(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 February 2011 (03.02.2011)

PCT

(10) International Publication Number
WO 2011/012269 A2

(51) International Patent Classification:
***C07D 213/82* (2006.01)** ***C07D 473/16* (2006.01)**
***C07D 401/04* (2006.01)**

(21) International Application Number:
PCT/EP20 10/004522

(22) International Filing Date:
23 July 2010 (23.07.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09166455.7 27 July 2009 (27.07.2009) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* **ARIPO (BW, GH,** GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, **FI,** FR, GB, GR, HR, HU, IE, IS, **IT, LT,** LU, LV, MC, MK, MT, NL, NO, PL, **PT,** RO, SE, SI, SK, SM, TR), OAPI (BF, **BJ,** CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4Λ 7(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: METHOD AND SUBSTANCES FOR PREPARATION OF N-SUBSTITUTED PYRIDINIUM COMPOUNDS

(57) Abstract: The present invention relates to a method for the synthesis of N-substituted pyridinium compounds by using an N-heteroaryl substituted pyridinium salt (Zincke salt) and reacting it with a nucleophilic amine. In this reaction the pyridinium ring of the Zincke salt reacts with the amine which induces ring opening followed by ring closing, whereby the nitrogen of the amine becomes part of the N-substituted pyridinium ring. Preferably the amine is a primary amine. Novel purine-substituted pyridyl compounds, which can e.g. used in the above reaction, are also disclosed.

WO 2011/012269 A2

Method and substances for preparation of N-substituted pyridinium compounds

Background of the Invention

The present invention relates to a method for the synthesis of N-substituted pyridinium compounds by using an N-heteroaryl substituted pyridinium salt (Zincke salt) and reacting it with a nucleophilic amine. In this reaction the pyridinium ring of the Zincke salt reacts with the amine which induces ring opening followed by ring closing, whereby the nitrogen of the amine becomes part of the N-substituted pyridinium ring. Preferably the amine is a primary amine. Novel purine-substituted pyridyl compounds, which can e.g. used in the above reaction, are also disclosed.

Pyridinium compounds are of special interest, e.g. in drug design, or as general intermediates for organic syntheses, especially in natural product synthesis (Cheng, W.-C. et al., Organic Preparations and Procedures International 34 (2002) 585-608).

Certain substituted pyridinium compounds are of great utility in the synthesis of NAD or NAD analogs, respectively (Walt, D.R. et al., Journal of the American Chemical Society 106 (1984) 234-239; WO 2007/012494; DE 10 2006 035 020; Hockova, D. et al., Collection of Czechoslovak Chemical Communications 61 (1996) 1538-1548).

Certain heteroaryl substituted pyridinium compounds are known (Bredereck, H. et al., Angewandte Chemie 72 (1960) 708) and have e.g. been studied for solvatochromism (Masternak, A. et al., Journal of Physical Chemistry A 109 (2005) 759-766).

Triazinyl reactive dyes with carboxypyridine as leaving group are known as dyestuff for coloration of cotton (Sugimoto, T., Journal of the Society of Dyers and Colourists 108 (1992) 497-500). In this case the pyridinium moiety acts as a leaving group when the triazinyl dye is reacted with nucleophils during the dying procedure. A Zincke like pathway with ring opening would not result in fixation of the dye. Therefore the heteroaryl substituted pyridinium salts used in the dying of cotton are not supposed to be useful in the Zincke reaction.

The standard synthetic route in the production of substituted pyridinium compounds is via alkylation of pyridine derivatives. However, this reaction is only convenient when using primary alkyl halides. When secondary or tertiary alkyl halides are used elimination occurs as an unwanted side reaction and yields are generally low. Moreover when the alkylation is performed with alkyl halides with the halogen atom attached to an asymmetric carbon atom racemization can occur during the nucleophilic displacement reaction.

All these limitations are overcome by using the "Zincke reaction" which is based on the reaction of Zincke salts with alkyl or aryl amines. Zincke salts are activated pyridinium salts which are capable of reacting with a primary amine (R-NH2). In this reaction ring opening is induced which in turn is followed by ring closing to an R substituted pyridinium compound. The Zincke reaction can also be performed with hydrazines, hydroxyl amine and carboxylic or sulfonic acid hydrazides. These types of Zincke reactions are used for in solution and for solid phase organic syntheses (Eda, M. et al., J. Org. Chem. 65 (2000) 5131 - 5135).

In the art the predominant way for preparing the desired Zincke salts is by reacting a pyridinium compound with 2,4 dinitro halobenzol preferably with 2,4 dinitrochlorbenzol and 2,4 dinitrobrombenzol.

As obvious from the above description of state of the art processes, the presently used activation reagents are either toxic, explosive or otherwise hazardous and therefore limited to small scale research applications. There are scattered attempts to perform the Zincke reaction in a eco friendly manner, e.g., by using microwave assisted synthesis. However this attempt still relies on explosive dinitrophenyl compounds and it is not possible to scale up this method without taking expensive precautionary measures (Vianna, G.H.R. et al., Letters in Organic Chemistry 5 (2008) 396-398).

Therefore there is quite a need to improve the synthesis of N-substituted pyridinium compounds, e.g. by avoiding hazardous activation reagents. Novel less critical activation reagents should allow for safer production procedures and for easier, less risky and more efficient production of such compounds at much larger scale.

Summarv of the Invention

It now has been found by the inventors of the present invention that pyridinium compounds can be reacted with appropriate aromatic heterocycles thereby forming a Zincke-type salt. It could surprisingly be shown that these heteroaryl substituted pyridinium salts are useful for reaction with primary amine nucleophils, i.e. in Zincke-type reactions. Unexpectedly both the formation of the Zincke salt as well as Zincke reaction of primary amines with N-heteroaryl pyridinium compounds shows high yields. Advantageously both the Zincke salt formation as well as the Zincke reaction can be performed under less vigorous reaction conditions as compared to state of the art procedure and they can easily be scaled up. It is a further advantage that after the Zincke reaction is completed the heteroaryl byproduct of the Zincke-type reaction usually shows a low solubility and precipitates. Therefore it can be easily separated from the reaction mixture, which helps in isolation of the N-substituted pyridinium compound.

Based on all these findings many of the problems known from the art can be avoided and overcome.

The present invention relates to a method for synthesis of an N-substituted pyridinium compound comprising the steps of a) providing a N-heteroaryl substituted pyridinium salt (Zincke salt) b) reacting the Zincke salt of step (a) with an amine (R-NH2) under appropriate conditions and c) thereby obtaining an N-substituted pyridinium compound substituted with the R residue of the primary amine.

Also disclosed are novel Zincke-type salts. These Zincke-type salts can e.g. be used in the synthesis of N-substituted pyridinium compounds.

Certain substituted pyridinium compounds produced in a method as disclosed in the present invention are of great utility in the synthesis of NAD or NAD analogs, like carba-NAD, respectively.

Detailed Description of the Invention

In a first embodiment the present invention relates to a method for synthesis of an N-substituted pyridinium compound comprising the steps of providing a N-heteroaryl substituted pyridinium salt (Zincke salt) b) reacting the Zincke salt of step (a) with a primary amine (R-NH2) under appropriate conditions and c) thereby obtaining an N-substituted pyridinium compound substituted with the R residue of the primary amine.

Zincke type salts are prepared by reacting pyridines with electron deficient heteroaromates which are substituted with a leaving group.

An "electron deficient heteroaromate" or "electron poor heteroaromate" according to this invention is a 6-membered heteroaromate characterized by an unsaturated aromatic ring system with a minimum of two sp2 N atoms which are in ortho or para position to a leaving group.

A "leaving group" is an appropriate group that is attached to the reactive center of the 6-membered unsaturated aromatic ring system. The reactive center carrying the leaving group is an sp2 carbon atom which is adjacent to a sp2 nitrogen atom (in ortho position to an sp2 N).

