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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 July 2016 (21.07.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/114670 A1

(51) International Patent Classification:
C07C 269/04 (2006.01) *C07C 271/58* (2006.01)
C07C 273/18 (2006.01) *C07C 275/28* (2006.01)
C07C 271/28 (2006.01)

(21) International Application Number:
PCT/NL2016/050042

(22) International Filing Date:
18 January 2016 (18.01.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
15151464.3 16 January 2015 (16.01.2015) EP
1041160 29 January 2015 (29.01.2015) NL

(71) Applicant: **NEDERLANDSE ORGANISATIE VOOR TOEGEPAST-NATUURWETENSCHAPPELIJK ONDERZOEK TNO** [NL/NL]; Anna van Buerenplein 1, 2595 DA 's-Gravenhage (NL).

(72) Inventors: **VAN DER HEIJDEN, Antonius Eduard Dominicus Maria**; c/o TNO / IP & Contracting, Anna van Buerenplein 1, 2595 DA 's-Gravenhage (NL). **VAN GEEST, Erik**; c/o TNO / IP & Contracting, Anna van Buerenplein 1, 2595 DA 's-Gravenhage (NL). **VAN DEN ELSHOUT, Jos Johan Matthijs Hugo**; c/o TNO / IP & Contracting, Anna van Buerenplein 1, 2595 DA 's-Gravenhage (NL).

(74) Agents: **JANSEN, C.M.** et al.; V.O., P.O. Box 87930, 2508 DH Den Haag (NL).

(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, BN, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, 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, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: SYNTHESIS OF CARBAMATE OR UREA COMPOUNDS

(57) Abstract: The invention pertains to the synthesis of carbamate and urea compounds. In particular the invention is directed to the synthesis of carbamate and urea compounds which may be used in the production of compounds that are used to stabilize nitrocellulose. The method of the invention comprises preparing a carbamate or urea derivative comprising reacting an amine and a carbonate or carbamate in the presence of an ionic liquid.

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Title: SYNTHESIS OF CARBAMATE OR UREA COMPOUNDS

The invention pertains to the synthesis of carbamate and urea compounds. In particular the invention is directed to the synthesis of carbamate and urea compounds which may be used in the production of compounds that are used to stabilize nitrocellulose.

Nitrocellulose is used as a propellant in ammunition and is made by the nitration of cellulose. Due to the high content of nitrate esters, nitrocellulose is intrinsically thermodynamically unstable. The nitrate esters decompose over time into RO- and NO_2-radicals (B. Vogelsanger, *Chimia* **2004**, *58,* 401-408). These radicals catalyze further decomposition of nitrocellulose. The decomposition of nitrocellulose is therefore classified as autocatalytic, which means that decomposition of nitrocellulose may lead to a runaway reaction resulting in self-ignition of the nitrocellulose (J. Rychlý *et al.*, *J. Therm. Anal. Calorim.* **2012**, *107*, 1267-1276).

The decomposition of nitrocellulose may be slowed down by using stabilizers as additives. These stabilizers scavenge radicals and/or protons, thereby limiting the autocatalytic reaction and preventing a runaway reaction. Stabilizers are typically classified into the class of aromatic amines or into the class of aromatic urea derivatives. The aromatic urea derivatives comprise of symmetric alkyl-aryl substituted ureas and unsymmetric diaryl substituted ureas. Typical examples of the symmetric alkyl-aryl substituted ureas are Centralite I (diethyl-*N,N'*-diphenylurea) and Centralite II (dimethyl-*N,N'*-diphenylurea). Typical examples of unsymmetric diaryl substituted ureas are Akardite I (*N',N'*-diphenylurea) and Akardite II (*N*-methyl-*N',N'*-diphenylurea).

Decomposition or degradation of nitrocellulose is sometimes also referred to as ageing. Ammunition and thus the nitrocellulose comprised therein has to meet certain standards. The performance requirements for NATO ammunition are set forth in Standardization Agreement (STANAG)

4582 (NATO, **2004**. STANAG 4582 (Edition 1) - Ratification Draft 1 - Explosives, nitrocellulose based propellants, stability test procedure and requirements using heat flow calorimetry), which is incorporated herein by reference. STANAG 4582 also describes methods to determine the performance of the stabilizer in slowing down the ageing of the propellant.

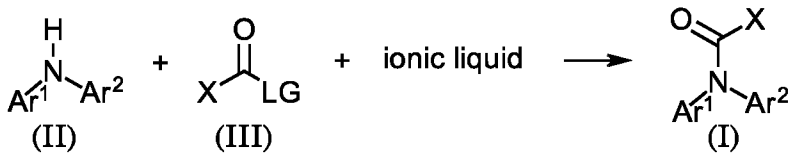
S. Wilker *et al.*, *Propellants Explos. Pyrotech.*, **2007**, *32*, 135-148 describe that in particular Akardite II has shown favorable stabilizing properties. Another advantage is that Akardite II and its reaction products are known to be the least toxic of the conventional stabilizers. Like most other aromatic urea-derived stabilizers, Akardite II is typically produced via a precursor (*e.g.* a carbamoyl halide) that is obtained by reacting phosgene ($COCl_2$) with a corresponding amine. Since phosgene is highly toxic, a production process with this chemical requires extensive safety measures. It is therefore desirable to have a method for the production of aromatic urea derived stabilizers without requiring phosgene, *e.g.* by using a phosgene surrogate.

