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Chinese Chemical Letters 23 (2012) 883–886

CHINESE CHEMICAL LETTERS

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# A novel and efficient strategy for the synthesis of various carbamates using carbamoyl chlorides under solvent-free and grinding conditions using microwave irradiation

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Received 17 February 2012
Available online 4 July 2012

**Abstract**

We present an efficient, fast and simple strategy of generating the intermediate carbamoyl chlorides from secondary amines using stoichiometric amounts of bis(trichloromethyl)carbonate (BTC) in solution and solvent-free conditions with excellent yields. The results obtained showed the yield increasing on whether a base was used. Finally, an efficient and rapid synthesis of variety carbamate derivatives was developed by the reaction with a high variety of different alcohols, phenols, diols and this intermediate at room temperature with grinding and in solvent-free conditions under microwave irradiation. The presence of various safe bases is shown to be effective in reducing the reaction times, increasing the yields and easing purification. The present method does not involve any hazardous phosgene.



*Keywords:* Bis(trichloromethyl)carbonate; Carbamoyl chloride; Carbamate; Microwave irradiation; Solvent-free; Grinding

Carbamoyl chlorides are starting material for production the various classes of compounds such as carbamates and urea derivatives [1]. They are to be employed to synthesize various compounds in pharmaceutical, medical, agrochemical, and polymer chemistry, which possess biologically desirable properties such as superior inhibitors of TryR or HIV, anticancer, anticonvulsants, antibacterials, antiepileptics, and enzyme inhibitors. They are also useful chemical intermediates for many industrial products such as fine chemicals, cosmetics, and pesticides [2–6]. Typically, aliphatic and aromatic carbamoyl chlorides are generated from amines reacting with phosgene or phosgene equivalents [7]. Carbamoyl chlorides and carbamates are generated by other processes, such as, the oxidative and reductive carbonylation of amines with CO or $CO_2$ in the presence of transition metal catalysts, even with photocatalysis [8]. These routes were always suffered from the hazards in using of carbon monoxide and phosgene under high pressure. Also, these routes were limited due to low yields, longer reaction times, stringent conditions, and use of expensive reagents. Another approach to the preparations of carbamates is using the reaction of urea with symmetrical carbonates [9]. This process can be used only when the two components (urea and carbonate) are either

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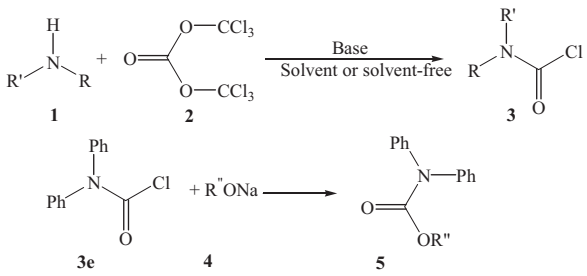
1001-8417/$ – see front matter 
http://dx.doi.org/10.1016/j.cclet.2012.06.025




Scheme 1. Synthesis of compounds **3**, **5**.

both aliphatic or both aromatic [2], which limits the possible number of accessible products. All these facts prompted us to find a new nontoxic method and to employ safe bases for the synthesis of the carbamoyl chlorides in a solvent-free environment. As a solution to these problems, we envisaged the use of BTC. This capable compound has replaced its gaseous congener, phosgene and diphosgene, in terms of its lower vapor pressure, reactivity, higher stability and safe handling [10]. As part of our current studies on the development of new compounds, [11–15] we now report a novel and efficient synthesis of carbamoyl chlorides **3** and carbamates **5** (Scheme 1).

## 1. Experimental

Amines **1**, bis(trichloromethyl)carbonate **2**, alcohols, phenols and diols were obtained from Merck and were used without further purification. Alkoxides and phenoxides **4** were prepared by known methods [16]. Melting points (uncorrected) were measured on an Electrothermal 9100 apparatus. The microwave oven used for this work was an ETHOS-MR (800 W, 180 °C) operating at 2450 MHz. Elemental analyses for C, H, N and S were performed using a Heraeus CHN-O-Rapid analyzer. The experimental data were in good agreement with the calculated values. $^{1}H$ and $^{13}C$ NMR spectra ($CDCl_3$) were measured with a Bruker DRX-300 Avance spectrometer. IR spectra were recorded on a Bruker tensor FT-IR 27 spectrometer. Mass spectra were recorded on a Hewleet-Packard 5993C spectrometer.

