d, *J* = 7.7 Hz, 1H), 6.78-6.74 (m, 4H), 6.19 (s, 1H), 3.75 (s, 3H), 3.45 (m, 2H), 2.62-2.43 (m, 3H), 2.10 (m, 1H), 1.20 (t, *J* = 7,3, 3H).^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.0 (C_q), 168.9 (C_q), 158.2 (C_q), 151.2 (C_q), 140.4 (CH), 139.2 (C_q), 133.9 (C_q), 130.2 (CH), 130.1 (C_q), 129.4 (CH), 129.3 (CH), 129.2 (CH), 123.5 (CH), 113.9 (CH), 112.3 (CH), 63.5 (CH), 55.2 (CH_3), 48.1 (CH_2), 35.4 (CH_2), 26.7 (CH_2), 9.4 (CH_3). IR (neat): *v*max (cm^{-1}) = 3238 (w), 2937 (w), 1705 (m), 1618 (s), 1568 (s), 1512 (s), 1431 (s), 1153 (s), 787 (m). HRMS (ESI): *m/z* calculated for $C_{25}H_{27}BrN_3O_3$ (M+H) 496.1130, found 496.1123.

6p: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.18 (bs, 7.83 (d, *J* = 8.1 Hz, 1H), 7.51 (d, *J* =2.5 Hz, 1H), 7.46-7.41 (m, 2H), 7.27-7.17 (m, 6H), (t, *J* = 4.4 Hz, 1H), 5.04 (d, *J* =17.1 Hz, 1H), 5.02 (t, *J* = 7.3 Hz, 1H), 4.82 (d, *J* =16.8 Hz, 1H), 1.99 (m, 1H), 1.75 (m, 1H), 1.61 (m, 1H), 0.90 (m, 6H).^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.3 (C_q), 166.7 (C_q), 151.2 (C_q), 140.1 (CH), 139.4 (C_q), 137.1 (C_q), 136.5 (C_q), 130.8 (CH), 130.0 (CH), 128.7 (CH), 127.7 (CH), 127.3 (CH), 127.2 (CH), 123.6 (CH), 112.5 (CH), 59.2 (CH), 51.5 (CH_2), 37.1 (CH_2), 25.2 (CH). 22.6 (CH_3), 22.5 (CH_3). IR (neat): *v*max (cm^{-1}) = 3240 (w), 2957 (w), 1697 (s), 1562 (s), 1517 (s), 1427 (s), 1387 (s), 1155 (s), 1120 (s), 727 (s). HRMS (ESI): *m/z* calculated for $C_{23}H_{25}BrN_3O_2S$ (M+H) 486.0845, found 486.0831.

6q: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.23 (bs, 1H), 8.20 (d, *J* = 8.3 Hz, 1H), 7.53 (t, *J* = 8 Hz, 1H), 7.34 (m, 2H), 7.27 (m, 3H), 7.18 (m, 4H), 6.98 (d, *J* = 7.3 Hz, 2H), 6.12 (s, 1H), 4.75 (d, *J* = 17.6 Hz, 1H), 4.53 (d, *J* = 17.6, 1H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8 (C_q), 168.6 (C_q), 151.1 (C_q), 140.5 (CH), 139.2 (C_q), 137.1 (C_q), 133.3 (C_q), 130.1 (CH), 129.2 (CH), 129.1 (CH), 128.4 (CH), 127.0 (CH), 126.0 (CH), 123.6 (CH), 112.3 (CH), 63.9 (CH), 50.5 (CH_2), 22.4 (CH_3). IR (neat): *v*max (cm^{-1}) = 3238 9w), 3030 (w), 1703 (s), 1634 (s), 1568 (s), 1431 (m), 1153 (s), 698 (m), 631 (s), 530 (s), 500 (s). HRMS (ESI): *m/z* calculated for $C_{22}H_{21}BrN_3O_2$ (M+H) 438.0812, found 438.0804.

6r: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.04 (bs, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.22-7.13 (m, 6H), 4.89 (d, *J* = 16.3 Hz, 1H), 4.66 (t, *J* = 7.4 Hz, 1H), 4.56 (d, *J* = 16.3 Hz, 1H), 1.85 (m, 1H), 1.69 (m, 1H), 1.54 (m, 1H), 1.38 (s, 9H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.3 (C_q), 169.8 (C_q), 151.2 (C_q), 140.0 (CH), 139.3 (C_q), 134.7 (C_q), 133.6 (C_q), 128.9 (CH), 128.8 (CH), 123.3 (CH), 112.3 (CH), 59.1 (CH), 49.9 (CH_2), 40.2 (C_q), 36.7 (CH_2), 28.9 (CH_3), 24.9 (CH), 22.8 (CH_3), 22.3 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1701 (s), 1562 (s), 1431 (s), 1155 (s), 787 (s). HRMS (ESI): *m/z* calculated for $C_{23}H_{30}BrClN_3O_2$ (M+H) 494.1204, found 494.1201.

6s: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.26 (bs, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.21-7.12 (m, 6H), 4.78 (m, 1H), 4.68 (d, *J* = 17.2 Hz, 1H), 4.61 *J* = 17.2 Hz, 1H), 2.28 (m, 1H), 2.17 (s, 3H), 1.75-1.60 (m, 6H), 1.20-1.14 (m, 2H), 1.03-0.99 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.2 (C_q), 168.8 (C_q), 151.2 (C_q), 140.2 (CH), 139.3 (C_q), 136.7 (C_q), 128.7 (CH), 127.3 (CH), 126.1 (CH), 123.5 (CH), 112.4 (CH), 60.4 (CH), 50.1 (CH_2), 35.6 (CH), 30.2 (CH_2), 28.9 (CH_2), 26.2 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 22.4 (CH_3). IR (neat): *v*max (cm^{-1}) = 3198 (w), 2924 (w), 1628 (s), 1568 (s), 1431 (s), 773 (m), 631 (s),534 (m), 494 (s), 405 (s). HRMS (ESI): *m/z* calculated for $C_{22}H_{27}BrN_3O_2$ (M+H) 444.1281, found 444.1266.

6t: Product 1 (a white solid): m.p.: 158 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.45 (bs, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.49-7-31 (m, 5H), 7.17 (d, *J* = 7.6 Hz, 1H), 5.15 (q, *J* = 6.5 Hz, 1H), 3.75 (m, 1H), 2.49 (m, 1H), 2.35 (s, 3H), 1.66 (d, *J* = 7.0 Hz, 3H), 1.26 (m, 1H) 1.17 (m, 1H), 0.63 (d, *J* = 6.5 Hz, 3H), 0.41 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.4 (C_q), 171.4 (C_q), 151.8 (C_q), 140.1 (CH), 139.5 (C_q), 138.8 (C_q), 128.8 (CH), 128.2 (CH), 127.3 (CH), 123.4 (CH), 112.5 (CH), 61.3 (CH), 57.3 (CH), 39.2 (CH_2), 25.1 (CH), 23.9 (CH_3), 23.0 (CH_3), 21.0 (CH_3), 17.6 (CH_3). IR (neat): *v*max (cm^{-1}) = 2966 (w), 1693 (m), 1556 (s), 1529 (s), 1429 (s), 1391 (s), 1319 (m), 1155 (s), 1128 (s), 993 (m), 794 (s), 698 (s), 554 (m), 522 (m). HRMS (ESI): *m/z* calculated for $C_{21}H_{27}BrN_3O_2$ (M+H) 432.1281, found 432.1264. Product 2 (a light brown oil): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.31 (bs, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.40-7.32 (m, 5H), 7.12 (d, *J* = 8.0 Hz, 1H), 5.17 (q, *J* = 7.0 Hz, 1H), 3.93 (bs, 1H), 2.49 (m, 1H), 2.27 (s, 3H), 1.71 (d, *J* = 7.0 Hz, 3H), 1.64 (m, 1H), 1.49 (m, 1H), 0.95 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.0 (C_q), 169.7 (C_q), 151.6 (C_q), 140.1 (CH), 139.3 (C_q), 139.1 (C_q), 129.2 (CH), 128.4 (CH), 126.9 (CH), 123.1 (CH), 112.2 (CH), 59.2 (CH), 56.6 (CH), 39.2 (CH_2), 25.7 (CH), 23.6 (CH_3), 23.3 (CH_3), 22.1 (CH_3), 17.5 (CH_3). IR (neat): *v*max (cm^{-1}) = 3227 (w), 3040 (w), 1701 (s), 1623 (m), 1568 (s), 1431 (s), 1155 (s), 1128 (s), 789 (s), 729 (s). HRMS (ESI): *m/z* calculated for $C_{21}H_{27}BrN_3O_2$ (M+H) 432.1281, found 432.1272.

6u: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.81 (bs, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.33 (bs, 4H), 7.17 (d, *J* = 7.5, 1H), 6.11 (s, 1H), 3.25 (t, *J* = 8.0 Hz, 2H), 2.25 (s, 3H), 1.45 (m, 1H), 1.05 (m, 1H), 0.69 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.1 (C_q), 168.6 (C_q), 151.2 (C_q), 140.4 (CH), 139.3 (C_q), 135.0 (C_q), 132.8 (C_q), 131.0 (CH), 123.6 (CH), 112.3 (CH), 62.6 (CH), 49.2 (CH_2), 23.0 (CH_2), 21.8 (CH_3) 11.1 (CH_3). IR (neat): *v*max (cm^{-1}) = 2968 (w), 1703 (m), 1616 (m), 1566 (s), 1533 (m), 1427 (s), 1391 (s), 1300 (m), 1155 (s), 1128 (s), 789 (s), 731 (s), 548 (s). HRMS (ESI): *m/z* calculated for $C_{18}H_{20}BrN_3O_2$ (M+H) 424.0422, found 424.0418.

6v: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.69 (bs, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.18-7-04 (m, 6H), 5.36 (bs, 1H), 5.19 (d, *J* = 17.5 Hz, 1H), 4.74 (d, *J* = 17.5 Hz, 1H), 2.39 (m, 1H), 2.22 (m, 1H), 1.14 (s, 9H), 1.10 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz)

δ 176.7 (C_q), 168.3 (C_q), 150.8 (C_q), 140.2 (CH), 139.2 (C_q), 138.1 (C_q), 128.6 (CH), 126.7 (CH), 125.3 (CH), 123.6 (CH), 112.4 (CH) 49.6 (CH_2), 36.7 (C_q), 27.6 (CH_3), 27.4 (CH_2), 9.8 (CH_3). IR (neat): *v*max (cm^{-1}) = 2960 (w), 1630 (s), 1566 (s), 1529 (m), 1431 (s), 1389 (s), 1153 (s), 1128 (s), 789 (s), 731 (s). HRMS (ESI): *m/z* calculated for $C_{21}H_{27}BrN_3O_2$ (M+H) 432.1281, found 432.1267.

