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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

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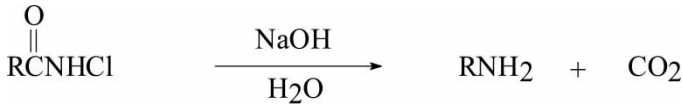


Scheme 1.

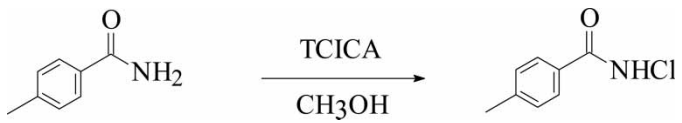
TCICA, a stable solid, has been developed. Consequently, we undertook an investigation of the reaction between amides and TCICA.

First, a study of the effect of solvent on the *N*-chlorination of *p*-toluamide was carried out using acetonitrile, methylene chloride, methyl acetate, acetone, and methanol. As determined by TLC, complete conversion at room temperature took 1.5 h, 24 h, 6 h, 5 h, and 0.5 h, respectively. Then, using a 1-h reaction time and methanol as the solvent, it was determined that an equivalent ratio of amide to TCICA of 1 to 1.10 gave a high yield of crude product of high purity (Scheme 2). Although preliminary studies with *p*-toluamide in methanol showed that the reaction was complete in 30 min, a 1-h reaction time was used for subsequent reactions.

A simple general procedure was developed for the preparation of *N*-chloroamides. After the amide dissolved in methanol, TCICA was added and the solution stirred for 1 h at room temperature. The solid cyanuric acid that formed was removed by filtration, and after evaporation of the methanol, the crude product was purified by flash chromatography or recrystallization. The results for a number of *N*-chloroamides are shown in Table 1.

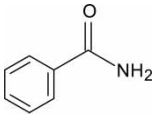
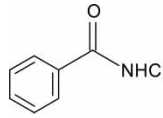
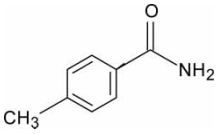
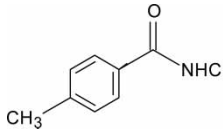
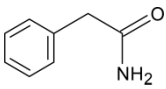
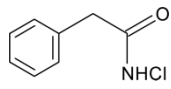
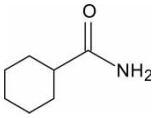
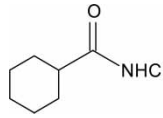
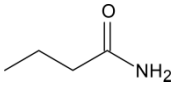
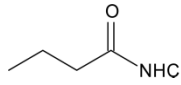
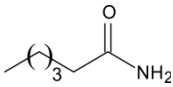
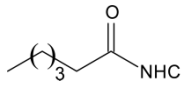
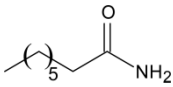
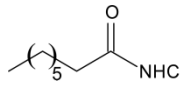
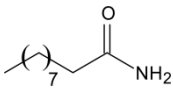
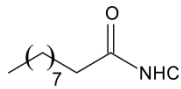
EXPERIMENTAL

All reagents were used as received unless otherwise stated. Reagent-grade acetone, anhydrous methanol, anhydrous acetonitrile, *p*-toluamide, and cyclohexanecarboxamide were obtained from Aldrich Chemical Co. Hexanamide, octanamide, decanamide, 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



Scheme 2.

Table 1. Preparation of *N*-chloroamides from amides

Amide	*N*-Chloroamide	Purified yield	Melting point[a]
		95%[b] 92%[c]	114.0–115.0°C 115.0–116.0°C
		95%[b] 94%[c]	146.0–146.8°C 147.0–147.8°C
		97%[b] 75%[c]	129.0–130.0°C 129.5–130.0°C
		68%[c]	139.0–140.0°C
		94%[b]	One spot on TLC[d]
		89%[b]	One spot on TLC[d]
		86%[b]	One spot on TLC[d]
		97%[c]	40.5–41.5°C

[a]Melting points are uncorrected.
[b]Purified by flash chromatography.
[c]Purified by recrystallization.
[d]Liquid.

from benzene (mp 112.0–112.8°C). Trichloroisocyanuric acid (99%) was obtained from Chem Lab Products.

^{1}H FT-NMR spectra were recorded in $CDCl_3$, CD_3CN, or CD_3COCD_3 using an Anasazi-modified Varian EFT 90-MHz spectrometer. FT-IR spectra were recorded using a Perkin Elmer 1650 spectrometer. TLC was performed using Bakerflex silica-gel IB-F plates, 2.5 × 7.5 cm from J. T.

Baker using diethyl ether as the solvent. Melting points were taken using a Thomas Hoover Uni-Melt capillary melting-point apparatus and are uncorrected. Flash chromatography was performed using silica gel, grade 9385, 230–400 mesh, 60 Å from Aldrich Chemical Co.