A suitable alternative for phosgene may be for instance dimethyl carbonate. An example is provided by Fu *et al.* in *Catalysis Communications* **2009**, *10*, 665-668 who describe a reaction of an N-heterocyclic moiety with dimethyl carbonate catalyzed by ionic liquids (*i.e.* the N-methylcarboxylation of N-heterocyclic compounds). Unfortunately, the non-heterocyclic amine (aniline) shows no reaction. It would be desirable to have a process where non-heterocyclic amines would react with compounds like dimethyl carbonate.

Wang Na *et al.* in *Petrochemical Technologies,* 2008, 1255-1259 describe the preparation of methyl *N*-phenyl carbamate of analine and dimethylcarbonate catalyzed by 1,1,3,3-tetramethylguanidine. The use of analine makes this reaction not suitable for the production of nitrocellulose stabilizers such as Akardite I and II.

It would desirable to provide a process wherein urea or carbamate compounds are prepared that can be used for the production of nitrocellulose stabilizers such as Akardite I and II.

The present inventors have surprisingly found a solution to at least one of these problems by preparing a compound according to formula I, in particular a carbamate or urea derivative according to formula I, comprising reacting an amine according to formula II and a carbonate or carbamate according to formula III, in the presence of a catalyst;



wherein

Ar^1 is an aryl that is optionally substituted with one or more halide, alkoxy, alkyl, nitro, sulfonate, ester, amide and/or carboxylate;

Ar^2 is Ar^1 or an aryl that is optionally substituted with one or more halide, alkoxy, alkyl, nitro, sulfonate, ester, amide, carboxylate;

X is an alkoxy, an aryloxy or an amine and is optionally substituted with one or more halide, alkoxy, alkyl, nitro, sulfonate, ester, amide and/or carboxylate;

LG is a leaving group.

It will be appreciated that because Ar^1 is an aryl, the present invention may be applicable to all aromatic urea derived stabilizers. It may further be appreciated that the carbonate or carbamate in accordance with formula III may be regarded as a phosgene surrogate, *viz.* it provides the carbonyl moiety present in the stabilizer.

The typical nitrocellulose-stabilizing compounds as described herein are ureas based on non-heterocyclic, secondary amines. Therefore, it is preferred that the amine according to formula II is a non-heterocyclic

secondary amine. With non-heterocyclic secondary amine is meant any secondary amine of which the nitrogen atom of the amine is not present in a cycle.

For sake of clarity and conciseness, the carbamate or urea derivative according to formula I is herein also referred to as compound I, the amine according to formula II is herein also referred to as compound II, and the carbonate or carbamate according to formula III is herein also referred to as compound III.

It is preferred that the catalyst comprises an ionic liquid. An ionic liquid (IL) is a salt in the liquid state, typically salts whose melting point is relatively low, for instance 200 °C or less. The ionic liquid in accordance with the present invention may comprise a cation and an anion. Without wishing to be bound by theory, the inventors believe that when the cation comprises a proton which may form a hydrogen bond with the carbonyl of compound III, the reaction between compound II and III may be accelerated (*i.e.* catalyzed) by the ionic liquid. Said proton, which may be considered electron poor due to the electron withdrawing effect of the positively charged cation (preferably an imidazolium group), may therefore be regarded as being Lewis acidic. Therefore, the ionic liquid preferably comprises an electron poor hydrogen. Typically, the cation is an *N,N*-dialkyl imidazolium, preferably a 1-alkyl-3-methylimidazolium such as a 1-ethyl-methylimidazolium or a 1-butyl-3-methylimidazolium. Most preferably the cation is 1-butyl-3-methylimidazolium (BMIm).

Preferably, the anion of the ionic liquid is a small anion. It was found that smaller anions leads to better catalytic properties of the ionic liquid. Without wishing to be bound by theory, it is believed that the cation of the present invention is soft and that a harder anion results in weaker electrostatic bounding between the cation and anion. Such an effect is in general known by the “hard and soft Lewis acid and base” (HSAB) concept, also known as the Pearson acid base concept. Hence, a hard anion is

preferred for the present invention. Small anions are typically hard anions. Therefore, the anion is preferably selected from the group consisting of hydroxide, chloride, bromide, iodate, acetate, hexafluorophosphate, tetrafluoroborate and combinations thereof. More preferably the anion is a hydroxide or a chloride.

Hence in view of the above, preferred ionic liquids are BMImCl, BMImOH or a combinations thereof.

