An improved one-pot cost-effective synthesis of N,N-disubstituted carbamoyl halides and derivatives

K. Adeppa, D.C. Rupainwar, and Krishna Misra

Abstract: A convenient one-pot procedure is reported for preparing N,N-disubstituted carbamoyl chlorides by using chlorocarbonylsulfenyl chloride as a carbonylating agent. It comprises the reaction of secondary amines with chlorocarbonylsulfenyl chloride in the presence of an aprotic organic solvent to produce the corresponding N,N-disubstituted carbamoyl halides. Insertion of the carbonyl group without using phosgene is the novelty of this method.

Key words: carbonylsulfenyl chloride, secondary amines, dichloromethane, carbamoyl halides.

Résumé : On a développé une méthode monotope pour préparer des chlorures de carbamoyle N,N-disubstitués qui fait appel au chlorure de chlorocarbonylsulfényle comme agent de carbonylation. Elle implique la réaction d'amines secondaires avec le chlorure de chlorocarbonylsulfényle en présence d'un solvant organique aprotique qui conduit à la formation des halogénures de carbamoyles N,N-disubstitués correspondants. La nouveauté de cette méthode correspond à l'insertion d'un groupe carbonyle sans faire appel au phosgène.

Mots-clés : chlorure de chlorocarbonylsulfényle, amines secondaires, dichlorométhane, halogénures de carbamoyle.

Introduction

Carbamoyl halides[1] are an important class of commercially viable chemicals. These are useful intermediates in the preparation of thiolcarbamate herbicides via their reaction with thiols such as sodium alkyl mercaptides. Carbamoyl halides, particularly chlorides, are useful in the preparation of 1,4-disubstituted 5-(4*H*)-tetrazolinones;[2] imidazole derivatives;[3] Reissert analogs;[4] phenylcarbamates;[5] unsymmetrical ureas; pyrrole-*N*-carbonyl compounds;[6] *O*-®-oxoalkylcarbamates;[7] *O*-allylic urethanes and carbonates;[8] in the synthesis of carbamates;[9] phthalides;[10] in the preparation of arylisocyanates;[11] *N*,*N*-dimethyl carbamoyloxy-3-thiodiazoles-1,2,4;[12] and *N*,*N*-dialkylcarbamate esters. Carbamoyl chlorides are also used for Friedel–Crafts acylation[13] followed by treatment with ammonia or amines to produce aromatic amides or substituted amides, which on hydrolysis yield corresponding acids. For example, *N*,*N*-dimethyl carbamoyl chloride has been used in the production of herbicides[14] such as isoproturon, fenuron, diuron, and metoxuron, and with drugs such as neostigmine bromide, neostigmine methylsulfate,[15] and pyridostigmine, which is the intermediate for the antihistaminic bulk drug loratidine. *N*,*N*-Diethyl carbamoyl chloride has been used as an intermediate for the antifilarial bulk drug diethlycarbamazine citrate. *N*-Ethyl-*N*-methyl carbamoyl chloride is used as an intermediate for the bulk drugs rivistigmine and β-propiolactone.

So far, the most prevalent commercial method for producing carbamoyl chlorides is phosgenation of ammonia or amines.[16,17] The main objective of the present work was to develop an efficient and economically viable procedure for preparing N,N-disubstituted carbamoyl chlorides. A further objective was to exploit the procedure for the preparation of unsymmetrical ureas[18] and N,N-disubstituted carbamate esters,[19] aromatic amides,[20] and thiolcarbamate herbicides. For the preparation of N,N-disubstituted carbamoyl chlorides, the commercial process involves the phosgenation of secondary amines. The use of phosgene, however, has several disadvantages. The phosgenation route is long and energy-intensive, and requires handling highly corrosive materials and highly toxic reagents and intermediates, especially phosgene and chlorine. Furthermore, the phosgenation route requires the use of process equipment that can withstand high temperatures and highly corrosive conditions, resulting in increased capital cost.