A "Zincke salt" or Zincke-type salt" is a pyridinium compound which bears an electron withdrawing moiety at the nitrogen atom of the pyridinium ring. In Zincke-type salts according to the present invention the electron withdrawing group is an electron deficient heteroaromatic moiety.

An "electron deficient heteroaromatic moiety" or "electron poor heteroaromatic moiety" according to this invention is a 6-membered heteroaromatic moiety characterized by an unsaturated aromatic ring system with a minimum of two sp2 N atoms which are in ortho or para position to the pyridinium ring of the Zincke type salt.

The term Zincke reaction" or "Zincke-type reaction" relates to the reaction of a Zincke salt with an amine nucleophil resulting in formation of an N-substituted pyridinium compound.

As the skilled artisan will appreciate, a prerequisite for the heteroaromatic compound is that it is an electron deficient heteroaromate carrying a substituent which acts as a leaving group. The electron deficiency of the aromatic heterocycle favors nucleophilic substitution reactions and allows for reaction with pyridines, i.e. for the formation of a Zincke salt.

In order to allow for a reaction under non vigorous conditions, e.g. avoiding very high temperature, and in order to avoid non scalable methods like microwave synthesis, the reaction center, i.e. the atom to which the leaving group is bound must be activated in such a way that the reaction with pyridines performs quite easily. Activation of the leaving group is achieved by choosing heterocycles which have in ortho and para position to the leaving group an sp2 nitrogen atom, since in this case the reactive center where the nucleophilic attack of the pyridine nitrogen atom occurs is more positively charged.

Such N-heteroaryl substituted pyridinium compounds are in principle capable of two reaction pathways when reacted with amine nucleophils: ring opening of the pyridinium moiety or nucleophilic displacement wherein the pyridinium moiety acts as a leaving group. Therefore the extend of activation of the leaving group must be well balanced. We found that especially useful as heteroaryl moieties are purines and substituted triazines. The substituents on the purine or triazine carbon atoms are chosen in such a manor that reactivity towards pyridinium nucleophils is high enough and that the ring open/ring closure pathway is preferred over nucleophilic displacement. Another import role is that solubility in a given solvent is directed in such a manner that the amine substituted purine or triazine which is the result of the Zincke reaction precipitates and therefore is easy to separate from the desired N-substituted pyridinium compound, preferably by filtration. For large scale synthesis the costs of materials e.g. of the heterocycle used are a further selection criterion. It is obvious to the skilled artisan that for different pyridine compounds different combinations with heterocycles and different solvents may be the best choice. Without any undue experimentation the skilled artisan will be able to select such appropriate combinations of desired pyridinium compounds and candidate aromatic heterocycles.

In one embodiment of the present invention a Zincke-type salt is generated by reaction of an electron deficient aromatic heterocycle having an unsaturated aromatic ring system with a minimum of two sp2 N atoms which are in ortho or para position to a substituent acting as a leaving group with a pyridine of interest. In this reaction a Zincke-type salt according to Formula I is formed.

A Zincke-type salt consists of the positively charged heteroaryl substituted pyridinium moiety as depicted in Formula I and a counter ion.

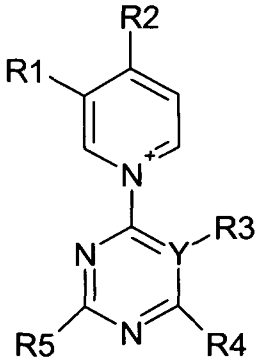
Typical and preferred examples of heteroaromates used in the generation of Zincke salts are chlorotriazines, 6-chloro-purines, 4-chloro-pyrimidines and 4-chloro - quinazolines. The 6 membered heteroaromatic ring may be substituted on the sp2 carbon atoms, other than the sp2 carbon atom of the reactive center, with substituents independently selected from amino, alkyl amino, aryl amino, alkoxy, hydroxyl, alkyl, aryl and halogen or two adjacent sp2 carbon atoms can be members of a further aromatic or heteroaromatic ring, like in purines or quinazolines. These heteroaromates also represent preferred heteroaromates for use in synthesis of a Zincke salt and thereby in a subsequent Zincke-type reaction according to the present invention.

As mentioned above, the electron deficient heteroaromate carries a leaving group. Preferred leaving groups are Cl, Br, 4-methylphenyl-sulfonyloxy, trifluormethyl-sulfonyloxy, and methyl-sulfonyloxy. Preferably Cl is used as a leaving group.

The kind of the counter ion is determined by the leaving group. Therefore appropriate and preferred counter ions are chloride, bromide, tosylate, mesylate and triflate. In some reactions it is useful and also represents a preferred embodiment to exchange the counter ion to a non-nucleophilic counter ion like dodecyl sulfate or tetrafluoroborate.

In one embodiment the present invention relates to a method for synthesis of an N-substituted pyridinium compound comprising the steps of (a) providing a Zincke salt according to Formula I

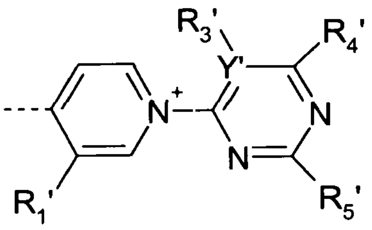
Formula I



having a counter ion,

wherein R1 is selected from H, alkyl, aryl, 2-methyl-l,3-dioxolan-2-yl, aryloxy, alkyloxy, hydroxyalkyl, arylalkyl, N-protected aminoalkyl, alkenyl, alkinyl, arylalkenyl, arylalkinyl C=XNH2, C=XNHalkyl, C=XN(alkyl)2 C=XNHaryl, C=XN(aryl)2, C=Xaryl, C=X alkyl, COO alkyl,

wherein R2 is selected from H, alkyl, aryl, pyrid-4-yl, alkylpyridinium-4-yl, 2-methyl-l,3-dioxolan-2-yl, aryloxy, alkyloxy, hydroxyalkyl, arylalkyl, protected amino alkyl, alkenyl, alkinyl, arylalkenyl, arylalkinyl, C=XNH2, C=XNHalkyl, C=XN(alkyl)2, C=XNHaryl, C=XN(aryl)2, C=Xaryl, C=Xalkyl, COOalkyl, alkylsulfanyl and



wherein at least one of R1 or R2 is H or alkyl or the residues R1 and R2 together are a butan-1,4 diyl, or a butadiene- 1,4-diyl moiety linked to each other forming a 6-membered cycle,

wherein independently in R1 or R2 alkyl is linear or branched C1-C6 alkyl or C5-C6 cycloalkyl, alkenyl is linear or branched C2-C6 alkenyl, alkinyl is linear or branched C2- C6 alkinyl and aryl is phenyl or naphthyl,

wherein X = S or O,

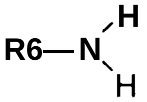
wherein Y is N or C; in case Y is N no R3 is present and in case Y is C, then R3 is H, C1-C3 alkyl, or forming together with R4 and the two sp2 carbon atoms to which R3 and R4 are attached a 5- or 6-membered aromatic ring system, optionally comprising 1 or 2 nitrogen atoms,

wherein R4 is H, C1-C3 alkyl, hydroxy, 0-C1-C3 alkyl, amino, C1-C3 alkyl-amino, phenylamino, phenyl or forming together with R3 and the two sp2 carbon atoms to which R3 and R4 are attached a 5 or 6-membered aromatic ring system, optionally comprising 1 or 2 nitrogen atoms, wherein R5 is H, C1-C3 alkyl, hydroxy, O-C1-C3 alkyl, amino, C1-C3 alkyl-amino, phenylamino, phenyl or halogen,

and wherein each of Y', Rl', R3', R4'and R5', in case Formula I represents a bipyridyl compound, are the same as the corresponding Y, Rl, R3, R4 and R5,

(b) reacting the Zincke salt of step (a) with a primary amine of Formula II

Formula II

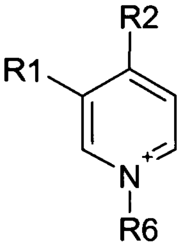


wherein R6 is part of a primary organic amine comprising an sp2 or an sp3 carbon atom which is bound to the -NH2 moiety,

or wherein R6 is a residue which together with -NH2 is a hydrazine, a hydroxyl amine, a sulfonyl hydrazide or a carbohydrazide,

(c) thereby obtaining an N-substituted pyridinium compound of Formula III

Formula III



having a counter ion and wherein Rl, R2, and R6 are as defined above.