In a particular embodiment, the catalyst comprises a non-nucleophilic base such that undesired side reactions of *e.g.* compound II with the base are limited. An example of such a base is N,N-diisopropylethylamine (DIPEA). Preferably a superbase is applied, yet more preferably an organic superbase is applied. Superbases are known in the art as compounds having a very high basicity. Suitable superbases can be found for instance in "Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts" (Tsutomu Ishikawa; 2009; John Wiley & Sons, Ltd; ISBN: 978-0-470-51800-7). Superbase catalysts can be applied as solid-supported compounds. The organic superbase can be selected from the group consisting of amidines, phosphazenes, (poly)guanidines and or proton sponge type materials.

Phosphazenes that can be used for the present invention may be selected from the group consisting of *tert*-butylimino-tri(pyrrolidino)phosphorane (BTTP), *tert*-butylimino-tris(dimethylamino)phosphorane (*t*-Bu-P_1), 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), *tert*-octylimino-tris(dimethylamino)phosphorane (P_1-*t*-Oct), tetramethyl(tris(dimethylamino)phosphoranylidene)phosphorictriamid-Et-imin (P_2-Et), 1-*tert*-butyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^5,4λ^5-catenadi(phosphazene) (P_2-*t*-Bu), 1,1,1,3,3,3-hexakis(dimethylamino)diphosphazenium fluoride (P_2-F), tetrakis[tris(dimethylamino)phosphoranylidenamino]phosphonium fluoride

(P_5-F), 1-*tert*-octyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)phosphoranylidenamino]-2λ^5,4λ^5-catenadi(phosphazene) (P_4-*t*-Oct) and 1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamino]-2λ^5,4λ^5-catenadi(phosphazene) (P_4-*t*-Bu).

A suitable guanidine is for instance a tetra-alkyl guanidine such as 1,1,3,3-tetramethylguanidine. Other examples of guanidines that could be selected for use in the present invention include 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), 7-ethyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (ETBD), 7-isopropyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (ITBD)

Examples of amidines that can be used for the present invention include vinamidines, formamidines, acetamidines, benzamidines, EtN_2-acetamidines, (poly)cyclic amidines, for instance 1,5-diazabicyclo[4.4.0]dec-5-ene (DBD), 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]dec-1-ene (PMDBD), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Particularly good results have been obtained with DBU, so it is preferred that the catalyst comprises DBU.

Proton sponge type materials are known in the art to have at least two basic nitrogen atoms in their structure positioned such that one proton can be taken up resulting in a stabilized intramolecular hydrogen bond. Examples of proton sponge type materials that may be applied in the present invention include 1,8-Bis(dimethylamino)naphthalene (DMAN), 1,8-bis(hexamethyltriaminophosphazenyl)naphthalene (HMPN), 1,8-bis(tetramethylguanidino)naphthalene (TMGN).

It has further been found that the ionic liquid may be present in catalytic amounts. In this respect, with catalytic amounts is meant any amount which would be insufficient for the ionic liquid to be a solvent, *e.g.* a substoichiometric amount with respect to compound II, but the amount is still sufficient to acceptably catalyze the reaction. With substoichiometric

amount is meant any molar amount that is less than the molar amount of compound II. A lower amount of ionic liquid may be beneficial for the purification of compound I and may also be economically attractive. A higher amount will result in a faster reaction. Therefore, the ionic liquid is preferably present in less than 50 mol%, more preferably less than 25 mol%, even more preferably less than 10 mol% and most preferably less than 5 mol%, for instance from 1 to 4 mol% with respect to compound II. The ionic liquid may be recycled, *viz.* it may be separated from the reaction mixture when the reaction is complete and may be re-used in a new reaction of compounds II and III.

It is known that in particular certain aromatic urea derived stabilizers are effective in stabilizing nitrocellulose. Therefore, it is preferable that Ar^1 is a phenyl that is optionally substituted with one or more halide, alkoxy, alkyl, nitro, sulfonate, ester, amide and/or carboxylate and Ar^2 is a phenyl or a C_1-C_8 alkyl and is optionally substituted with one or more halide, alkoxy, alkyl, nitro, sulfonate, ester, amide and/or carboxylate. More preferably, Ar^1 is phenyl and Ar^2 is phenyl or methyl such that compound II is *e.g.* methylphenylamine, more preferably wherein both Ar^2 and Ar^1 are phenyl such that compound II is diphenylamine.

In the context of the present invention, any alkyl may be linear or branched if possible. A C_1 alkyl consist of one carbon atom (*i.e.* a methyl), C_4 alkyl consist of four carbon atoms and may be linear or branched. C_1-C_4 alkyl means that the alkyl consists of one up to four carbon atoms. C_1-C_8 alkyl means that the alkyl consists of one up to eight carbon atoms.

In the reaction between compound II and III, the LG of compound III is replaced by the nitrogen of compound II and is therefore regarded as a leaving group. Typically, LG is an alkoxy, an aryloxy, an amine that is optionally substituted with one or two C_1-C_4 alkyl groups, an amide, a sulfonate such as tosylate, mesylate or nosylate, a halide, a nitrate, a

phosphate and/or a carboxylate. Preferably, LG is a C_1-C_4 alkoxy or a C_6-C_{10} aryloxy.