6w: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.60 (bs, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 5.31 (bs, 1H), 4.17 (m, 1H), 3.85 (m, 1H), 3.65 (s, 3H), 2.63-2.56 (m, 2H), 2.34 (s, 3H), 1.11 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8 (C_q), 171.3 (C_q), 169.1 (C_q), 151.3 (C_q), 140.4 (CH), 139.5 (C_q), 123.7 (CH), 112.6 (CH), 60.4 (CH_2), 51.9 (CH), 36.5 (C_q), 34.6 (CH_2), 27.8 (CH_3), 21.9 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1735 (s), 1628 (s), 1568 (s), 1431 (s), 1153 (s), 764 (m), 631 (s), 534 (m), 498 (s), 401 (s). HRMS (ESI): *m/z* calculated for $C_{17}H_{25}BrN_3O_4$ (M+H) 414.1023, found 414.1017.

3a: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.3). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.40 (bs, 1.3H), 7.42-7.18 (m, 6.5H), 5.05 (d, *J* = 15.6 Hz, 0.3H), 4.75-4.70 (m, 2H), 4.51 (d, *J* = 17.3 Hz, 1H), 4.42 (m, 0.3H), 4.22 (d, *J* = 15.6 Hz, 0.3H), 2.30 (s, 0.9H), 2.17 (s, 3H), 1.92 (m, 1H), 1.73 (m, 0.3H), 1.65-1.49 (m, 2.3H), 1.36 (m, 0.3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 0.9H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.59 (d, *J* = 6.7 Hz, 0.9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.4 (C_q), 174.4 (C_q), 173.3 (C_q), 173.0 (C_q), 138.2 (C_q), 136.5 (C_q), 128.8 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 126.9 (CH), 126.6 (CH), 59.5 (CH), 57.2 (CH), 51.7 (CH_2), 47.5 (CH_2), 38.4 (CH_2), 38.1 (CH_2), 25.2 (CH), 24.4 (CH), 22.2 (CH_3), 22.2 (CH_3), 22.2 (CH_3), 22.0 (CH_3), 22.0 (CH_3), 21.7 (CH_3). IR (neat): *v*max (cm^{-1}) = 2955 (w), 1735 (s), 1718 (s), 729 (s), 632 (s), 546 (s), 501 (s). HRMS (ESI): *m/z* calculated for $C_{15}H_{22}NO_3$ (M+H) 264. 1594, found 264.1603.

3b: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.7). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.45 (bs, 1.7H), 7.59-7.16 (m, 17H), 5.19 (d, *J* = 14.3 Hz, 0.7H), 4.69 (d, *J* = 15.6 Hz, 1H), 4.4.49 (m, 1.7H), 4.21 (d, *J* = 14.6 Hz, 0.7H), 4.14 (m, 1H), 2.19 (m, 1H), 1.83-1.52 (m, 3.1H), 1.30 (m, 1H), 0.98-0.82 (m, 6H), 0.60-0.40 (m, 4.2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.0 (C_q), 175.5 (C_q), 173.7 (C_q), 173.6 (C_q), 138.3 (C_q), 135.8 (C_q), 135.7 (C_q), 135.2 (C_q), 130.3 (CH), 130.1 (CH), 129.7 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.4 (CH), 127.0 (CH), 126.6 (CH), 60.6 (CH), 58.7 (CH), 54.6 (CH_2), 47.4 (CH_2), 38.2 (CH_2), 29.7 (CH_2), 25.4 (CH), 24.2 (CH), 22.4 (CH_3), 22.2 (CH_3), 21.4 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1713 (m), 1593 (m), 1447 (m), 1246 (m), 733 (m), 633 (s), 536 (s), 494 (s), 403 (s). HRMS (ESI): *m/z* calculated for $C_{20}H_{24}NO_3$ (M+H) 326.1751, found 326.1748.

3c: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.4). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.60 (bs, 1.4H), 7.39-7.19 (m, 7H), 4.66 (s, 0.8H), 4.63 (s, 2H), 4.09 (s, 2H), 3.94 (s, 0.8H), 2.25 (s, 3H), 2.16 (s, 1.2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7 (C_q), 172.6 (C_q), 172.3 (C_q), 172.1 (C_q), 136.31 (C_q), 135.4 (C_q), 129.1 (CH), 128.7 (CH), 128.4 (CH), 128.0 (CH),

127.7 (CH), 126.7 (CH), 53.0 (CH_2), 49.5 (CH_2), 48.8 (CH_2), 47.1 (CH_2), 21.3 (CH_3), 21.1 (CH_3). IR (neat): *v*max (cm^{-1}) = 2927 (w), 1732 (m), 1599 (m), 1431 (m), 1201 (m), 633 (s), 532 (m), 498 (s), 403 (s). HRMS (ESI): *m/z* calculated for $C_{11}H_{14}NO_3$ (M+H) 208.0968, found 208.0964.

3d: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.14). ^1H NMR ($CDCl_3$, 500 MHz) δ 10.71 (bs, 1.14H), 7.42 (m, 5.7H), 6.75 (m, 4.56H), 6.03 (s, 1H), 5.74 (s, 0.14H), 3.75 (s, 3.42H), 3.65 (m, 0.14H), 3.42 (m, 1H), 3.35 (m, 1H), 3.17 (m, 0.14H), 2.75 (m, 0.14H), 2.58 (m, 1H), 2.50-2.31 (m, 2.28H), 2.13 (m, 1H), 1.92 (m, 0.14H), 1.16 (t, *J* =7.0 Hz, 3.42H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.6 (C_q), 174.0 (C_q), 158.2 (C_q), 133.9 (C_q), 129.9 (C_q), 129.8 (CH), 129.4 (CH), 128.9 (CH), 113.9 (CH), 62.5 (CH), 55.2 (CH_3), 48.4 (CH_2), 35.2 (CH_2), 26.6 (CH_2), 9.4 (CH_3). IR (neat): *v*max (cm^{-1}) = 2937 (w), 1736 (m), 1610 (m), 1512 (s), 1421 (m), 1246 (s), 1178 (s), 1157 (s), 1036 (m), 727 (m), 702 (s). HRMS (ESI): *m/z* calculated for $C_{20}H_{24}NO_4$ (M+H) 342.1700, found 342.1687.

3e: ^1H NMR ($CDCl_3$, 500 MHz) δ 10.35 (bs, 1H), 7.49 (s, 1H), 7.47-7.30 (m, 6H), 7.00 (s, 1H), 4.99 (d, *J* =16.5 Hz, 1H), 4.79 (bs, 1H), 4.16 (bs, 1H), 2.17 (m, 1H), 1.65 (m, 2H), 0.91-0.63 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.8 (C_q), 166.4 (C_q), 136.9 (C_q), 129.5 (CH), 128.8 (CH), 127.8 (CH), 127.4 (CH), 127.2 (CH), 60.0 (CH), 38.3 (CH_2), 29.7 (CH_2), 25.3 (CH), 22.5 (CH_3), 22.1 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1715 (s), 1591 (m), 1522 (s), 1425 (m), 1352 (m), 1319 (m), 1245 (m), 1173 (m), 968 (m), 908 (m), 858 (m), 729 (s). HRMS (ESI): *m/z* calculated for $C_{18}H_{22}NO_3S$ (M+H) 332.1315, found 332.1305.

3f: ^1H NMR ($CDCl_3$, 500 MHz) δ 10.40 (bs, 1H), 7.37-7.17 (m, 8H), 6.99 (m, 2H), 5.92 (s, 1H), 4.68 (d, *J* = 17.6 Hz, 1H), 4.45 (d, *J* = 17.6 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.8 (C_q), 173.4 (C_q), 136.7 (C_q), 133.5 (C_q), 129.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.1 (CH), 126.1 (CH), 62.6 (CH), 50.6 (CH_2), 22.1 (CH_3). IR (neat): *v*max (cm^{-1}) = 2922 (w), 1732 (m), 1597 (m), 1418 (m), 1204 (m), 729 (s), 698 (s), 634 (s), 530 (s), 496 (s), 401 (s). HRMS (ESI): *m/z* calculated for $C_{17}H_{18}NO_3$ (M+H) 284.1281, found 284.1274.

3g: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34 (d, *J* = 7.4 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 4.91 (d, *J* = 16.5 Hz, 1H), 4.55 (d, *J* = 15.0 Hz, 1H), 3.49 (m, 1H), 2.19 (m, 1H), 1.59 (m, 1H), 1.43 (m, 1H), 1.34 (s, 9H), 0.86 (d, *J* = 6.5 Hz, 1H), 0.73 (d, *J* = 6.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.6 (C_q), 174.7 (C_q), 129.0 (CH), 128.9 (CH), 60.6 (CH), 39.3 (CH_2), 38.7 (C_q), 29.7 (CH_2), 28.4 (CH_3), 25.4 (CH), 22.8 (CH_3), 22.0 (CH_3). IR (neat): *v*max (cm^{-1}) = 2959 (w), 1734 (m), 1716 (m), 1636 (m), 1493 (s), 1182 (m), 790 (m), 516 (s), 430 (s). HRMS (ESI): *m/z* calculated for $C_{18}H_{27}ClNO_3$ (M+H) 140.1674, found 340.1650.

3h: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.2). ^1H NMR ($CDCl_3$, 500 MHz) δ 10.78 (bs, 1.2H), 7.38-7.11 (m, 6H), 4.74 (d, *J* = 16.8 Hz, 1H), 4.67 (d, *J* = 15.5 Hz, 0.2H), 4.60 (d, *J* = 15.5 Hz, 0.2H), 4.40 (d, *J* = 16.8 Hz, 1H), 3.99 (d, *J* = 11.0 Hz, 0.2H), 3.87 (d, *J* = 10.5 Hz, 1H), 2.32 (m, 1H), 2.26 (s, 0.6H), 2.20 (s, 3H), 1.93 (m, 0.2H), 1.81-1.56 (m,

4.8H), 1.48 (m, 0.2H), 1.36-1.04 (m, 4.6H), 1.01-0.68 (m, 2.4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.7 (C_q), 173.5 (C_q), 172.5 (C_q), 171.8 (C_q), 137.9 (C_q), 135.2 (C_q), 129.0 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 126.8 (CH), 126.7 (CH), 70.6 (CH), 66.2 (CH), 55.4 (CH_2), 46.2 (CH_2), 36.7 (CH), 36.0 (CH), 30.3 (CH_2), 30.1 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 25.3 (CH_2), 22.6 (CH_3), 22.3 (CH_3). IR (neat): *v*max (cm^{-1}) = 2926 (m), 1728 (m), 1601 (s), 1450 (s), 1421 (m), 1240 (m), 1184 (m), 910 (m), 729 (s), 696 (s). HRMS (ESI): *m/z* calculated for $C_{17}H_{24}NO_3$ (M+H) 290.1751, found 290.1733.