The skilled artisan will have no difficulty at all in choosing appropriate reaction conditions for carrying out the method according to the present invention. A range of appropriate reaction conditions is e.g. described by means of the Examples given.

In a preferred embodiment in R1 or R2, independently of each other, alkyl is linear or branched C1-C6 alkyl or C5-C6 cyclo alkyl, alkenyl is linear or branched C2-C6 alkenyl, alkinyl is linear or branched C2- C6 alkinyl and aryl is phenyl or naphthyl.

As the skilled artisan will readily note the method according to the present invention may be used with great advantage for N-substitution of a large variety of pyridinium based chemical compounds. It is quite likely that even compounds not covered by the above definitions of Rl and R2, respectively, of Formula I can be used.

Preferred examples of a pyridinium moiety in a Zincke-type salt for use in a method according to the present invention are a) para substituted pyridines like pyrid-4-yl, alkylpyridinium-4-yl, 2-methyl-l,3-dioxolan-2-yl, C=ONH2, C=ONEt2, COOalkyl, naphthyl, phenyl, anthracen-9-yl, 2-(9-anthracenyl)ethenyl, methyl, propyl, t.-butyl, N-trifluoracetyl-2-amino-ethyl, 3-hydroxypropyl, methylsulfanyl, or "dimeric Zincke" salts resulting from reacting bipyridines on both N atoms with an electron deficient heterocycle; b) Meta-substituted pyridines carrying substituents like phenyl, methyl, C=ONH2, C=ONEt2. [(methoxyimino)methyl]-, COOEt, methoxy, (13-hydroxytridecyl)-, [(9E)-12-N boc-amino]-9-dodecen-l-yl], hydroxymethyl, (2-methyl-l,3-dioxolan-2-yl)-; c) pyridines having para and meta substituents, e.g. with Rl and R2 being methyl or forming together a ring, e.g. the Isoquinolinium-Zincke salts and derivatives thereof, e.g. the 8-methyl or 6,7-dimethoxy isoquinolinium derivatives.

In one preferred embodiment the para and meta substituent are linked to each other thereby together with the pyridinium ring forming an isoquinolinium ring or a derivative thereof.

In one preferred embodiment the pyridine moiety used in a method according to the present invention does not fall into the definition of Formula I but has two methyl groups in meta position.

Preferably either R1 or R2 of Formula I is selected from phenyl, CONH2, CSNH2, carboxy-(Cl-C6)-alkyl, (Cl-C ό)-alkyl and 2-methyl-l,3-dioxolan-2-yl. Also preferred either R1 or R2 is CONH2 or CSNH2 and the other is hydrogen, respectively. Also preferred R1 is CONH2 and R2 is H.

In one preferred embodiment the pyridinium ring according to Formula I bears only one substituent in the meta position. Preferably this substituent in meta position is selected from C=ONH2, C=SNH2, C=OCH3, 2-methyl-l,3-dioxolan-2-yl, (Cl-C6)-alkyl or phenyl.

In a preferred embodiment in the synthesis of the N-substituted pyridinium compound a Zincke-type salt according to Formula I is used wherein Y is N and both R4 and R5 are alkoxy each independently with a Cl to C3 alkyl group. Preferably the Zincke-type salt for use in a method according to the present invention is based on 2-chloro-4,6-dimethoxy-triazine, and 2-chloro-4,6-diamino - triazine. As the skilled artisan will appreciate also an N-substituted derivative thereof (e.g. a simazine, atrazine, anilazine, propazine) can be used in a method according to the present invention.

In a further preferred embodiment in a method according to the present invention a Zincke-type salt according to Formula I is used wherein X is C, i.e. it is based on an appropriate pyrimidine. In one preferred embodiment both R3 and R4 are hydrogen or Cl to C3 alkyl and R5 is NH2 or N-dialkyl (Cl to C3). Other preferred pyrimidines for use in the production of a Zincke-type salt and later use of said salt in method according to the present invention are selected from the group consisting of 6-chloro-2,4-dimethoxypyrimidine, 2,4-dichloropyrimidine, 4 chloro-2,6-diaminopyrimidine, 4-amino-2,6-dichloropyrimidine, 4-chloro-2,6-dimethylpyrimidine and 2-amino-4-chloro-pyrimidines.

In a further preferred embodiment in a method according to the present invention a Zincke-type salt according to Formula I is used wherein X is C and R3 and R4 form an aromatic cycle.

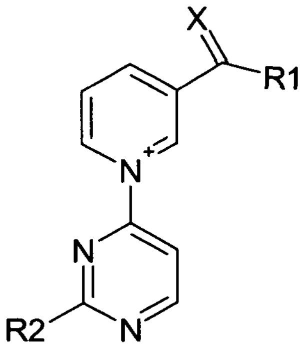
In a further preferred embodiment in a method according to the present invention a Zincke-type salt according to Formula I is used wherein Y is C and R3 and R4 are linked to each other to form together with the sp2 carbon atoms to which R3 and R4 are attached an imidazole ring, i.e. in this case the Zincke salt is based on a purine ring system. Preferably the Zincke-type salt used in a method according to the present invention is based on activation of a purine or substituted purine. Preferably 6-chloro purine, 2-amino-6-chloro purine or 2,6 dichloro purine is used.

In a further preferred embodiment in a method according to the present invention a Zincke-type salt according to Formula I is used wherein Y is C, and R3 and R4 are linked to each other to form together with the sp2 carbon atoms to which R3 and R4 are attached an aromatic 6-membered ring system, i.e. in this case the Zincke salt is based on a quinazoline ring system. Preferred quinazolines for use in a method according to the present invention are 2,4-dichloro-6,7-dimethoxyquinazoline and 4-chloro-6,7-dimethoxy-quinazoline.

Due to environmental aspects preferably a Zincke-type salt is used in a method according to the present invention that bears only one halogen atom in order to avoid halogenated organic waste.

In a preferred embodiment the present invention relates to a Zincke-type salt selected from the group consisting of compounds as defined by Formulas IV, V, VI and VII.

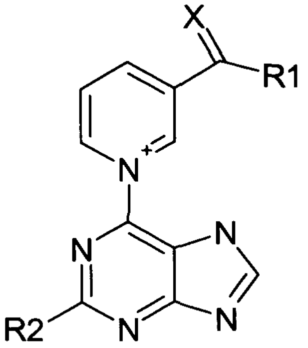
Formula IV



wherein

X is O or S,
R1 **is** methyl, ethyl, O-methyl, O-ethyl, NH2, N-dimethyl, N-diethyl,
R2 is NH2;

Formula V



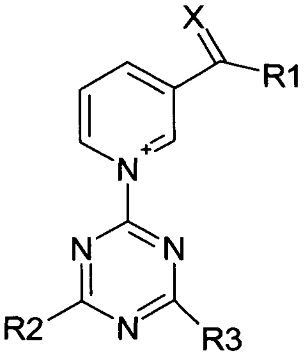
wherein

X is O or S,

R1 is methyl, ethyl, O-methyl, O-ethyl, NH2, N-dimethyl, N-diethyl,

R2 is NH2 or Cl;

Formula VI



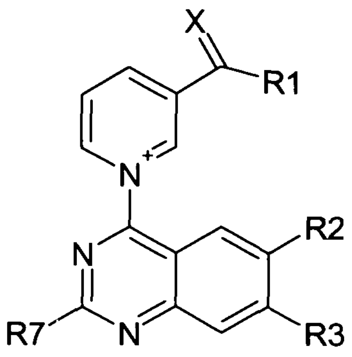
wherein

X is O or S,

R1 is methyl, ethyl, O-methyl, O-ethyl, NH2, N-dimethyl, N-diethyl,

R2 and R3 independently are O-C1-C3 alkyl or NH2;

Formula VII



wherein

X is O or S,

R1 is methyl, ethyl, O-methyl, O-ethyl, NH2, N-dimethyl, N-diethyl,

R2 and R3 independently are O-C1-C3 alkyl and R7= H or Cl.