N-Chloroamides were characterized by FT-IR and ^{1}H FT-NMR spectra and by comparison of the melting point with the literature data or by conversion back to the amide using sodium hydrogen sulfite. The recovered amides were then compared with the starting amides by mixture melting points and FT-IR and ^{1}H FT-NMR spectra. IR bands characteristic of the N-Cl linkage in benzamide derivatives occur at 1250–1272 and 882–910 cm^{-1}.[4]

***N*-Chlorination of *p*-toluamide:** In a 200-mL, round-bottom flask were placed 100 mL methanol and 7.576 (56.05 mmol) of *p*-toluamide, and the mixture was allowed to stir until the solid dissolved. TCICA, 4.780 g (20.57 mmol, 61.70 meq), was added and a precipitate of cyanuric acid formed in 8 min. After stirring for 1 h, the mixture was vacuum filtered and the solid was washed with methylene chloride. The solvent was removed from the filtrate using a rotary evaporator to give 9.857 g (103.7%) of crude solid product. Recrystallization from benzene gave 8.938 g (94.0%) of *N*-chloro-*p*-toluamide: mp 147.0–147.8°C (Lit.[4] mp 147°C); FT-IR (mull) 3125 (m, br, NH), 1661 (s, C═O), 1267 (m, NCl), 894 (m, NCl) cm^{-1}; ^{1}H NMR δ 7.69 (m, 2H, ArH), 7.24 (m, 2H, ArH, 1H, NH), 2.39 (s, 3H, CH_3).

***N*-Chlorination of hexanamide:** In a 15-mL, round-bottom flask were placed 5 mL of methanol and 0.5154 g (4.475 mmol) of hexanamide, and the mixture was allowed to stir until the solid dissolved. TCICA, 0.3811 g (1.604 mmol, 4.919 meq), was added and a precipitate formed in 3 min. After stirring for 1 h, the mixture was filtered and the solid was washed with methylene chloride. The solvent was removed from the filtrate using a rotary evaporator to give a solid/liquid crude product. The mixture was vacuum filtered and the solid washed with methylene chloride. The solvent was removed from the filtrated using a rotary evaporator to give 0.6836 g (102.2%) of liquid crude product. Flash chromatography with 1:1 pentane–ether gave 0.5936 g (89.2%) of *N*-chlorohexanamide: FT-IR (film) 3134 (s, br, NH), 2942 (s, CH), 2840 (s, CH), 1664 (s, C═O), 1468 (s), 1250 (m, NCl), 1099 (w), 913 (w), 910 (w, NCl) 745 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.06 (s, br 1H, NH), 2.43 (t, $J = 7.4$, 2H, CH_2CO), 1.69 (m, 2H, $\mathbf{CH_2}CH_2CO$), 1.35 (m, 4H, CH_2), 0.89 (t, $J = 5.7$, 3H, CH_3). For conversion back to the amide, 0.309 g (2.06 mmol) of *N*-chloroamide was dissolved in 3 mL of methanol and 2 mL of water, and 0.292 g (2.80 mmol) of $NaHSO_3$ was added. After stirring for 50 min, a negative test for oxidizing power was obtained using wet KI-starch test paper. The methanol was removed with a rotary evaporator, the water was saturated with NaCl, and the solution was extracted with ether (4 × 10 mL). After drying and removal of the ether, the crude amide was recrystallized from cyclohexane to give 0.192 g (65.2%) of

hexanamide: mp 98.8–99.6°C; mmp 98.5–99.9°C. The melting point of the starting amide was 100.2–100.8°C. The FT-IR and ^{1}H FT-NMR spectra of the recovered and the starting amides were identical.

***N*-Chlorination of benzamide:** The reaction of 4.764 g (39.328 mmol) of benzamide with 3.352 g (14.423 mmol, 43.27 meq) of TCICA gave 5.630 g (92.0%) of *N*-chlorobenzamide after recrystallization from benzene: mp 115.0–116.0°C (Lit.[7] mp 117–118°C); FT-IR (mull) 3134 (m, br, NH), 1663 (s, C═O), 1270 (m, NCl), 887 (m, NCl) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.09 (s, br, 1H, NH), 7.84 (m, 2H, ArH), 7.44 (m, 3H, ArH).

