ORGANIC LETTERS

2009
Vol. 11, No. 2
273−275

A Facile Method for the Preparation of MOM-Protected Carbamates

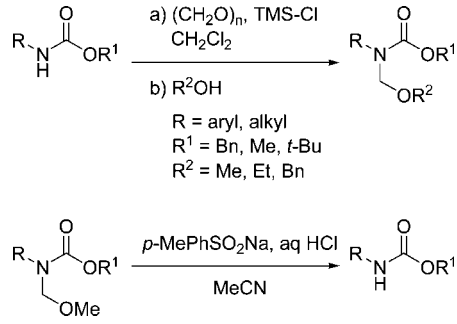
David M. Barnes,* Jufang Barkalow, and Daniel J. Plata

GPRD Process Research and Development, Abbott Laboratories, Building R13/3, 1401 Sheridan Road, North Chicago, Illinois 60064

david.barnes@abbott.com

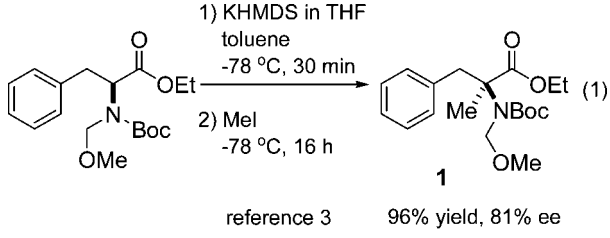
Received September 30, 2008

ABSTRACT



A novel method for the preparation of MOM-protected carbamates is described that avoids the use of MOM-Cl, a regulated carcinogen. The two-step, one-pot procedure generates a reactive *N*-chloromethyl carbamate that is quenched with methanol to afford MOM-protected carbamates. The process is tolerant of a variety of functionalities, including Boc, sulfonamide, and acetamide protecting groups. Mild conditions for the removal of the MOM group are also described; selective deprotection of the MOM group in the presence of a Boc group has been demonstrated.

The methoxymethyl (MOM) group is a well-known base-stable protecting group that can also act as a useful formaldehyde synthon. While commonly employed for the protection of alcohols,[1] the MOM group has also been used as a protecting group of amides[2] and carbamates. A notable example of the latter is found in the work of Kawabata, where the MOM group functions not only as a protecting group but also as a key design feature in the authors' memory of chirality chemistry (eq 1).[3] In addition, it can function as a methylene precursor in iminium ion chemistry.[4]



Most methods for the installation of a MOM-group onto acylated nitrogen groups employ a base-mediated alkylation with MOM-Cl.[2,3,5] However, utilization of this strategy is complicated by incompatibility with base-sensitive molecules, and by the fact that MOM-Cl is a regulated

(1) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.

(2) (a) Kirby, G. W.; Robins, D. J.; Stark, W. M. *J. Chem. Soc., Chem. Commun.* **1983**, 812–813. (b) Schollkopf, U.; Beckhaus, H. *Angew. Chem.* **1976**, *88*, 296–297.

(3) (a) Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2155–2157. (b) Kawabata, T.; Kawakami, S.-p.; Shimada, S.; Fuji, K. *Tetrahedron* **2003**, *59*, 965–974. (c) Kawabata, T.; Chen, J.; Suzuki, H.; Fuji, K. *Synthesis* **2005**, 1368–1377.

(4) (a) Shono, T.; Matsumura, Y.; Uchida, K.; Kobayashi, H. *J. Org. Chem.* **1985**, *50*, 3243–3245. (b) Brands, K. M. J.; Pandit, U. K. *Tetrahderon Lett.* **1989**, *30*, 1423–1426. (c) Esch, P. M.; Hiemstra, H.; Spekamp, W. N. *Tetrahderon Lett.* **1988**, *29*, 367–370. (d) Mooiweer, H. H.; Hiemstra, H.; Spekamp, W. N. *Tetrahedron* **1991**, *47*, 3451–3462. (e) See also Kawabata et al. (Kawabata, T.; Ozturk, O.; Suzuki, H.; Fuji, K. *Synthesis* **2005**, 505–508), where the MOM-group takes part in a Pictet−Spengler cyclization following its use in the memory of chirality alkylation.

