A Practical Synthesis of *tert*-Alkylamines via the Ritter Reaction with Chloroacetonitrile

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Received 11 May 2000; revised 22 July 2000

Abstract: Ritter reaction of tertiary alcohols with chloroacetonitrile and subsequent cleavage of chloroacetyl group in the resulting chloroacetamide with thiourea is an efficient procedure for synthesis of *tert*-alkylamines.

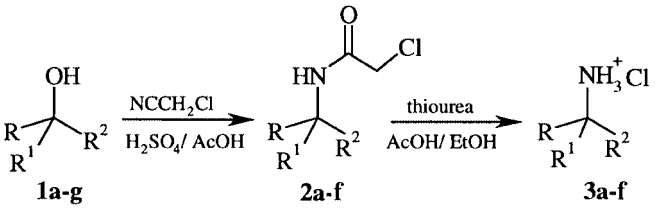
Key words: Ritter reaction, tertiary alcohols, amides, amines, cleavage

The reaction of nitriles or hydrogen cyanide with in situ generated carbocations giving *N-tert*-alkylamides (Ritter reaction[1]) is one of the few methods for introduction of the amino functionality at a tertiary carbon atom. Nevertheless the synthesis of *tert*-alkylamines via the Ritter reaction is limited to the use of the highly toxic hydrogen cyanide (HCN) because the formyl group in resulting formamide can be easily cleaved by either acidic or basic hydrolysis.[1b–d] In contrast to formamides, *N-tert*-alkylacetamides undergo retro-Ritter reaction during acidic hydrolysis[1a,2] and can be cleaved only by drastic alkaline hydrolysis[1a,d] or by a two step procedure involving *O*-alkylation of acetamide with triethyloxonium tetrafluoroborate.[3]

In connection with the development of a series of 1,3,5-alkyl-substituted cyclohexylamines acting as *N*-methyl-D-aspartate receptor antagonists,[4] we searched for a convenient approach toward *tert*-alkylamines avoiding the use of hazardous hydrazoic acid or HCN. We turned our attention to chloroacetamides as precursors of *tert*-alkylamines taking into account the smooth cleavage of the chloroacetyl group with thiourea.[5] Synthesis of *N-tert*-alkylchloroacetamides by the Ritter reaction with chloroacetonitrile ($ClCH_2CN$) has already been reported.[1c] Herein we report an extension of this reaction to the synthesis of *tert*-alkylamines.

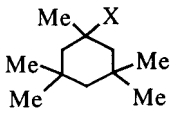
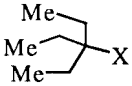
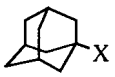
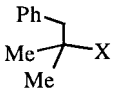
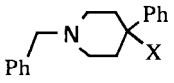
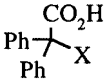
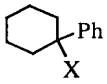
The Ritter reaction with $ClCH_2CN$ was carried out with structurally diverse tertiary alcohols **1a–g** (Scheme). Typically, high yields of chloroacetamides **2a–f** (Table 1) were obtained showing that amide formation with $ClCH_2CN$ is at least as efficient as with HCN or MeCN.[6]

In the case of 1-phenylcyclohexanol **(1g)**, formation of amide **2g** was not observed; instead, 1-phenylcyclohexene was isolated as the major product. The poor ability of cyclohexanol **1g** to form the corresponding amides in the Ritter reaction with PhCN and HCN has been reported previously and is apparently due to the low electrophilicity of the intermediate carbenium ion.[7] 4-Phenylpiperidin-4-ol **(1e)** reacts efficiently with MeCN,[8] and this was also found to be the case with $ClCH_2CN$.



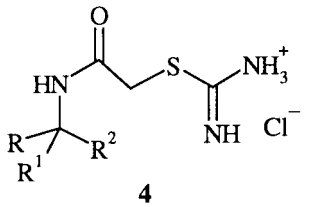
Scheme

Table 1 Yields of Chloroacetamides **2** and *tert*-Alkylamines **3**[a]

RR^1R^2CX	X = $NHCOCH_2Cl$ Yield (%)	X = $NH_3^+Cl^-$ Yield (%)
	**2a**, 86	**3a**, 89
	**2b**, 84	**3b**, 80
	**2c**, 95	**3c**, 85
	**2d**, 78	**3d,** 84
	**2e**, 73	**3e**, 74[b]
	**2f**, 91	**3f**, 61
	**2g**, –	**3g,** –

[a] Satisfactory microanalyses obtained: C ±0.47, H ±0.16, N ±0.19.
[b] Isolated in the base form due to high hygroscopicity of dihydrochloride.