3i: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.22 (bs, 1.1H), 5.17 (m, 1.1H), 3.56 (m, 0.1H), 3.47 (m, 1H), 2.34 (m, 4.4H), 1.67 (d, *J* =7.0 Hz, 3.3H), 1.26 (m, 1.1H), 0.91 (m, 0.6H), 0.76 (m, 1.1H), 0.60 (d, *J* =6.5 Hz, 3H), 0.22 (d, *J* =6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.4 (C_q), 173.0 (C_q), 172.8 (C_q), 172.6 (C_q), 138.0 (C_q), 137.9 (C_q), 128.8 (CH), 128.8 (CH), 128.4 (CH), 128.4 (CH), 127.7 (CH), 127.3 (CH), 58.0 (CH), 57.8 (CH), 57.7 (CH), 57.6 (CH), 39.9 (CH_2), 39.2 (CH_2), 25.6 (CH), 24.9 (CH), 23.5 (CH_3), 23.3 (CH_3), 23.0 (CH_3), 22.7 (CH_3), 21.7 (CH_3), 20.5 (CH_3), 17.6 (CH_3), 16.9 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (w), 1715 (m), 1635 (m), 1593 (m), 1450 (m), 1313 (m), 1246 (m), 1205 (s), 904 (s), 725 (s), 648 (s). HRMS (ESI): *m/z* calculated for $C_{16}H_{24}NO_3$ (M+H) 278.1751, found 278.1738.

3j: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.1). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.15 (bs, 1.1H), 7.99 (d, *J* =7.5 Hz, 0.1H), 7.42 (d, *J* =7.5 Hz, 0.1H), 7.30 (m, 4H), 5.67 (s, 1H), 5.54 (s, 0.1H), 3.37 (m, 0.1H), 3.24 (m, 1H), 3.12 (m, 1H), 3.02 (m, 0.1H), 2.20 (s, 3.3H), 1.45 (m, 1.1H), 1.14 (m, 1.1H), 0.73 (t, *J* = 7.3 Hz, 3H), 0.63 (m, 0.3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8 (C_q), 172.7 (C_q), 172.4 (C_q), 170.1 (C_q), 140.1 (C_q), 134.6 (C_q), 132.8 (C_q), 131.5 (CH), 130.8 (CH), 130.2 (CH), 128.8 (CH), 127.9 (C_q), 64.1 (CH), 62.1 (CH), 49.9 (CH_2), 47.3 (CH_2), 29.7 (CH_2), 22.6 (CH_2), 22.2 (CH_3), 21.4 (CH_3), 11.3 (CH_3), 11.1 (CH_3). IR (neat): *v*max (cm^{-1}) = 2968 (w), 1734 (m), 1595 (s), 1493 (s), 1421 (m), 1194 (m), 1092 (s), 1016 (s), 734 (m). HRMS (ESI): *m/z* calculated for $C_{13}H_{17}ClNO_3$ (M+H) 270.0891, found 270.0886.

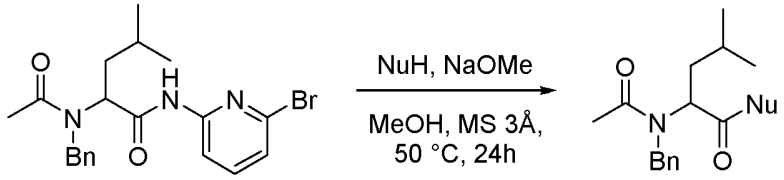
3k: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (t, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 2H), 4.96 (d, *J* = 17.0 Hz, 1H), 4.40 (d, *J* = 17.0 Hz, 1H), 4.29 (bs, 1H), 2.37 (m, 2H), 1.12 (m, 12H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.2 (C_q), 171.4 (C_q), 136.0 (C_q), 129.1 (CH), 127.8 (CH), 126.0 (CH), 36.9 (CH_2), 29.7 (C_q), 28.4 (CH_3), 28.0 (CH_2), 9.5 (CH_3). IR (neat): *v*max (cm^{-1}) = 2961 (w), 1733 (m), 1604 (m), 1465 (m), 1452 (m), 1213 (m), 1163 (s), 966 (m), 731 (s), 696 (s). HRMS (ESI): *m/z* calculated for $C_{16}H_{24}NO_3$ (M+H) 278.1751, found 278.1742.

3l: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.5). ^{1}H NMR (MeOD, 500 MHz) δ 4.26 (bs, 0.5H), 3.95 (m, 1H), 3.63 (m, 2H), 2.82-2.58 (m, 3H), 2.17 (s, 4.5H), 1.14 (s, 4.5H), 1.10 (s, 9H). ^{13}C NMR (MeOD, 125 MHz) δ 175.6 (C_q), 174.9 (C_q), 174.9 (C_q), 174.1 (C_q), 172.5 (C_q), 172.2 (C_q), 69.6 (CH), 69.5 (CH), 42.9 (CH_2), 37.1 (CH_2), 36.6 (CH_2), 34.6

(CH_2), 33.2 (C_q), 30.8 (C_q), 28.5 (CH_3), 28.3 (CH_3), 22.7 (CH_3), 21.7 (CH_3). IR (neat): *v*max (cm^{-1}) = 2962 (w), 1717 (m), 1607 (m), 1419 (m), 1367 (s), 1209 (m), 1165 (s), 797 (s), 540 (m). HRMS (ESI): *m/z* calculated for $C_{11}H_{20}NO_5$ (M+H) 246.1336, found 246.1327.

3.1.1 Transformations under basic conditions.

[46] The nucleophilic displacement of the 2-amino-6-bromopyridine moiety from the Ugi products under basic conditions gave good results, therefore other transformations were evaluated starting from the Ugi product of **5l**, acetic acid, isovaleraldehyde and benzylamine. It was found that this Ugi product (**6l**) was readily converted to the corresponding methyl ester **3a**, as well as secondary and tertiary amides (**2ba** and **2aa**, respectively).

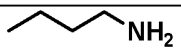


6l **3a, 4a, 2aa, 2ba**

Scheme 8:

Nucleophilic substitution of Ugi product **6l** with various nucleophiles under basic conditions.

Table 2. Yields of nucleophilic substitution of Ugi product **6l** with various nucleophiles under basic conditions.

Entry	NuH	Product	Yield
1	H_2O	**3a**	99%
2	MeOH	**4a**	80%
3		**2ba**	61%
4		**2aa**	70%

[47] Analytical data:

4a: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.35). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.17 (m, 6.75H), 4.95 (t, *J* =6.9 Hz, 1H), 4.66 (d, *J* = 17.6 Hz, 1.35H), 5.51 (d, *J* = 17.6 Hz, 1.35H), 4.41 (dd, *J* = 8.6 Hz, 6.1 Hz, 0.35H), 3.60 (s, 3H), 3.49 (s, 1.05H), 2.28 (s, 1.05H), 2.13 (s, 3H), 1.86-1.74 (m, 1.35H), 1.66 (m, 0.35H), 1.54 (m, 2H), 1.41 (m, 0.35H), 0.90 (m, 4.05H), 0.79 (d, *J* = 6.3Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 1.05H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.2 (C_q), 171.9 (C_q), 171.7 (C_q), 171.3 (C_q), 138.0 (C_q), 137.0 (C_q), 128.6 (CH), 128.1 (CH), 128.0 (CH), 127.4 (CH), 127.0 (CH), 126.4 (CH), 58.8 (CH), 55.6 (CH), 52.1 (CH_3), 51.9 (CH_3), 50.5 (CH_2), 46.2 (CH_2), 38.3 (CH_2), 29.6 (CH_2), 25.1 (CH), 24.3 (CH), 22.4 (CH_3), 22.4 (CH_3), 22.2 (CH_3), 22.2 (CH_3), 22.1 (CH_3), 21.9 (CH_3). IR (neat): *v*max (cm^{-1}) =

2955 (m), 1738 (s), 1649 (s), 1410 (s), 1200 (s), 729 (s), 633 (s), 498 (s). HRMS (ESI): *m/z* calculated for $C_{16}H_{24}NO_3$ (M+H) 278.1751, found 278.1742.

2ba: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.1). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 6.56 (bs, 1H), 5.04 (m, 1H), 4.65 (d, *J* = 17.8 Hz, 1H), 4.59 (d, *J* = 17.7 Hz, 1H), 3.23-3.11 (m, 2H), 2.06 (s, 3H), 1.84 (m, 1H), 1.51-1.34 (m, 4H), 1.33-1.28 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9 (C_q), 170.6 (C_q), 137.5 (C_q), 128.6 (CH), 127.2 (CH), 125.9 (CH), 55.7 (CH), 48.9 (CH_2), 38.9 (CH_2), 37.0 (CH_2), 31.4 (CH_2), 25.1 (CH), 22.8 (CH_3), 22.4 (CH_3), 22.3 (CH_3), 20.0 (CH_2), 13.7 (CH_3). IR (neat): *v*max (cm^{-1}) = 3298 (m), 2957 (m), 1630 (s), 1547 (s), 633 (s), 532 (s), 498 (s). HRMS (ESI): *m/z* calculated for $C_{19}H_{31}N_2O_2$ (M+H) 319.2380, found 319.2369.

2aa: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.16). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39-7.08 (m, 5.8H), 5.58 (t, *J* = 7.0 Hz, 1H), 5.08 (d, *J* = 15.0 Hz, 0.16H), 4.73 (d, *J* = 17.5 Hz, 1H), 4.68 (d, *J* = 17.5 Hz, 1H), 4.27 (m, 0.16H), 4.05 (d, *J* = 15.0 Hz, 0.16H), 3.71 (m, 1H), 3.51 (m, 1H), 3.35 (m, 1H), 3.21 (m, 0.32H), 3.12 (m, 0.16H), 3.00 (m, 1H), 2.70 (m, 0.16H), 2.35 (m, 0.16H), 2.27 (s, 0.48H), 2.07 (s, 3H), 2.00-1.69 (m, 5.64H), 1.63-1.41 (m, 2.32H), 0.99-0.80 (m, 6.96H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.9 (C_q), 170.7 (C_q), 168.9 (C_q), 166.0 (C_q), 138.4 (C_q), 138.0 (C_q), 128.4 (CH), 128.4 (CH), 127.8 (CH), 126.9 (CH), 126.8 (CH), 125.8 (CH), 57.8 (CH), 52.1 (CH), 47.9 (CH_2), 46.4 (CH_2), 45.7 (CH_2), 45.6 (CH_2), 45.4 (CH_2), 45.1 (CH_2), 39.2 (CH_2), 38.6 (CH_2), 25.9 (CH_2), 25.6 (CH_2), 24.8 (CH), 24.6 (CH), 24.0 (CH_2), 23.4 (CH_3), 23.4 (CH_2), 22.9 (CH_3), 22.6 (CH_3), 22.3 (CH_3), 21.8 (CH_3), 21.7 (CH_3). IR (neat): *v*max (cm^{-1}) = 2955 (m), 1636 (s), 1439 (m), 1408 (m), 698 (m), 621 (m). HRMS (ESI): *m/z* calculated for $C_{19}H_{29}N_2O_2$ (M+H) 317.2224, found 317.2200.