## 2. Results and discussion

The reaction of stoichiometric amounts of BTC with diphenyl amine in various solvents and solvent-free conditions was revisited and it was shown that the formation of carbamoyl chlorides in high yields required careful adjustments of experimental conditions and the use of the base as an HCl scavenger. We investigated comparatively the activities of some representatives of various bases which are nonvolatile, noncorrosive, and very popularly studied recently in green catalysis, diphenyl carbamoyl chloride synthesis from BTC and diphenyl amine, and the results are listed in Table 1.

Given the fact that some carbamoyl chlorides are unstable and best used without any purification, we searched for a cleaner and more efficient approach to synthesis them. BTC appeared as a good reagent for generating carbamoyl chlorides but this reagent used in the presence of triethylamine [17] or pyridine [18]. The disadvantages of these routes are always suffered from the byproducts [19]. Herein, we describe the approach to the synthesis of various carbamoyl chlorides as a single product by the reaction of stoichiometric amounts of BTC with secondary amines in solvents and

Table 1
Chlorocarbonylation of diphenyl amine using BTC in solvent (I) and in solvent free condition (II): influence of the added base.

| Base | Time (min) | | Yield (%) | |
|---|---|---|---|---|
| | I | II | I | II |
| NaOH | 30 | 5 | 90 | 96 |
| $CaCO_3$ | 60 | 20 | 60 | 65 |
| $CaHCO_3$ | 45 | 20 | 72 | 80 |
| $Na_2CO_3$ | 40 | 20 | 75 | 85 |
| None | 180 | 30 | 70 | 75 |

Table 2
Synthesis of various carbamoyl chlorides **3a–f**.

| Substrate | Product | R | R′ | Solvent | Time (min) | | Yield[b] (%) | | Mp (°C) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | I | II | I | II | Found | Reported[a] |
| **1a** | **3a** | Me | Me | $CH_2Cl_2$ | 10 | 2 | 80 | 88 | White oil | White oil |
| **1b** | **3b** | *n*-Pr | *n*-Pr | $CH_2Cl_2$ | 10 | 2 | 85 | 92 | White oil | White oil |
| **1c** | **3c** | Ph | Me | Benzene-xylene | 20 | 5 | 95 | 99 | 86–88 | 87–90 |
| **1d** | **3d** | Ph | Et | Benzene-xylene | 20 | 5 | 92 | 98 | 56–58 | – |
| **1e** | **3e** | Ph | Ph | Benzene-xylene | 30 | 5 | 90 | 96 | 81–83 | 83–85 |
| **1f** | **3f** | Benzyl | Benzyl | Benzene-xylene | 30 | 7 | 85 | 90 | White oil | White oil |

[a] All the products were characterized on the basis of their IR, $^1$H NMR and $^{13}$C NMR spectral analysis and compared with the literature data [19,20].
[b] Isolated yields.

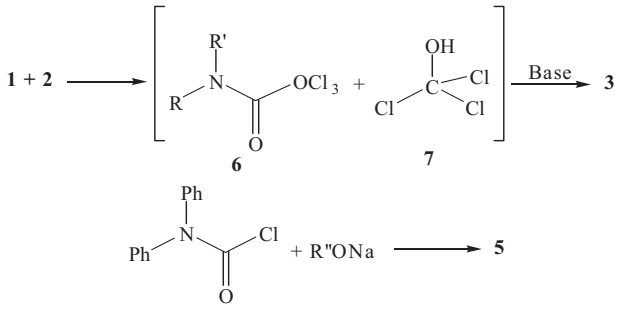
solvent-free conditions using NaOH with temperature and time control in excellent yields (see the supporting information and Table 2).

The advantage procedure is there can be use a broad spectrum of variety aromatic or aliphatic alcohols and diols to react with carbamoyl chloride to the synthesis respective carbamates. The data obtained will help to establish a scale of entering groups that will extend our knowledge on the reactivity of alcohols with carbamoyl chlorides for the synthesis of carbamates. The reaction of carbamoyl chlorides with alcohols under solvent-free conditions at room temperature on microwave and grinding generated carbamates in moderate purity and high yields (Table 3).