Cleavage of the chloroacetyl group with thiourea was optimized using amide **2a** as an example. Conversion of amide **2a** to amine **3a** was monitored by TLC with isothiouronium salt **4**[5b,9] as a reference standard (prepared alternatively). The conversion was very slow when traditional reaction conditions, e.g. boiling in neat ethanol were applied.[5a,b] Evidently, this could be attributed to the steric crowding in amides derived form *tert*-amines when compared with the less branched secondary and tertiary amides.[5] It was observed, however, that the decomposition rate of **4** depends strongly on the concentration of acetic acid in the reaction mixture[5c,d] (Table 2).



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Boiling the amide **2a** and thiourea in a mixture of ethanol and acetic acid (5:1) for 10 hours were optimal and provided a high yield of amine **3a** (Table 1). These cleavage conditions proved to be effective also in the case of chloroacetamides **2b–f** providing *tert*-alkylamines **3b–f** in good to excellent yields (Scheme, Table 1).

In summary, it was demonstrated that the Ritter reaction with $ClCH_2CN$ and subsequent cleavage of the chloroacetyl group with thiourea is an efficient approach toward *tert*-alkylamines avoiding the use of the highly toxic hydrogen cyanide.

Melting points were measured in capillary tubes on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 580B spectrometer. Microanalyses were performed on a Carlo Erba Instrument EA1108. ^1H and ^{13}C NMR spectra were determined on a Varian Mercury 200BB spectrometer with TMS as an internal standard. Preparative chromatography was carried out on Kieselgel 63–100 μm by flash column method.[10] TLC analysis was performed on Kieselgel 60 F_{254} plates (Merck). All chemicals were purchased from Aldrich. 1-Benzyl-4-hydroxy-4-phenylpiperidine **1e** was obtained by a known procedure.[8]

Chloroacetamides **2c**,[11] **2d**,[12] **2f**[13] and amines **3b**,[14] **3d**,[15] **3e**[8] are known. Amines **3c** and **3f** were identical with authentic samples obtained from Aldrich.

Table 2 Optimization Studies of Chloroacetyl Group Cleavage in Amide **2a**

Entry	EtOH/AcOH Ratio	Disappearance of **4** (h)	Yield of **3a** (%)
1	20:1	18	81
2	10:1	11	85
3	5:1	7	88

***N*-Chloroacetyl-*tert*-alkylamines 2a-f; General Procedure**

To the alcohol **1** (5 mmol) and $ClCH_2CN$ (10 mmol) was added AcOH (0.8 mL) and the mixture was cooled to 0–3 °C. H_2SO_4 (0.80 mL, 15 mmol) was added dropwise keeping the temperature below 10 °C (in the case of alcohols **1d** and **1f** the amounts of $ClCH_2CN$, AcOH and H_2SO_4 were tripled, otherwise the reaction mixture was too thick to stir). The reaction mixture was allowed to reach r.t., stirred for 5 h and poured into ice water (20 mL). Further workup procedure for individual amides was as follows.

Compounds **2a–c** formed a precipitate which was filtered. The filter cake was washed with sat. aq $NaHCO_3$ (2 × 10 mL), H_2O (3 × 10 mL), dried in vacuo over NaOH, and purified by Kugelrohr short path distillation.

Compound **2d** was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with sat. aq Na_2CO_3 and brine, and dried ($MgSO_4$) After solvent evaporation, the residue was purified by column chromatography eluting with 10% EtOAc in petroleum ether followed by 20% EtOAc in petroleum ether.

To isolate compound **2e**, the aqueous solution was made strongly basic with aq 20% NaOH. The resulting precipitate was collected on a filter, washed with H_2O (3 × 10 mL) followed by hexane (3 × 5 mL), and dried in vacuo over NaOH. Amide **2e** is stable in base form at r.t. for several months.

Compound **2f** formed precipitate which was collected on a filter and washed with H_2O (5 × 10 mL), then with EtOH (5 mL) and Et_2O (3 × 5 mL) and dried in vacuo over NaOH.

***N*-Chloroacetyl-1,3,3,5,5-pentamethylcyclohexanamine (2a)**

Mp 86–88 °C; TLC (hexane/EtOAc, 6: 1); R_f 0.38.