In a preferred embodiment the LG is X. This way compound III is a symmetrical compound which has shown to generally give good yields in the reaction between compounds II and III.

In another preferred embodiment, X is a C_1-C_4 alkoxy, an C_6-C_{10} aryloxy or an amine optionally substituted with one or two C_1-C_4 alkyl groups. Preferably X is methoxy, ethoxy, *tert*-butoxy, phenoxy, amino (*i.e.* NH_2) or methylamine. More preferably X and LG are both methoxy or phenoxy. These groups have shown to give good reaction rates and yields.

It may be appreciated that in a particular embodiment of the present invention when compound III is *O*-methyl-*N*-methyl carbamate (*i.e.* X is NHMe and LG is OMe) and compound II is diphenyl amine (*i.e.* Ar^2 and Ar^1 are both phenyl), Akardite II may immediately be obtained. Compound III in accordance with this particular embodiment may for instance be obtained by the reaction of dimethylurea and dimethylcarbonate as is described in Shivarkar, A.B., S.P. Gupte, and R.V. Chaudhari, *J. Mol. Catal. A-Chem.*, **2004**, *223*, 85-92.

The inventors have found that the reaction compounds II and III may be influenced by the reaction temperature (*i.e.* the temperature at with compounds II and III are reacted). Preferably, the reaction temperature is at least 90 °C, more preferably at least 125 °C, for instance the reaction temperature is about 130 °C. However, the reaction temperature may also be even higher than 130 °C as the reaction temperature may be dependent on LG and/or X. In a particular embodiment of the present invention, the temperature may be up to about 170 °C or higher. Generally the reaction temperature is below 200 °C.

The inventors have further found that the ratio of compound II to compound III (calculated by dividing the molar amount of compound II by the molar amount of compound III and herein further referred to as the

II/III ratio) may influence the yield of compound I. For instance, the reaction of diphenyl amine (*i.e.* compound II wherein Ar^2=Ar^1=Ph) and dimethyl carbonate (*i.e.* compound III wherein X=LG=OMe) at 90 °C for 24 h, gave a yield of *O*-methyl-*N*,*N*-diphenyl carbamate (*i.e.* a compound I) of 13% when the II/III ratio was 5. The corresponding yield was 18% when the II/III ratio was 10. The II/III ratio is therefore preferably at least 5, more preferably at least 10.

These observations may suggest that the reaction of compounds II and III into compound I is an equilibrium reaction. An equilibrium reaction has a forward and a reverse reaction. The inventors found that the yield be improved by countering the reverse reaction (*i.e.* the reaction of compound I into compounds II and III) by removal of the protonated LG that is liberated upon the formation of compound I. For instance, when LG is methoxy, the reaction of compounds II and III give methanol together to compound I. This methanol may react with formed compound I to form compounds II and III in the reverse reaction. Hence, in a preferred embodiment, the protonated LG that is also formed by the reaction of compound II and compound III is removed during the reaction. This may typically be effected by techniques such as evaporation, distillation, absorption, use of a membrane and the like. Preferably, the membrane is a semi-permeable membrane that is selectively permeable to LG-H and is thus not permeable to other reagents present in the reaction mixture.

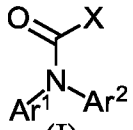
In a particular embodiment of the present invention, typically when X is an alkoxy, *e.g.* methoxy, ethoxy or *tert*-butoxy or when X is an aryloxy, *e.g.* phenoxy, it is preferred that compound I is further converted into an urea. This is preferably effected by a conversion with an amine such as methylamine. As such a methyl-substituted urea may for instance be obtained. In a preferred embodiment, when Ar^2 and Ar^1 are both phenyl for compound I, this compound may further be converted into Akardite II, preferably by reacting compound I with methylamine.

Further converting compound I into an urea may simultaneously result in partial decomposition of compound I into and compound II. Without wishing to be bound by theory, this may proceed through a nucleophilic attack of the amine (*e.g.* methylamine) onto the carbonyl of compound I and subsequent leaving of compound II from the reactive intermediate and the formation of the corresponding carbamate or urea derivative. To obtain a higher overall yield, compound II resulting from the decomposition may be reused in a reaction with compound III. Hence, in a preferred embodiment, the resulting compound II is recycled back into the reaction of compound II and compound III. In such an embodiment, this compound II may be referred to as recycled compound II.

Hence, in a preferred embodiment, at least part of the total amount of compound II that is reacted to compound I is recycled compound II, *i.e.* compound II as obtained by the decomposition of compound I in its conversion into an urea as defined in the previous paragraph.

In a further preferred embodiment, the process of reacting compounds II and III into compound I and reacting compound I further into a urea is a continuous process. In such a process it is preferred that no intermediate purification of compound I is required.