A non-phosgene process for preparing N,N-disubstituted carbamoyl chlorides, which is economical and commercially viable and that can produce N,N-disubstituted carbamoyl chlorides with good yields under extremely mild reaction conditions and short reaction times, is highly desirable. Such an attempt has been made during the present work.

Results and discussion

To develop a general method for the synthesis of carbamoyl chlorides and their derivatives, experiments were conducted through the carbonylation of secondary amines with chlorocarbonylsulfenyl chloride at ~40 °C for 3 h and

Received 25 March 2010. Accepted 17 August 2010. Published on the NRC Research Press Web site at canjchem.nrc.ca on 1 December 2010.

K. Adeppa and D.C. Rupainwar. U.P. Technical University, Lucknow (U.P.)-226000, India.
K. Misra.[1] Indian Institute of Information Technology, Allahabad (U.P.)-211002, India.

[1]Corresponding author (e-mail: kmisra@iiita.ac.in).

Scheme 1. Probable reaction mechanism for the preparation of N,N-disubstituted carbamoyl chlorides from secondary amines.

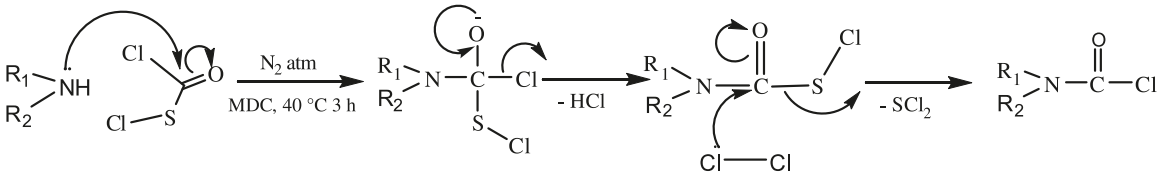
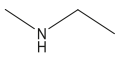
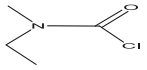
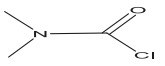
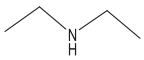
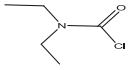
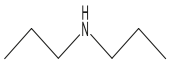
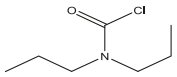
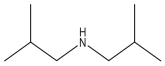
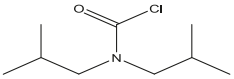
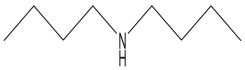
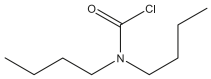
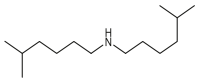
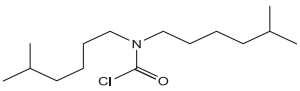
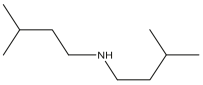
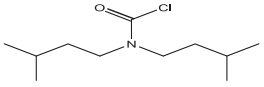
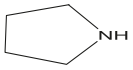
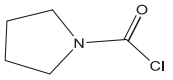
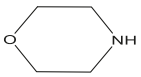
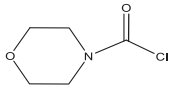
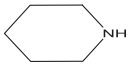
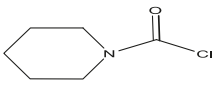
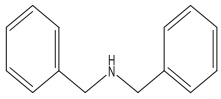
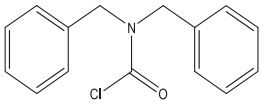


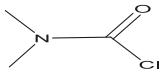
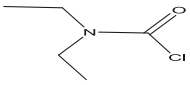
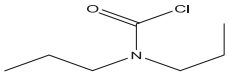
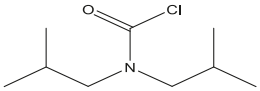
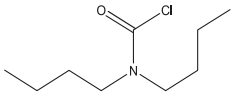
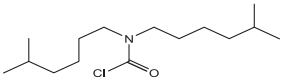
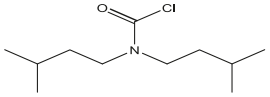
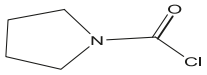
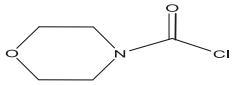
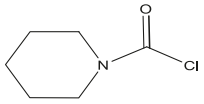
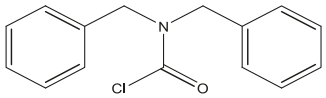
Table 1. Reaction conditions and boiling points of the prepared N,N-disubstituted carbamoyl chlorides.