In a preferred embodiment the present invention relates to a Zincke-type salt according to Formula IV.

In a preferred embodiment the present invention relates to a Zincke-type salt according to Formula V.

In a preferred embodiment the present invention relates to a Zincke-type salt according to Formula VI.

In a preferred embodiment the present invention relates to a Zincke-type salt according to Formula VII.

In a further preferred embodiment in a method according to the present invention a Zincke-type salt according to Formula IV, V, VI or VII is used

In a further preferred embodiment in a method according to the present invention a Zincke-type salt according to Formula I is used wherein R1 is hydrogen and R2 is CONH2. If such Zincke-type salt is used the synthesis method according to the present invention leads an N-substituted nicotinamide derivative. In the generation of substituted nicotinamide preferably Zincke-type salts based on 2-amino-6-chloro-purine, 2-amino-4-chloropyrimidine, 4-chloro-6,7-dimethoxquinazoline or 2-chloro-4,6-dimethoxy triazine are used.

In one preferred embodiment in a method according to the present invention a 6-chloro purine is reacted with a pyridinium compound and the resulting 1-(purin-6-yl)-pyridinium salt is reacted with a primary amine.

In a further preferred embodiment nicotine amide is reacted with 2-amino-6-chloro-purine to produce the Zincke salt l-(2 amino-purin-6yl) 3 carboxamidopyridinium chloride and subsequent this Zincke salt is reacted with a primary amine.

As mentioned above the Zincke reaction can be performed with any appropriate nucleophilic amine (R-NH2). The nature of R in the amine R-NH2 can be very broad. As the skilled artisan will appreciate R will preferably be selected in such a manner that the amino group attached to it has a nucleophilicity that is high enough to attack the C2 or C6 carbon atom of the pyridinium moiety of a Zincke salt in a method according to the present invention.

Even though the empirical concepts of basicity and nucleophilicity are related but not strictly proportional, chemists are using pKa values for obtaining at least a rough insight into the relative reactivity of amines (see e.g. Jaramillo, P. et al., Journal of Physical Organic Chemistry 20 (2007) 1050-1057).

pKa values are known for a plurality of amines (cf.: Dissociation Constants of Organic Bases in Aqueous Solution, (Pure and Applied Chemistry), Perrin, D.D., London (1965) pp. 473).

In a preferred embodiment the amine R-NH2 has a pKa-value of from 1.7 (inclusive) to 12 (inclusive).

Preferably R is chosen such that the amine is a primary amine as defined in Formula II (R6-NH2). The skilled artisan will have no difficulty to choose an appropriate primary amine R6-NH2 for use in a method according to the present invention. This way it is possible to generate the desired pyridinium compound with an R6-substituted nitrogen.

Typically primary alkyl amines have an pKa from 10-1 1. Primary alkyl amines (R6-NH2) having an sp3 carbon atom in R6 bound to the amino group represent a preferred embodiment according to the present invention.

In case the primary amine R6-NH2 has an sp2 carbon atom in R6 bound to the amino group, the nucleophilicity of such primary amine can easily be evaluated by comparison to a reference compound.

In a preferred embodiment according to the present invention the pKa-value for the arylic or heteroarylic amine R6-NH2, the later not comprising a basic ring nitrogen atom, is the same as determined for 4-cyano aniline or it is above the pKa as measured for this compound. pKa value determination by titration is a well established method and automated tritrators specialized on pKa measurements are commercially are available. In a preferred embodiment the pKa is determined with Sirius T3 according to the instructions provided by the manufacturer (Sirius Analytical Ltd. Riverside, East Sussex, UK).

For amino substituted nitrogen heterocycles with a ring nitrogen atom, the ring nitrogen atom being the most basic site, direct measurement of the basicitiy of the exocyclic amino group is not possible. In this case the procedure as described in Deady, L.W. et al., Aust. J. Chem 37 (1984) 1625-1630 has to be applied. In case the heteroarylamine is an amino substituted nitrogen heterocycle with a basic ring nitrogen atom the pKa preferably is the same as determined for 4 amino pyridine or it is above the pKa as measured for this compound.

In one embodiment R6 is part of a primary organic amine comprising an sp2 or an sp3 carbon atom which is bound to the -NH2 moiety, or R6 is a residue that together with -NH2 is a hydrazine, a hydroxylamine, a sulfonyl hydrazide or a carbohydrazide.

Preferably R6 together with -NH2 is a primary organic amine, or R6 is selected from the group consisting of -OH, -NH2, -N(Cl-C6alkyl)2, -NHC=Oaryl, -NHSO2aryl, -NHSO2-(C 1-C6)alkyl, -NHC=O(C4-C 13)-heteroaryl comprising one optionally substituted heteroatom selected from N, O, S or N-(Cl-C6)-alkyl or protected N, -NHSO2, C4-C13-heteroaryl comprising one substituted heteroatom selected from N, O, S or N-Cl-C alkyl or protected N, wherein N is protected by a tosyl- or boc- protecting group.

A primary organic amine is an amino group that is bound via a single valency bond to an sp3 or to an sp2 carbon atom.

In case R6 is part of a primary organic amine comprising an sp2 or an sp3 carbon atom which is bound to the -NH2 moiety, said sp2 carbon atom preferably is part of an aromatic or a heteroaromatic moiety, or said sp3 carbon atom preferably is part of a carboacyclic moiety, a heteroacyclic moiety, a carbocyclic or a heterocyclic moiety.

In a preferred embodiment either R6 is selected from the group consisting of alkyl, alkenyl, alkinyl, heterocycloalkyl, aryl, heteroaryl, or Formula II represents an amino alcohol, an amino acid, a furanosylamine or a cyclopentylamine.

As the skilled artisan will appreciate even compounds having an additional principally nucleophilic group in R6 can be used. In this case a further nucleophilic group has to be protected by an appropriate protecting group. Protecting groups are well known from the art and reviewed in standard text books (Greene, T., Protective groups in organic synthesis, John Wiley&Sons, Inc. (1981) New York, Chichester, Brisbane, Toronto). Preferably, amino groups, e.g. in N-protected alkyl, are protected by tosyl-, boc-, phthaloyl- or trifluoracetyl-protecting groups. Mercapto groups preferably are protected as disulfide.

In R6 alkyl preferably is a linear or branched (C1-C20)- alkyl or a mono-, bi- or tricyclo (C3-C10)-alkyl; alkenyl preferably is a linear or branched (C3-C20)alkenyl or a mono-, bi- or tricyclo (C5-C10)-alken-l-yl with the amino group attached to an sp3 carbon atom; alkinyl preferably is a linear or branched (C3-C20)-alkinyl with the amino group attached to an sp3 carbon atom; a heterocycloalkyl preferably is (C5-C6)-cycloalkyl comprising one optionally substituted heteroatom selected from O, NC1-C3 alkyl, protected N; aryl preferably is a C6-C14 aryl moiety; heteroaryl preferably is a C4-C13 heteroaryl moiety comprising one optionally substituted heteroatom selected from N, O, S or N-C1-C6 alkyl or protected N. The nomenclature C4 to C13 relates to heteroaryl rings with a total number of 5 to 14 ring atoms of which one is a hetero atom as mentioned above.