A compound according to the present invention is thus a compound in accordance with formula I



(I)

wherein

Ar^1 is an aryl that is optionally substituted with one or more halide, alkoxy, alkyl, nitro, sulfonate, ester, amide and/or carboxylate;

Ar^2 is hydrogen, an aryl or an alkyl and optionally substituted with one or more halide, alkoxy, alkyl, nitro, sulfonate, ester, amide and/or carboxylate; and

X is an alkoxy, aryloxy (such as phenoxy or derivatives thereof) or an amine and is optionally substituted with one or more halide, alkoxy, alkyl, nitro, sulfonate, ester, amide and/or carboxylate.

The compound in accordance with formula I (herein also referred to as compound I), may be prepared in accordance with the present invention. It may also be converted into a nitrocellulose-stabilizing compound such as Akardite II in accordance with the present invention.

In a preferred embodiment of compound I, Ar^1 is an aryl that is optionally substituted with one or more halide, alkoxy, alkyl, nitro, sulfonate, ester, amide and/or carboxylate and Ar^2 is an aryl or a C_1-C_8 alkyl and optionally substituted with one or more halide, alkoxy, alkyl, nitro, sulfonate, ester, amide and/or carboxylate, and X is a C_1-C_4 alkoxy, an C_6-C_{10} aryloxy or an amine optionally substituted with one or two C_1-C_4 alkyl groups, preferably X is methoxy, ethoxy, *tert*-butoxy, phenoxy, amino or methylamine.

Preferably Ar^1 is phenyl, and Ar^2 is phenyl, methyl or ethyl and/or X is C_1-C_4 alkoxy or C_6-C_{10} aryloxy, preferably Ar^1 is phenyl and Ar^2 is

phenyl or methyl and/or X is methoxy or phenoxy, more preferably wherein both Ar^1 and Ar^2 phenyl.

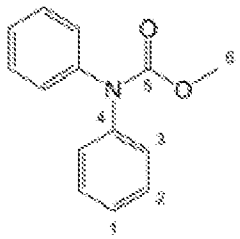
Hence it may be appreciated that compound I is very suitable for use in the production of a nitrocellulose-stabilizing compound, in particular for use in the production of Akardite II. It may further be appreciated that urea compounds, in particular Akardite II readily crystallize from ethanol, which is also a suitable solvent for the formation of urea compounds, *e.g.* Akardite II, from compound I.

The present invention is further illustrated with a number of examples.

Experimental examples

All chemicals were purchased from Sigma Aldrich and used without further purification. Nitrogen gas (N50) was purchased from Air Liquide. Water was obtained by the purification of tap water using a Mili-Q Direct-Q 5. Methylamine was purchased as a solution of 40 wt% in H_2O and 33 wt% in absolute ethanol. Ionic liquid BMImCl was dried in a vacuum stove (Heraeus vacuum oven, Thermo Scientific) at 100 °C for 3 hours and stored under N_2 atmosphere before use. Ace pressure tubes were purchased from Sigma Aldrich and fitted with a Teflex® O-ring, purchased from Eriks. Teflon tape was wrapped around the screw-thread of the pressure tube cap for extra grip. ^1H and ^{13}C NMR spectra were recorded on a Bruker Ascend 400 (400 MHz). Mass spectra were recorded on a Finnigan MAT900 using an electrospray ionization technique (ESI-MS), with methanol as the eluent. MS samples were prepared by dissolving a few milligrams of compound in HPLC-grade acetone. IR spectra were recorded on a PelkinElmer Spectrum Two FT-IR spectrometer.

Example 1. Synthesis of *O*-methyl-*N,N*-diphenyl carbamate (compound I, wherein Ar^2=Ar^1=Ph and X=OMe)



In a round-bottomed flask (3-neck, 50 ml, fitted with reflux equipment and a valve), the ionic liquid BMImCl (0.5 mmol, 88 mg), diphenyl amine (5.0 mmol, 0.85 g) and anhydrous dimethyl carbonate (5 ml) were mixed under an N_2 atmosphere. The mixture was heated to 130°C and stirred for 7 hours, while allowing the alcoholic reaction product to escape through the opened valve. It was then cooled to room temperature, the solvent was evaporated and the resulting crude product was purified on a SiO_2 column (the eluent was a mixture of ethyl acetate (EtOAc) and petroleum ether (PetEt):EtOAc/PetEt 10:90). The pure product was obtained as a colorless liquid, which crystallized quickly into a white solid when pressurized air was passed over the liquid. *O*-methyl-*N,N*-diphenyl carbamate was obtained in a yield of 80%.

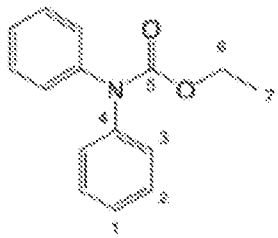
^{1}H NMR ($CDCl_3$): δ 7.40-7.35 (m, 4H, 2 or 3), 7.30-7.22 (m, 6H, 1 and 2 or 3), 3.78 (s, 3H, 6).

^{13}C NMR: δ 155.31 (5), 142.59 (4), 128.95 (1, 2, or 3), 126.95 (1, 2, or 3), 126.18 (1, 2, or 3), 53.14 (6).