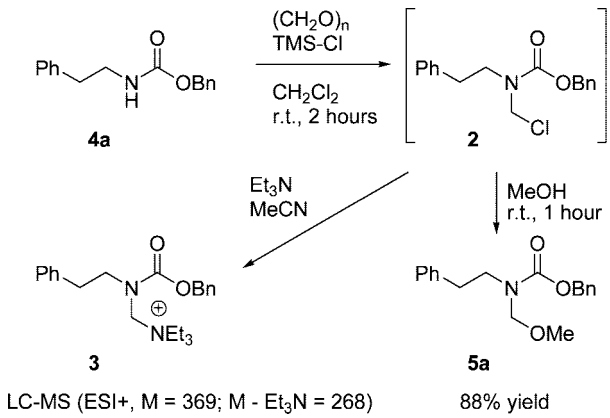
(5) For an example of the electrochemical oxidation of trimethylsilylmethyl carbamates to methoxymethyl carbamates, see: Yoshida, J.; Isoe, S. *Tetrahedron Lett.* **1987**, *28*, 6621–6624.

10.1021/ol8022769 CCC: $40.75
Published on Web 12/15/2008

carcinogen. In this paper, we describe an alternate approach to the preparation of MOM-protected carbamates, which proceeds via the *N*-chloromethyl derivative. This methodology avoids the use of MOM-Cl and employs mildly acidic conditions that are tolerant of a range of functionalities.

The reaction of carbamates with TMS-Cl and paraformaldehyde in the presence of $MgSO_4$ in toluene have been reported to afford the corresponding *N*-chloromethyl carbamates.[6] Treatment of Cbz-phenethylamine (**4a**) with TMS-Cl and paraformaldehyde in dichloromethane[7] led to a new peak by HPLC when samples were diluted with Et_3N in MeCN (Scheme 1). LC-MS analysis suggested that this new

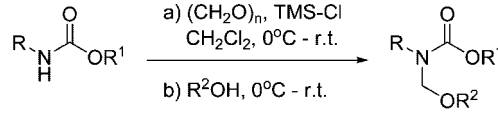
Scheme 1. Preparation and Reactions of *N*-Chloromethyl Carbamate **2**

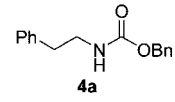
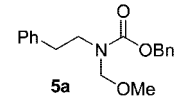
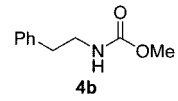
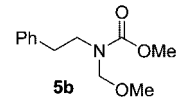
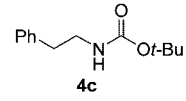
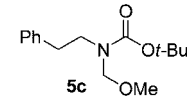
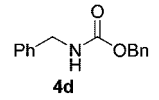
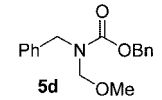
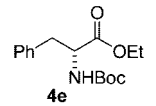
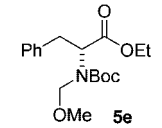
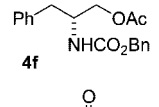
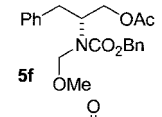
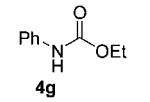
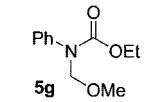
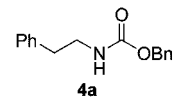
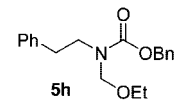
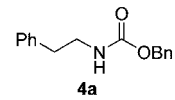
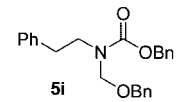


peak was the quaternary salt **3** (ESI+: M = 369; M − Et_3N = 268). The facility with which the putative *N*-chloromethyl carbamate alkylated a tertiary amine encouraged us to investigate its reactivity toward other nucleophiles, and we were pleased to find that on addition of methanol to the reaction mixture, *N*-methoxymethyl (MOM) carbamate **5a** was obtained cleanly. After an aqueous workup and chromatography the product was obtained in 88% yield.