For amines derived from alkylalkenyl, cycloalkenyl, cycloalkanyl, polycycloalkan, or heterocycloalkanes the following selected examples represent preferred embodiments for a primary organic amine according to Formula II and its use in a method according to the present invention:

a) alkyl and alkenyl amines are preferably selected from the group consisting of (S)-Phenylalaninol, D-Phenylethylamine, 4-Pyridinemethanamine, Propylamine, 2-Amino- 1-phenyl- 1,3-propanediol, 3-Pyridinetridecanamine, (3-Vinyl-4-isopropoxybenzyl)amine, 2-Phenylglycine, Serine, Isoleucin, beta-Alanyl- L-Histidine, 9-(3-Pyridinyl)-,3-nonen-l -amine, 6-Amino-beta-(aminornethyl)-9H-purine-9-butanol and p-(Aminomethyl)benzenesulfonamide;

b) cycloalken preferably is (lR,4S,6S)4-amino-6-hydroxy-2-Cyclohexene-l-methanol- 1-(dihydrogen phosphate),

c) cycloalkan preferably is cyclohexylamine, trans-2-Phenylcyclopropylamine, or (1S,2R,3S,5S)- 3-Amino-5-(hydroxymethyl)-l,2-Cyclopentanediol,

d) polycycloalkan preferably is tricyclo[3 .3.1. 13,7]decan- 1-amine and

e) heterocycloalkans preferably is selected from 4-Amino-3 -methyl- 1-(phenylmethyl)-3-Piperidinol, (2S)-2-Aminomethylpyrrolidine- 1-carboxylic acid tert-butyl ester; 2-Amino-l,5-anhydro-2-deoxy- 6-(dihydrogen phosphate) D-altritol; 2-Amino-1,5-anhydro-2,3-dideoxy-, and 6-(dihydrogen phosphate) D-arabino-hexitol.

In case R6 represents an aryl moiety the corresponding arylamine according to Formula II preferably is selected from 4-Aminobenzonitrile, 2-Hydroxy-4-aminobenzoic acid; p-Hexadecylaniline, 2,5-Dimethylaniline; p-Phenylenediamine, l,4-Diamino-2,5-dimethylbenzene, 4-Halogenoaniline; 3-Bromo-4-isopropoxyaniline, 4-Isopropoxy-3-vinylaniline, 1-Naphthylamine, 4-(Aminobenzyl)phosphonic acid diethyl ester; p-Aminophenol; p-Aminobenzyl alcohol, 4-(Pyridin-4-ylmethyl)phenylamine; 4-Aminophenylsulfonic acid, 4-Aminobenzoic acid; 4-(Acetylamino)aniline; Dimethyl-5-aminoisophthalate; p-Aminoacetophenone; 2,2-dimethyl-l ,3-Benzodioxol-5-amine.

Preferably, in case R6 is a heteroaryl moiety, i.e. the compound according to Formula II is a heteroaryl, the compound according to Formula II is preferably selected from the group consisting of 6-amino-quinoline, 4 -amino-pyridine and 3-amino-pyridine.

Preferably the primary amine used in a method according to the present invention is a pure enantiomeric primary amine wherein the amino group is attached to a stereocenter. This is preferred because the method according to the present invention allows for a stereospecific production of the desired pyridinium compound.

As the skilled artisan appreciates such primary amines can comprise further substituents which do not interfere with the Zincke reaction or are unstable under conditions of the Zincke reaction. In a preferred embodiment the compound according to Formula II used in a method according to the present invention is a substituted alkyl amine.

Preferred compounds according to Formula II for use in a method according to the present invention are pure stereoisomers of amino alcohols and amino acids.

Preferably an amino alcohol is derived from any naturally occurring or any commercially available non-natural amino acid Preferably the amino alcohol is selected from the group consisting of serinol, threoninol, phenylalaninol, 2,5 diamino 1-Pentanol, (from ornithin) 2,6 diamino-1-hexanol (from lysine).

In case the compound according to Formula II is an amino acid, the amino acid may be selected from any naturally occurring or any commercially available non-natural amino acid. In a preferred embodiment the amino acid either is a naturally occurring amino acid or a non-naturally occurring amino acid. Preferably the compound according to Formula II is an amino acid selected from serine, threonine, phenylalanine, ornithin, lysine, leucine.

If desired, in a further alternative embodiment di- or polyamines where no amino group is protected can be reacted with two or more equivalents of Zincke type salts, in order to form di-pyridinium or poly-pyridinium compounds.

Also preferred primary amines are amines substituted with furanosyl sugar moieties or analogs of such furanosyl sugar moieties, which optionally are phosphorylated at an OH group or compromise protected hydroxyl groups, whereas the protecting groups are benzyl, acetal, silyl and trityl or compromise F or methoxy groups instead of OH groups. Preferably a furanosyl sugar or such analogs which are suitable for the synthesis of NAD or Nicotinamidmononucleosid and analogs thereof are used.

Synthesis of NAD or Nicotinamidmononucleosid and analogs thereof using furanosylamines in combination with the dinitrophenyl Zincke salt is described in detail in the following references: Kam, B.L. et al., Biochemistry 26 (1987) 3453-3461; Sicsic, S. et al., European Journal of Biochemistry 155 (1986) 403-407; Kam, B.L. et al., Carbohydrate Research 77 (1979) 275-280, and US 4,41 1,995.

Preferred furanosylamines are the beta and alpha anomers of D and L ribose, xylose and arabinose.

Also preferred are cyclopentylamines which are the carba analogs of furanosylamines. Preferably these analogs are selected from the group consisting of Beta-D-ribofuranosyl amines, -2-deoxyribofuranosylamine, or -2,3-dideoxy ribosylfuranosylamine the later preferably selected from (lR,2S,3R,4R)-2,3 Dihydroxy-4-hydroxymethyl-l-aminocyclopentane, (lS,3R,4R)-3-Amino-4-hydroxy-cyclo-pentanemethanol, or (1R-cis)-3-amino-Cyclopentane-methanol.

In a further preferred embodiment in a method according to the present invention a Zincke-type salt is reacted with a primary amine (R6-NH2), wherein said primary amine is (lR,2S,3R,4R)-2,3 Dihydroxy-4-hydroxymethyl-l aminocyclopentane). Reacting an appropriate Zincke salt of the present invention with this primary amine leads to the formation of nicotinamido-carba riboside (3-Carbamoyl-1-((lR,2S,3R,4R)-2,3-dihydroxy-4-hydroxymethyl-cyclopentyl)-pyridinium chloride). Nicotinamido-carba riboside is a compound which is key to the synthesis of the carba analog to NAD. Carba-NAD and its preferred uses are described in detail in WO 2007/012494. The full disclosure of WO 2007/012494 is herewith included by reference.

Other preferred substituted primary amines are selected from 3-Amino tetrahydrofuranes or protected 3-Amino-pyrollidines, e.g. (2R, 4R)-4-Aminotetrahydrofuran-2-methanol (a heterocyclic analog of 2,3-dideoxyribosylamine) cyclohexylamines and Cyclohex-2-enyl amines, e.g. 6 ring sugar analogs as disclosed in Goulioukina, N. et al., Helvetica Chimica Acta 90 (2007) 1266-1278.

Preferred examples of phosphorylated amino sugars are (lR,4S,6S)4-Amino-6-hydroxy-2-Cyclohexene- 1-methanol- 1-(dihydrogen phosphate), 2-Amino- 1,5-anhydro-2-deoxy- 6-(dihydrogen phosphate) D-Altritol, 2-Amino-l,5-anhydro-2,3-dideoxy-and 6-(dihydrogen phosphate) D-arabino-Hexitol.

As the skilled artisan will appreciate even compounds having an additional principally nucleophilic group in R6 can be used. In this case a further nucleophilic group has to be protected by an appropriate protecting group. Protecting groups are well known from the art and reviewed in standard text books (Greene, T., Protective groups in organic synthesis, John Wiley&Sons, Inc. (1981) New York, Chichester, Brisbane, Toronto). Preferably, amino groups are protected by boc-, phthaloyl- or trifluoracetyl-protecting groups, mercapto groups are protected as disulfide.