(ESI)-MS (calc.): 250.0 (250.3, $[M-Na]^+$) 282.1 (282.3, $[M-Na-MeOH]^+$, 308.0 (308.4, $[M-Na-Me_2CO]^+$, 475.2 (475.6, $[M_2-Na]^+$).

IR (cm^{-1}): 3100-3000 (w, C-H stretch, Ph), 2900-3000 (w, C-H stretch, CH_3), 1708 (s, C=O stretch, NC(=O)N), 1588, 1492 and 1439 (m, C=C stretch, Ph).

Example 2. Synthesis of *O*-ethyl-*N,N*-diphenyl carbamate (compound I, wherein Ar^1=Ar^2=Ph and X=OEt)



Example 1 was repeated, only diethyl carbonate (5 ml) was used instead of dimethyl carbonate (5 ml). *O*-Ethyl-*N,N*-diphenyl carbamate was obtained in a yield of 57%.

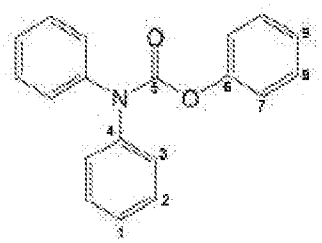
^{1}H NMR ($CDCl_3$): δ 7.39-7.33 (m, 4H, 2 or 3), 7.28-7.20 (m, 6H, 1 and 2 or 3), 4.26 (q, 2H, 6), 1.27 (t, 3H, 7).

^{13}C NMR ($CDCl_3$): δ 154.86 (5), 142.70 (4), 128.87 (1, 2, or 3), 126.98 (1, 2, or 3), 126.01 (1, 2, or 3), 62.06 (6), 14.47 (7).

(ESI)-MS (calc.): 242.1 (242.3, $[M-H]^+$), 264.1 (264.3, $[M-Na]^+$), 296.1 (296.3, $[M-Na-MeOH]^+$), 322.0 (322.4, $[M-Na-Me_2CO]^+$), 505.2 (505.6, $[M_2-Na]^+$).

IR (cm^{-1}): 3100-3000 (w, C-H stretch, Ph), 3000-2900 (w, C-H stretch, CH_2, CH_3), 1715 (s, C=O stretch, NC(=O)O), 1590, 1491 and 1465 (m, C=C stretch, Ph).

Example 3. Synthesis of *O*-phenyl-*N,N*-diphenyl carbamate (compound I, wherein Ar^1=Ar^2=Ph and X=OPh)



Example 1 was repeated, only diphenyl carbonate (7.5 mmol, 1.61 g) was used instead of dimethyl carbonate (5 ml). *O*-Phenyl-*N,N*-diphenyl carbamate was obtained in a yield of 9%.

^{1}H NMR ($CDCl_3$): δ 7.439-7.34 (m, 9H), 7.31-7.15 (m, 6H)

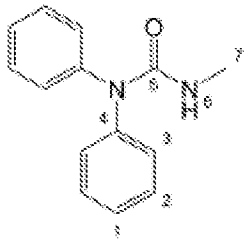
^{13}C NMR ($CDCl_3$): δ 153.12 (5), 151.12 (6), 142.28 (4), 129.26 (2 or 8), 129.06 (2 or 8), 126.91 (1 or 9), 126.48 (1 or 9), 125.50 (3), 121.52 (7).

Example 4. Influence of reaction temperature on formation of *O*-methyl-*N,N*-diphenyl carbamate (compound I, wherein Ar^1=Ar^2=Ph and X=OMe)

To investigate the influence of temperature on the reaction of compounds II and III, experiments according to example 1 were performed, with the only difference that the mixture was heated to different temperatures and stirred for different time periods. The experiments gave the following results.

- heated to 90 °C for 24 h: 18% yield
- heated to 110 °C for 7 h: 55% yield
- heated to 130 °C for 7 h: 80% yield
- heated to 130 °C for 16 h: 84% yield

Example 5. Synthesis of *N*-methyl-*N'*,*N'*-diphenylurea (Akardite II)



A solution of methylamine (MMA) in EtOH/H_2O in a ratio of 3:1 was prepared by mixing 3.5 ml of 33 wt% MMA in EtOH and 10.5 ml of 40 wt% MMA in H_2O. The freshly prepared MMA solution was mixed with *O*-methyl-*N*,*N*-diphenyl carbamate (2.0 mmol, 0.45 g) in a pressure tube (21 ml, fitted with Teflex® O-ring). After sealing the tube, the reaction mixture was heated to 100 °C and stirred until the carbamate was completely consumed. This occurred overnight. The reaction mixture was then cooled to room temperature, and the tube was left open to allow MMA to evaporate. Next, the solvent was evaporated, which turned the reaction mixture into an emulsion. EtOAc was added and the two phases were separated. The aqueous phase was washed with EtOAc. Both EtOAc solutions were combined and the solvent was evaporated. The contents of the resulting liquid were separated using a SiO_2 column (eluent: EtOAc/PetEt 25:75). The AK II fractions were combined and the solvent was evaporated. The remaining solid was washed with PetEt and pure Akardite II was obtained as a white solid in a yield of 17 mg, *i.e.* 3.8%.