IR (nujol): ν = 3415, 3300, 1690, 1660 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.91 (6 H, s), 1.07 (2 H, d, *J* = 14 Hz), 1.14 (6 H, s), 1.37 (3 H, s), 1.0–1.45 (2 H, m), 2.16 (2 H, d, *J* = 14 Hz), 3.94 (2 H, s), 6.4 (1 H, br s).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 28.70, 30.62, 32.18, 37.15, 43.95, 48.59, 52.23, 55.90, 165.70.

***N*-Chloroacetyl-3-ethylheptane-3-amine (2b)**

Mp 56–57 °C; TLC (hexane/EtOAc, 6: 1); R_f 0.31.

IR (nujol): ν = 3270, 3080, 1685, 1660 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.81 (9 H, t, *J* = 7 Hz), 1.73 (6 H, d, *J* = 7 Hz), 3.97 (2 H, s), 6.0 (1 H, br s).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 7.44, 26.36, 42.88, 60.14, 164.50.

***N*-Chloroacetyladamantane-1-amine (2c)**

Mp 121–122 °C; TLC (hexane/EtOAc, 6: 1); R_f 0.30.

IR (nujol): ν = 3260, 3080, 1660 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.69 (6 H, s), 2.03 (6 H, s), 2.10 (3 H, s), 3.94 (2 H, s), 6.2 (1 H, br s).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.09, 36.10, 41.13, 42.81, 52.26, 67.40, 164.49.

***N*-Chloroacetyl-1,1-dimethyl-2-phenylethylamine (2d)**

Mp 57–58 °C; TLC (hexane/EtOAc, 6: 1); R_f 0.30.

IR (nujol): ν = 3300, 1650 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.38 (6 H, s), 3.03 (2 H, s), 3.95 (2 H, s), 6.2 (1 H, br s), 7.1–7.4 (5 H, m).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.72, 42.90, 41.13, 44.99, 54.40, 126.47, 128.08, 130.30, 137.15, 165.09.

***N*-Benzyl-4-chloroacetamido-4-phenylpiperidine (2e)**

Mp >135 °C (dec.); TLC ($MeCN/H_2O/AcOH$, 10:1: 0.3); R_f 0.35.

IR (nujol): ν = 3280, 1665 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.0−2.4 (6 H, m), 2.7−2.9 (2 H, m), 3.55 (2 H, s), 4.00 (2 H, s), 6.75 (1 H, s), 7.1−7.4 (10 H, m).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 35.43, 43.01, 49.39, 56.68, 63.06, 124.97, 127.0, 128.36, 129.08, 138.12, 144.82, 164.41.

***N*-Chloroacetyldiphenylglycine (2f)**
Mp 213−214 °C (dec.); TLC ($CHCl_3$/MeOH/H_2O, 7: 2: 1 bottom layer); R_f 0.15.

IR (nujol): ν = 3340, 1710, 1640 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 4.26 (2 H, s), 7.1−7.4 (10 H, m).

^{13}C NMR (50 MHz, DMSO-d_6) δ = 42.90, 69.91, 127.53, 127.91, 128.32, 140.45, 165.58, 171.89.

***tert*-Alkylamines 3a-f; General Procedure**
A solution of amide **2** (5 mmol) and thiourea (0.46 g, 6 mmol) in a mixture of EtOH (10 mL) and AcOH (2 mL) was refluxed for 10 h. The workup procedure for individual amines was as follows.

To isolate amines **3a−e**, H_2O (50 mL) was added to the reaction mixture and the resulting precipitate was filtered. The filtrate was made alkaline with aq 20% NaOH. The product was extracted with hexane (3 × 30 mL), the combined extracts were washed with brine (30 mL) and dried (NaOH). The solution of amine in hexane was filtered through a Celite pad, and a solution of 1.6 M HCl in Et_2O (6 mL) was added. The solvent and the excess of HCl were removed in vacuo. The residue was treated with Et_2O, filtered and dried (NaOH). Amine **3e** was isolated as a free base after evaporation of hexane.

To isolate amino acid **3f**, the mixture was evaporated, and H_2O (20 mL) was added to the residue. The resulting mixture was acidified to pH ~1 and filtered. The filtrate was neutralized to pH 6−7 with 20% aq NaOH solution. The resulting precipitate was collected on a filter, washed with H_2O (1 mL) and dried in vacuo over NaOH.