In an alternative embodiment the Zincke-type salt according to Formula I is used in a Zincke reaction with a compound having a free NH2 group. In this alternative embodiment R6 is selected from -OH, -NH2, -N(Cl-C6alkyl)2, -NHC=Oaryl, -NHSO2aryl, -NHSO2-(C1-C6) alkyl, -NHC=O(C4-C13)-heteroaryl comprising one optionally substituted heteroatom selected from N, O, S or N-C1-C6 alkyl or protected N, -NHSO2-(C4- C13)-heteroaryl comprising one optionally substituted heteroatom selected from N, O, S or N-Cl-C alkyl or protected N. In this embodiment Formula II preferably represents a hydrazine, a hydroxylamine or a hydrazide. In this embodiment preferably the following compounds are used in a Zincke-type reaction: a) hydrazides; e.g. 2-(Pyridin-3-yl)acetohydrazide, 3-Indolylacetic acid hydrazide; l,3-Benzodioxole-5-acetic acid hydrazide, 3-Phenylpropanoic acid hydrazide, Phenoxyacetic hydrazide, Cyclohexanecarboxylic hydrazide or Heptanoic acid hydrazide; Benzoic acid hydrazide; 4-Aminobenzoic acid hydrazide; 3-(Aminosulfonyl)-4-chloro-benzoic acid hydrazide; 4-Pyridinecarboxylic acid hydrazide; 3-Pyridinecarboxylic acid hydrazide; 2-Pyridinecarboxylic acid hydrazide; or acetic acid hydrazide, b) Sulfonic acid hydrazides, e.g., phenylsulfonic acid hydrazide, 4-Methoxybenzenesulfonic acid hydrazide; Methylsulfonic acid hydrazide, and c) hydrazines, e.g., l-Amino-2-(methoxymethyl)pyrrolidine, 2-hydrazinyl-pyridine or 2 hydrazinyl isoquinoline.

In a further preferred embodiment 4,4'-bipyridines are reacted with two equivalents of an electron deficient heteroaromate to produce an N,N'-bisheteroaryl bispyridinium salt. Such "bis Zincke salts" can be reacted with amines to N, N' bisubstituted bipyridines, which are known as viologens. Viologens exhibit very interesting electrochemical properties. Synthesis of viologens is described by Inagaki, Y. et al., Journal of Materials Chemistry 16 (2006) 345-347; Liu, Y. et al., Organic Letters 10 (2008) 765-768.

If the N,N'-bisheteroaryl bispyridinium salts are reacted with bisamines, polyviologens will result, which have a broad range of applications as electrochromic materials or as semiconductors (see e.g. WO 2008/022966; EP 2 023 418 and US 2009/128882). In a further preferred embodiment the present invention thus relates to method for producing a polyviologen by reacting a N,N'-bisheteroaryl bispyridinium salt with a bisamine.

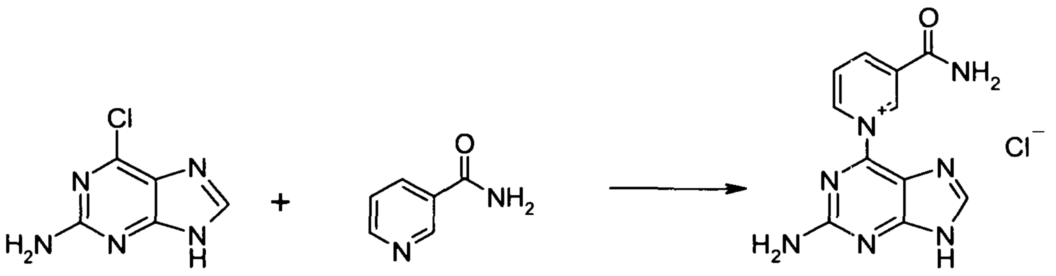
From the above it is obvious that a lot of different compounds according to Formula II are compatible with the Zincke reaction.

The novel procedures disclosed in the present invention have several advantages compared to the standard procedure with 2,4-Dinitrophenyl Zincke salts. Aromatic heterocycles like 2-amino-6-chloro purine or 2-chloro-4,6-dimethoxy triazine are cheap and readily available. They are non-explosive compounds and therefore the Zincke salt formations and Zincke reaction can easily be scaled up without any undue precautionary measures.

The following examples are provided to aid the understanding of the present invention, the true scope of which is set forth in the appended claims. It is understood that modifications can be made in the procedures set forth without departing from the spirit of the invention.

Example 1

1-(2 amino-purin-6yl) **3** carboxamidopyridinium **chloride**



967 g (5.7 mol) 2-Amino-6-chlorpurin (Carbosynth Batch FA025810801) and 562 g (4.6 mol) Nicotinamide (Fluka 72340) were heated in 5 l dimethylformamide for 7h under stirring at 95-97 °C. The mixture was stored at room temperature overnight. The mixture was filtrated and the residue was suspended in 3 l acetone;

the suspension was stirred for Ih at room temp. The mixture was filtrated and the residue was dried for 2 days in vacuum.

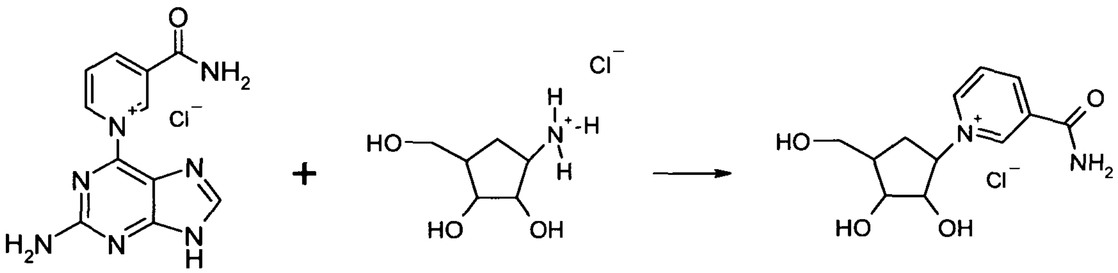
Yield 120O g
TLC (HPTLC-Diol Plates, Merck-Nr. 1.12668.0001) 1-butanol/acetic acid/water 10/3/5, Rf= 0.41

Using 2-amino-6-chloro-pyridine as heteroaromatic compound in reaction with nicotine amide can easily be performed in DMF at 100 °C or even below. The product simply precipitates after cooling to room temperature and could be easily separated by filtration. The Zincke reaction of the resulting Zincke salt with (lR,2S,3R,4R)-2,3 Dihydroxy-4-hydroxymethyl-l aminocyclopentane was performed in an polar solvent (see Example2).

The resulting "by-product" 2,6 diaminopurine is easily removed by adjusting the pH and subsequent filtration.

Example 2

3-Carbamoyl-l-((lR,2S,3R,4R)-2,3-dihydroxy-4-hydroxymethyl-cyclopentyl)-pyridinium; **chloride**



537 g (2.93 mol) (lR,2S,3R,4R)-2,3-dihydroxy-hydroxymethyl-l-amino-cyclopentanhydrochlorid (Chirotec 004-003), 90Og (3.09 mol) l-(2 amino-purin-6yl) 3 carboxamidopyridinium chloride ("Purine Zincke salt") and 1.1 L (9.1 mol) N-ethyldiisopropylamine (Fluka 03440) were given to 7.5 L Methanol. The mixture was heated under stirring to 60°C for 2 h. After cooling to room temperature the mixture was filtrated by using a Seitz filter.

