One-Pot Conversion of Trimethylsilyl Ethers into Urethanes Using Chlorosulfonyl Isocyanate: Application to the Synthesis of a Novel Neuromodulator Carisbamate

Guang Ri Dong, Qing Ri Li, Seol Hee Woo, In Su Kim, and Young Hoon Jung
College of Pharmacy, Sungkyunkwan University, Suwon 440-746, Korea

(Received October 21, 2008/Accepted November 7, 2008)

This paper reports a novel synthetic method for the preparation of various urethanes and the application to the synthesis of carisbamate. The reaction of primary (2a, 2e and 2f) or secondary (2g-2i) trimethylsilyl ethers with chlorosulfonyl isocyanate afforded the corresponding urethanes in good yields without affecting the olefin moiety. However, in the case of secondary benzylic trimethylsilyl ether 2j, the corresponding urethane 3j was obtained in low yield. From the difference in reactivity between the primary and secondary benzylic trimethylsilyl ethers, the one-pot synthesis of carisbamate 1 from bis-trimethylsilyl ether 2l was achieved.

Key words: Chlorosulfonyl isocyanate, Urethane, Carisbamate, Carbamate, Trimethylsilyl ether, One-pot synthesis

INTRODUCTION

Urethanes (carbamates) are a useful and interesting class of compounds due to their widespread use in industry, such as insecticides (Thompson, 2002; Baron, 1994) and polymers (Feldman and Barbalata, 1996). Moreover, these compounds have received considerable attention as potential medical agents on account of their interesting pharmacological properties (Finkel et al., 2004; Bar-On et al., 2002; Thal et al., 1983). Consequently, the development of a new synthetic method for urethanes has been the subject of intensive research in synthetic and industrial fields. Accordingly, a number of synthetic methods have been reported for the preparation of urethanes. For a typical example, phosgene is commonly used in the synthesis of urethanes. However, this reagent has many limitations such as its high toxicity and flammability (Dibenedetto et al., 2002). Alternative conventional methods have been attempted to overcome this disadvantage, such as, the use of carbon dioxide, trichloroacetyl isocyanate (Ichikawa et al., 1997), Chloroformates (Raucher and Jones, 1985), sodium cyanate/trichloroacetic acid (Modarresi-Alam et al., 2006), and cyanogen chloride (Fuks and Hartemink, 1973).

Carisbamate (1: Fig. 1) is a novel neuromodulator with a broad range of anticonvulsant activity (ED₅₀ 5-60 mg/kg) in rodent seizure models that is under development by Johnson & Johnson Pharmaceutical Research and Development, for the treatment of epilepsy (Deshpande et al., 2008; Rogawski, 2006; Novak et al., 2007; Mannens et al., 2007). Despite its relatively simple structure, there are few synthetic approaches for the target compound reported in the literature. For an example, Choi et al. demonstrated the synthesis of enantiomeric carisbamate analogs through the addition of liquid ammonia to a carbonate intermediate. However, this method is not particularly amenable to practical production due to the excess waste of the regioisomer and the moderate overall yield (45-52%) (Choi et al., 1998). Recently, Otten et al. developed a novel process to avoid the separation steps and concomitant loss of undesired regioisomer. However, the lack of efficiency, such as multi-step synthesis (4 steps) preclude large scale production (Rey et al., 2003).

Recently, we have reported the stereoselective amination of a variety of allylic ethers using chlorosulfonyl isocyanate (CSI) (Kim et al., 2003) and its application to the synthesis of polyhydroxylated alkaloids (Kim et al.,
As a part of an ongoing research program aimed at the development of new methodologies using CSI and their application to the synthesis of biologically active compounds, we became interested in developing an efficient synthetic route to carisbamate (1). Here, we report the chemo-selective introduction of a carbamate moiety into trimethylsilyl ethers and the one-pot preparation of compound 1 from a bis-trimethylsilyl ether compound using CSI.