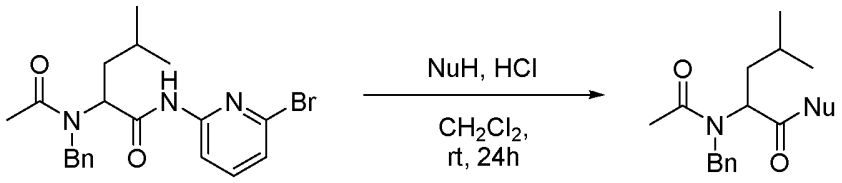
General procedure IV: Nucleophilic substitution of Ugi products derived from 5l under basic conditions.

[48] To a flame dried Schlenk 3Å MS, NaOMe in MeOH (0.5M, 5 mL, 2.5 mmol, 5.0 eq.) and a nucleophile (2.5 mmol, 5.0 eq.) were added and predried for 1 hour under nitrogen atmosphere. The Ugi-product 2-(*N*-benzylacetamido)-*N*-(6-bromopyridin-2-yl)-4-methylpentanamide (209 mg, 0.5 mmol, 1.0 eq.) was added and the mixture was stirred for 24h at 50°C. The crude mixture was cooled to 0°C and acidified at once to pH=1 with 6M HCl and extracted with EtOAc. The organic layer was washed with 1M HCl and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography (cyclohexane : EtOAc) to yield the corresponding product.

3.1.2 Transformations under acidic conditions

[49] The 2-amino-6-bromopyridine moiety in the above Ugi products may also be

displaced by non-basic nucleophiles under acidic conditions (scheme 9). It was found that conversion of Ugi product **6l** to various esters **4a-d** was efficient (quantitative yield). Also thioesters **4e** and **4f** were obtained in this manner.

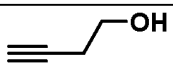
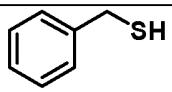


6l **3a**, **4a-f**

Scheme 9:

Nucleophilic substitution of Ugi product **6l** with various nucleophiles under acidic conditions.

Table 3. Yields of nucleophilic substitution of Ugi product **6l** with various nucleophiles under acidic conditions.

Entry	NuH	Product	Yield
1	**H_2O**	**3a**	99%
2	**MeOH**	**4a**	99%
3	**BuOH**	**4b**	99%
4	***i*PrOH**	**4c**	99%
5		**4d**	65%[a]
6	**EtSH**	**4e**	86%[b]
7		**4f**	36%[c]

a) 2 Equivalents of the corresponding alcohol were used, b) EtSH was used as a co-solvent, c) 4Å MS were added to the reaction mixture.

General procedure V: Nucleophilic substitution of Ugi products derived from 5l under acidic conditions.

[50] The Ugi-product 2-(*N*-benzylacetamido)-*N*-(6-bromopyridin-2-yl)-4-methylpentanamide (209 mg, 0.5 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (2 mL) and HCl in Et_2O solution (1M, 2.5 mL, 2.5 mmol, 5.0 eq.) was added. Subsequently, the nucleophile (2.5 mmol, 5.0 eq.) was added and the resulting mixture stirred for 16 hours at room temperature. The crude mixture was acidified to pH=1 with 1M HCl and extracted with CH_2Cl_2. The organic layer was washed with 1M HCl and brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield the corresponding product.

Analytical data:

4b: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.4). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34-7.12 (m, 7H), 4.80 (t, *J* = 6.6 Hz, 1H), 4.65 (m, 1.4H), 4.43 (m, 1.4H), 4.37 (m, 0.4H), 4.00 (m, 1H), 3.93 (m, 1.4H), 3.76 (m, 0.4H), 2.23 (s, 1.2H), 2.06 (s, 3H), 1.82-1.75 (m, 1.4H), 1.56-1.43 (m, 5.6H), 1.33-1.24 (m, 2.8H), 0.89-0.83 (m, 8.4H), 0.73 (d, *J* = 6.5 Hz, 3H), 0.65 (d, *J* = 6.7 Hz, 1.2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8 (C_q), 171.7 (C_q), 171.5 (C_q),170.8 (C_q), 137.9 (C_q), 137.0 (C_q), 128.5 (CH), 128.0 (CH), 127.8 (CH), 127.3 (CH), 126.8 (CH), 126.3 (CH), 65.1 (CH_2), 64.7 (CH_2), 58.9 (CH), 56.00 (CH_2), 50.6 (CH_2), 46.3 (CH_2), 38.3 (CH_2), 38.1 (CH_2), 30.3 (CH_2), 30.1 (CH_2), 25.0 (CH), 24.3 (CH), 22.2 (CH_3), 22.1 (CH_3), 22.0 (CH_3), 21.9 (CH_3), 21.8 (CH_3), 18.9 (CH_2), 18.9 (CH_2), 13.5 (CH_3), 13.5 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (m), 1734 (s), 1653 (s), 633 (s), 536 (s), 498 (s). HRMS (ESI): *m/z* calculated for $C_{19}H_{30}NO_3$ (M+H) 320.2220, found 320.2206.

4c: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.4). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.15 (m, 7H), 4.94 (septet, *J* = 6.3 Hz, 1H), 5.89-5.80 (m, 1.8H), 4.70 (d, *J* = 17.5 Hz, 1H), 4.47 (d, *J* = 17.5 Hz, 1H), 4.33 (t, *J* = 6.3 Hz, 0.4H), 4.28 (d, *J* = 15.5 Hz, 0.4H), 2.56 (s, 1,2H), 2.09 (s, 3H), 1.84 (m, 1H), 1.73 (m, 0.4H), 1.64-1.35 (m, 2.8H), 1.21 (d, *J* = 6.0 Hz, 6H), 1.19 (d, *J* = 6.0 Hz, 1.2H), 1.13 (d, *J* = 6.0 Hz, 1.2H), 0.88 (m, 4.2H), 0.78 (d, *J* = 6.5 Hz, 3H), 0.67 (d, *J* = 6.5 Hz, 1.2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.0 (C_q), 171.9 (C_q), 171.2 (C_q), 170.5 (C_q), 138.4 (C_q), 137.4 (C_q), 128.7 (CH), 128.2 (CH), 127.9 (CH), 127.4 (CH), 126.9 (CH), 126.5 (CH), 69.3 (CH), 68.6 (CH), 59.5 (CH), 56.5 (CH), 50.8 (CH_2), 46.8 (CH_2), 38.6 (CH_2), 25.3 (CH), 24.5 (CH), 22.5 (CH_3), 22.4 (CH_3), 22.3 (CH_3), 22.3 (CH_3), 22.2 (CH_3), 22.0 (CH_3), 21.7 (CH_3), 21.6 (CH_3), 21.5 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (m), 1730 (s), 1653 (s), 1410 (m), 1177 (m), 1105 (s), 968 (m), 727 (s), 698 (s). HRMS (ESI): *m/z* calculated for $C_{18}H_{28}NO_3$ (M+H) 306.2064, found 306.2051.

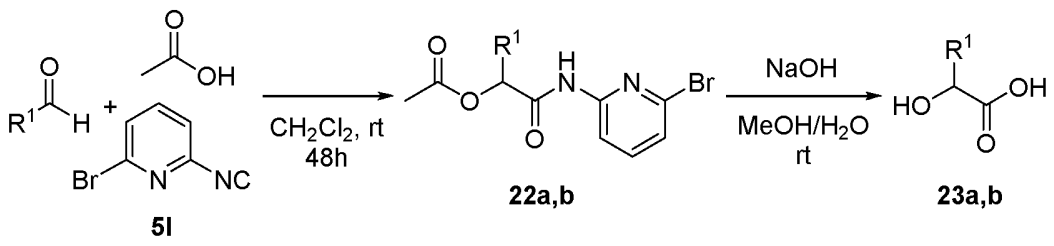
4d: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.35). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.18 (m, 6.75H), 4.77 (t, *J* = 7.0 Hz, 1H), 4.75 (m, 1.35H), 4.50 (m, 1.35H), 4.41 (t, *J* = 7.0 Hz, 0.35H), 4.13 (m, 2H), 4.03 (m, 0.35H), 3.87 (m, 0.35H), 2.48 (m, 2H), 2.39 (m, 0.70H), 2.29 (s, 1H), 2.12 (s, 3H), 1.99 (s, 1.05H), 1.98 (0.35H), 1.89 (m, 1H), 1.78 (m, 0.35H), 1.71-1.38 (m, 2.7H), 0.89 (d, *J* = 6.5 Hz ,4.05H), 0.78 (d, *J* = 6.5 Hz, 3H), 0.73 (d, *J* = 6.5 Hz, 1.05H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.9 (C_q), 171.8 (C_q), 171.4 (C_q),170.7 (C_q), 138.1 (C_q), 137.1 (C_q), 128.7 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.0 (CH), 126.6 (CH), 80.1 (C_q), 70.2 (CH), 69.8 (CH), 62.8 (CH_2), 62.6 (CH_2), 58.9 (CH), 56.2 (CH), 51.1 (CH_2), 46.3 (CH_2), 38.4 (CH_2), 38.2 (CH_2), 25.2 (CH), 24.4 (CH), 22.5 (CH_3), 22.4 (CH_3), 22.4 (CH_3), 22.3 (CH_3), 22.2 (CH_3), 22.0 (CH_3), 18.8 (CH_2), 18.7 (CH_2). IR (neat): *v*max (cm^{-1}) = 3279 (m), 2957 (m), 1736 (s), 1647 (s), 1410 (m), 1240 (m), 1171 (m), 729 (s), 698 (s), 638 (m), HRMS (ESI): *m/z* calculated for $C_{19}H_{26}NO_3$ (M+H) 316.1907, found 316.1892.