The filtrate was evaporated by using a rotary evaporator and the resulting residue was dissolved in 7.5 L water. After adjusting to pH 4.2 with 2 M HCl a yellow precipitate formed. The mixture was stored overnight at 4°C, filtrated and to the filtrate were added activated charcoal. After stirring for 30 min at room temp the mixture was filtrated using a Seitz filter. The slightly yellow filtrate was evaporated by using a rotary evaporator, yielding 800 g of an orange oil, which was pure enough for further reactions.

For further purification, the residue can be dissolved in methanol and precipitated with ethyl acetate.

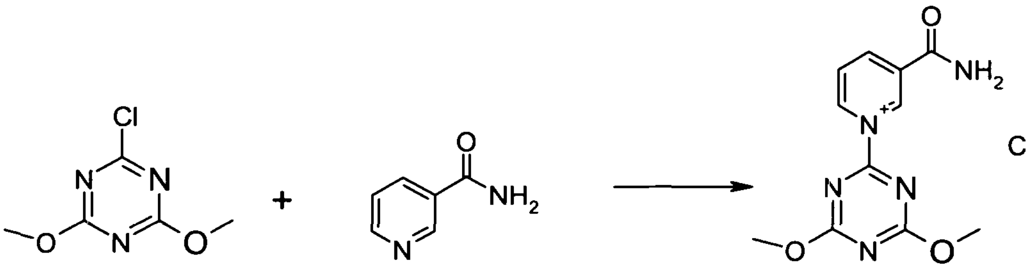
TLC: (HPTLC-Diol plates, Merck-Nr. 1.12668.0001) 1-butanol/acetic acid/water 10/3/5 Rf= 0.39

This crude product is suitable for synthesis of a NAD analog as shown in Examples 5 and 6.

Higher purities were obtained by ion exchange chromatography using a cation exchanger and eluting with water.

Example 3

1-(4,6dimethoxy-traizine **-2** yl) **3** carboxamidopyridinium **chloride**



9.2 g (51.5 mol) 2 chloro 4.6 dimethoxy triazine and 6.2 g (5.0 mol) Nicotinamide (Fluka 72340) were heated in 40 ml dimethylformamide for 0.5h under stirring at 80°C. The mixture was stored at room temperature for 2h. The mixture was filtrated and the residue was washed two times with acetone. The product was dried for 2 days in vacuum.

Yield 12, 4 g

Using 2-chloro-4,6-dimethoxy triazine as heteroaromatic compound in the reaction with nicotine amide the reaction can be performed in DMF at far below 100 °C, e.g. at 80 ^{0}C as shown above. The product precipitates after cooling to room temperature and thus could be easily separated by filtration. The Zincke reaction of the resulting Zincke salt with (lR,2S,3R,4R)-2,3 Dihydroxy-4-hydroxymethyl-l aminocyclopentane was performed in an polar solvent (see Example 4).

Example 4

3-CarbamoyI-l-((lR,2S,3R,4R)-2,3-dihydroxy-4-hydroxymethyl-cyclopentyl)-pyridinium; **chloride**

1.6 g (8.5 mmol) (lR,2S,3R,4R)-2,3-dihydroxy-hydroxymethyl-l-amino-cyclopentanhydrochlorid (Chirotec 004-003), 3.4g (10 mmol) 1-(4,6dimethoxy-traizine -2 yl) 3 carboxamidopyridinium chloride ("Triazine Zincke salt") and 3.2 ml N-ethyldiisopropylamine (Fluka 03440) were given into 50 ml Methanol. The mixture was heated under stirring to 60°C for 2 h. After cooling to room temperature the mixture was filtrated by using a D4-frit.

The filtrate was evaporated by using a rotary evaporator and the resulting residue was dissolved in 30 ml Methanol. and dropped under vigorous stirring in 250 ml ethyl acetate. The mixture was stored at one hour at room temp. The supernatant was removed by decantation. The crude product was dried under vacuum (1 mbar).

Example 5

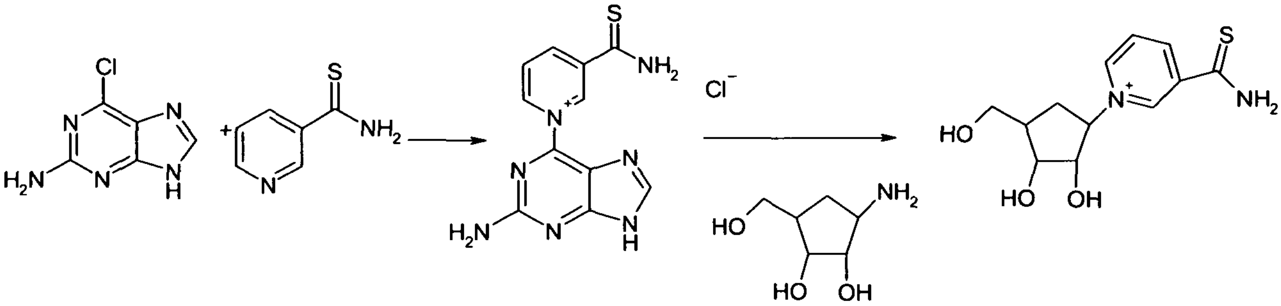
Conversion of 3-Carbamoyl-l-((lR,2S,3R,4R)-2,3-dihydroxy-4-hydroxymethyl-cyclopentyl)-pyridinium; **chloride to carba nicotinamide**

1 g (2.16 mmol) of 3-Carbamoyl-l-((lR,2S,3R,4R)-2,3-dihydroxy-4-hydroxymethyl-cyclopentyl)-pyridinium; chloride, 0.242 g (0.4mmol) ATP di sodium salt, 300 mg MgC12 x 6H2O (l.,45 mmol) 16 U Ribosylkinase, 1.45 g (4.43 mmol) creatinphosphate and 4.27 kU creatinkinase were dissolved in 25 ml sterile water. The mixture was incubated at 35 °C overnight. Then 2.42 g (4mmol) ATP di sodium salt, 440 mg MgC12 x 6H2O (2.16 mmol) and 32 U nicotine amide mononucleotide adenosyl transferase (NMN-AT) were added. The mixture was incubated at 35 °C overnight. Then it was heated to 90 ^{0}C for 5min and after cooling filtrated. Purification was performed by using ion exchange chromatography as described in WO 2007/0 12494.

For 3-Carbamoyl-l-((lR,2S,3R,4R)-2,3-dihydroxy-4-hydroxymethyl-cyclopentyl)-pyridinium; chloride as e.g. obtained in Examples 2 or 4, respectively, the correct mass of carba NAD was found in HPLC MS /ESI negative mode.

Example 6

l-(2 amino-purin-6yl) **3** thiocarboxamidopyridinium **chloride and 3-** ThiocarbamoyI-l-((lR,2S,3R,4R)-2,3-dihydroxy-4-hydroxymethyl-cyclopentyl)-pyridinium; **chloride**



Using the same method as described in Example 1 thionicotinamide could be converted to l-(2 amino-purin-6yl) 3 thiocarboxamidopyridinium chloride, which is then converted to 3-thiocarbamoyl-l-((lR,2S,3R,4R)-2,3-dihydroxy-4-hydroxymethyl-cyclopentyl)-pyridinium; chloride by the method described in Example 2.

Example 7

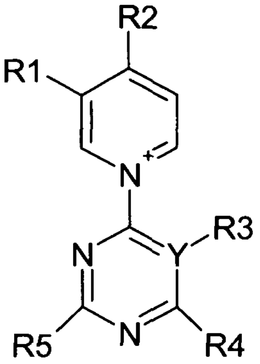
Other aromatic heterocycles **for formation of** Zincke-type **salts**

Using an analogous method as described in Example 1 and Example 3, respectively, different aromatic heterocycles were tested in combination with nicotinamide in order to obtain a Zincke salt appropriate for use in a method according to the present invention. 2-amino-4-chloro-pyrimidine and 1,4-dichloro-6,7 dimethoxyquinazoline also could be converted into the a Zincke salt according to the invention and these Zincke salts could thereafter be reacted to the 3-Carbamoyl-l-((lR,2S,3R,4R)-2,3-dihydroxy-4-hydroxymethyl-cyclopentyl)-pyridinium; chloride in analogy to the methods shown in Examples 2 and 4.

