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Synthesis of Carbamoyl Azides from Primary Amines and Carbon Dioxide under Mild Conditions

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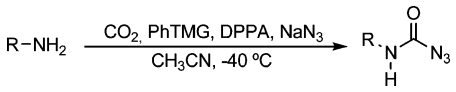


Treatment of amines under a carbon dioxide atmosphere with tetramethylphenylguanidine (PhTMG) and diphenylphosphoryl azide (DPPA) in acetonitrile below 0 °C provides carbamoyl azides in high to excellent yields. In addition, epimerization is not observed when optically pure α-amino esters are used as substrates.

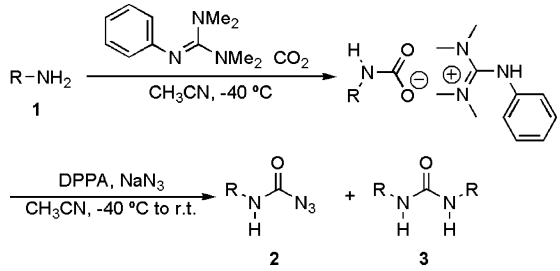
Caution: Carbamoyl azides are potentially explosive compounds. Reactions must be carried out behind a safety shield.

Knowledge of the carbamoyl azide functionality dates back to the end of the last century. However, the use of these compounds as useful synthetic intermediates has been limited, mainly because of their presumed instability and the harsh conditions necessary for their preparation.[1] In fact, some carbamoyl azides, as other azides, are considered to be powerful explosives. In addition, carbamoyl azides are sensitive to heat and to both acidic and basic conditions. As a consequence, examples of the use of carbamoyl azides in synthesis have been very scarce over the past few years.[2] However, one of the most outstanding examples is the synthesis of biotin carried out by De Clerck.[3]

There are three standard procedures for carbamoyl azide synthesis: (a) diazotization of semicarbazides and related compounds; (b) treatment of isocyanates with hydrazoic acid; (c) reaction of carbamoyl chlorides with sodium azide. However, all of these methods have several drawbacks, especially with sensitive substrates. First, yields are poor to moderate in most cases. Second, the reagents are toxic and explosive (hydrazoic acid). In addition, several intermediates, such as carbamoyl chlorides and isocyanates, are rather unstable toward nucleophilic attack.

More efficient preparations of carbamoyl azides have been achieved from carboxylic acids and carboxylic acid chlorides via a Curtius rearrangement,[4] as well as by radical azidonation of aldehydes.[5] In addition, they have also been prepared by degradation of tertiary amines.[6]

SCHEME 1



In this paper, we present a new method for the preparation of carbamoyl azides under mild conditions through the one-pot carbamoylation of primary amines using carbon dioxide, a guanidine as a base and diphenyl phosphoryl azide (DPPA) (Scheme 1).

It is well-known that an amine and carbon dioxide are in equilibrium with a carbamate anion in a basic medium. If this equilibrium is sufficiently shifted toward the carbamate, the anion can be alkylated in good yield with several electrophiles.[7] One approach to shift the equilibrium is the use of a pentaalkyl guanidine as the base. Guanidines are non-nucleophilic and relatively strong bases.[8] Their basicity has been explained on the basis of the exceptional stability of the guanidinium cation. This cation has a highly delocalized charge, which has allowed its use for the stabilization of polydentate anions.[9] It is accepted that in the aforementioned equilibrium, guanidinium cations stabilize the carbamate anions effectively, thus increasing their concentration in solution.

We chose 1,1,3,3-tetramethyl-2-phenylguanidine (PhTMG) as the base in the reaction because we found that the structure of the guanidine has a negligible effect on the outcome of the reaction. In addition, PhTMG could be easily prepared in high yield by slightly modifying the procedure of Bredereck.[10]

The reaction was carried out in acetonitrile. Several studies indicated that guanidines have a higher basicity in acetonitrile than in other solvents.[11] Furthermore, since the anions are only weakly solvated by acetonitrile, the stabilization of the carbamate anion by the guanidinium cation is favored.[12] In addition,

