Synthetic Communications®, 35: 2091–2098, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1081/SCC-200066695

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Preparation of Methyl *N*-Substituted Carbamates from Amides through *N*-Chloroamides

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Abstract: Amides are chlorinated on the nitrogen using trichloroisocyanuric acid, and the *N*-chloroamides are then rearranged to the corresponding methyl *N*-substituted carbamates by sodium methoxide in methanol.

Keywords: Amides, *N*-chloroamides, methyl *N*-substituted carbamates, preparation, rearrangement, synthesis, trichloroisocyanuric acid

N-Chloramides are easily prepared from amides using trichloroisocyanuric acid [TCICA; 1,3,5-trichloro-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione; $C_3Cl_3N_3O_3$], a stable solid.[1] Treatment of *N*-chloroamides with aqueous hydroxide gives amines with one less carbon in a reaction known as the Hofmann degradation.[2] An intermediate in this reaction is the isocyanate, and that reacts with hydroxide followed by decarboxylation to give the corresponding amine (Scheme 1). We report that treatment of *N*-chloroamides with sodium methoxide in methanol gives the corresponding methyl *N*-substituted carbamates (Scheme 2). Although similar reactions have been reported using *N*-bromoamides,[3] a search of the chemical literature did not turn up previous examples using *N*-chloroamides. The results are summarized in Table 1. Carbamates can be hydrolyzed to the corresponding amines, reduced to *N*-methylamines with lithium aluminum hydride,[4] converted

Received in the USA March 28, 2005
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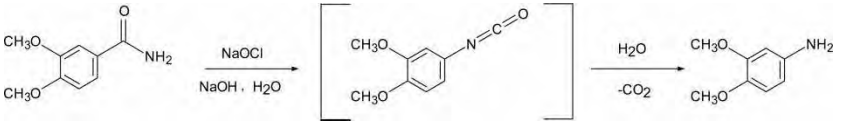


Scheme 1.

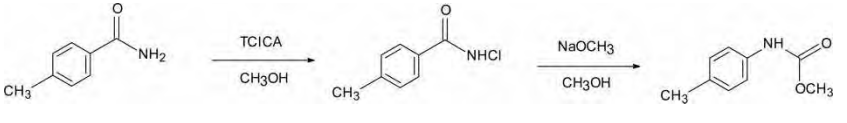
into the corresponding isocyanates with chlorocatecholborane and triethylamine,[5] and converted to dimethyl acetals by anodic methoxylation.[6]

All carbamates were characterized by their FT-IR and ^{1}H NMR spectra and by comparison with carbamate standards through FT-IR and ^{1}H NMR spectra and by mixture melting points when appropriate. Carbamate standards were prepared from the amines by reaction with dimethyl carbonate and sodium methoxide in methanol (Scheme 3).[7] The data for carbamates prepared from the amines are shown in Table 2.

EXPERIMENTAL

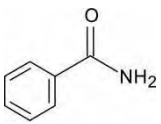
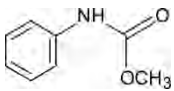
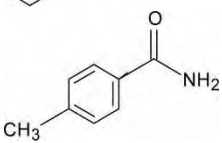
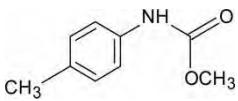
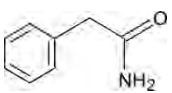
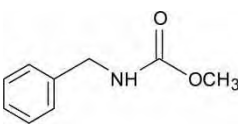
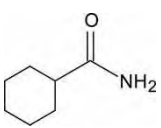
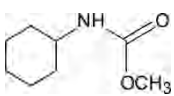
All reagents were used as received unless otherwise stated. Reagent-grade acetone, anhydrous methanol, anhydrous acetonitrile, *p*-toluamide, cyclohexanecarboxamide, dimethyl carbonate, benzylamine, and cyclohexylamine were obtained from Aldrich Chemical Co. Hexanamide, octanamide, decanamide, propylamine, pentylamine, heptylamine, nonylamine, and 2-phenylacetamide were obtained from TCI Chemical Co. Anhydrous diethyl ether and reagent-grade dichloromethane were obtained from EM Science. Benzamide (practical) was obtained from Acros Chemical Co. and was recrystallized from benzene (mp 125.0–125.8°C). *p*-Toluidine was obtained from Avocado Chemical Co. Butanamide (practical) was obtained from Eastman Chemical Co. and was recrystallized from benzene (mp 112.0–112.8°C). Aniline was obtained from Spectrum Chemical Co. Trichloroisocyanuric acid (99%) was obtained from Chem Lab Products.