Although we have not yet established experimental proof for the mechanism of the formation of compounds **3** and **5**, a plausible mechanism was proposed as shown in Scheme 2. It is reasonable to assume that carbamoyl chlorides **3** results from the initial addition amines to the BTC and subsequent deprotonation of the intermediate, followed by rearrangement of **6**, to from the carbamoyl chlorides **3**. These compounds undergo a substitution reaction to produce the final products **5** (Scheme 2).

Table 3
Synthesis of carbamates and hydroxyl carbamates using carbamoyl chloride and corresponding alcohols in solvent (I), and by grinding in solvent free condition (II), and under microwave-irradiated condition (III).

| Substrate | Product | R″ | Time (h) | | | Yield (%) | | | Mp (°C) |
|---|---|---|---|---|---|---|---|---|---|
| | | | I | II | III | I | II | III | |
| **4a** | **5a** | Me | 0.01 | 0.005 | 0.002 | 97 | 99 | 99 | 58 |
| **4b** | **5b** | Et | 0.05 | 0.009 | 0.004 | 95 | 99 | 99 | 70 |
| **4c** | **5c** | *n*-Propyl | 8 | 0.21 | 0.14 | 80 | 76 | 90 | 214 |
| **4d** | **5d** | *sec*-Butyl | 10 | 0.26 | 0.17 | 75 | 69 | 85 | Oil |
| **4e** | **5e** | *t*-Butyl | 9.5 | 0.25 | 0.16 | 76 | 71 | 87 | Oil |
| **4f** | **5f** | Benzyl | 4 | 0.10 | 0.07 | 80 | 82 | 92 | 108 |
| **4g** | **5g** | 4-*t*-Bu benzyl | 6.5 | 0.17 | 0.11 | 75 | 77 | 86 | 140 |
| **4h** | **5h** | 4-Methoxy benzyl | 5.5 | 0.14 | 0.09 | 78 | 80 | 88 | 121 |
| **4i** | **5i** | $C_6H_5$ | 5 | 0.13 | 0.08 | 91 | 93 | 99 | 105 |
| **4j** | **5j** | 4-$CH_3$ $C_6H_4$ | 7 | 0.18 | 0.12 | 90 | 92 | 98 | 82 |
| **4k** | **5k** | 4-$CH_3O$ $C_6H_4$ | 6 | 0.15 | 0.10 | 93 | 95 | 99 | 102–103 |
| **4l** | **5l** | 4-Cl $C_6H_4$ | 9.5 | 0.25 | 0.16 | 85 | 87 | 96 | 104–106 |
| **4m** | **5m** | 4-$NO_2$ $C_6H_4$ | 12 | 0.31 | 0.21 | 81 | 83 | 93 | 113 |
| **4n** | **5n** | 3-$NO_2$ $C_6H_4$ | 11 | 0.28 | 0.19 | 76 | 78 | 89 | 84 |
| **4o** | **5o** | $CH_2CH_2OH$ | 8 | 0.21 | 0.14 | 83 | 85 | 96 | 67–68 |
| **4p** | **5p** | $CH_2CH_2CH_2OH$ | 11.5 | 0.30 | 0.20 | 75 | 77 | 87 | Oil |
| **4q** | **5q** | $CH_2CH$ $OHCH_3$ | 10 | 0.26 | 0.17 | 78 | 80 | 90 | 106 |
| **4r** | **5r** | 3-Hydroxynaphthalen-2-olate | 14 | 0.37 | 0.24 | 73 | 75 | 85 | 162 |
| **5o** | **6o** | $CH_2CH_2OCON(C6H_5)_2$ | 12 | 0.31 | 0.21 | 76 | 80 | 88 | 160 |
| **5q** | **6q** | $CH_2CH(CH_3)OCON(C6H_5)_2$ | 13 | 0.34 | 0.22 | 73 | 77 | 84 | 202–205 |
| **5r** | **6r** | Naphtalen-2-yl diphenyl carbamate | 14.5 | 0.38 | 0.25 | 69 | 71 | 80 | 208 |




Scheme 2. A plausible mechanism for the formation of compounds **3**, **5**.

## 3. Conclusion

The reaction of BTC, amines and NaOH provides a simple one-pot entry into the synthesis of carbamoyl chloride of potential synthetic interest. Carbamoyl chlorides **3a–f** can be considered as potentially useful synthetic intermediates. The advantages that can be the reaction performed under neutral conditions and the starting materials and reagents can be mixed without any activation or modification.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2012.06.025.

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