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TABLE 1. Yields of Carbamoyl Azides from Various Amines

entry	amine (**1**)	**2**
1	pentane-1,5-diamine (**a**)	69
2	benzylamine (**b**)	74
3	2-(1-cyclohexenyl)ethylamine (**c**)	84
4	cyclohexylamine (**d**)	76
5	homoveratrylamine (**e**)	76
6	allylamine (**f**)	71
7	isobutylamine (**g**)	80
8	HCl·L-Val-OMe (**h**)	90
9	HCl·D-Val-OMe (**i**)	88
10	HCl·L-Glu(OMe)-OMe (**j**)	88
11	HCl·L-Trp-OMe (**k**)	86
12	pTsOH·LAsp(OBn)-OBn (**l**)	79
13	HCl·L-Ile-OMe (**m**)	90
14	TFA·L-Met-OMe (**n**)	81
15	TFA·L-Phe-OMe (**o**)	84
16	HCl·D-Phe-OMe (**p**)	82

the high solubility of carbon dioxide in acetonitrile also facilitates the reaction.

A few problems had to be overcome in order to obtain optimal yields. Initially, the reaction was performed at 0 °C by bubbling carbon dioxide into dry acetonitrile at atmospheric pressure until saturation was achieved. The amine, the guanidine, and the DPPA were then added sequentially. Although the carbamoyl azide was formed in rather good yield, in some experiments a substantial amount of the symmetrical urea appeared as a byproduct. The characterization of this byproduct, which has ^{1}H NMR and ^{13}C NMR spectra that are almost identical to the carbamoyl azide spectra but had lost the intense IR azide band around 2150 cm^{-1}, was only possible by MS. This result indicated that carefully designed experimental conditions had to be used in order to avoid undesired side-reactions and to improve the yield of the carbamoyl azide.

First, the need for anhydrous solvent and carbon dioxide was established as we confirmed that the presence of small amounts of water led to lower yields, presumably due to hydrolysis of the carbamoyl azide.

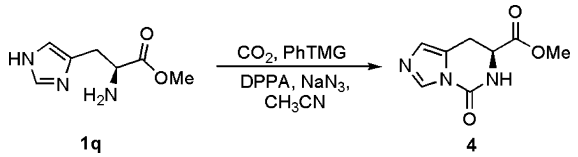
The appearance of the urea was attributed to the reaction between either the formed carbamoyl azide or a previous intermediate and the free amine in the reaction medium. In an effort to minimize the amount of urea, several modifications were made: the initial temperature of the reaction was kept below −35 °C, the order of addition of reagents was reversed, the amine was added slowly, and excess sodium azide was added to the reaction medium.

The results of the reactions on a 1 mmol scale for several simple primary amines are given in Table 1 (entries 1−7). Yields correspond to isolated and purified products. The yields for the carbamoyl azides vary between 69 and 84%, whereas the amount of isolated urea was kept below 2% (except for **1c**, 8%). Other products were not detected in these experiments.

Entries 8−16 represent the reaction results starting from amino ester salts of proteinogenic amino acids. Yields of isolated carbamoyl azides are somewhat higher. The yield of urea is also slightly higher although, in most cases, this was kept well below 5%. The reason why yields from simple amines are to some extent lower than from amino esters is unclear. We attributed several low yields for small amines to losses in isolation due to the volatility of the carbamoyl azides of low molecular weight amines.

Compound **2e** was isolated as a crystalline solid and this allowed a single-crystal X-ray analysis to be carried out. The results of this analysis confirm the carbamoyl azide structure for all the compounds and show the typical structural measurements for the carbamoyl azide functionality. The azide is nearly linear with an insignificant distortion in the lattice.

SCHEME 2



1q **4**

When the reaction was carried out with L-histidine methyl ester **1q** as the substrate (Scheme 2) the carbamoyl azide was not isolated. Instead, the major compound from the reaction mixture was the cyclic urea **4**, presumably obtained by intramolecular attack of the imidazole nitrogen on either the carbamoyl azide or one of its precursors (see below). Compound **4** was characterized by spectroscopic methods and by single-crystal X-ray analysis.