^{1}H FT-NMR spectra were recorded in $CDCl_3$ using an Anasazi-modified Varian EFT 90 MHz spectrometer. FT-IR spectra were recorded using a Perkin Elmer 1650 spectrometer. GC analyses were carried out with a Hewlett-Packard 5890 Series II instrument on a 6 ft × 1/8 in 10% Carbowax 20M column. Melting points were taken using a Thomas Hoover Uni-Melt capillary melting-point apparatus and are uncorrected.



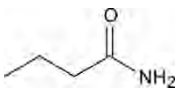
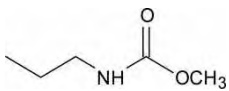
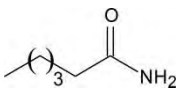
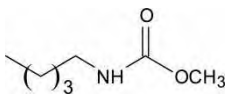
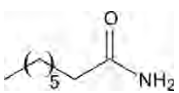
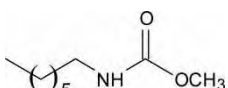
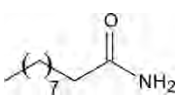
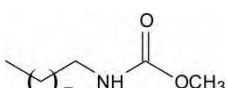
Scheme 2.

Table 1. Preparation of methyl *N*-substituted carbamates from amides

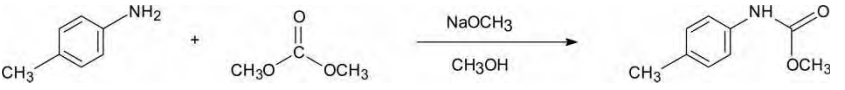
Amide	Carbamate	Yield	Mp[a]/bp (press)	Mixture mp[b]/ GC purity
		85%	46.0–46.8°C	45.0–45.5°C
		85%	97.5–98.2°C	97.2–97.8°C
		92%	63.9–64.5°C	64.3–65.0°C
		94%	74.0–74.6°C	74.0–74.6°C

(*continued*)

Table 1. Continued

Amide	Carbamate	Yield	Mp[a]/bp (press)	Mixture mp[b]/ GC purity
		98%[c] 68%[d]	137.5°C (6.5 torr)	97.7%
		95%[c] 89%[d]	178.5°C (15.6 torr)	99.6%
		103%[c] 90%[d]	205.1°C (6.7 torr)	99.6%
		84%[c] 92%[d]	195.0°C (1.82 torr)	95.9%

[a]Melting points are uncorrected.
[b]Mixture mp with carbamate standards.
[c]Crude yield.
[d]Percent recovery of distilled carbamate (Hickman apparatus).

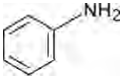
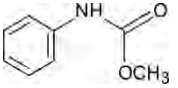
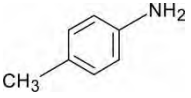
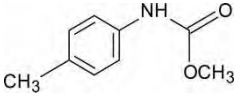
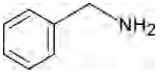
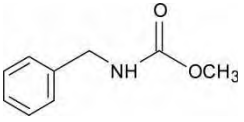
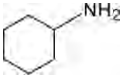
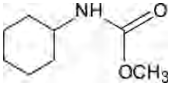
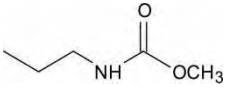
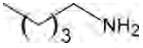
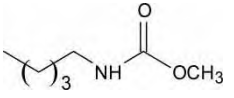
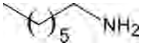
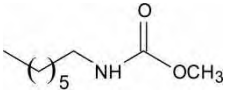
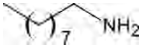
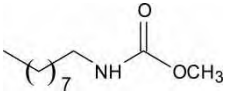


Scheme 3.

