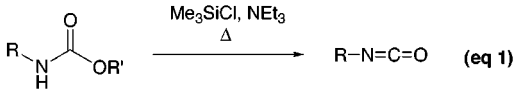
Diiodosilane: A Reagent for Mild, Efficient Conversion of Carbamates to Ureas via Isocyanates

Stéphane Gastaldi,† Steven M. Weinreb,*,‡ and Didier Stien§

LCMO-UMR 6517, Université d'Aix-Marseille III, Avenue Escadrille Normandie-Niemen, 13397 Marseille, Cedex 20, France, Department of Chemistry, The Pennsylvania State University, University Park, Pennsylania 16802, and LAPP-UMR 5810, Université de Montpellier II, Place E. Bataillon, 34095 Montpellier, Cedex 5, France

Received December 28, 1999

About 30 years ago, Greber and Kricheldorf found that trimethylchlorosilane promotes the conversion of carbamates into isocyanates (eq 1).[1] Subsequent work by Pirkle and co-workers demonstrated that highly chlorinated silanes are even more effective at inducing this transformation.[2] In addition, some reagents other than



silanes have been shown to effect the reaction.[3] Recently, Petillo et al. have reported a nice systematic study of the reaction of carbamates with various chlorosilanes.[4] It was found that in general the silane reactivity increases in the order $Me_3SiCl < Me_2SiCl_2 < MeSiCl_3 < HSiCl_3$. In addition, as the carbamate alkoxyl group becomes bulkier, the reaction slows down, and with *N*-Boc carbamates, isocyanate production is quite sluggish. In the cases involving *O*-alkyl carbamates the reactions normally need to be conducted between room temperature and 70 °C. It is believed that the transformation probably involves an initial *N*-silylated carbamate **1**, which presumably collapses via **2** to the isocyanate **3** and a stable alkoxysilane **4**, thereby preventing readdition of the alcohol to **3** (Scheme 1).

In the course of a project in alkaloid total synthesis, we were interested in converting an *N*-Boc carbamate to a urea via an isocyanate, but due to the lability of our substrate were concerned that the usual thermal conditions required for the chlorosilane-induced reaction would lead to extensive decomposition. We therefore prospected for alternative reagents which might allow isocyanate formation under milder reaction conditions, particularly from *N*-Boc systems. We now wish to report that commercially available diiodosilane is a particularly useful reagent for this transformation.[5]

Scheme 1

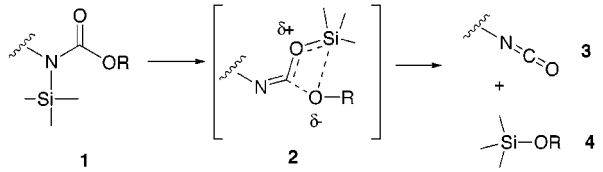
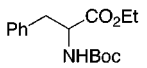
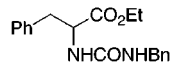
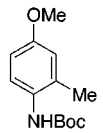
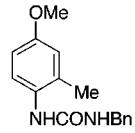
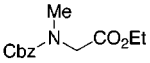


Table 1. Conversion of Carbamates to Ureas via Isocyanates formed with SiI_2H_2

entry	carbamate[a]	urea	isolated yield (%)
1a	CyNHBoc	R, R' = Bn, H	84
1b		R, R' = Bn, allyl	76
1c		R, R' = *i*-Pr	57
1d		R, R' = Ph, H	68
2	CyNHCbz	CyNHCONHBn	94
3	$CyNHCO_2Me$	CyNHCONHBn	89
4	$CyNHCO_2Ph$	CyNHCONHBn	87
5			78
6	$Ph(CH_2)_2NHBoc$	$Ph(CH_2)_2NHCONHBn$	91
7			74
8	PhNHBoc	PhNHCONHBn	83
9			78
10		recovered SM (91%)	

[a] Cy = cyclohexyl.

Thus, treatment of a carbamate with 1.2 equiv of Hünig's base and 1.2 equiv of diiodosilane for 30 min from −30 to −5 °C in methylene chloride led to complete disappearance of the starting material as determined by TLC analysis. Formation of an isocyanate was established in the case of *N*-*tert*-butoxycarbonyl-4-methoxy-2-methylaniline (entry 9) by the observation of the characteristic isocyanate IR absorption at 2289 cm^{-1} (KBr pellet) in the crude product before the addition of benzylamine. However, in general the isocyanates were not isolated, but could be trapped in situ with amines affording ureas in good to excellent yields, depending on the nature of the starting carbamate as well as the amine used.[6] The generality of the method has been assessed using a variety of aliphatic and aromatic carbamates,

† Université d'Aix-Marseille III.
‡ The Pennsylvania State University.
§ Université de Montpellier II.

(1) Greber, G.; Kricheldorf, H. R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 941.

(2) (a) Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **1974**, *39*, 3904. (b) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2781. (c) Mironov, V. F.; Kozyukov, V. P.; Orlov, G. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1981**, *51*, 1555.