4e: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.4). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.18 (m, 7H), 5.30 (t, *J* = 7.0 Hz, 1H), 5.10 (d, *J* = 15.5 Hz, 0.4H), 4.70 (d, *J* = 17.5 Hz, 1H), 4.44 (d, *J* = 17.5 Hz, 1H), 4.40 (t, *J* = 7.0 Hz, 0.4H), 4.02 (d, *J* = 15.5 Hz, 0.4H), 2.85 (m, 2.8H), 2.29 (s, 1.2H), 2.13 (s, 3H), 1.80 (m, 1.4H), 1.54 (m, 1.4H), 1.43 (m, 1H), 1.3 (m, 0.4H), 1.23 (m, 4.2H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 1.2H), 0.74 (d, *J* = 6.5 Hz, 3H), 0.53 (d, *J* = 6.5 Hz, 1.2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.4 (C_q), 199.2 (C_q), 172.4 (C_q), 171.9 (C_q), 138.5 (C_q), 137.3 (C_q), 128.7 (CH), 128.3 (CH), 127.8 (CH), 127.4 (CH), 127.0 (CH), 126.2 (CH), 66.9 (CH), 62.1 (CH), 50.2 (CH_2), 47.7 (CH_2), 38.3 (CH_2), 37.8 (CH_2), 25.3 (CH), 24.5 (CH), 23.6 (CH_2), 23.4 (CH_2), 22.4 (CH_3), 22.4 (CH_3), 22.3 (CH_3), 21.8 (CH_3), 14.4 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (m), 1681 (m), 1655 (s), 1402 (s), 972 (m), 727 (s), 698 (s). HRMS (ESI): *m/z* calculated for $C_{17}H_{26}NO_2S$ (M+H) 308,1679, found 308,1659.

4f: Two rotamers were present on NMR timescale (R^1 : R^2 = 1 : 0.4). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29-7.11 (m, 14H), 5.24 (m, 1H), 5.05 (d, *J* = 15.5 Hz, 0.4H), 4.63 (d, *J* = 17.6, 1H), 4.36 (m, 1.4H), 4.03 (m, 3.2H), 2.21 (s, 1.2H), 2.06 (s, 3H), 1.81-1.70 (m, 1.4H), 1.54-1.36 (m, 2.8H), 0.82 (d, *J* = 6.5 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 1.2H), 0.67 (d, *J* = 6.6 Hz, 3H), 0.46 (d, *J* = 6.6 Hz, 1.2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.9 (C_q), 198.6 (C_q), 172.3 (C_q), 171.8 (C_q), 138.3 (C_q), 137.1 (C_q), 136.9 (C_q) 136.6 (C_q), 128.8 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.8 (CH), 127.4 (CH), 127.4 (CH), 127.2 (CH), 127.0 (CH), 126.14 (CH), 66.8 (CH), 62.2 (CH), 50.3 (CH_2), 47.8 (CH), 38.2 (CH_2), 37.8 (CH_2), 33.5 (CH_2), 33.3 (CH_2), 25.2 (CH), 24.4 (CH), 22.4 (CH_3), 22.3 (CH_3), 22.3 (CH_3), 22.2 (CH_3), 22.2 (CH_3), 21.7 (CH_3). IR (neat): *v*max (cm^{-1}) = 2957 (m), 1684 (s), 1655 (s), 1240 (s), 606 (s), 579 (s), 459 (s). HRMS (ESI): *m/z* calculated for $C_{22}H_{28}NO_2S$ (M+H) 370.1835, found 370.1821.

3.2 Passerini reactions with 5l

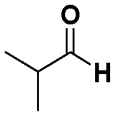
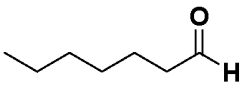
[51] We next investigated the utility of **5l** in the Passerini reaction (scheme 10). Subsequent basic hydrolysis of the Passerini products **22** obviously also cleaves the ester moiety to give the corresponding α-hydroxy carboxylic acids **23**.



Scheme 10:

Passerini reactions with **5l** and subsequent saponification to α-hydroxy acids **23**

Table 4. Passerini reactions with **5l** and subsequent saponification to α-hydroxy acids

Entry	Aldehyde R^1CHO	Passerini 3CR		Hydrolysis	
		Product	Yield	Product	Yield
1		**22a**	98%	**23a**	99%
2		**22b**	80%	**23b**	99%

General procedure VI: Passerini reaction and subsequent saponification to α-hydroxy acids

[52] The aldehyde (1.0 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (3 mL), acetic acid (86 µL, 1.5 mmol, 1.5 eq.) and 2-bromo-6-isocyanopyridine (201 mg, 1.1 mmol, 1.1 eq.) were added subsequently. Additional CH_2Cl_2 (1mL) was added and the resulting mixture stirred for 48 hours at room temperature. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (cyclohexane : EtOAc) to yield the Passerini-products.

[53] The Passerini product (0.2 mmol, 1.0 eq.) was dissolved in MeOH (0.9 mL) and 10M NaOH (0.1 mL, 1 mmol, 5.0 eq.) was added. The resulting mixture stirred at room temperature for 48 hours. Conversion of the amide to the α-hydroxy acid was monitored by TLC, indicated by formation of 6-bromopyridin-2-amine (a characteristic blue spot appears without stain). Water was added to the crude reaction mixture. The water later was washed with EtOAc (2x), acidified to pH=1 with 1M HCl and extracted with EtOAc (3x). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to yield the corresponding α-hydroxy carboxylic acid.

[54] Analytical data:

22a: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.29 (bs, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 5.17 (d, *J* = 4.5 Hz, 1H), 2.36-2.29 (m, 1H), 2.24 (s, 3H), 1.02 (d, *J* = 3.8 Hz, 3H), 0.99 (d, *J* = 3.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7 (C_q), 168.2 (C_q), 150.5 (C_q), 140.7 (CH), 139.3 (C_q), 124.1 (CH), 112.5 (CH), 78.1 (CH), 31.0 (CH_3), 21.0 (CH), 18.6 (CH_3), 17.1 (CH_3). IR (neat): *v*max (cm^{-1}) = 3296 (w), 1743 (m), 1708 (s), 1566 (s), 1519 (m), 1429 (s), 1389 (m), 1232 (m), 789 (m). HRMS (ESI): *m/z* calculated for $C_{12}H_{16}BrN_2O_3$ (M+H) 315.0339, found 315.0314.

22b: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.35 (bs, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 5.26 (t, *J* = 6.0 Hz), 2.23 (s, 3H), 1.90 (m, 2H), 1.37-1.27 (m,

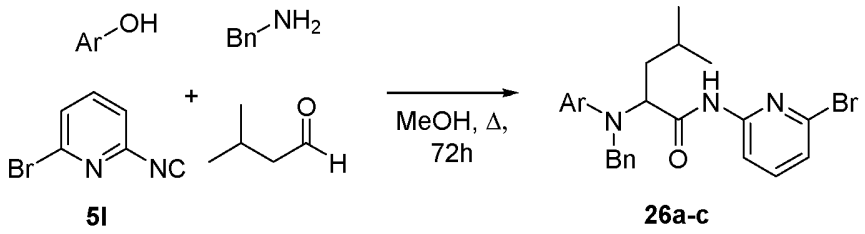
8H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.6 (C_q), 168.7 (C_q), 150.6 (C_q), 140.7 (CH), 139.3 (C_q), 124.1 (CH), 112.6 (CH), 74.1 (CH), 32.0 (CH_2), 31.5 (CH_2), 28.8 (CH_2), 24.6 (CH_2), 22.5 (CH_2), 21.1 (CH_3), 14.0 (CH_3). IR (neat): *v*max (cm^{-1}) = 2928 (w), 1717 (m), 1568 (s), 1431 (s), 787 (m), 631 (s), 536 (s), 498 (s). HRMS (ESI): *m/z* calculated for $C_{15}H_{22}BrN_2O_3$ (M+H) 357.0808, found 357.0800.

23a: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.15 (d, *J* = 3,4 Hz, 1H), 2.16 (m, 1H), 1.05 (d, *J* = 7.0 Hz, 1H), 0.91 (d, *J* = 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.3 (C_q), 74.8 (CH), 31.9 (CH), 18.8 (CH_3), 15.9 (CH_3).

23b: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.28 (dd, *J* = 7.5, 4.2 Hz, 1H), 1.87 (m, 1H), 1.72 (m, 1H), 1.47-1.41 (m, 8H) 0.88 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.6 (C_q), 70.2 (CH), 34.2 (CH_2), 31.6 (CH_2), 28.9 (CH_2), 24.7 (CH_2), 22.5 (CH_2), 14.0 (CH_3).

3.3 Other MCRs with 5l

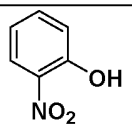
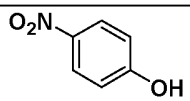
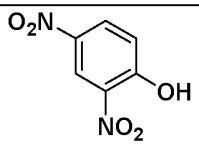
[55] Isocyanides of the present invention such as **5l** are also suitable for other IMCRs such as the Ugi-Smiles reaction (scheme 11).



5l **26a-c**

Scheme 11. Ugi-Smiles reactions with **5l**

[56] **Table 5.** Yields of Ugi-Smiles reactions with **5l**

Entry	ArOH	Ugi-Smiles 4CR	
		Product	Yield
1		**26a**	34%
2		**26b**	21%
3		**26c**	78%

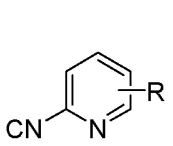
General procedure VII: Ugi-Smiles reactions (scheme 11)

[57] Under nitrogen atmosphere benzylamine (109 µL, 1.0 mmol, 1.0 eq.) and isovaleraldehyde (108 µL, 1.0 mmol, 1,0 eq.) were dissolved in the MeOH (3 mL) and prestirred for 2 hours at room temperature. The nitrophenol (1.5 mmol, 1.5 eq.) and 2-bromo-6-isocyanopyridine (220 mg, 1.2 mmol, 1.2 eq.) were added subsequently. Additional MeOH (1 mL) was added and the resulting mixture was refluxed for 72 hours. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (cyclohexane : EtOAc) to yield the Ugi-Smiles products as foamy solids.

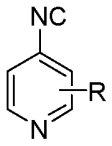
CLAIMS

1. Method for performing isocyanide-based multicomponent reaction (IMCR) comprising a step of reacting

a substituted 2- or 4-isocyanopyridine of the general formula **5** or **19**, preferably **5**,



5



19

with a carbonyl-containing compound selected from the group consisting of an aldehyde and a ketone;

in the presence of an acidic carbon compound selected from the group consisting of a (thio)carboxylic acid and a (thio)phenolic compound

and/or a primary or secondary amine,

wherein R is selected from the group consisting of H, halogen, C_1-C_4-alkyl such as C_1-, C_2-, n-C_3-, i-C_3- alkyl,, halogenated C_1-C_4 alkyl, halogen (F, Cl, Br, I), (thio)ethers, sulfoxides, sulfones, esters, (substituted) (hetero)aryl, (substituted) cycloalkyl, alkoxy/(hetero)aryloxy, and mono-di-alkyl/(hetero)arylamino.

