Synthesis of Sterically Hindered α-Aminocarboxamides from α-Bromocarboxamides

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As part of an investigation on base-promoted reactions of α-halocarboxamides[1,2,3], we studied the nucleophilic substitution at C-2 of 2-haloalkanamides.

The synthesis of α-substituted hindered carboxamides from α-halocarboxamides is encumbered by difficulties, mainly due to competition between α-substitution and α,β-dehydrohalogenation[4]. A recent report on the synthesis of α-*t*-butylaminocarboxamides[5] prompts us to report some of our results obtained in the synthesis of sterically hindered α-aminocarboxamides.

2-Bromoalkanamides **(1)** react with equimolecular amounts of primary or secondary, hindered or unhindered amines **(2)** either in tetrahydrofuran in the presence of sodium hydride (Method A) or under phase-transfer catalysis (aqueous 50% sodium hydroxide/tetrabutylammonium bromide/dichloromethane; Method B) to afford the corresponding 2-aminoalkanamides **(3)** in high yields (Table 1).

As was found for *N*-benzyl-2-bromo-2-methylpropanamide (**1**, $R^1=CH_3$, $R^2=—CH_2—C_6H_5$), the reaction does not proceed in the desired manner with diisopropylamine (**2**, $R^3=R^4=i\text{-}C_3H_7$); using Method A, the previously described[1] self-condensation product of the amide is obtained, whereas Method B leads to the formation of *N*-benzyl-2-hydroxy-2-

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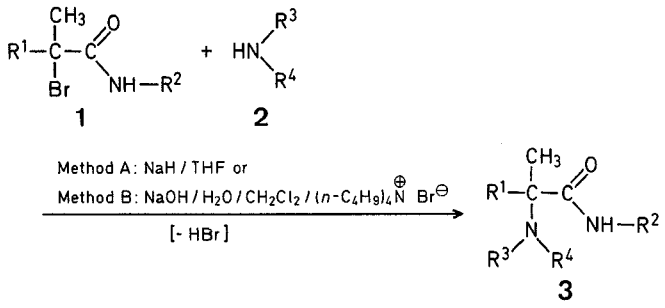
Table 1. 2-Aminoalkanamides (**3**) prepared

3	R^1	R^2	R^3	R^4	Yield [%] Method A	Yield [%] Method B (time [h])	b.p./torr or m.p. [°C]	Molecular formula[a] or m.p. [°C] reported
a	CH_3	t-C_4H_9	t-C_4H_9	H	72		m.p. 69–71°	m.p. 68–70°[5]
b	CH_3	—CH_2—C_6H_5	1-adamantyl	H		68 (10)	m.p. 88–90°	$C_{21}H_{30}N_2O$ (326.5)
c	CH_3	C_6H_5	C_6H_5	H	67		m.p. 156–158°	m.p. 157–159°[5]
d	CH_3	—CH_2—C_6H_5	—CH_2—C_6H_4—Cl-4	H	86		b.p. 200°/1.5[b]	$C_{18}H_{21}ClN_2O$ (316.8)
e	CH_3	CH_3	C_2H_5	C_2H_5		73 (6)	b.p. 80°/1.5[b]	$C_9H_{20}N_2O$ (172.3)
f	CH_3	—CH_2—C_6H_5	C_2H_5	C_2H_5		74 (4)	b.p. 125°/1.5[b]	$C_{15}H_{24}N_2O$ (248.4)
g	CH_3	—CH_2—C_6H_5	C_2H_5	C_6H_5	88		m.p. 78–79°	$C_{19}H_{24}N_2O$ (296.4)
h	CH_3	—CH_2—C_6H_5	—CH_2—CH_2—O—CH_2—CH_2—		86	80 (4)	m.p. 65–66°	$C_{15}H_{22}N_2O_2$ (262.35)
i	C_2H_5	—CH_2—C_6H_5	t-C_4H_9	H	66		b.p. 150°/1.5[b]	$C_{16}H_{26}N_2O$ (262.4)
j	C_2H_5	—CH_2—C_6H_5	C_2H_5	C_2H_5		80 (8)	b.p. 179°/1.5[b]	$C_{16}H_{26}N_2O$ (262.4)

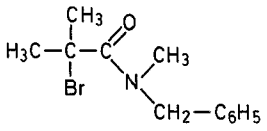
[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.35; H, ±0.23; N, ±0.21. Exception: **3i**, C, −0.43.