S. No	Secondary amine	*N,N*-Disubstituted carbamoyl chloride	Reaction time	Yield (%)	Boiling point (°C)
1			5h	90.00	bp_{40}: 88-89
2			5h 20min	88.00	bp_{175}: 167-168
3			5h 50min	88.60	bp_{15}: 60-62
4			6h 50min	82.20	bp_{10}: 115-116
5			6h 25min	84.00	bp_{15}: 114-118
6			5h 20min	85.00	bp_{4}: 99-101
7			6h 35min	88.20	bp_{2}: 140-142
8			4h 55min	91.20	bp_{15}: 136-140
9			6h 20min	86.40	bp_{20}: 124-125
10			7h 10min	82.00	bp_{8}: 101-103
11			7h 30min	85.60	bp_{13}: 111-112
12			7h 15min	84.1	$bp_{0.1}$: 150-152

chlorination at room temperature for 2 h under nitrogen using dichloromethane as a solvent. To explore the general method developed for the synthesis of carbamoyl chloride derivatives, the experiments were conducted with chlorocarbonylsulfenyl chloride and a variety of secondary alkyl amines followed by chlorination to give the corresponding N,N-disubstituted carbamoyl chloride derivatives in substantial yields.

We found that this one-step reaction is general and is applicable to most secondary alkyl amines. The reaction conditions for the preparation of N,N-disubstituted carbamoyl chlorides starting from different secondary alkyl amines are summarized in Table 1, and the GC analysis as compared with the standard samples are summarized in Table 2. A probable mechanism for the preparation of N,N-disubstituted carbamoyl chlorides from different secondary alkyl amines

Table 2. Comparative GC retention time data of prepared compounds vs standard compounds

Serial No.	*N*,*N*-Disubstituted carbamoyl chloride	Retention time (min) Sample	Standard
1		5.62	5.62
2		4.32	4.32
3		6.56	6.56
4		6.75	6.75
5		5.95	5.95
6		5.86	5.86
7		6.43	6.43
8		7.32	7.32
9		6.52	6.52
10		7.20	7.20
11		6.32	6.32
12		6.50	6.50

Note: GC, THERMO Fischer model GC 1000; 8 ft glass (0.8 mm ID); 10% SE-30 on Chromosorb W (80–100 mesh); initial column temperature, 70 °C for 2 min; temperature rise rate, 25 °C/min; final column temperature, 240 °C held for 5 min; injector temperature, 240 °C; detector temperature, 250 °C. Two hundred milligrams of the sample and the standard were dissolved in 5 mL of toluene and 0.5 µL of each solution was injected.

has been suggested in Scheme 1. The present method has obvious advantages, compared with those reported in the literature, namely milder reaction conditions, use of less toxic materials, and better yields resulting in cost effectiveness of the procedure and general applicability.

Experimental details

Dimethylamine, diethylamine, di-*n*-propylamine, diisopropyl amine, *N*,*N*-ethyl-methylamine, di-*n*-butylamine, piperidine, and dichloromethane were sponsored by Merck (India), and perchloromethyl mercaptan was sponsored by India Pesticides Limited (Lucknow, India). All the products gave satisfactory boiling points. Gas chromatographic analysis was performed on a Thermo Fisher model GC-1000 gas chromatograph, and the results were consistent with the literature data.