1,3,3,5,5-Pentamethylcyclohexanamine Hydrochloride (3a)
Mp 235−237 °C; TLC (CH_3Cl/MeOH/25% aq NH_3, 6:1:1, bottom layer); R_f 0.50.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (6 H, s), 1.07 (6 H, s), 1.23 (1 H, d, *J* = 14 Hz), 1.30 (1 H, d, *J* = 14 Hz), 1.64 (3 H, s), 1.66 (2 H, d, *J* = 14 Hz), 1.76 (2 H, d, *J* = 14 Hz), 8.25 (3 H, br s).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.19, 30.72, 32.41, 36.05, 48.43, 51.19, 57.53.

3-Ethylheptane-3-amine Hydrochloride (3b)
Mp >280 °C; TLC ($CHCl_3$/MeOH/25% aq NH_3, 6:1:1, bottom layer); R_f 0.64.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.01 (9 H, t, *J* = 7.5 Hz), 1.73 (6 H, d, *J* = 7.5 Hz), 8.3 (3 H, br s).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.45, 28.03, 60.62.

Adamantane-1-amine Hydrochloride (3c)
Mp >300 °C; TLC ($CHCl_3$/MeOH/25% aq NH_3, 6:1:1, bottom layer); R_f 0.50.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.68 (6 H, s), 2.03 (6 H, s), 2.14 (3 H, s), 8.3 (3 H, br s).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.87, 35.30, 40.49, 52.87.

1,1-Dimethyl-2-phenylethylamine Hydrochloride (3d)
Mp 196−200 °C; TLC ($CHCl_3$/MeOH/25% aq NH_3, 6:1:1, bottom layer); R_f 0.68.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.46 (6 H, s), 3.09 (2 H, s), 7.1−7.4 (5 H, m), 8.5 (3 H, br s).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.07, 46.23, 55.77, 127.24, 128.44, 130.61, 134.68.

***N*-Benzyl-4-amino-4-phenylpiperidine (3e)**
Mp 60-61 °C; TLC ($CHCl_3$/MeOH/25% aq NH_3, 6:1:1, bottom layer); R_f 0.78.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.48 (2 H, br s), 1.70 (2 H, d, *J* = 13 Hz) 2.1−2.3 (2 H, m), 2.4−2.6 (2 H, m), 2.70 (2 H, dt, *J* = 14, 2 Hz), 3.56 (2 H, s), 7.2−7.4 (8 H, m), 7.45−7.6 (2 H, m).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 37.72, 49.78, 52.02, 63.14, 124.92, 126.41, 126.94, 128.14, 129.10, 138.54.

Diphenylglycine (3f)
Mp 245−247 °C (dec.); TLC (EtOAc/H_2O/BuOH/AcOH, 1:1:1:1); R_f 0.74.

^{1}H NMR (200 MHz, D_2O): δ = 7.4−7.6 (m).

^{13}C NMR (50 MHz, D_2O): δ = 71.83, 130.28, 131.81, 132.53, 138.30, 174.11.

***N*-Aminoiminomethylthioacetyl-1,3,3,5,5-pentamethylcyclohexanamine Hydrochloride (4)**
A solution of amide **2a** (0.245 g, 1 mmol) and thiourea (0.092 g, 1.2 mmol) in EtOH (2 mL) was refluxed for 10 min. EtOH was evaporated and the residue treated with MeCN (10 mL). The precipitate formed was collected by filtration and dried in vacuo to give **4** (0.120 g, 37%); mp 209−211 °C; TLC ($CHCl_3$/MeOH/25% aq NH_3, 6:1:1, bottom layer); R_f 0.25.

IR (nujol): ν = 3200, 3070, 1660 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 0.86 (6 H, s), 1.05 (6 H, s), 1.20 (3 H, s), 0.8−1.31 (4 H, m), 2.18 (2 H, d, *J* = 14 Hz), 3.93 (2 H, s), 7.86 (1 H, s), 8.34 (4 H, br s).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 28.23, 29.95, 31.18, 34.62, 35.92, 46.48, 51.37, 54.64, 167.42, 170.36.

Acknowledgement

We acknowledge I. Dipans for recording IR spectra and E. Sarule for obtaining microanalyses. We also wish to thank Dr. A. Klapars for valuable comments during the preparation of the manuscript.

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Article Identifier:
1437-210X,E;2000,0,12,1709,1712,ftx,en;Z04000SS.pdf