The scope of the reaction is illustrated in Table 1.[8] In general, *N*-MOM carbamates are obtained in good yield with 95−98% consumption of starting material as determined by

Table 1. Scope of the Alkoxymethylation of Carbamates



entry	substrate	R^2OH	product	Yield
1	 **4a**	MeOH	 **5a**	88%
2	 **4b**	MeOH	 **5b**	80%
3[a,b]	 **4c**	MeOH	 **5c**	74%
4	 **4d**	MeOH	 **5d**	98%
5[b]	 **4e**	MeOH	 **5e**	82%
6[a,b]	 **4f**	MeOH	 **5f**	93%
7	 **4g**	MeOH	 **5g**	96%
8	 **4a**	EtOH	 **5h**	93%
9[c]	 **4a**	BnOH	 **5i**	91%

[a] The reaction was run at 0 °C. [b] The reaction was quenched into Et_3N/MeOH. [c] The reaction was quenched into DIPEA/BnOH.

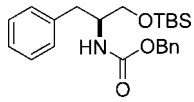
HPLC analysis. A variety of carbamate protecting groups are tolerated (entries 1−3), though due to the acid lability of the Boc group, reactions of substrates containing that functionality need to be quenched with a methanol/triethylamine mixture (entries 3 and 5). Other aliphatic amine derivatives are also good substrates, such as benzylamine (entry 4) and branched derivatives (entries 5 and 6). Of particular note is entry 5 in which the product (**5e**) is one employed in the Kawabata chiral-memory-effect alkylations (eq 1).[3] The ability of an acetate group to survive the reaction (entry 6) attests to the mildness of the conditions, though primary TBS ether **6** underwent significant deprotection under the reaction conditions at 0 °C. The reaction also works well with a protected aniline derivative (entry 7). Finally, the intermediate chloromethyl carbamate can react with other alcohols. Trapping with ethanol affords the ethoxymethyl

(6) (a) Ortiz, J.; Guijarro, A.; Yus, M. *Tetrahedron* **1999**, *55*, 4831–4842. (b) Smith, M. B.; Dembofsky, B. T.; Son, Y. C. *J. Org. Chem.* **1994**, *59*, 1719–1725.

(7) The conditions described in ref 6a additionally employed $MgSO_4$ in toluene. In our experience, the $MgSO_4$ has little effect on the outcome of the reaction. We observed differences in reaction rates when reactions in toluene were stirred magnetically or mechanically; these differences were not seen when the reaction was run in dichloromethane.

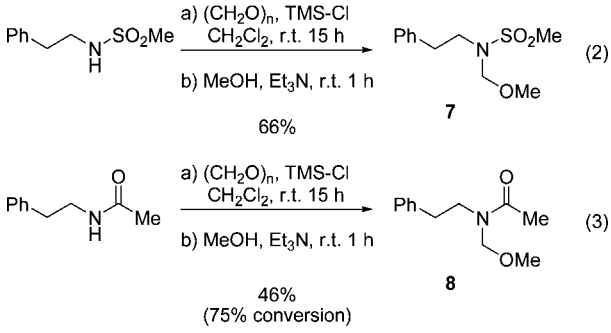
(8) General experimental: A flask was charge with *N*-benzyloxycarbonyl phenethylamine (**4a**, 1 g, 3.9 mmol), paraformaldehyde (0.18 g, 6.0 mmol, 1.5 equiv), and 10 mL of CH_2Cl_2. TMSCl (1.28 g, 11.7 mmol, 3 equiv) was charged and the reaction was stirred at room temperature for 2 h, at which point HPLC analysis indicated that the reaction was complete. To the flask was charged 3 mL of MeOH, and the reaction was stirred for 1 h. The reaction mixture was quenched into 15 mL of saturated aqueous $NaHCO_3$ solution, mixed, and separated. The aqueous phase was extracted with 10 mL of CH_2Cl_2 and the combined organic phases were washed with 10 mL of brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography afforded 1.03 g (88% yield) of benzyl *N*-methoxymethyl(phenethyl)carbamate **5a**.

derivative in good yield (entry 8); likewise, benzyl alcohol delivers the BOM-protected carbamate in 91% yield (entry 9).