^{1}H NMR ($CDCl_3$): δ 7.36 – 7.32 (m, 4H, 2 or 3), 7. 30 – 7.20 (m, 6H, 1 and 2 or 3), 4.51 (s, 1H, 6), 2.84 (s, 3H, 7).

^{13}C NMR: 156.82 (5), 142.90 (4), 129.37 (1, 2, or 3), 127.42 (1, 2, or 3), 126.12 (1, 2, or 3), 27.48 (7).

(ESI)-MS (calc.): 227.1 (227.3, $[M-H]^+$), 249.1 (249.3, $[M-Na]^+$), 281.1 (281.3, $[M-Na-MeOH]^+$), 307.1 (307.4, $[M-Na-Me_2CO]^+$), 475.2 (475.6, $[M_2-Na]^+$).

IR (cm^{-1}): 3339 (m, N-H stretch, H-NMe), 3100-3000 (w, C-H stretch, Ph), 3000-2900 (w, C-H stretch, CH_3), 1653 (s, C=O stretch, NC(=O)N), 1587, 1486 and 1449 (m, C=C stretch, Ph), 1512 (N-H bend, H-NMe).

Example 6. Synthesis of *N*-methyl-*N'*,*N'*-diphenylurea (Akardite II)

Example 5 was repeated, only *O*-ethyl-*N*,*N*-diphenyl carbamate (2.0 mmol, 0.48 g) was used instead of *O*-methyl-*N*,*N*-diphenyl carbamate. In this particular example, the carbamate was completely consumed during 12 days of stirring at 100 °C. Akardite II was obtained in a yield of 17 mg, *i.e.* 3.8%.

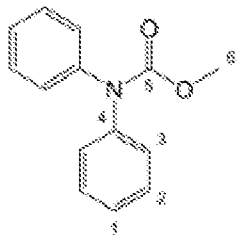
Example 7. Synthesis of *N*-methyl-*N'*,*N'*-diphenylurea (Akardite II)

O-Phenyl-*N*,*N*-diphenyl carbamate (0.35 mmol, 100 mg) was dissolved in 2 mL of MMA solution, 33wt% in absolute ethanol. The mixture was stirred at room temperature for 2 days. Next, the solvent was evaporated. The contents of the resulting liquid were separated using a SiO_2 column (eluent: EtOAc/PetEt 25:75). The AK II fractions were combined and the solvent was evaporated. The remaining solid was washed with PetEt and pure Akardite II was obtained as a white solid in a yield of 54 mg, *i.e.* 68%.

Example 8. Synthesis of *N*-methyl-*N'*,*N'*-diphenylurea (Akardite II)

Example 7 was repeated, only the reaction mixture was stirred for 5 days instead of 2 days. Akardite II was obtained as a white solid in a yield of 64 mg, *i.e.* 81%.

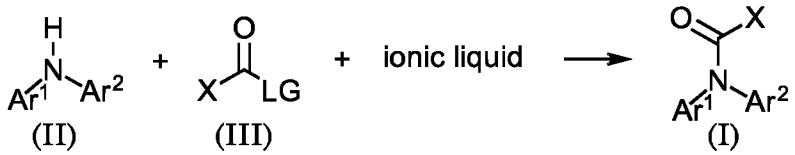
Example 9. Synthesis of *O*-methyl-*N,N*-diphenyl carbamate (compound I, wherein Ar^1=Ar^2=Ph and X=OMe)



In a round-bottomed flask (3-neck, 50 ml, fitted with reflux equipment and a valve), 'superbase' 1,8-diazabicyclo[5.4.0]undec-7-ene DBU (0.5 mmol, 88 mg), diphenyl amine (5.0 mmol, 0.85 g) and anhydrous dimethyl carbonate (5 ml). The mixture was heated to 130°C and stirred for 7 hours, while allowing the alcoholic reaction product to escape through the opened valve. It was then cooled to room temperature, the solvent was evaporated and the resulting crude product was purified on a SiO_2 column (the eluent was a mixture of ethyl acetate (EtOAc) and petroleum ether (PetEt):EtOAc/PetEt 10:90). The pure product was obtained as a colorless liquid, which crystallized quickly into a yellowish solid when pressurized air was passed over the liquid. The solid was washed with diethyl ether (Et_2O). *O*-methyl-*N,N*-diphenyl carbamate was obtained in a yield of 11%.

Claims

1. Method for preparing a carbamate or urea derivative according to formula I, comprising reacting an amine according to formula II and a carbonate or carbamate according to formula III, in the presence of a catalyst



(II) (III) (I)

wherein

Ar^1 is an aryl that is optionally substituted with one or more halide, alkoxy, alkyl, nitro, sulfonate, ester, amide and/or carboxylate;

Ar^2 is Ar^1 or an aryl that is optionally substituted with one or more halide, alkoxy, alkyl, nitro, sulfonate, ester, amide and/or carboxylate;

X is an alkoxy, aryloxy or an amine and is optionally substituted with one or more halide, alkoxy, alkyl, nitro, sulfonate, ester, amide and/or carboxylate.