Chlorocarbonylsulfenyl chloride (CCSC)[21]

Perchloromethyl mercaptan (PCMM) (294 mL, 500 g, 2.7 mol) was taken in a 2 L reaction flask equipped with a reflux condenser, a thermometer, and a stirrer, and a mixture

of water (54 mL, 3.0 mol) in concd sulfuric acid (620 mL) was added. The heterogenous mixture was vigorously stirred for 6 h at 45–50 °C as HCl evolved, and then stirred overnight at 25 °C to ensure complete reaction of PCMM at the expense of a decreased yield of chlorocarbonylsulfenyl chloride (CCSC), which can hydrolyze. The upper phase (280 g, 80%) was separated and distilled through a column, bp 98–101 °C (lit.,[21] bp 98 °C) to yield 230 g (65%) of the clear light yellow liquid of CCSC (65%).

General procedure for the preparation of *N*,*N*-dialkylcarbamoyl chlorides

A stirred solution of secondary amine (0.47 mol) in 800 mL dichloromethane in a 2 L reaction flask equipped with a reflux condenser and a stirrer was heated at ~40 °C under nitrogen. CCSC (65.50 g, 0.50 mol) at ~40 °C under nitrogen was added with stirring. The reaction mixture was stirred for an additional 3 h under reflux until evolution of HCl gas was completed. After cooling to room temperature (RT), the dark green liquid was chlorinated with chlorine (35.5 g, 0.50 mol) and the reaction mass was stirred for an additional 2 h under these conditions, followed by distillation at atmospheric pressure to remove solvent and sulfur dichloride. This reddish brown material was transferred into a 100 mL capacity distillation flask and distilled under reduced pressure (10 mm Hg; 1 mmHg = 133.3224 Pa). The total yield of N,N-disubstituted carbamoyl chloride was 80%–86%. Retention times in GLC as compared with the standard are given in Table 2.

Conclusion

The present method describes a simple, efficient one-pot method for the synthesis of commercially important N,N-disubstituted carbamoyl chlorides from the corresponding secondary amines and chlorocarbonylsulfenyl chloride. The process is economically viable;the enhanced rate of reaction, negligible byproducts, and cleaner reaction profiles make it a useful and attractive process for synthesis. The generalized and simple product-isolation procedures play an important role in the development of this novel method. It is an important step toward developing a greener and more efficient commercial synthesis for a group of compounds that are used to make important intermediates for the synthesis of a large number of commercially important products. This is an improvement over the phosgenation method being used at present.

Acknowledgements

The authors gratefully acknowledge the Centre for Biomedical Magnetic Resonance (CBMR), the Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGI), Lucknow, India, for NMR spectra, and the Central Drug Research Institute (CDRI), Lucknow, India, for IR spectra. One of the authors (K. Adeppa) is grateful to India Pesticides Limited, Lucknow, India, for providing all laboratory facilities and financial support, which enabled the present work to be completed successfully.