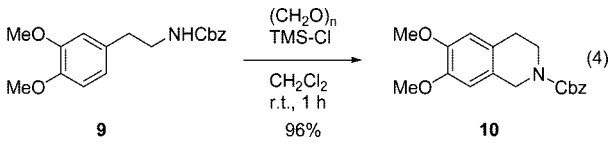


6

In addition to carbamates, we have found that the reaction works with other nitrogen protecting groups. The protection of a methanesulfonamide proceeded in 66% isolated yield (eq 2). The reaction with the corresponding acetamide stalled at about 75% conversion. After workup and isolation, MOM-protected acetamide **8** was isolated in 46% yield (eq 3).[9]

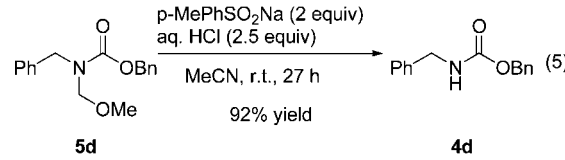


The reactivity of the putative chloromethyl intermediate[10] toward poorly nucleophilic reagents such as triethylamine and methanol suggests that the iminium ion formed by chloride ionization is an intermediate in the displacement process. Thus, a notable limitation of this methodology includes substrates which contain nucleophilic functionality that can undergo intramolecular trapping of the *N*-acyl iminium species. For example, treatment of Cbz-protected dimethoxyphenethylamine **9** under the reaction conditions led to Cbz-protected tetrahydroisoquinoline **10** in 96% yield via a Pictet−Spengler reaction (eq 4).[11]



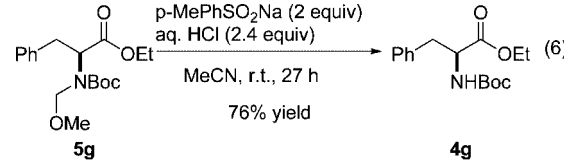
9 **10**

Deprotection of *N*-MOM protected amides has been accomplished by using strong acids.[12] However, we have found that chemoselective cleavage of a MOM group from carbamates can be achieved under relatively mild conditions, employing toluenesulfinic acid as a formaldehyde scavenger.[13] For example, deprotection of Cbz-derivative **5d** (2 equiv of *p*-$MePhSO_2Na$, 2.5 equiv of HCl in MeCN) afforded the deprotected carbamate **4d** in 92% yield (eq 5).



5d **4d**

Deprotection of Boc-derivative **5g** under these conditions led to some loss of the *tert*-butyl carbamate. However, the deprotected carbamate **4g** was still isolated in 76% yield (eq 66). In conclusion, we have described new conditions for the *N*-methoxymethylation of carbamates which avoid the use of MOM-Cl.[14] The mild nature of these reaction conditions grants the methodology a wide breadth of substrate scope; acetate and Boc groups are not affected during the protecting group installation. We have also developed mild deprotection conditions which are compatible with acid-sensitive functionality. Thus the MOM-group can be considered an orthogonal protecting group to carbamates.



5g **4g**

Acknowledgment. The authors thank Prof. David MacMillan and Dr. Tony Haight for helpful discussions.

Supporting Information Available: Experimental and characterization data for compounds **4f**, **5a**−**g**, **7**, **8**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8022769

(9) These reactions were not further optimized.

(10) NMR analysis of a reaction run in CD_2Cl_2 on carbamate **4a** supported the *N*-chloromethyl structure shown in Scheme 1 relative to that of the imminium ion. See the Supporting Information.

(11) This transformation has previously been accomplished in two steps in 14% overall yield. Kim, H. J.; Yoon, U. C.; Jung, Y.-S.; Park, N. S.;Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 860–863.

(12) Reference 2a (BBr_3): (a) Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2934–2936 (conc. HCl). (b) Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 4073–4075 (TMS-Cl, NaI). (c) Sotelo, E.; Coelho, A.; Ravina, E. *Tetrahedron Lett.* **2001**, *42*, 8633–8636 ($AlCl_3$ or BBr_3). (d) Baran, P. S.; Guerrero, C. A.; Hafensteiner, B. D.; Ambhaikar, N. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3892–3895 (bromocatecholborane).

(13) For the reaction of toluene sulfinic acid with formaldehyde, see: Brederek, H.; Bader, E. *Chem. Ber.* **1954**, *87*, 129–139.

(14) Although the conditions described in this paper do not employ MOM-Cl as a reagent, it is possible that upon MeOH quench some MOM-Cl is in fact generated from the activated formaldehyde.