LG is a leaving group.

2. Method according to claim 1, wherein the catalyst comprises an ionic liquid.

3. Method according to claim 2, wherein the ionic liquid comprises a cation and an anion and wherein the cation is a *N,N*-dialkyl imidazolium, preferably a 1-alkyl-3-methylimidazolium, preferably 1-ethyl-3-methylimidazolium or 1-butyl-3-methylimidazolium (BMIm) and/or the anion is selected from the group consisting of hydroxide, chloride, bromide,

iodate, acetate, hexafluorophosphate, tetrafluoroborate and combinations thereof, preferably the anion is a hydroxide or a chloride.

4. Method according to claim 1, wherein the catalyst comprises a non-nucleophilic base, preferably a superbase, more preferably a superbase selected from the group consisting of amidines, phosphazenes and guanidines, even more preferably amidines, most preferably 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

5. Method according to any of the previous claims, wherein Ar^1 is a phenyl, optionally substituted with one or more halide, alkoxy, nitro, sulfonate, ester, amide, carboxylate and Ar^2 is Ar^1 or a phenyl and is optionally substituted with one or more halide, alkoxy, nitro, sulfonate, ester, amide, carboxylate, preferably both Ar^1 and Ar^2 are phenyl such that the amine according to formula II is diphenylamine.

6. Method according to any of the previous claims, wherein X is a C_1-C_4 alkoxy, an C_6-C_{10} aryloxy or an amine optionally substituted with one or two C_1-C_4 alkyl groups and LG is X, an alkoxy, an aryloxy, an amine optionally substituted with one or two C_1-C_4 alkyl groups, an amide, a sulfonate such as tosylate, mesylate or nosylate, a halide, a nitrate, a phosphate or a carboxylate, preferably X is methoxy, ethoxy, *tert*-butoxy, phenoxy, amino or methylamine and/or LG is X, more preferably X and LG are both methoxy or phenoxy.

7. Method according to any of the previous claims, wherein the amine according to formula II and carbonate or carbamate according to formula III are reacted at a temperature of at least 90 °C, preferably at least 125 °C, more preferably at about 130 °C.

8. Method according to any of the previous claims, wherein protonated LG that is also formed by the reaction of the amine according to formula II and the carbonate or carbamate according to formula III is removed during said reaction, preferably by using a membrane or by evaporation.

9. Method according to any of the previous claims, wherein the catalyst is present in less than 50 mol%, more preferably less than 25 mol%, most preferably about 10 mol% with respect to the amine according to formula II.

10. Method according to any of the previous claims, wherein the carbamate or urea derivative according to formula I is further converted into an urea, preferably into Akardite II, typically by reacting the carbamate or urea derivative according to formula I with ammonia or methylamine.

11. Method according to any of the previous claims, wherein at least part of the total amount of the amine according to formula II that is reacted to give the carbamate or urea derivative according to formula I is a recycled product resulting from the conversion as defined in claim 10.

12. Method according to any of claims 1 - 9, wherein the carbamate or urea derivative according to formula I is Akardite II.

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2016/050042

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C269/04 C07C273/18 C07C271/28 C07C271/58 C07C275/28
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STEPHEN L. MACNEIL ET AL: "Anionic N -Fries Rearrangement of N -Carbamoyl Diarylamines to Anthranilamides. Methodology and Application to Acridone and Pyranoacridone Alkaloids", ORGANIC LETTERS, vol. 8, no. 6, 1 March 2006 (2006-03-01), pages 1133-1136, XP055269898, US ISSN: 1523-7060, DOI: 10.1021/ol053162e Supporting info p. 3 ----- -/--	1,4,5

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 May 2016	18/05/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Tabanella, Stefania

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Version 2.3.3: "International Union of Pure and Applied Chemistry Compendium of Chemical Terminology Gold Book", , 24 February 2014 (2014-02-24), XP055166808, Retrieved from the Internet: URL:http://goldbook.iupac.org/PDF/goldbook.pdf [retrieved on 2015-02-03] page 1486	1-12
X	SUNITHA ET AL: "An efficient and chemoselective Bronsted acidic ionic liquid-catalyzed N-Boc protection of amines", TETRAHEDRON LETTERS, PERGAMON, GB, vol. 49, no. 16, 4 March 2008 (2008-03-04), pages 2527-2532, XP022541919, ISSN: 0040-4039, DOI: 10.1016/J.TETLET.2008.02.126 entry 24; table I page 2532	1-12
X	A. VELAVAN ET AL: "Unsymmetrical tetrasubstituted ureas from tertiary carbamoylimidazole: activation by AlMe3", ORGANIC & BIOMOLECULAR CHEMISTRY, vol. 10, no. 31, 1 January 2012 (2012-01-01), page 6420, XP55269907, GB ISSN: 1477-0520, DOI: 10.1039/c2ob25412c N,N-diphenylimidazole-1-carboxamide (9b); page 6426	1,4,6