**MATERIALS AND METHODS**

Commercially available reagents were used without additional purification, unless otherwise stated. All anhydrous solvents were distilled over CaH₂ or P₂O₅ or Na/benzophenone prior to reaction. All reactions were performed under an inert atmosphere of nitrogen or argon. Melting points were measured on a Gallenkamp melting point apparatus or Electrothermal IA9300 melting point apparatus and were not corrected. Nuclear magnetic resonance spectra (¹H- and ¹³C-NMR) were recorded on a Varian Unity Inova 500 and 300 MHz spectrometer for CDCl₃ solutions and chemical shifts are reported as parts per million (ppm) relative to, respectively, residual CHCl₃ δ⁻⁷.26 ppm and CDCl₃ δ⁻⁷.7 ppm as internal standards. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (J) are reported in hertz (Hz). IR spectra were recorded on a Nicolet 205 Infrared spectrophotometer or Bruker Vector 22 Infrared spectrophotometer and are reported as cm⁻¹. Optical rotations were measured with a Jasco P1020 polarimeter. Thin layer chromatography was carried out using plates coated with Kieselgel 60F₂₅₄ (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. High-resolution mass spectra (HRMS) were recorded on a JEOL, JMS-505, or JMS-600 spectrometer.

**General procedure for the preparation of trimethylsilyl ethers (2a and 2e-2j)**

To a stirred solution of alcohols (1.00 mmol) in anhydrous CH₂Cl₂ (2 mL) was added Et₃N (3.00 mmol) and TMSCI (1.50 mmol) at 0°C under N₂. The reaction mixture was allowed to stir at 0°C until complete consumption of starting material was observed, at which point the reaction mixture was quenched with H₂O (2 mL). The aqueous layer was extracted with CH₂Cl₂ (10 mL) and the organic layer was washed with H₂O and brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc) to afford corresponding products 2a and 2e-2j.

**Materials and Methods**

1. **Phenethoxy trimethylsilane (2a)**
   - ¹H NMR (500 MHz, CDCl₃) δ 0.79 (s, 3H), 2.86 (t, J = 7.5 Hz, 2H), 3.80 (t, J = 7.5 Hz, 2H), 7.21-7.32 (m, 5H);
   - ¹³C NMR (125 MHz, CDCl₃) δ -0.31, 39.76, 77.0 ppm.

2. **Cyclohexylmethoxy trimethylsilane (2e)**
   - ¹H NMR (300 MHz, CDCl₃) δ 0.13 (s, 3H), 0.84-0.97 (m, 2H), 1.64-1.81 (m, 9H), 3.39 (d, J = 6.6 Hz, 2H);
   - ¹³C NMR (125 MHz, CDCl₃) δ 2.15, 26.07, 26.83, 29.80, 40.74 ppm.

3. **Benzyloxy trimethylsilane (2f)**
   - ¹H NMR (300 MHz, CDCl₃) δ 0.17 (s, 3H), 4.72 (s, 2H), 7.34-7.36 (m, 5H);
   - ¹³C NMR (125 MHz, CDCl₃) δ -0.11, 64.92, 126.80, 127.35, 128.54, 141.26.

4. **1-Phenylpropan-2-yloxy trimethylsilane (2g)**
   - ¹H NMR (300 MHz, CDCl₃) δ 0.02 (s, 3H), 1.22 (d, J = 6.0 Hz, 3H), 2.67-2.84 (m, 2H), 3.97-4.02 (m, 1H), 7.21-7.35 (m, 5H);
   - ¹³C NMR (125 MHz, CDCl₃) δ 0.11, 23.94, 46.55, 71.27, 126.27, 128.32, 129.88, 139.72.

5. **(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyloxy trimethylsilane (2h)**
   - ¹H NMR (300 MHz, CDCl₃) δ 0.16 (s, 3H), 0.77 (d, J = 7.2 Hz, 3H), 0.84-1.22 (m, 10H), 1.37-1.45 (m, 1H), 1.37-1.71 (m, 2H), 1.45-1.93 (m, 1H), 2.16-2.22 (m, 1H), 3.43 (dt, J = 10.5, 4.5 Hz, 1H);
   - ¹³C NMR (125 MHz, CDCl₃) δ 0.75, 16.16, 21.42, 22.48, 23.22, 25.46, 31.92, 34.80, 45.72, 50.29, 72.68.