***N*-Chlorination of 2-phenylacetamide:** The reaction of 0.3966 g (2.934 mmol) of 2-phenylacetamide with 0.2495 g (1.074 mmol, 3.221 meq) of TCICA gave 0.4977 g (97.5%) of *N*-chloro-2-phenylacetamide after flash chromatography using 1:1 methylene chloride–diethyl ether: mp 129.0–130.0°C; FT-IR (mull) 3115 (m, br, NH), 1663 (s, C═O), 1314 (w), 1129 (w), 1266 (w, NCl), 1088 (w), 966 (m), 935 (w), 917 (w), 764 (m), 729 (m), 695 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33 (s, br, 5H, ArH), 7.26 (s, 1H, NH), 3.72 (s, 2H, CH_2). Reaction with $NaHSO_3$ followed by recrystallization from ethyl acetate gave 61.0% 2-phenylacetamide: mp 158.2–158.6°C; mmp 158.1–158.6°C; mp of starting amide 158.4–158.8°C.

***N*-Chlorination of cyclohexanecarboxamide:** Reaction of 0.4090 g (3.22 mmol) of cyclohexanecarboxamide with 0.2747 g (1.18 mmol, 3.55 meq) of TCICA gave 0.3545 g (68.2%) of *N*-chlorocyclohexanecarboxamide: mp 139.0–140.0°C; FT-IR (mull) 3174 (s, NH), 1664 (s, C═O), 1250 (w, NCl), 1189 (m), 1134 (m), 951 (m), 898 (m, NCl) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.28 (s, 1H, NH), 2.20–2.66 (m, 1H, CHCO), 1.04–2.11 [m, 10H, $(CH_2)_5$]. Reaction with $NaHSO_3$ followed by recrystallization from benzene gave 83.6% cyclohexanecarboxamide: mp 186.0–186.4°C; mmp 186.0–186.5°C; mp of starting amide 186.0–186.8°C.

***N*-Chlorination of butanamide:** Reaction of 0.3943 g (4.526 mmol) of butanamide with 0.3873 g (1.666 mmol, 4.999 meq) of TCICA gave 0.5182 g (94.2%) of liquid *N*-chlorobutanamide after flash chromatography with 1:2 pentane–ether: FT-IR (film) 3134 (m, br, NH), 2949 (s, CH), 2865 (s, CH), 1669 (s, C═O), 1466 (m), 1391 (w), 1274 (w), 1258 (m, sh, NCl), 1198 (m), 1098 (w), 905 (m, NCl) 793 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.56 (s, br 1H, NH), 2.45 (t, $J = 7.0$, 2H, CH_2CO), 1.73 (sex, $J = 7.0$, 2H, CH_2), 0.98 (t, $J = 7.3$, 3H, CH_3). Reaction with $NaHSO_3$ followed by recrystallization from ethyl acetate/cyclohexane gave 95.8% butanamide: mp 112.5–112.8°C; mmp 112.6–112.8°C; mp of starting amide 112.5–112.9°C.

***N*-Chlorination of octanamide:** Reaction of 0.4280 g (2.988 mmol) of octanamide with 0.2546 g (1.095 mmol, 3.286 meq) of TCICA gave 0.4590 g

(86.5%) of liquid *N*-chlorooctanamide after flash chromatography using 1:1 pentane–ether: FT-IR (film) 3134 (s, br, NH), 2906 (s, CH), 2824 (s, CH), 1669 (s, C═O), 1468 (s), 1269 (m, NCl), 1105 (w), 971 (w), 886 (w, NCl), 745 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.90 (s, br 1H, NH), 2.44 (t, $J = 7.3$ Hz, 2H, CH_2CO), 1.74 (m, 2H, $\mathbf{CH_2}CH_2CO$), 1.31 (m, 8H, CH_2), 0.89 (t, $J = 5.1$ Hz, 3H, CH_3). Reaction with $NaHSO_3$ followed by recrystallization from ethyl acetate/cyclohexane gave 61.6% octanamide: mp 104.5–105.2°C; mmp 104.8–105.4°C; mp of starting amide 105.1–105.6°C.

***N*-Chlorination of decanamide:** Reaction of 0.8484 g (4.953 mmol) of decanamide with 0.4217 g (1.814 mmol, 5.443 meq) of TCICA gave 0.9926 g (97.5%) of *N*-chlorodecanamide after recrystallization from pentane: mp 40.5–41.5°C; FT-IR (mull) 3205 (m, NH), 2932 (s, CH), 2849 (s, CH), 1664 (s, C═O), 1267 (w, NCl), 1105 (w), 962 (m), 893 (w, NCl), 719 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (s, br 1H, NH), 2.36 (t, $J = 7.1$ Hz, 2H, CH_2CO), 1.69 (m, 2H, $\mathbf{CH_2}CH_2CO$), 1.26 (m, 12H, CH_2), 0.87 (t, $J = 6.1$ Hz, 3H, CH_3). Reaction with $NaHSO_3$ followed by recrystallization from hexane/cyclohexane gave 77.2 % decanamide: mp 97.8–98.2°C; mmp 97.9–98.2°C.; mp of starting amide 97.8–98.1°C.

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