[b] Bulb-to-bulb distillation.



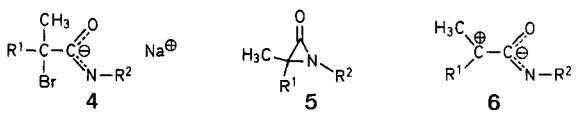
1 **2** **3**

methylpropanamide together with traces of *N*-benzylmethacrylamide. Non-ionizable *N,N*-dialkyl-2-bromoalkanamides, e.g.,



are only dehydrobrominated to the corresponding acrylamides under the conditions of Method A.

We assume that the key step in the formation of products **3** is the conversion of the 2-bromoalkanamide **1** into the conjugated anion **4** which then undergoes nucleophilic substitution via an S_N1-like mechanism. Since stabilized α-lactams (**5**) are not expected to be formed generally from 2-bromoalkanamides **1**[3] under the reaction conditions, zwitterions of the type **6** having a positive charge on C-2 and a stabilizing negative charge on the amide moiety may be regarded as intermediates in the conversion **1**→**3**[6].



4 **5** **6**

Some merits of the present synthesis of amides **3** are:

- use of components **1** and **2** in equimolecular amounts;
- mild reaction conditions;
- suppression of elimination reactions;
- no limitations from the physical state of the amine **2**;
- salts of low-boiling amines can be used directly under phase-transfer conditions.

The reaction pattern of carboxamides **1** with tertiary amines and other neutral or ionic nucleophiles will be reported elsewhere.

