ORGANIC LETTERS

2006
Vol. 8, No. 15
3263−3265

One-Pot Transformation of Trichloroacetamide into Readily Deprotectable Carbamates

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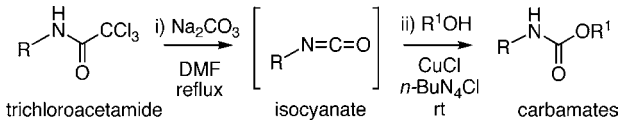
Received May 8, 2006

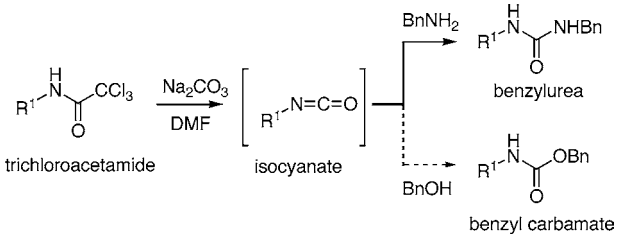
ABSTRACT



A trichloroacetamide group was converted to an isocyanate, which was in situ captured by a variety of alcohols in the presence of CuCl and *n*-BuN_4Cl to afford the corresponding carbamates. The scope and limitation of this transformation are also described.

The rearrangement of allylic trichloroacetimidates into trichloroacetamides (Overman rearrangement) has been widely used for the synthesis of a variety of nitrogen-containing compounds.[1,2] Recent development of a catalytic version of the asymmetric Overman rearrangement has increased the importance.[3] The resulting trichloroacetamides have been deprotected under hydrolytic conditions with 4−6 N HCl or 6 N NaOH in hot ethanol and reductive conditions with $NaBH_4$[4] or DIBAL-H.[5] However, in the early stages of our synthetic studies on tetrodotoxin analogues, deprotection of trichloroacetamide from our advanced intermediates was extremely difficult under the precedent conditions because of various sensitive functional groups in the substrates.[6] Therefore, conventional procedures for guanidinylation of amines could not be employed. To overcome the above problem, we developed a new synthetic route of guanidines from trichloroacetamides not through the unprotected amines;[7] thus, trichloroacetamides were heated with benzylamine in the presence of Na_2CO_3 to give benzylureas (Scheme 1),

Scheme 1



which were eventually transformed into dibenzylguanidinium compounds. In fact, the method was successfully employed in the total synthesis of 5,11-dideoxytetrodotoxin[6] and 11-deoxytetrodotoxin.[8] We supposed that the benzylurea was formed by addition of benzylamine to an isocyanate gener-

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(1) Reviews on the Overman rearrangement: (a) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218−224. (b) Ritter, K. In *Houben-Weyl. Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; E 21, Vol. 9, pp 5677−5699. (c) Sato, H.; Oishi, T.; Chida, N. *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 693−704. (d) Overman, L. E.; Carpentaer, N. E. *Org. React.* **2005**, *66*, 1−107.

(2) For improved conditions for facile Overman rearrangement, see: Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188−192.

(3) (a) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412−12413. (b) Kirch, S. F.; Overman, L. E.; Watson, M. P. *J. Org. Chem.* **2004**, *69*, 8101−8104.

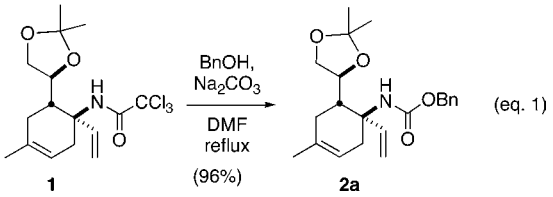
(4) Weygand, F.; Frauendorfer, E. *Chem. Ber.* **1970**, *103*, 2437−2449.

(5) Oishi, T.; Ando, K.; Inomoya, K.; Sato, H.; Iida, M.; Chida, N. *Org. Lett.* **2002**, *4*, 151−154.

10.1021/ol061123c CCC: $33.50
Published on Web 06/20/2006

ated from the trichloroacetamide under the conditions,[9] although the intermediate had not been detected. We anticipated that in situ trapping of the unstable isocyanate with alcohol (ROH) instead of amine would afford the corresponding carbamate.[10] This report discloses realization of the protective group transformation of trichloroacetamide into several carbamates under mild conditions.

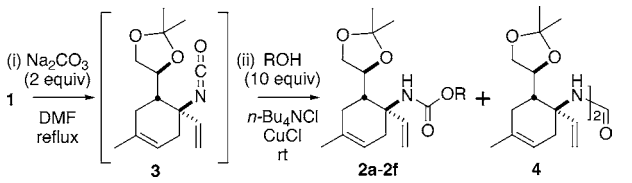
According to the synthesis of benzylurea, a key intermediate **1**[11] for tetrodotoxin synthesis in this laboratory was heated with benzyl alcohol (5 equiv) in the presence of Na_2CO_3 (2 equiv) under a reflux temperature of dry DMF[12] to give benzyl carbamate **2a** in excellent yield (eq 1). Unfortunately, the procedure was found not to be general for some other alcohols such as trichloroethanol, *tert*-butyl alcohol, and 9-fluorenylmethanol (vide infra). Therefore, a more general procedure was required for the transformation.