Conversion of *p*-toluamide to methyl *N*-*p*-tolylcarbamate: In a 250-mL, round-bottom flask were placed 50 mL of methanol and 9.187 g (67.96 mmol) of *p*-toluamide. The mixture was allowed to stir until the solid dissolved. TCICA, 5.791 g (24.92 mmol, 74.76 meq), was added and a precipitate of cyanuric acid formed in 4 min. After stirring for 1 h, the mixture was vacuum filtered and the solid was washed with methanol. The filtrate was transferred to a dry, 250-mL, round-bottom flask, and the solvent was removed using a rotary evaporator to give 11.811 g (102.5%) of crude solid *N*-chloroamide product. A magnetic stir bar and 10 mL of methanol were added to the crude product, and the flask was fitted with a Claisen adapter containing condenser and a 50-mL addition funnel. A nitrogen line was attached to the addition funnel and the system was flushed with nitrogen. The apparatus was placed in an ice-water bath, then 55 mL (137.5 mmol) of 2.5 N sodium methoxide in methanol was added through the addition funnel at a rate of 5 mL every 5 min while stirring. The addition funnel was rinsed into the flask with 10 mL of methanol, and stirring was continued for 20 h at room temperature. The reaction mixture was concentrated using a rotary evaporator and then 100 mL of ether and 50 mL of water were added. After shaking and separation, the aqueous layer was extracted further with ether (3×50 mL). The combined ether solution was washed with saturated NaCl solution (50 mL) and dried over $MgSO_4$. After filtration and evaporation, the crude product was recrystallized from cyclohexane to give 9.573 g (85.3%) of methyl *N*-*p*-tolylcarbamate: mp 97.5–98.2°C; mmp 97.2–97.8°C; FT-IR (mull) 3322 (m, NH), 1700 (s, C═O), 1600 (m), 1540 (m), 1512 (m), 1317 (m), 1236 (s, C–O), 1073 (m), 816 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (m, 2H, ArH), 7.06 (m, 2H, ArH), 6.71 (s, br, 1H, NH), 3.75 (s, 3H, OCH_3), 2.29 (s, 3H, CH_3).

Preparation of methyl *N*-*p*-tolylcarbamate from *p*-toluidine: In a 15-mL, round-bottom flask with condenser and nitrogen line were placed 2 mL of methanol, 1.015 g (9.476 mmol) of *p*-toluidine, and 0.973 g (10.80 mmol) of dimethylcarbonate. Sodium methoxide in methanol, 4.1 mL of 2.5 N (10.25 mmol), was added over 1 min. After refluxing for 24 h under N_2, the mixture was concentrated to a solid using a rotary evaporator. The solid crude product was mixed with 10 mL of water and 10 mL of ether. After shaking and separation, the aqueous layer was further extracted with ether (3×10 mL). The combined ether solution was washed with 1 N HCl (25 mL) and saturated NaCl solution (25 mL) and then dried over $MgSO_4$.

Table 2. Preparation of methyl *n*-substituted carbamates from amines

Amine	Carbamate	Yield	Mp[a]/bp (press)	GC purity
		52%	46.0–46.8°C	
		46%	97.2–97.8°C	
		80%	64.3–65.0°C	
		83%	74.0–74.6°C	
		76%[b] 88%[c]	155.1°C (13.4 torr)	99.6%
		85%[b] 91%[c]	184.9°C (11.5 torr)	99.8%
		91%[b] 88%[c]	199.2°C (4.1 torr)	99.5%
		94%[b] 84%[c]	185.1°C (0.68 torr)	99.7%

[a]Melting points are uncorrected.
[b]Crude yield.
[c]Percent recovery of distilled carbamate (Hickman apparatus).