Patent Claims

1. A method for synthesis of an N-substituted pyridinium compound comprising the steps of

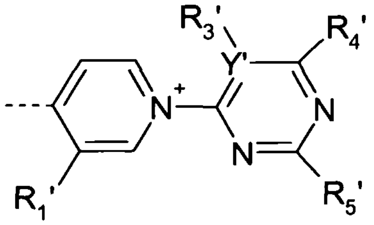
   a) providing a Zincke salt according to Formula I
   Formula I



having a counter ion,

wherein R1 is selected from H, alkyl, aryl, 2-methyl-l,3-dioxolan-2-yl, aryloxy, alkyloxy, hydroxyalkyl, arylalkyl, N-protected aminoalkyl, alkenyl, alkinyl, arylalkenyl, arylalkinyl C=XNH2, C=XNHalkyl, C=XN(alkyl)2 C=XNHaryl, C=XN(aryl)2, C=Xaryl, C=X alkyl, COO alkyl,

wherein R2 is selected from H, alkyl, aryl, pyrid-4-yl, alkylpyridinium-4-yl, 2-methyl-l,3-dioxolan-2-yl, aryloxy, alkyloxy, hydroxyalkyl, arylalkyl, protected amino alkyl, alkenyl, alkinyl, arylalkenyl, arylalkinyl, C=XNH2, C=XNHalkyl, C=XN(alkyl)2, C=XNHaryl, C=XN(aryl)2, C=Xaryl, C=X alkyl, COO alkyl, alkylsulfanyl and



wherein at least one of R1 or R2 is H or alkyl or the residues R1 and R2 together are a butan-1,4 diyl, or a butadiene-1,4-diyl moiety linked to each other forming a 6-membered cycle,

wherein independently in R1 or R2 alkyl is linear or branched C1-C6 alkyl or C5-C6 cyclo alkyl, alkenyl is linear or branched C2-C6 alkenyl, alkinyl is linear or branched C2- C6 alkinyl and aryl is phenyl or naphthyl,

wherein X = S or O,

wherein Y is N or C, in case Y is N no R3 is present and in case Y is C, then R3 is H, C1-C3 alkyl, or forming together with R4 and the two sp2 carbon atoms to which R3 and R4 are attached a 5- or 6-membered aromatic ring system, optionally comprising 1 or 2 nitrogen atoms,

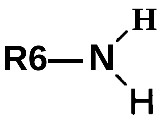
wherein R4 is H, C1-C3 alkyl, hydroxy, O-C1-C3 alkyl, amino, C1-C3 alkylamino, phenylamino, phenyl or forming together with R3 and the two sp2 carbon atoms to which R3 and R4 are attached a 5 or 6-membered aromatic ring system, optionally comprising 1 or 2 nitrogen atoms,

wherein R5 is H, C1-C3 alkyl, hydroxy, O-C1-C3 alkyl, amino, C1-C3 alkylamino, phenylamino, phenyl or halogen,

wherein each of Y', R1', R3', R4'and R5' in case Formula I represents a bipyridyl compound are the same as the corresponding Y, R1, R3, R4 and R5,

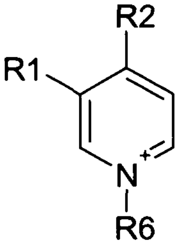
b) reacting the Zincke salt of step (a) with a primary amine of Formula II

Formula II



wherein R6 is part of a primary organic amine comprising an sp2 or an sp3 carbon atom which is bound to the -NH2 moiety, or wherein R6 is a residue which together with -NH2 is a hydrazine, a hydroxylamine, a sulfonyl hydrazide or a carbohydrazide,

c) thereby obtaining an N-substituted pyridinium compound of Formula III Formula III



having a counter ion and wherein Rl, R2, and R6 are as defined above.

2. The method according to claim 1, wherein Y is N and both R4 and R5 are alkoxy each independently with a Cl to C3 alkyl group.

3. The method according to claim 1, wherein when Y is C then R3 is hydrogen.

4. The method of claim 1, wherein Y is C, both R3 and R4 are hydrogen and R5 is NH2.

5. The method of claim 1, wherein Y is C, R3 and R4 form together with the two sp2 carbon atoms to which R3 and R4 are attached a 5- or 6-membered aromatic cycle or heterocycle and R5 is NH2.

6. The method of claim 5, wherein Y is C, R3 and R4 together with the two sp2 carbon atoms to which R3 and R4 are attached form an imidazole ring and R5 is NH2.

7. The method according to any of claims 1 to 6, wherein either Rl or R2 is CONH2 or CSNH2 and the other is hydrogen, respectively.

8. The method according to any of claims 1 to 7, wherein R2 is CONH2 and Rl is hydrogen.

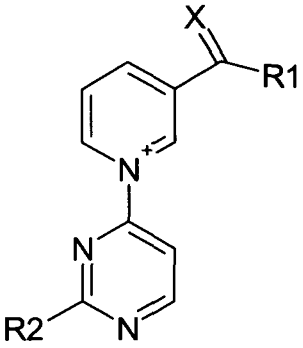
9. The method according to claim 1, wherein R5 is Cl.

10. The method according to any of claims 1 to 9, wherein R6 is selected from the group consisting of alkyl, alkenyl, alkinyl, heterocycloalkyl, aryl, heteroaryl, or wherein Formula II represents an amino alcohol, an amino acid, a furanosylamine or a cyclopentylamine.

11. The method according to any of claims 1 to 10, wherein the primary amine according to Formula II is 3-amino-5-hydroxymethyl-cyclopentane-l,2-diol.

12. A Zincke-type salt selected from the group consisting of compounds as defined by Formulas IV, V, VI and VII.

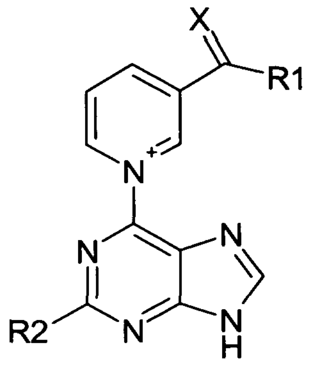
Formula IV



wherein

X is O or S,
Rl is methyl, ethyl, O-methyl, O-ethyl, NH2, N-dimethyl, N-diethyl,
R2 is NH2;

Formula V



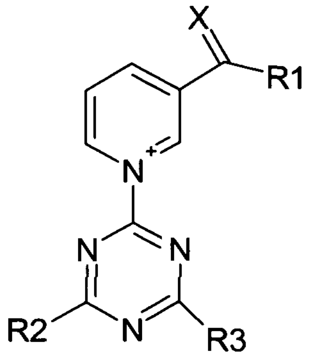
wherein

X is O or S,

R1 is methyl, ethyl, O-methyl, O-ethyl, NH2, N-dimethyl, N-diethyl,

R2 is NH2 or Cl;

Formula VI



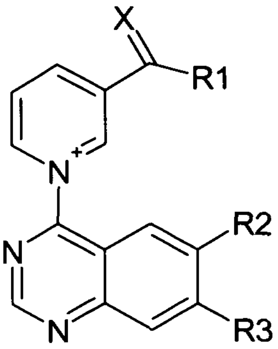
wherein

X is O or S,

R1 is methyl, ethyl, O-methyl, O-ethyl, NH2, N-dimethyl, N-diethyl,

R2 and R3 independently are O-C1-C3 alkyl or NH2;

Formula VII



wherein

X is O or S,

R1 is methyl, ethyl, O-methyl, O-ethyl, NH2, N-dimethyl, N-diethyl,

R2 and R3 independently are O-C1-C3 alkyl and R7= H or Cl.

13. Use of a Zincke-type salt according to claim 12 in a method according to claim 1.