6. **((3S,10R,13R,17R)-10,13-Dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradehydro-1H-cyclopenta[a]phenanthren-3-yl)oxy) trimethylsilane (2i)**
   - mp 115-117°C; ¹H NMR (300 MHz, CDCl₃) δ 0.16 (s, 3H), 0.72 (s, 3H), 0.90-2.34 (m, 40H), 3.49-3.57 (m, 1H), 5.36-5.39 (m, 1H);
   - ¹³C NMR (125 MHz, CDCl₃) δ 0.99, 12.09, 18.97, 19.61, 21.31, 22.80, 23.04, 24.08, 24.54, 28.25, 28.47, 32.17, 32.19, 32.24, 36.02, 36.46, 36.82, 37.66, 39.78, 40.07, 42.58, 42.95, 50.50, 56.43, 57.06, 72.62, 121.55, 141.66.
1-Phenylpropan-2-yl carbamate (3j)  
1H NMR (300 MHz, CDCl₃) δ 1.07 (s, 3H), 0.93 (t, J = 7.2 Hz, 3H), 1.70-1.78 (m, 2H), 4.59 (t, J = 7.2 Hz, 1H), 7.25-7.37 (m, 5H); 13C NMR (125 MHz, CDCl₃) δ -0.38, 10.55, 33.77, 76.64, 126.20, 127.13, 128.29, 145.73.

General procedure for the preparation of urethanes (3a and 3e-3j)  
To a stirred solution of 2a or 2e-2j (0.50 mmol) in anhydrous toluene (2.5 mL) was added CSI (0.75 mmol) at 0°C under N₂. The reaction mixture was allowed to stir at 0°C until complete consumption of starting material was observed, at which point the reaction mixture was quenched with H₂O (2 mL). The aqueous layer was acidified with 6 N HCl (pH 2-3) and extracted with EtOAc (10 mL×2). The aqueous layer was observed, at which point the reaction mixture was extracted with EtOAc (10 mL×2). The organic layer was washed with H₂O and brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc) to afford corresponding products 3a or 3e-3j.

Phenethyl carbamate (3a)  
mp 91-93°C; IR (CHCl₃) ν 3419, 3334, 3272, 2965, 1686, 1608, 1498, 1475, 1455, 1411, 1340, 1122, 1079, 1047, 784, 752, 702 cm⁻¹; 1H NMR (300 MHz, CDCl₃) δ 1.27 (d, J = 6.3 Hz, 3H), 2.81 (dd, J = 13.8, 6.6 Hz, 1H), 2.99 (dd, J = 13.8, 6.3 Hz, 1H), 4.65 (br, 2H), 5.07 (dt, J = 6.6, 6.3 Hz, 1H), 7.24-7.37 (m, 5H); 13C NMR (125 MHz, CDCl₃) δ 19.80, 42.57, 72.41, 126.66, 128.55, 129.70, 137.84, 157.03; HRMS (FAB) Calcd for C₁₀H₁₄NO₂ [M+H⁺] 180.1025, found 180.1025.

Cyclohexylmethyl carbamate (3e)  
mp 95-97°C; IR (CHCl₃) ν 3435, 3260, 2929, 2855, 1686, 1616, 1460, 1419, 1356, 1067, 756 cm⁻¹; 1H NMR (300 MHz, CDCl₃) δ 0.94-1.06 (m, 2H), 1.16-1.35 (m, 4H), 1.62-1.79 (m, 5H), 3.90 (d, J = 7.2 Hz, 2H), 4.62 (br, 2H); 13C NMR (125 MHz, CDCl₃) δ 25.88, 26.61, 29.81, 97.57, 70.58, 157.53; HRMS (FAB) Calcd for C₇H₁₄NO₂ [M+H⁺] 158.1181, found 158.1183.

Benzyl carbamate (3f)  
mp 87-89°C; IR (CHCl₃) ν 3416, 3333, 3273, 2360, 1689, 1608, 1446, 1403, 1343, 1121, 1072, 910, 733, 697 cm⁻¹; 1H NMR (300 MHz, CDCl₃) δ 4.90 (br, 2H), 5.15 (s, 2H), 7.30-7.43 (m, 5H); 13C NMR (125 MHz, CDCl₃) δ 67.18, 128.36, 128.47, 128.80, 136.47, 157.02; HRMS (FAB) Calcd for C₈H₁₄NO₂ [M+H⁺] 152.0712, found 152.0714.