After filtration and evaporation, the crude product was recrystallized from cyclohexane to give 0.735 g (46.9%) of methyl *N*-*p*-tolylcarbamate: mp 97.2–97.8°C; FT-IR (mull) 3322 (m, NH), 1700 (s, C═O), 1600 (m), 1540 (m), 1512 (m), 1317 (m), 1236 (s, C-O), 1073 (m), 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (m, 4H, ArH), 6.67 (s, br, 1H, NH), 3.75 (s, 3H, OCH_3), 2.29 (s, 3H, $ArCH_3$).

Conversion of benzamide to methyl *N*-phenylcarbamate: From 8.633 g of the amide were obtained 9.451 g (85.5%) of methyl *N*-phenylcarbamate after

recrystallization from cyclohexane: mp 46.0–46.8°C; mmp 45.0–45.5°C; FT-IR (mull) 3322 (m, NH), 1709 (s, C═O), 1615 (m), 1605 (s), 1543 (s), 1503 (m), 1451 (s), 1324 (s), 1248 (s, C–O), 1072 (s), 1031 (m), 905 (m), 730 (m), 710 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46–6.92 (m, 5H, ArH; 1H, NH), 3.74 (s, 3H, OCH_3).

Conversion of 2-phenylacetamide to methyl *N*-benzylcarbamate: From 2.428 g of the amide were obtained 1.824 g (66.0%) of methyl *N*-phenylcarbamate after recrystallization from cyclohexane: mp 63.9–64.5°C; mmp 64.0–64.6°C; FT-IR (mull) 3344 (m, NH), 1692 (s, C═O), 1536 (s), 1495 (m), 1273 (s, C-O), 1144 (w), 999 (w), 739 (w), 704 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26 (s, 5H, ArH), 5.21 (s, br, 1H, NH), 4.32 (d, J = 5.9 Hz, 2H, CH_2), 3.65 (s, 3H, CH_3).

Conversion of cyclohexanecarboxamide to methyl *N*-cyclohexylcarbamate: From 5.105 g of the amide were obtained 5.528 g (94.9%) of methyl *N*-cyclohexylcarbamate after recrystallization from cyclohexane: mp 74.0–74.6°C; mmp 74.0–74.6°C; FT-IR (mull) 3333 (m, NH), 1694 (s, C═O), 1533 (s), 1451 (s), 1351 (s), 1282 (s), 1233 (s, C–O), 1053 (s), 893 (m), 778 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.81 (s, br, 1H, NH), 3.65 (s, 3H, OCH_3), 1.41 [m, 11H, (ring CH, CH_2)].

Conversion of butanamide into methyl *N*-propylcarbamate: From 4.193 g of the amide, 5.567 g (98.9%) of crude liquid carbamate were obtained. A 1.402-g portion was distilled using a Hickman apparatus to give 1.090 (77.8% recovery) of methyl *N*-propylcarbamate: bath temp. 137.5°C (6.5 torr); 97.7% pure by GC; FT-IR (film) 3333 (m, NH), 2949 (s, CH), 2865 (m, CH), 1697 (s, C═O), 1538 (s), 1466 (m), 1371 (w), 1267 (s, C-O), 1193 (m), 1146 (m), 1117 (m), 1051 (m), 1011 (m), 981 (w), 781 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.29 (s, br, 1H, NH), 3.67 (s, 3H, OCH_3), 3.12 (m, 2H, CH_2N), 1.47 (m, 2H, $\mathbf{CH}_2CH_3$), 0.91 (t, $J = 7.3$ Hz, 3H, CH_3).