2. Method according to claim 1, wherein the acidic carbon compound is a carboxylic acid (Passerini reaction).
3. Method according to claim 1, wherein further a primary amine is present (Ugi reaction).
4. Method according to claim 1, wherein the acidic carbon compound is a phenolic compound (Ugi-Smiles reaction).
5. Method according to claim 1, wherein R is positioned at the 3, 4 ,5 and/or 6 position in the 2-isocyanopyridine or wherein R is positioned at the 2, 3, 5 or 6 position in the 4-isocyanopyridine.

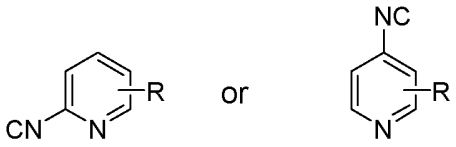
6. Method according to claim 1, wherein R is selected from the group consisting of C_1-, C_2-, *n*-C_3-, *i*-C_3- alkyl, halogen (F, Cl, Br, I), CF_3 .

7. Method according to claim 6, wherein, for 2-isocyanopyridines, R is selected from the group consisting of 3-Me, 4-Me, 5-Me, 6-Me, 3-Br, 4-Br, 5-Br, 6-Br, 3-Cl, 4-Cl, 5-Cl, 6-Cl, 3-F, 4-F, 5-F, 6-F, 3-CF_3, 4-CF_3, 5-CF_3, 6-CF_3 and wherein for 4-isocyanopyridines , R is selected from the group consisting of 2-Me, 3-Me, 5-Me, 6-Me, 2-Br, 3-Br, 5-Br, 6-Br, 2-Cl, 3-Cl, 5-Cl, 6-Cl, 2-F, 3-F, 5-F, 6-F, 2-CF_3, 3-CF_3, 5-CF_3, 6-CF_3 .

8. Method according to claim 7, wherein, for 2-isocyanopyridines, R is selected from the group consisting of 3-Me, 4-Me, 5-Me, 6-Me, 3-Br, 4-Br, 5-Br, 5-Cl, 5-CF_3, 6-Br, 6-Cl.

9. Method according to claim 8, wherein R is Br, preferably 6-Br.

10. Substituted 2-isocyanopyridine or 4-isocyanopyridine having the general formula



5 **19**

wherein R is selected from the group consisting of H, C_1-C_4-alkyl such as C_1-, C_2-, n-C_3-, i-C_3- alkyl,, halogenated C_1-C_4 alkyl, halogen (F, Cl, Br, I), (thio)ethers, sulfoxides, sulfones, esters, (substituted) (hetero)aryl, (substituted) cycloalkyl, alkoxy/(hetero)aryloxy, and mono-di-alkyl/(hetero)arylamino.

11. Substituted 2-isocyanopyridine or 4-isocyanopyridine according to claim 10, wherein for 2-isocyanopyridines, R is selected from the group consisting of 3-Me, 4-Me, 5-Me, 6-Me, 3-Br, 4-Br, 5-Br, 6-Br, 3-Cl, 4-Cl, 5-Cl, 6-Cl, 3-F, 4-F, 5-F, 6-F, 3-CF_3, 4-CF_3, 5-CF_3, 6-CF_3 and wherein for 4-isocyanopyridines , R is selected from the group consisting of 2-Me, 3-Me, 2-Br, 3-Br, 2-Cl, 3-Cl, 2-F, 3-F, 2-CF_3, 3-CF_3.

12. Substituted 2-isocyanopyridine or 4-isocyanopyridine according to claim 11, wherein for 2-isocyanopyridines, R is selected from the group consisting of 3-Me, 4-Me, 5-Me, 6-Me, 3-Br, 4-Br, 5-BR, 5-Cl 5-CF_3, 6-Br, 6-Cl and wherein for 4-isocyanopyridines R is selected from the group consisting of 2-Me, 2-Br, 2-CF_3, 2-Cl.

13. Substituted 2-isocyanopyridine or 4-isocyanopyridine according to claim 12, wherein for 2-isocyanopyridines R is Br, preferably 6-Br and wherein for wherein for 4-isocyanopyridines is R is Br or Cl, preferably 2-Br or Cl.

14. Method for the conversion of the *N*-2-pyridylamide- or *N*-4-pyridylamide- containing product of the Ugi reaction of claim 3 to the corresponding carboxylic acid under basic conditions.

15. Method for the nucleophilic substitution of the *N*-2-pyridylamide or *N*-4-pyridylamide-group of the *N*-2-pyridylamide- or *N*-4-pyridylamide- containing product of the Ugi reaction of claim 3 in the presence of a nucleophile under acidic or basic conditions.

16. Method according to claim 15, wherein the nucleophile is selected from the group consisting of water, alcohols, thiols, primary or secondary amines.

17. Method according to claim 15 or 16, wherein the conditions are basic and the nucleophile is selected from the group consisting of water, primary C_1-C_4-alcohols, primary C_1-C_8 alkylamines, secondary C_2-C_8 alkylamines and C_4-C_8 cycloalkylamines.

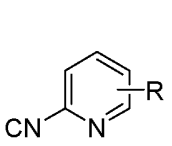
18. Method according to claim 15 or 16, wherein the conditions are acidic and the nucleophile is selected from the group consisting of water, primary C_1-C_4-alcohols, secondary C_3-C_8-alcohols, alkylthiols, benzylthiols.

19. Method for the conversion of the *N*-2-pyridylamide- or *N*-4-pyridylamide- containing product of the Passerini reaction of claim 2 under basic conditions to provide the corresponding alpha-hydroxy carboxylic acid.

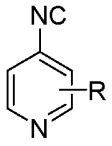
20. Use of substituted 2-isocyanopyridines or substituted 4-isocyanopyridines as defined in claim 10 in multicomponent reactions.

Conclusies

1. Methode voor het uitvoeren van isocyanide gebaseerde multicomponent reactie (IMCR) bestaande uit een stap van het laten reageren van een gesubstitueerd 2 - of 4-isocyanopyridine van de algemene formule 5 of 19, bij voorkeur 5,



5



19

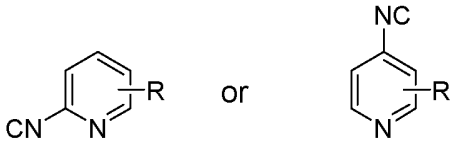
met een carbonyl-bevattende stof geselecteerd uit de groep bestaande een aldehyde of een keton;
in aanwezigheid van een zure koolstof verbinding geselecteerd uit de groep bestaande uit een (thio) carbonzuur en een (thio) fenolische verbinding en/of een primair of secundair amine,
waarin R wordt geselecteerd uit de groep bestaande uit H, halogeen, C1-C4-alkyl zoals C_1-, C_2-, *n*-C_3-, *i*-C_3- alkyl gehalogeneerde C_1-C_4 alkyl, halogeen (F, Cl, Br, I), (thio) ethers, sulfoxiden, sulfonen , esters, (gesubstitueerd) (hetero) aryl, (gesubstitueerd) cycloalkyl, alkoxy / (hetero) aryloxy en mono-di-alkyl / (hetero) arylamino.

2. De methode volgens conclusie 1, waarin de zure koolstof verbinding een carbonzuur is (Passerini reactie).
3. De methode volgens conclusie 1, waarin verder een primair amine aanwezig is (Ugi reactie
4. De methode volgens conclusie 1, waarin de zure koolstof verbinding een fenolische verbinding is (Ugi-Smiles reactie).
5. De methode volgens conclusie 1, waarin R gelegen is op de 3, 4, 5 of 6 positie in de 2-isocyanopyridine of waarin R gelegen is op de 2, 3, 5 of 6 positie in de 4-isocyanopyridine.
6. Methode volgens conclusie 1, waarin R is geselecteerd uit de groep bestaande uit C_1-, C_2-, *n*-C_3-, *i*-C_3- alkyl, halogeen (F, Cl, Br, I), CF_3 .
7. De methode volgens conclusie 6, waarin, voor 2-isocyanopyridines, R is geselecteerd uit de groep bestaande uit 3-Me, 4-Me, 5-Me, 6-Me, 3-Br, 4-Br, 5-Br, 6-Br, 3-Cl, 4-Cl, 5-Cl, 6-Cl, 3-F, 4-F, 5-F, 6-F, 3-CF_3, 4-CF_3, 5-CF_3, 6-CF_3 en waarin voor 4-isocyanopyridines , R is geselecteerd uit de groep bestaande uit -Me, 3-Me, 5-Me, 6-Me, 2-Br, 3-Br, 5-Br, 6-Br, 2-Cl, 3-Cl, 5-Cl, 6-Cl, 2-F, 3-F, 5-F, 6-F, 2-CF_3, 3-CF_3, 5-CF_3, 6-CF_3.

8. De methode volgens conclusie 7, waarin, voor 2-isocyanopyridines, R is geselecteerd uit de groep bestaande uit 3-Me, 4-Me, 5-Me, 6-Me, 3-Br, 4-Br, 5-Br, 5-Cl, 5-CF_3, 6-Br, 6-Cl.

9. De methode volgens conclusie 8, waarin R is Br, bij voorkeur 6-Br.

10. Gesubstitueerde 2-isocyanopyridine of 4-isocyanopyridine met de algemene formule



5 **19**

waarin R is geselecteerd uit de groep bestaande uit H, C_1-C_4-alkyl such as C_1-, C_2-, n-C_3-, i-C_3- alkyl, gehalogeneerde C_1-C_4 alkyl, halogeen (F, Cl, Br, I), (thio)ethers, sulfoxides, sulfonen, esters, (gesubstitueerde) (hetero)aryl, (gesubstitueerde) cycloalkyl, alkoxy/(hetero)aryloxy, en mono-di-alkyl/(hetero)arylamino.

11. Gesubstitueerde 2-isocyanopyridine of 4-isocyanopyridine volgens conclusie 10, waarin voor 2-isocyanopyridines, R is geselecteerd uit de groep bestaande uit 3-Me, 4-Me, 5-Me, 6-Me, 3-Br, 4-Br, 5-Br, 6-Br, 3-Cl, 4-Cl, 5-Cl, 6-Cl, 3-F, 4-f, 5-F, 6-F, 3-CF_3, 4-CF_3, 5-CF_3, 6-CF_3 en waarin voor 4-isocyanopyridines, R is geselecteerd uit de groep bestaande uit, 3-Me, 2-Br, 3-Br, 2-Cl, 3-Cl, 2-F, 3-F, 2-CF_3, 3-CF_3.

12. Gesubstitueerde 2-isocyanopyridine of 4-isocyanopyridine volgens conclusie 11, waarin voor 2-isocyanopyridines, R is geselecteerd uit de groep bestaande uit 3-Me, 4-Me, 5-Me, 6-Me, 3-Br, 4-Br, 5-CF_3, 6-Br, 6-Cl en waarin voor 4-isocyanopyridines R is geselecteerd uit de groep bestaande uit 2-Me, 2-Br, 2-CF_3, 2-Cl.