(eq. 1)

The generation of isocyanate **3** was confirmed by IR spectra (2272 cm^{-1}) of the crude product obtained from heating trichlroroacetamide **1** with Na_2CO_3 (2.0 equiv) in the absence of the alcohol. We then explored an alternative condition that allowed addition of various alcohols to the isocyanate generated from compound **1** in one pot. Considerable experimentation enabled us to find a satisfactory condition, giving the carbamate **2a** in a comparable yield (Table 1). Thus, trichloroacetamide **1** was heated with Na_2CO_3 (2.0 equiv) in DMF at the reflux temperature to give isocyanate **3**,[13] which was directly treated at room temperature with a large excess of benzyl alcohol (10 equiv)[14] in the presence of *n*-Bu_4NCl (2.0 equiv) and CuCl (2.0 equiv)[15] to furnish benzyl carbamate **2a** in 83% yield (entry 1). The

Table 1. Transformation of Trichloroacetamide to Carbamates



		additive (equiv)		products		
entry	ROH	CuCl	*n*-Bu_4NCl	carbamate	yield (%)	urea **4** (%)
1	BnOH	2	2	**2a** Cbz	83	0
2	BnOH	2	0	**2a** Cbz	47	0
3	BnOH	0	2	**2a** Cbz	0	55[a]
4	CCl_3CH_2OH	2	2	**2b** Troc	70	0
5	CH_2=HCH_2OH	2	2	**2c** Alloc	69	0
6	*t*-BuOH	2	2	**2d** Boc	38	22
7	TMS-CH_2CH_2OH	2	2	**2e** Teoc	69	0
8	9-fluorenyl-methanol	2	2	**2f** Fmoc	73	0

[a] Dimethylurea was obtained as a byproduct in 28% yield.

same reaction in the absence of *n*-Bu_4NCl gave a lower yield of the product **2a** (entry 2), while the reaction in the absence of CuCl did not give the desired product, but gave urea **4** as a major product (entry 3), indicating the importance of both the additives (CuCl and *n*-Bu_4NCl) in the addition of alcohol to the isocyanate.

The above one-pot, two-step procedure allowed the synthesis of a variety of carbamates as shown in Table 1; addition of trichloroethanol, allyl alcohol, 2-(trimethylsilyl)-ethanol and 9-fluorenylmethanol under the optimized conditions gave the corresponding carbamates such as Troc-, Alloc-, Teoc-, and Fmoc-protected amine (**2b**, **2c**, **2e**, and **2f**) in good yields (entries 4, 5, 7, and 8). The reaction with *tert*-butyl alcohol gave 38% of the desired Boc-protected product **2d** along with urea **4** in 22% yield, presumably due to steric reasons (entry 6). It is worthwhile to note that the procedure for eq 1 could not be applied to the synthesis of **2b**, **2d**, and **2f**.

With the suitable conditions for the protective group transformation in hand, we next examined some substrate generality (Table 2).[16] Trichloroacetamide **5** prepared from the Overman rearrangement of geraniol underwent the above transformation with benzyl alcohol to give the corresponding benzyl carbamate **10** in 82% yield. The same transformation of **6** and **7** in which trichloroacetamides were connected to secondary carbons gave the corresponding benzyl carbamates **11** and **12** in 79% and 43% yield, respectively, along with the corresponding symmetric urea in about 20% yield (entries 2 and 3). In the case of diacetone-D-glucose-derived substrate **8**, the desired benzyl carbamate **13** was obtained in 77% yield without the corresponding symmetric urea. When a similar

(6) (a) Nishikawa, T.; Asai, M.; Ohyabu, N.; Yamamoto, N.; Isobe, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3081−3084. (b) Asai, M.; Nishikawa, T.; Ohyabu, N.; Yamamoto, N.; Isobe, M. *Tetrahedron* **2001**, *57*, 4543−4558.

(7) (a) Yamamoto, N.; Isobe, M. *Chem Lett.* **1994**, 2299−2302. (b) Nishikawa, T.; Ohyabu, N.; Yamamoto, N.; Isobe, N. *Tetrahedron* **1999**, *55*, 4325−4340.

(8) Nishikawa, T.; Asai, M.; Isobe, M. *J. Am. Chem. Soc.* **2002**, *124*, 7847−7852.

(9) Atanassova, I. A.; Petrov, J. S.; Mollov, N. M. *Synthesis* **1987**, 734−736.

(10) In our recent report for a new deprotection of trichloroacetamide with Cs_2CO_3 at 100 °C in DMF, we proposed that an isocyante produced under the conditions would immediately react with the carbonate to give the corresponding amine. See: Urabe, D.; Sugino, K.; Nishikawa, T.; Isobe, M. *Tetrahedron Lett.* **2004**, *45*, 9405−9407.