(3) (a) Bal'on, Y. G. *J. Org. Chem. USSR (Engl. Transl.)* **1980**, *16*, 2233. (b) Valli, V. L. K.; Alper, H. *J. Org. Chem.* **1995**, *60*, 257. (c) Butler, D. C. D.; Alper, H. *J. Chem. Soc., Chem. Commun.* **1998**, 2575.

(4) Chong, P. Y.; Janicki, S. Z.; Petillo, P. A. *J. Org. Chem.* **1998**, *63*, 8515 and references cited.

(5) For other synthetic uses of this silane, see: *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, U.K., 1995; Vol. 3, p 1905.

(6) For a review on synthesis of ureas, see: Petersen, U. *Methoden Org. Chem. (Houben-Weyl)* **1983**, *E4*, 334.

10.1021/jo9919714 CCC: $19.00
Published on Web 04/12/2000

some bearing other functional groups potentially reactive toward electrophiles (Table 1). As can be seen, the reaction proceeds rapidly with all types of carbamates, including *N*-Boc derivatives. The ethyl ester functionality in the example in entry 7 proved compatible with the reagent. Carbamates of secondary amines are not affected under the reaction conditions (entry 10).

A tertiary alkylamine base is required to effect the desired transformation. When pyridine is used, the reaction simply affords the parent amine from the carbamate instead of the isocyanate.[7] Since in exploratory runs with the model carbamate *N*-Boc-cyclohexylamine slightly better yields of urea were produced with Hünig's base compared to triethylamine, which is the common base in the chlorosilane reactions, the former base was generally used in our work.

In conclusion, isocyanates are formed under very mild low temperature reaction conditions from a wide variety of carbamates by treatment with commercially available SiI_2H_2 and Hünig's base. In situ trapping of the isocyanate with primary or secondary amines efficiently leads to ureas.

Experimental Section

General Experimental Procedure. Diiodosilane (0.6 mmol, Aldrich) was added to a −30 °C solution of the carbamate (0.5 mmol) and DIPEA (0.6 mmol) in 3 mL of dichloromethane. The reaction temperature was then slowly elevated to −5 °C (30 min). The solution was recooled to −50 °C, and the amine was added (2.5 mmol). The mixture was then allowed to warm to room temperature. The solution was diluted with AcOEt, washed with 1 N HCl solution and brine, and dried over Na_2SO_4. The crude product was purified by flash chromatography. All compounds in Table 1 are known except for those listed below.

1-Allyl-1-benzyl-3-cyclohexylurea (entry 1b): ^{1}H NMR ($CDCl_3$) δ 0.80−1.90 (m, 10H), 3.58 (m, 1H), 3.77 (d, 2H, J = 5.3 Hz), 4.22 (d, 1H, J = 7.3 Hz), 4.40 (s, 2H), 5.12 (m, 2H), 5.71 (m, 1H), 7.20 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.8, 25.6, 33.7, 49.3, 49.6, 50.2, 116.8, 127.3, 127.4, 128.7, 134.1, 138.2, 157.7.

1-Benzyl-3-cyclopropylurea (entry 5): ^{1}H NMR ($CDCl_3$) δ 0.65 (m, 2H), 0.73 (m, 2H), 2.42 (m, 1H), 4.42 (d, 2H, J = 5.9 Hz), 5.00 (bs, 1H), 5.40 (bs, 1H), 7.25 (m, 5H);^{13}C NMR ($CDCl_3$) δ 7.5, 22.4, 44.2, 127.3, 127.4, 130.9, 139.4, 159.1.

2-(3-Benzylureido)-3-phenylalanine ethyl ester (entry 7): ^{1}H NMR ($CDCl_3$) δ 1.11 (t, 3H, J = 7.0 Hz), 2.99 (m, 2H), 4.02 (q, 2H, J = 7.0 Hz), 4.27 (AB of ABX, 2H, J_{AB} = 15.2 Hz), 4.75 (q, 1H, J = 6.0 Hz), 5.30 (m, 2H), 7.05 (m, 2H), 7.22 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 14.1, 38.7, 44.3, 54.0, 61.3, 126.9, 127.2, 127.4, 128.4, 128.5, 129.4, 136.3, 139.1, 157.4, 173.1.

1-Benzyl-3-(4-methoxy-2-methylphenyl)urea (entry 9): ^{1}H NMR (DMSO-d_6) δ 2.11 (s, 3H), 3.39 (d, 1H, J = 5.1 Hz), 3.69 (s, 3H), 4.28 (d, 2H, J = 5.1 Hz), 6.71 (m, 3H), 7.29 (m, 4H), 7.55 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 18.0, 42.9, 55.1, 111.1, 115.3, 123.7, 126.7, 127.1, 128.9, 130.5, 130.9, 140.5, 155.0, 155.9.

Acknowledgment. We are grateful to the National Science Foundation (CHE-97-32038) for financial support of this research. We also thank the Ministry of Foreign Affairs (France) for a Lavoisier Postdoctoral Fellowship to D.S.

Supporting Information Available: Copies of proton and carbon NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9919714

(7) It should be noted that iodotrimethylsilane cleaves Boc carbamates to amines: Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun*. **1978**, 315. Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun*. **1979**, 495. Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett*. **1985**, *26*, 5543.