1-Phenylpropan-2-yl carbamate (3g)  
mp 63-66°C; IR (CHCl₃) ν 3484, 3348, 3063, 3029, 2979, 2933, 1710, 1600, 1497, 1454, 1379, 1325, 1217, 1131, 1068, 1028, 906, 783 cm⁻¹; 1H NMR (300 MHz, CDCl₃) δ 1.27 (d, J = 6.3 Hz, 3H), 2.81 (dd, J = 13.8, 6.6 Hz, 1H), 2.99 (dd, J = 13.8, 6.3 Hz, 1H), 4.65 (br, 2H), 5.07 (dt, J = 6.6, 6.3 Hz, 1H), 7.24-7.37 (m, 5H); 13C NMR (125 MHz, CDCl₃) δ 19.80, 42.57, 72.41, 126.66, 128.55, 129.70, 137.84, 156.77; HRMS (CI) Calcd for C₁₀H₁₄NO₂ [M+H⁺] 180.1024, found 180.1025.

(S)-4-(2-Chlorophenyl)-2,2,7,7-tetramethyl-3,6-dioxo-2,7-disilaoctane (2l)  
To a stirred solution of (S)-(+-)-1-(2-chlorophenyl)-1,2-ethanediol (0.2 g, 1.159 mmol) in anhydrous CH₂Cl₂ (5.8 mL) was added Et₃N (0.97 mL, 6.954 mmol) and TMSCl (0.44 mL, 3.477 mmol) at 0°C under N₂. The reaction mixture was stirred for 4 h at 0°C and quenched with H₂O (5 mL). The aqueous layer was extracted with CH₂Cl₂ (20 mL) and the organic layer was washed with H₂O and brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc) to afford corresponding products 3a or 3e-3j.
to afford 0.35 g (95%) of \(2l\) as colorless oil.

\[ \text{H NMR (300 MHz, CDCl}_3 \text{)} \delta 0.76 (s, 3H), 0.79 (s, 3H), 3.51 (dd, \text{J} = 10.8, 7.5 Hz, 1H), 3.70 (dd, \text{J} = 10.8, 3.3 Hz, 1H), 5.14 (dd, \text{J} = 7.5, 3.3 Hz, 1H), 7.15-7.32 (m, 3H), 7.56-7.60 (m, 1H); \text{C NMR (125 MHz, CDCl}_3 \text{)} \delta 0.19, 67.11, 72.30, 127.06, 128.54, 128.94, 129.45, 131.80, 138.88. \]

**General procedure for the preparation of 3k and 1**

To a stirred solution of \(2k\) or \(2l\) (0.10 mmol) in anhydrous toluene (0.5 mL) was added CSI (0.30 mmol) at 0°C under \(\text{N}_2\). The reaction mixture was allowed to stir at 0°C until complete consumption of starting material was observed, at which point the reaction mixture was quenched with \(\text{H}_2\text{O}\) (0.5 mL). The aqueous layer was extracted with EtOAc (5 mL×2). The aqueous layer was acidified with 6 N HCl (pH 2-3) and extracted with EtOAc (5 mL×2). The organic layer was washed with \(\text{H}_2\text{O}\) and \(\text{brine}\), dried over \(\text{MgSO}_4\) and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc) to afford corresponding products \(3k\) or \(1\).

\((S)-1-(2\text{-Chlorophenyl})\text{ethane-1,2-diyl dicarbamate (3k)} [\alpha]_D^{29} +50.7 (c 0.4, \text{MeOH}); \text{mp} 132-136°C; \text{IR} (\text{CH}_2\text{Cl}_2) \nu 3416, 3295, 3214, 2956, 2361, 1898, 1636, 1464, 1416, 1349, 1315, 1126, 1096, 1060, 1035, 945, 903, 816, 786, 754, 726 cm\(^{-1}\); \text{H NMR (300 MHz, DMSO-d}_6\text{)} \delta 3.54 (s, 2H), 4.14 (d, \text{J} = 5.4 Hz, 2H), 6.04 (t, \text{J} = 12.0, 2.7 Hz, 1H), 6.59 (br, 2H), 7.35-7.51 (m, 4H); \text{C NMR (125 MHz, DMSO-d}_6\text{)} \delta 64.69, 70.75, 128.17, 128.35, 130.07, 130.34, 132.00, 136.42, 136.51, 156.21, 156.82; \text{HRMS (CI)} \text{Calcd for C}_{10}\text{H}_{13}\text{N}_2\text{O}_4 \text{[M+H]+} 259.0485, \text{found} 259.0487.