References

(1) Lide, D. R. Properties of dimethylcarbamoyl chloride. In *CRC Handbook of Chemistry and Physics;* 87th ed.; CRC Press: Boca Raton, FL 2006–2007; p 4002.
(2) Yanagi, A.; Watanabe, Y.; Narabu, S.-i. Process for the Preparation of 1-4-Disubstituted-5 (4*H*)-Tetrazolinones. U.S. Patent 5,767,286, 1998.
(3) Ngochindo, R. I. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1645. doi:10.1030/P19900001645.
(4) Badawey, E.-S. A. M.; Kappe, T. *J. Heterocycl. Chem.* **1991**, *28* (4), 995. doi:10.1002/jhet.5570280427.
(5) Enz, A. Process for the Preparation of Phenyl Carbamate. U.S. Patent 5,602,176, 1997.
(6) Boger, D. L.; Patel, M. *J. Org. Chem.* **1987**, *52* (11), 2319. doi:10.1021/jo00387a046.
(7) Bruneau, C.; Dixncuf, P. H. *Tetrahedron Lett.* **1987**, *28* (18), 2005. doi:10.1016/S0040-4039(00)96031-3.
(8) McGhee, W. D.; Riley, D. P.; Christ, M. E.; Christ, K. M. *Organometallics* **1993**, *12* (4), 1429. doi:10.1021/om00028a069.
(9) Sang, C. S.; Jin, O. B.; Chil, H. D.; Young, Z. Y.; Tae, J. K. *Bull. Korean Chem. Soc.* **1990**, *11* (5), 467.
(10) Paleo, M. R.; Lamas, C.; Castedo, L.; Dominguez, D. *J. Org. Chem.* **1992**, *57* (7), 2029. doi:10.1021/jo00033a024.
(11) Bacaloglu, R.; Bunton, C. A. *Tetrahedron* **1973**, *29* (18), 2725. doi:10.1016/S0040-4020(01)93393-9.
(12) Taliani, L.; Pcrronnet, J. *J. Heterocycl. Chem.* **1979**, *16* (5), 961. doi:10.1002/jhet.5570160527.
(13) Olah, G. A.; Reddy, V. P.; Prakash, G. K. S. Friedel–Crafts Reactions. In *Kirk–Othmer Encyclopedia of Chemical Technology;* 3rd ed.; John Wiley and Sons, Inc.: New York, 1982; Vol. 11, p 286.
(14) Plimmer, J. R.; Bradow, J. M.; Dionigi, C. P.; Johnson, R. M.; Wojkowski, S. Herbicides. In *Kirk–Othmer Encyclopedia of Chemical Technology;* 3rd ed.; John Wiley and Sons, Inc.: New York, 1982; Vol. 12, pp 324–325.
(15) Finklea, J. F. *Correspondence — Current Intelligence Bulletin 11, Dimethylcarbamoyl chloride (DMCC);* National Institute for Occupational Safety and Health: Cincinnati, OH, 1976; Revised.
(16) Tilles, H. *J. Am. Chem. Soc.* **1959**, *81* (3), 714. doi:10.1021/ja01512a052.
(17) Hoshino, O.; Saito, K.; Ishizaki, M.; Umezawa, B. *Synth. Commun.* **1987**, *17* (16), 1887. doi:10.1080/00397918708057799.
(18) Van Gool, M.; Bartolomé, J. M.; Macdonald, G. J. *Tetrahedron Lett.* **2008**, *49* (50), 7171. doi:10.1016/j.tetlet.2008.09.171.
(19) Rosin, M. W.; Chorev, M. T. Process for the preparation of phenyl carbamate. U.S. Patent 4,948,807, 1990.
(20) Lemoucheux, L.; Seitz, T.; Rouden, J.; Lasne, M. C. *Org. Lett.* **2004**, *6* (21), 3703. doi:10.1021/ol0487130.
(21) Weiss, W. German Patent 1224720, 1964.

This article has been cited by:

1. Wen Yuan, Zhipei Shang, Xiaoming Qiang, Zhenghuai Tan, Yong Deng. 2013. Synthesis of pterostilbene and resveratrol carbamate derivatives as potential dual cholinesterase inhibitors and neuroprotective agents. *Research on Chemical Intermediates* . [CrossRef]
2. D. M. Manidhar, K. Uma Maheswara Rao, C. Suresh Reddy, Ch. Syamasunder, K. Adeppa, Krishna Misra. 2012. An improved method for the preparation of alkyl/arylurea derivatives using chlorocarbonylsulfenyl chloride as carbonylating agent. *Research on Chemical Intermediates* **38**:9, 2479-2489. [CrossRef]
3. Alex M. Schrader, Alayne L. Schroll, George Barany. 2011. Synthetic Routes to, Transformations of, and Rather Surprising Stabilities of (N -Methyl- N -phenylcarbamoyl)sulfenyl Chloride, ((N -Methyl- N -phenylcarbamoyl)dithio)carbonyl Chloride, and Related Compounds. *The Journal of Organic Chemistry* **76**:19, 7882-7892. [CrossRef]
4. K. Adeppa, D. C. Rupainwar, Krishna Misra. 2011. ChemInform Abstract: An Improved One-Pot Cost-Effective Synthesis of N,N-Disubstituted Carbamoyl Halides and Derivatives. *ChemInform* **42**:20, no-no. [CrossRef]