Table 2. Spectral Data of Compounds **3**

3	I.R. $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
a	(KBr) 1665	7.52 (br s, 1H, CO—NH); 1.34 [s, 15H, CO—NH—C(CH_3)$_3$ and 2CH_3]; 1.26 [s, 9H, C—NH—C(CH_3)$_3$]; 0.98 (br s, 1H. NH)
b	(KBr) 1660	7.79 (br t, 1H, CO—NH); 7.4–7.2 (m, 5H_{arom}); 4.40 (d, 2H, J=5.8 Hz, CO—NH—CH_2); 2.0–1.4 (m, 10$H_{adamantyl}$); 1.4 (s, 6H, 2CH_3); 1.13 (br s, 1H, NH)
c	(KBr) 1680	8.95 (br s, 1H, CO—NH); 7.6–6.6 (m, 10H_{arom}); 3.86 (br s, 1H, NH); 1.56 (s, 6H, 2CH_3)
d	(neat) 1655	7.62 (br t, 1H, CO—NH); 7.3–7.0 (m, 9H_{arom}); 4.42 (d, 2H, J=5.8 Hz, CO—NH—CH_2); 3.6 (s, 2H, C—N—CH_2); 1.53 (br s, 1H, NH); 1.42 (s, 6H, 2CH_3)
e	(neat) 1668	7.22 (br q, 1H, CO—NH); 2.80 (d, 3H, J=5.0 Hz, CO—NH—CH_3); 2.49 (q, 4H, J=7.0 Hz, 2CH_2—CH_3); 1.21 (s, 6H, 2CH_3); 1.03 (t, 6H, J=7.0 Hz, 2CH_2—CH_3)
f	(neat) 1670	7.69 (br t, 1H, CO—NH); 7.5–7.2 (m, 5H_{arom}); 4.42 (d, 2H, J=5.8 Hz, CO—NH—CH_2); 2.46 (q, 4H, J=7.0 Hz, 2CH_2—CH_3); 1.23 (s, 6H, 2CH_3); 0.94 (t, 6H, J=7.0 Hz, 2CH_2—CH_3)
g	(KBr) 1665	7.80 (br t, 1H, CO—NH); 7.5–7.0 (m, 10H_{arom}); 4.49 (d, 2H, J=5.8 Hz, CH_2—NH—CO); 2.99 (q, 2H, J=7.0 Hz, CH_2—CH_3); 1.23 (s, 6H, 2CH_3); 0.78 (t, 3H, J=7.0 Hz, CH_2—CH_3)
h	(KBr) 1665	7.52 (br t, 1H, CO—NH); 7.3–7.2 (m, 5H_{arom}); 4.43 (d, 2H, J=5.8 Hz, CO—NH—CH_2); 3.7–3.5, 2.5–2.3 (2m, 8H, CH_2—CH_2—O—CH_2—CH_2); 1.22 (s, 6H, 2CH_3)
i	(KBr) 1655	7.73 (br, 1H, CO—NH); 7.3–7.2 (m, 5H_{arom}); 4.6–4.2 (m, 2H, CO—NH—CH_2); 1.8–1.4 (m, 2H, CH_2—CH_3); 1.75 (br s, 1H, NH); 1.43 (s, 3H, CH_3); 1.10 [s, 9H, C(CH_3)$_3$]; 0.85 (t, 3H, J=7.0 Hz, CH_2—CH_3)
j	(KBr) 1670	7.51 (br t, 1H, CO—NH); 7.4–7.2 (m, 5H_{arom}); 4.7–4.0 (m, 2H, CO—NH—CH_2); 2.8–2.1 [m, 4H, N(CH_2—CH_3)$_2$]; 1.73 (q, 2H, J=7.0 Hz, C—CH_2—CH_3); 1.15 (s, 3H, CH_3); 0.93 [t, 6H, J=7.0 Hz, N(CH_2—CH_3)$_2$]; 0.83 (t, 3H, J=7.0 Hz, CH_3—CH_2—C)

I.R. spectra were recorded with a Perkin-Elmer 157 G spectrophotometer. ^{1}H-N.M.R. spectra were recorded at 90 MHz on a Perkin-Elmer R-32 instrument.

2-Aminoalkanamides (3a–j); General Procedures:

Method A: Sodium hydride (55% dispersion in mineral oil; 10 mmol) is washed with light petroleum (b.p. 40–60 °C; 2 × 3 ml) and covered with anhydrous tetrahydrofuran (15 ml). The suspension is stirred, the amine **2** (5 mmol) is added in one portion, and stirring is continued for a few minutes. Then, a solution of the 2-bromoalkanamide **1** (4 mmol) in anhydrous tetrahydrofuran (5 ml) is added dropwise over 45 min and stirring is continued for a further 30 min. The suspension is centrifugated and the solution is evaporated in vacuo. The residual crude product **3** is column-chromatographed on silica gel using ethyl acetate as eluent, or recrystallized, or distilled in vacuo.

Method B: The 2-bromoalkanamide **1** (3 mmol), the amine **2** or its salt (3.5 mmol), and tetrabutylammonium bromide (97 mg, ~0.3 mmol) are added to a well stirred two-phase mixture of aqueous 50% sodium hydroxide (10 ml) and dichloromethane (12 ml). Stirring is continued for 4–10 h (see Table). Water (10 ml) is added to the emulsion, the layers are separated, the organic phase is washed with water (3 × 50 ml) and with 1 normal hydrochloric acid (3 × 30 ml), and the aqueous extracts are combined, neutralized with sodium hydrogen carbonate, and extracted with dichloromethane (3 × 50 ml). This organic extract is dried with sodium sulfate and evaporated to dryness. The residual crude product **3** is column-chromatographed on silica gel using ethyl acetate as eluent, or recrystallized, or distilled in vacuo.

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