13. Gesubstitueerde 2-isocyanopyridine of 4-isocyanopyridine volgens conclusie 12, waarin voor 2-isocyanopyridines R is Br, bij voorkeur 6-Br en waarin voor 4-isocyanopyridines R is Br of Cl , bij voorkeur 2-Br of 2-Cl.

14. Methode voor de omzetting van de N-2-pyridylamide - of N-4-pyridylamide-bevattende product van de Ugi reactie van conclusie 3 tot de overeenkomstige carbonzuur onder basische condities.

15. Methode voor de nucleofiele substitutie van de N-2-pyridylamide of N-4-pyridylamide-groep van het N-2-pyridylamide - of N-4-pyridylamide- product van de Ugi reactie van conclusie 3 in aanwezigheid van een nucleofiel onder zure of basische condities.

16. De methode volgens conclusie 15, waarin het nucleofiel is geselecteerd uit de groep bestaande uit water, alcoholen, thiolen, primaire of secundaire amines.

17. Methode volgens conclusie 15 of 16, waarin de condities basisch zijn en het nucleofiel is geselecteerd uit de groep bestaande uit water, primaire C_1-C_4-alcoholen, primaire C_1-C_8 alkylaminen, secundaire C_2-C_8 alkylaminen en C_4-C_8 cycloalkylamines.

18. Methode volgens conclusie 15 of 16, waarin de voorwaarden zuur zijn en het nucleofiel is geselecteerd uit de groep bestaande uit water, primaire C_1-C_4-alcoholen, secundaire C_3-C_8-alcoholen, alkylthiolen, benzylthiolen.

19. Methode voor de omzetting van het N-2-pyridylamide - of N-4-pyridylamide- product van de Passerini reactie van conclusie 2 onder basische condities om het overeenkomstige alpha-hydroxy carbonzuur te verkrijgen.

20. Toepassing van gesubstitueerde 2-isocyanopyridines of gesubstitueerde 4-isocyanopyridines zoals gedefinieerd in conclusie 10 in multicomponent reacties.

Fig 1

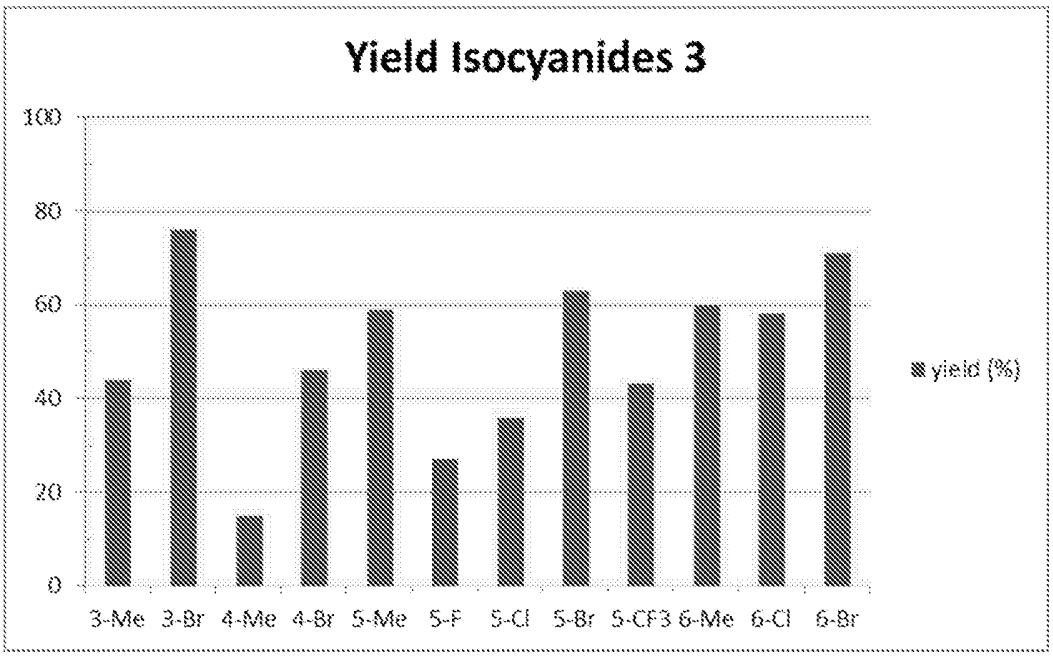

Yield Isocyanides 3
100
80
60
40
20
0
3-Me
3-Br
4-Me
4-Br
5-Me
5-F
5-Cl
5-Br
5-CF3
6-Me
6-Cl
6-Br
yield (%)

Fig 2

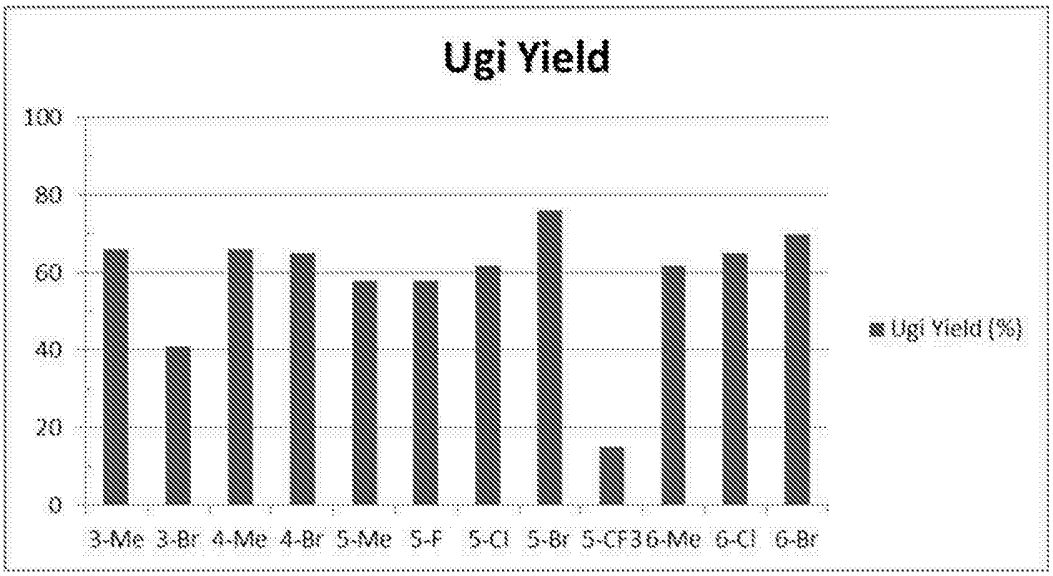
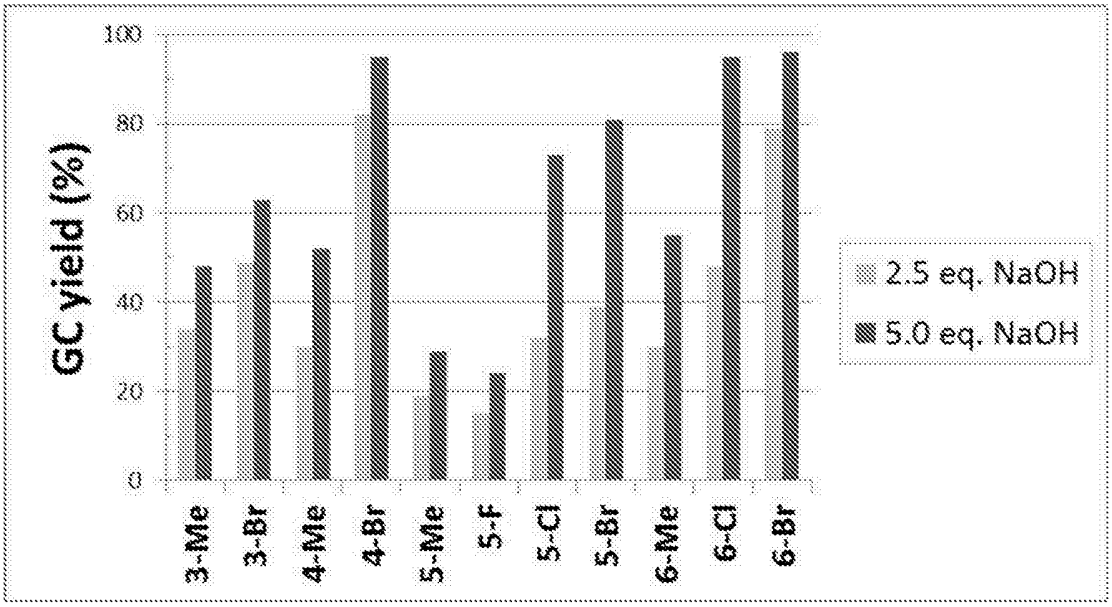
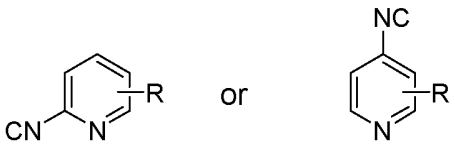

Ugi Yield
100
80
60
40
20
0
3-Me
3-Br
4-Me
4-Br
5-Me
5-F
5-Cl
5-Br
5-CF3
6-Me
6-Cl
6-Br
Ugi Yield (%)

Fig 3


GC yield (%)
100
80
60
40
20
0
3-Me
3-Br
4-Me
4-Br
5-Me
5-F
5-Cl
5-Br
6-Me
6-Cl
6-Br
2.5 eq. NaOH
5.0 eq. NaOH

A B S T R A C T

The present invention provide novel substituted 2-isocyanopyridines and their use in methods comprising reacting substituted isocyanopyridines of the general formula



5 **19**

with a carbonyl-containing compound selected from the group consisting of an aldehyde and a ketone; in the presence of an acidic carbon compound selected from the group consisting of a carboxylic acid and a (thio)phenolic compound and/or a primary or secondary amine, including their use in Ugi, Passerini and Ugi-Smiles reactions, and conversion of the resulting secondary amide products to (thio)carboxylic acids, (thio)esters and amides.