(11) For synthesis of the key intermediate, see: Nishikawa, T.; Asai, M.; Ohyabu, N.; Yamamoto, N.; Fukuda, Y.; Isobe, M. *Tetrahedron* **2001**, *57*, 3875−3883.

(12) Dry DMF was purchased as dehydrated DMF from Kanto Chemical Co., Inc.

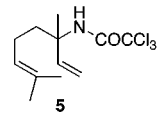
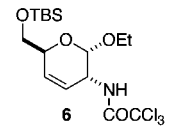
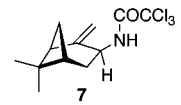
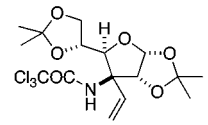
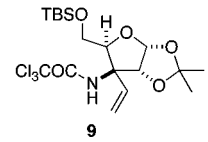
(13) In this specific case, the isocyanate **3** was detected on a silica gel TLC plate.

(14) Excess of benzyl alcohol was indispensable to prevent the formation of urea **4a** as the byproduct.

(15) Duggan, M. E.; Imagire, J. S. *Synthesis* **1989**, 131−132.

(16) (a) For preparation of **5**, **6**, and **7**, see ref 2. (b) For preparation of **8**, see: Tsujimoto, T.; Nishikawa, T.; Urabe, D.; Isobe, M. *Synlett* **2005**, 433−436. (c) For preparation of **9**, see the Supporting Information.

Table 2. Protective Group Transformation of Trichloroacetamides to Benzyl Carbamates

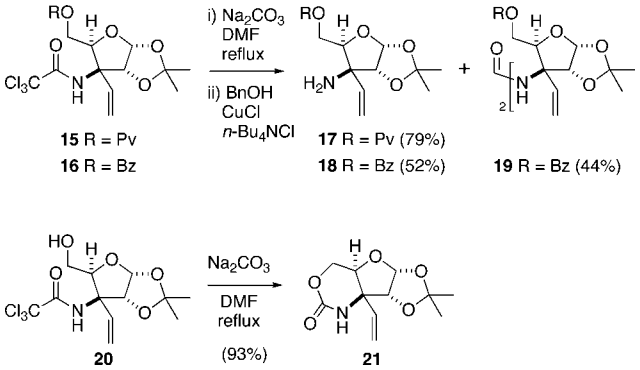
entry	substrate	products: benzyl carbamate	products: urea
1	 **5**	**10** 82%	0%
2 [a]	 **6**	**11** 79%	20%
3	 **7**	**12** 43%	24%
4	 **8**	**13** 77%	0%
5	 **9**	**14** 79%	0%

[a] The reaction was carried out by heating **6** with Na_2CO_3 in the presence of *n*-BuN_4Cl followed by addition of benzyl alcohol at rt.

substrate **9** with a silyl ether derived from **8** was subjected to the same reaction conditions, Cbz-protected amine **14** was obtained in about 80% yield.

In sharp contrast, the corresponding pivaloate **15** exhibited different reactivity (Scheme 2); when **15** was exposed to the same reaction sequence, unprotected amine **17** was exclusively obtained.[17] In the reaction of the benzoate **16**, amine **18** and urea **19** were obtained in 52% and 44% yields, respectively. These amines might be formed through neighboring group participation of the ester groups.[18] Thus, the proximate hydroxyl group of trichloroacetamide should be protected not as an ester but as a silyl ether such as **9**. As

Scheme 2



expected, the reaction of unprotected alcohol **20** gave cyclic carbamate **21** in high yield. These results indicate that acetals and silyl ethers are compatible with the conditions, while neighboring alcohols and esters should be avoided in the transformation.

In summary, we have developed a novel protective group transformation of trichloroacetamide into a variety of carbamates via an isocyanate in one pot. Since the milder deprotection procedures for the resulting carbamates have been established,[19] the present studies should increase the utility of trichloroacetamide and, therefore, the importance of the Overman rearrangement for the synthesis of nitrogen-containing compounds having a variety of functional groups.

Acknowledgment. We thank Professor Y. Ichikawa (Kochi University, Japan) for valuable discussions on the chemistry of isocyanate. Financial support provided by PRESTO of the Japan Science and Technology Agency (JST), a Grant-in-Aid Scientific Research, Specially Promoted Research (16002007) and the 21st century COE grant from MEXT, and the Fujisawa Foundation is gratefully acknowledged. We thank JSPS for a scholarship to D.U. Elemental analyses were performed by Mr. S. Kitamura in this departement, whom we thank.

Supporting Information Available: Preparation of substrates **9**, **15**, **16**, and **20**, experimental procedure for eq 1, typical experimental procedure exemplified for **1** to **2a**, and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The pivaloyl and benzoyl groups did not migrate to the amino group. The structures of these esters were confirmed by HMBC spectra.

(18) In the reaction of **15** and **16**, amines **17** and **18** and urea **19** were detected on silica gel TLC before addition of benzyl alcohol, CuCl, and *n*-Bu_4NCl.

(19) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; pp 503−550. (b) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme Verlag: Stuttgart, 2000; pp 502−542.