Conversion of hexanamide into methyl *N*-pentylcarbamate: From 0.955 g of the amide, 1.151 g (95.6%) of crude liquid carbamate were obtained. A 1.084-g portion was distilled using a Hickman apparatus to give 0.966 (89.1% recovery) of methyl *N*-pentylcarbamate: bath temp. 178.5°C (15.6 torr); 99.6% pure by GC; FT-IR (film) 3333 (m, NH), 2949 (s, CH), 2865 (m, CH), 1697 (s, C═O), 1540 (s), 1472 (m), 1379 (w), 1265 (s, C-O), 1197 (m), 1149 (m), 1100 (m), 781 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.21 (s, br, 1H, NH), 3.65 (s, 3H, OCH_3), 3.15 (m, 2H, CH_2N), 1.37 (m, 6H, $\mathbf{CH}_2CH_3$), 0.89 (t, $J = 5.8$ Hz, 3H, CH_3).

Conversion of octanamide into methyl *N*-heptylcarbamate: From 0.722 g of the amide, 0.908 g (103.9%) of crude liquid carbamate was obtained. A 0.799-g portion was distilled using a Hickman apparatus to give 0.722 (90.5% recovery) of methyl *N*-heptylcarbamate: bath temp. 205.1°C

(6.7 torr); 99.6% pure by GC; FT-IR (film) 3344 (m, NH), 2941 (s, CH), 2849 (m, CH), 1697 (s, C═O), 1540 (s), 1470 (m), 1383 (w), 1262 (s, C-O), 1195 (m), 1092 (w), 781 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.99 (s, br, 1H, NH), 3.66 (s, 3H, OCH_3), 3.15 (m, 2H, CH_2N), 1.29 (m, 10H, $\mathbf{CH_2}CH_3$), 0.88 (t, $J = 5.7$ Hz, 3H, CH_3).

Conversion of decanamide into methyl *N*-nonylcarbamate: From 0.950 g of the amide, 0.946 g (84.7%) of crude liquid carbamate was obtained. A 0.766-g portion was distilled using a Hickman apparatus to give 0.711 (92.9% recovery) of methyl *N*-nonylcarbamate: bath temp 195.0°C (1.82 torr); 95.9% pure by GC; FT-IR (film) 3333 (m, NH), 2898 (s, CH), 2816 (m, CH), 1700 (s, C═O), 1540 (s), 1470 (m), 1383 (w), 1262 (s, C–O), 1196 (m), 1149 (w), 1040 (w) 781 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.81 (s, br, 1H, NH), 3.66 (s, 3H, OCH_3), 3.15 (m, 2H, CH_2N), 1.27 (m, 14H, $\mathbf{CH_2}CH_3$), 0.88 (t, $J = 6.1$ Hz, 3H, CH_3).

ACKNOWLEDGMENT

This research was supported in part by a grant from the CSU Special Fund for Research, Scholarship, and Creative Activity.

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Synthetic Communications®, 35: 2099–2105, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1081/SCC-200066703

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Preparation of *N*-Chloroamides Using Trichloroisocyanuric Acid

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Abstract: Amides are efficiently converted to *N*-chloroamides by trichloroisocyanuric acid in methanol.

Keywords: Amides, chlorination, *N*-chloroamides, preparation, trichloroisocyanuric acid, synthesis

N-Chloramides can be an intermediate in the familiar Hoffmann degradation for the conversion of amides into amines containing one less carbon (Scheme 1).[1] The *N*-chloroamides used in the Hoffmann degradation were often prepared utilizing a high concentration of hypochlorite solution, which was made from chlorine gas generated by reacting hydrochloric acid with potassium permanganate.[2] *N*-Chloroamides have also been prepared using *t*-butyl hypochlorite,[3,4] calcium hypochlorite,[5] *N*-chlorobenzotriazole with microwave radiation,[6] *N*-chlorosuccinimide with *n*-butyllithium,[7] and chlorine gas.[8]

Several *N*-chloroamides and imides that are used as chlorinating agents[9] and *N*-chloro-Δ^1-4-azasteroids[10] were prepared using trichloroisocyanuric acid [TCICA; 1,3,5-trichloro-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione; $C_3Cl_3N_3O_3$]. However, no general procedure for the preparation of *N*-chloroamides using

Received in the USA April 11, 2005
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