\text{Carisbamate (1)} [\alpha]_D^{29} +81.7 (c 0.2, \text{CHCl}_3); \text{mp} 127-131°C; \text{IR} (\text{CH}_2\text{Cl}_2) \nu 3461, 3333, 3265, 2947, 1973, 1703, 1469, 1403, 1378, 1334, 1133, 1057, 923, 785, 756 cm\(^{-1}\); \text{H NMR (300 MHz, CDCl}_3 \text{)} \delta 1.72 (br, 1H), 4.26 (dd, \text{J} = 12.0, 7.8 Hz, 1H), 4.39 (dd, \text{J} = 12.0, 2.7 Hz, 1H), 4.77 (br, 2H), 4.41 (dd, \text{J} = 7.8, 2.7 Hz, 1H), 7.26-7.42 (m, 3H), 7.68 (dd, \text{J} = 7.5, 1.8 Hz, 1H); \text{C NMR (125 MHz, CDCl}_3 \text{)} \delta 69.05, 70.21, 127.36, 128.09, 129.37, 129.68, 132.21, 137.51, 157.53; \text{HRMS (CI)} \text{Calcd for C}_{9}\text{H}_{11}\text{NO}_3\text{Cl [M+H]+} 216.0427, \text{found} 216.0426.

**RESULTS AND DISCUSSION**

The initial experiments focused on the reaction of various silyl ethers \(2b-2d\) using CSI to give compound \(3a\) (Table I). As shown in entry 1, the reaction of CSI with alcohols is widely used for the preparation of carbamates. Next, the reaction of trimethylsilyl ether \(2b\) with CSI afforded the desired urethane \(3a\) in high yield (entry 2). TBDMS-ether \(2c\) was far less effective than TMS-ether under these reaction conditions (entry 3). The use of TBDPS-ether \(2d\) in this reaction gave only trace quantities of the urethane product \(3a\) (entry 4).

These results suggest that stable silylcation can be obtained during the reaction process (Lambert et al., 1994). In addition, steric hindrance of the alkyl moiety of silyl groups prevents the approach of CSI to the oxygen atom in the silyl ethers. Scheme 1 gives a plausible

![Scheme 1. Plausible reaction mechanism for the reaction of silyl ethers with CSI](image-url)
reaction mechanism. The stable silylcation formed by cleavage of the O-Si bond is trapped by a nitrogen anion to provide N-silyl carbamates, which can be converted into the desired urethane 3a by acidic work-up.

Next, the reactivity of aliphatic, allylic and benzylic silyl ethers was evaluated under the optimum reaction conditions cited in Table I. Our results are summarized in Table II. As shown in entry 1-3, the primary aliphatic TMS ethers (2a and 2e) and benzylic TMS ethers 2f were converted into the corresponding urethanes 3a, 3e, and 3f in high yields. The reaction of simple secondary TMS ethers (2g and 2h) under identical conditions provided the products in high yields. Moreover, secondary TMS ethers 2i with an olefin moiety afforded the desired product 3i in 80% yield. However, the product 3j was obtained in very low yield (11%) when benzylic secondary TMS ether 2j was used. These results suggest that the reaction outcome is controlled by the steric bulkiness of the substituents around the TMS ether.

Selective introduction of the carbamate moiety was attempted with the diol 2k under identical reaction conditions but only bis-carbamate 3k was isolated, as shown in Scheme 2. However, the results of 2a and 2j in Table II suggested that the regioselective synthesis of carisbamate (1) would be possible through the one-pot introduction of the carbamate moiety into the primary trimethylsilyl ether of compound 2l. As expected, the primary silyl ether moiety of compound 2l was converted selectively into the urethane moiety to give carisbamate (1) in 72% isolated yield.

In summary, the conversion of various TMS ethers to urethanes in the presence of chlorosulfonyl isocyanate was achieved in high yield. In addition, the one-pot preparation of antiepileptic carisbamate via a regioselective CSI reaction of the primary silyl ether moiety was described. A further examination of the scope of this reaction is underway and the results will be reported elsewhere.

ACKNOWLEDGMENTS

This research was supported by the Korean Research Foundation Grant funded by the Korean Government (MOEHRD) (KRF-2006-311-E00613) and the Brain Korea 21 Program.

REFERENCES


Deshpande, L. S., Nagarkatti, N., Sombati, S., and DeLorenzo, R. J., The novel antiepileptic drug carisbamate (RWJ333369) is effective in inhibiting spontaneous recurrent seizure discharges and blocking sustained repetitive firing in...


Thompson, A., Pest control on field vegetables threatened by the loss of organo-phosphorus (OP) and carbamate insecticides. *Pesticide Outlook*, 2, 84-86 (2002).