SAMENWERKINGSVERDRAG (PCT)

RAPPORT BETREFFENDE NIEUWHEIDSONDERZOEK VAN INTERNATIONAAL TYPE

IDENTIFICATIE VAN DE NATIONALE AANVRAGE	KENMERK VAN DE AANVRAGER OF VAN DE GEMACHTIGDE
	P32481NL00/RLA
Nederlands aanvraag nr. **2015814**	Indieningsdatum **19-11-2015**
	Ingeroepen voorrangsdatum
Aanvrager (Naam) **Stichting VU-VUmc**	
Datum van het verzoek voor een onderzoek van internationaal type **20-02-2016**	Door de Instantie voor Internationaal Onderzoek aan het verzoek voor een onderzoek van internationaal type toegekend nr. **SN65791**

I. CLASSIFICATIE VAN HET ONDERWERP (bij toepassing van verschillende classificaties, alle classificatiesymbolen opgeven)

Volgens de internationale classificatie (IPC)

C07D213/72;C07D213/75

II. ONDERZOCHTE GEBIEDEN VAN DE TECHNIEK

Onderzochte minimumdocumentatie

Classificatiesysteem	Classificatiesymbolen
IPC	**C07D**

Onderzochte andere documentatie dan de minimum documentatie, voor zover dergelijke documenten in de onderzochte gebieden zijn opgenomen

III.	☐ **GEEN ONDERZOEK MOGELIJK VOOR BEPAALDE CONCLUSIES**	(opmerkingen op aanvullingsblad)
IV.	☐ **GEBREK AAN EENHEID VAN UITVINDING**	(opmerkingen op aanvullingsblad)

ONDERZOEKSRAPPORT BETREFFENDE HET RESULTAAT VAN HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE

Nummer van het verzoek om een onderzoek naar de stand van de techniek
NL 2015814

A. CLASSIFICATIE VAN HET ONDERWERP
INV. C07D213/72 C07D213/75
ADD.

Volgens de internationale Classificatie van octrooien (IPC) of zowel volgens de nationale classificatie als volgens de IPC.

B. ONDERZOCHTE GEBIEDEN VAN DE TECHNIEK

Onderzochte minimum documentatie (classificatie gevolgd door classificatiesymbolen)
C07D

Onderzochte andere documentatie dan de minimum documentatie, voor dergelijke documenten, voor zover dergelijke documenten in de onderzochte gebieden zijn opgenomen

Tijdens het onderzoek geraadpleegde elektronische gegevensbestanden (naam van de gegevensbestanden en, waar uitvoerbaar, gebruikte trefwoorden)
EPO-Internal, WPI Data, CHEM ABS Data

C. VAN BELANG GEACHTE DOCUMENTEN

Categorie *	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.
X	EP 2 590 953 A1 (CONVERGENCE PHARMACEUTICALS [GB]) 15 mei 2013 (2013-05-15)	1,5-7, 10-12,20
Y	* Synthesis of cpd. 38 (p. 70-71) and 42 (p. 72-73) *	2-4,8,9, 14-19
	----- -/--	

[X] Verdere documenten worden vermeld in het vervolg van vak C.

[X] Leden van dezelfde octrooifamilie zijn vermeld in een bijlage

* Speciale categorieën van aangehaalde documenten

"A" niet tot de categorie X of Y behorende literatuur die de stand van de techniek beschrijft

"D" in de octrooiaanvrage vermeld

"E" eerdere octrooi(aanvrage), gepubliceerd op of na de indieningsdatum, waarin dezelfde uitvinding wordt beschreven

"L" om andere redenen vermelde literatuur

"O" niet-schriftelijke stand van de techniek

"P" tussen de voorrangsdatum en de indieningsdatum gepubliceerde literatuur

"T" na de indieningsdatum of de voorrangsdatum gepubliceerde literatuur die niet bezwarend is voor de octrooiaanvrage, maar wordt vermeld ter verheldering van de theorie of het principe dat ten grondslag ligt aan de uitvinding

"X" de conclusie wordt als niet nieuw of niet inventief beschouwd ten opzichte van deze literatuur

"Y" de conclusie wordt als niet inventief beschouwd ten opzichte van de combinatie van deze literatuur met andere geciteerde literatuur van dezelfde categorie, waarbij de combinatie voor de vakman voor de hand liggend wordt geacht

"&" lid van dezelfde octrooifamilie of overeenkomstige octrooipublicatie

Datum waarop het onderzoek naar de stand van de techniek van internationaal type werd voltooid	Verzenddatum van het rapport van het onderzoek naar de stand van de techniek van internationaal type
1 augustus 2016	

Naam en adres van de instantie	De bevoegde ambtenaar
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fritz, Martin

1

ONDERZOEKSRAPPORT BETREFFENDE HET RESULTAAT VAN HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE

Nummer van het verzoek om een onderzoek naar de stand van de techniek
NL 2015814

C.(Vervolg). VAN BELANG GEACHTE DOCUMENTEN

Categorie *	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.
X	SHAO N ET AL: "Dimerization of 2-pyridylisonitriles produces pi-extended fused heteroarenes useful as highly selective colorimetric and optical probes for copper ion", TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, deel 66, nr. 36, 4 september 2010 (2010-09-04), bladzijden 7302-7308, XP027205684, ISSN: 0040-4020 [gevonden op 2010-08-01] * tabel 1; verbindingen 1a-1h *	10-13
X	DE 37 19 424 A1 (MERCK PATENT GMBH [DE]) 22 december 1988 (1988-12-22) * bladzijde 14; voorbeeld 4 *	10-12
X	GUO ET AL.: "Transition metal complexes of isocyanopyridines, isocyanoquinolines and isocyanoisoquinolines", INORGANICA CHIMICA ACTA, deel 261, 1997, bladzijden 141-146, XP002760355, * verbindingen 1a,1c *	10
X	JIANG ET AL.: "Synthesis of 6-Alkylated Phenanthridine Derivatives Using Photoredox Neutral Somophilic Isocyanide Insertion", ANGEW. CHEM. INT. ED., deel 52, 2013, bladzijden 13289-13292, XP002760356, * verbinding 1 *	10
X	DÖMLING ET AL.: "Chemistry and Biology of Multicomponent Reactions", CHEMICAL REVIEWS, deel 112, 2012, bladzijden 3083-3135, XP002760357,	1-20
Y	* het gehele document *	2-4,8,9, 14-19

1

ONDERZOEKSRAPPORT BETREFFENDE HET RESULTAAT VAN HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE

Informatie over leden van dezelfde octrooifamilie

Nummer van het verzoek om een onderzoek naar de stand van de techniek
NL 2015814

In het rapport genoemd octrooigeschrift	Datum van publicatie	Overeenkomend(e) geschrift(en)	Datum van publicatie
EP 2590953 A1	15-05-2013	EP 2590953 A1	15-05-2013
		ES 2529233 T3	18-02-2015
		JP 5815029 B2	17-11-2015
		JP 2013535414 A	12-09-2013
		US 2013210796 A1	15-08-2013
		US 2016015687 A1	21-01-2016
		WO 2012004604 A1	12-01-2012
DE 3719424 A1	22-12-1988	GEEN	

WRITTEN OPINION

File No.	Filing date *(day/month/year)*	Priority date *(day/month/year)*	Application No.
SN65791	19.11.2015		NL2015814

International Patent Classification (IPC)
INV. C07D213/72 C07D213/75

Applicant
Stichting VU-VUmc

This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the application
- ☒ Box No. VIII Certain observations on the application

Examiner
Fritz, Martin

Application number

WRITTEN OPINION

NL2015814

Box No. I Basis of this opinion

1. This opinion has been established on the basis of the latest set of claims filed before the start of the search.

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ on paper

   ☐ in electronic form

   c. time of filing/furnishing:

   ☐ contained in the application as filed.

   ☐ filed together with the application in electronic form.

   ☐ furnished subsequently for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty	Yes:	Claims	2-4, 8, 9, 14-19
	No:	Claims	1, 5-7, 10-13, 20
Inventive step	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

Application number

WRITTEN OPINION

NL2015814

Box No. VII Certain defects in the application

see separate sheet

Box No. VIII Certain observations on the application

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Prior art

D1 EP 2 590 953 A1 (CONVERGENCE PHARMACEUTICALS [GB]) 15 mei 2013 (2013-05-15)

D2 SHAO N ET AL: "Dimerization of 2-pyridylisonitriles produces pi-extended fused heteroarenes useful as highly selective colorimetric and optical probes for copper ion",
TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL,
deel 66, nr. 36, 4 september 2010 (2010-09-04), bladzijden 7302-7308, XP027205684,
ISSN: 0040-4020
[gevonden op 2010-08-01]

D3 DE 37 19 424 A1 (MERCK PATENT GMBH [DE]) 22 december 1988 (1988-12-22)

D4 GUO ET AL.: "Transition metal complexes of isocyanopyridines, isocyanoquinolines and isocyanoisoquinolines",
INORGANICA CHIMICA ACTA,
deel 261, 1997, bladzijden 141-146, XP002760355,

D5 JIANG ET AL.: "Synthesis of 6-Alkylated Phenanthridine Derivatives Using Photoredox Neutral Somophilic Isocyanide Insertion",
ANGEW. CHEM. INT. ED.,
deel 52, 2013, bladzijden 13289-13292, XP002760356,

D6 DÖMLING ET AL.: "Chemistry and Biology of Multicomponent Reactions",
CHEMICAL REVIEWS,
deel 112, 2012, bladzijden 3083-3135, XP002760357,

Subject-matter claimed

Method for performing isocyanide-based multicomponent reaction employing an optionally substituted 2- or 4-isocyanopyridine of formulas 5 or 19 (claims 1-9, 14-19),

the optionally substituted 2- or 4-isocyanopyridines of formulas 5 and 19 (claims 10-13), and

the use of a compound 5 or 19 as defined in claim 10 in multicomponent reactions (claim 20).

Novelty and inventive step

The use of various isonitriles in multicomponent reactions is well known, cf. eg D6, representatives of the isonitrile compounds 5 and 19 are known (cf. D1-D5, cited passages) and also their use in multicomponent reactions (D1).

The subject-matter of claims 1, 5-7, 10-13 and 20 according to the present case is therefore not novel.

Claims 1, 5-7, 10-13 20 which are not novel do not offer a basis for the discussion of inventive step.

Closest prior art for claims 2-4, 8, 9, and 14-19 can be regarded D1.

The problem underlying the present case could be regarded as extending the scope of multicomponent reactions by providing other suitable isontrile compounds.

This problem has been solved by the method claimed.

A skilled person being aware of D1 would know from D6, that isontriles are suitable in all kinds of multicomponent reactions, and thus only have to combine the teaching of these two documents in order to solve the problem underlying the present case.

It must, from the above, be concluded, that the problem has been solved in an obvious manner, and an inventive step can therefore not be acknowledged for the subject-matter of claims 2-4, 8-9 and 14-19.

Re Item VII

Certain defects in the international application

The relevant background art disclosed in the documents D1-D6 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

The subject-matter of claim 1 lacks clarity:

The terms "(thio)ethers, sufoxides, sulfones, esters" designate generic classes of chemical compounds, not functional groups.

In order to fulfil the requirement of conciseness the terms in brackets should be deleted from claims 2-4.

The phrases starting with "preferably" employed in claims 1, 9, and 13 introduce technical features which are merely optional.

Consequently the subject-matter of these claims does not meet the requirement of conciseness.