Despite claims in the literature of carbamoyl azide instability, we did not observe decomposition of the compounds obtained here. Indeed, byproducts were not observed in pure carbamoyl azides stored for several months at low temperature in a freezer (−20 °C).

In order to assess the scope of the reaction, the possibility of epimerization under the reaction conditions was examined for enolizable α-protons. Thus, the carbamoyl azides of several amino esters were submitted to GC analysis on a chiral support in order to check their enantiomeric purity. Unfortunately, derivatization proved necessary because the chromatogram showed several peaks, probably due to thermal instability under GC conditions. Therefore, the carbamoyl azides of both enantiomers of valine methyl ester and phenylalanine methyl ester were treated with dimethylamine in acetonitrile for 10 min in order to form the dimethylurea. Each derivative showed only a single peak when submitted to GC. In addition, co-injection of enantiomers showed different retention times for each, proving that racemization (>99.5 ee) did not take place during either the synthesis of the carbamoyl azide or its derivatization. Moreover, the absence of epimerization could also be deduced by NMR spectra of the carbamoyl azide of isoleucine, since only a single set of peaks corresponding to a single diastereomer could be observed. This result is in agreement with the previously reported non racemization in the DPPA mediated coupling of acylamino acids with amino acids.[13]

When the reaction was carried out using the same conditions on dibutylamine, a completely different outcome was obtained. In this case, the mixed anhydride **5** was isolated in high yield (98%) as the only product. This compound was stable and could be easily purified and characterized. When the reaction mixture was heated under reflux overnight, a moderate yield (53%) of carbamoyl azide **6** was obtained (Scheme 3). Similar results were obtained on applying the same procedure to other secondary amines, with the yields of carbamoyl azides being low to moderate. These yields were not significantly improved on using harsher reaction conditions − longer times, adding more azide, raising the temperature, and/or adding a Lewis acid. Another significant difference with the behavior of primary amines is that urea was not detected when the reaction was carried out with secondary amines.

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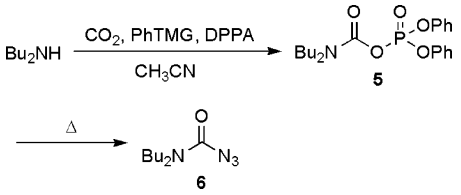
SCHEME 3



The different outcome of the reaction with primary and secondary amines suggests different mechanisms. Although the overall process is not well understood, the first step should involve nucleophilic attack of the carbamate anion to the phosphorus of DPPA to yield a mixed anhydride in the same way postulated for the conversion of carboxylates to acyl azides. In fact, this intermediate has been isolated for secondary amines although it could not be detected for primary ones. This mixed anhydride may evolve through different pathways with a variety of intermediates depending on the substrate. A possible explanation for the differences between primary and secondary amines in the experimental outcome of the reaction is that the mixed anhydride can evolve easily to an isocyanate, for primary amines, in the basic reaction medium. This isocyanate can then react with the nucleophiles present in the medium to yield either the carbamoyl azide or the symmetrical urea. Since the formation of the isocyanate is impossible for secondary amines, the substitution on the carbonyl carbon of the mixed anhydride must take place through a different mechanism.

In summary, a reliable method for the preparation of carbamoyl azides under very mild conditions is presented. The reaction provides very good yields of isolated products from a broad range of primary amines. Thus, the methodology fulfils the requirements for the preparation of carbamoyl azides either as intermediates or as final targets in organic synthesis.

Experimental Section

General Procedure for the Synthesis of Carbamoyl Azides from Primary Amines. A mixture of NaN_3 (0.200 g, 3.08 mmol, 302 mol %) and DPPA (0.280 g, 0.22 mL, 1.00 mmol) in dry acetonitrile (10 mL) was cooled in a dry ice/acetone bath at −41 °C. Carbon dioxide was slowly bubbled through the mixture until saturation was achieved. A solution of the amine (1.06 mmol, 106 mol %) and PhTMG (0.220 g, 1.15 mmol, 112 mol %) in dry acetonitrile (15 mL) was added dropwise (1.5−2.0 h). Once the addition was finished, the stream of CO_2 was stopped, and the mixture was stirred under a carbon dioxide atmosphere, allowing the temperature to rise to room temperature overnight (14−17 h). The mixture was dissolved in EtOAc (150 mL), and the solution was washed with water (3 × 15 mL) and with 5% aq HCl (3 × 15 mL). The resulting organic phase was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography.

Pentane-1,5-diyldicarbamoyl Azide (2a). Following the general procedure, 2.04 mmol of DPPA and 2.30 mmol of PhTMG were used. Thus, starting from 1.00 mmol of pentane-1,5-diamine, after purification by flash chromatography (EtOAc/hexanes from 1:9 to 1:1), the product was obtained as a white solid (0.160 g, 69% yield): R_f 0.60 (hex/EtOAc 1:1); mp 115.8 °C dec; ^{1}H NMR ($CDCl_3$, 400.13 MHz) (two rotamers, ratio 93:7) δ 5.12 (br s, 2H), 3.25 (q, 3.7H, J = 6.5 Hz), 3.13 (q, 0.3H, J = 6.5 Hz), 1.55 (q, 4H, J = 7.0 Hz), 1.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.62 MHz) (major rotamer) δ 156.3, 40.4, 28.7, 23.1; FTIR (KBr) ν_{max} 3256 (br), 2178, 2142, 1686, 1668, 1539, 1258, 1225 (br) cm^{-1}; HRMS (FAB+, mNBA matrix) calcd for $C_7H_{13}N_8O_2$ 241.1161, found 241.1154.

Dibutylcarbamic (Diphenylphosphoric) Anhydride (5). DPPA (0.20 mL, 0.93 mmol) was added to an ice-cooled solution of dibutylamine (0.168 mL, 1.0 mmol) and PhTMG (0.268 g, 1.4 mmol) in acetonitrile. CO_2 was bubbled through the solution for 30 min until saturation was achieved. The mixture was stirred for 5 h under a carbon dioxide atmosphere, allowing the temperature to rise to room temperature. The crude product was dissolved in EtOAc and washed with water and with 5% HCl. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Compound **5** was obtained as a yellowish oil (0.369 g, 98% yield): R_f 0.33 (EtOAc/hexanes 1:5); ^{1}H NMR ($CDCl_3$) δ 7.38−7.20 (m, 10H), 3.25 (t, 2H, J = 7.6 Hz), 3.08 (t, 2H, J = 7.6 Hz), 1.55 (m, 2H), 1.43−1.28 (m, 4H), 1.14 (m, 2H, J = 7.4 Hz), 0.93 (t, 3H, J = 7.3 Hz), 0.85 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 150.4, 150.4, 147.8, 129.7, 125.6, 120.3, 120.3, 48.0, 47.9, 30.5, 29.5, 19.8, 19.7, 13.7, 13.6; ^{31}P NMR ($CDCl_3$) δ −1.84; LRMS (EI) *m/z* (relative intensity), 405 (M^+, 2), 349 (39), 312 (48), 263 (88), 156 (80), 99 (79), 84 (100); HRMS (EI) calcd for $C_{21}H_{28}NO_5P$ (M^+) 405.1705, found 405.1716.

Dibutylcarbamoyl Azide (6). Dibutylamine (0.168 mL, 1.0 mmol) was submitted to the same procedure as described for the preparation of **5**. The mixture was heated at 60 °C for 14 h under a carbon dioxide atmosphere. The reaction mixture was dissolved in EtOAc and sequentially washed with water and 5% HCl. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/hexanes 1:12) to give **6** as a colorless oil (0.095 g, 53% yield): R_f 0.66 (EtOAc/hexanes 1:9); ^{1}H NMR ($CDCl_3$) δ 3.28 (t, 2H, J = 7.6 Hz), 3.16 (t, 2H, J = 7.5 Hz), 1.67−1.46 (m, 4H), 1.34−1.26 (m, 4H), 0.93 (t, 6H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 156.3, 48.7, 47.2, 30.7, 29.8, 20.1, 19.8, 13.8, 13.7; HRMS (FAB+, mNBA matrix) calcd for $C_9H_{19}N_4O$ $(M + 1)^+$ 199.1559, found 199.1566.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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