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LETTERS TO THE EDITOR

Addition of Cyclic Amines to α,β-Unsaturated Acids via the Aza-Michael Reaction

H. N. Khachatryan[a], G. A. Bagdasaryan[a], S. S. Hayotsyan[a*], O. S. Attaryan[a,b], and G. G. Danagulyan[a,b]

[a] *Institute of Organic Chemistry, Scientific-Technological Center of Organic and Pharmaceutical Chemistry, National Academy of Sciences of Armenia Azatutyan ave. 26, Yerevan, 0014 Armenia*
**e-mail: hasmikjasmin1@gmail.com*

[b] *Russian-Armenian (Slavonic) University, Yerevan, Armenia*

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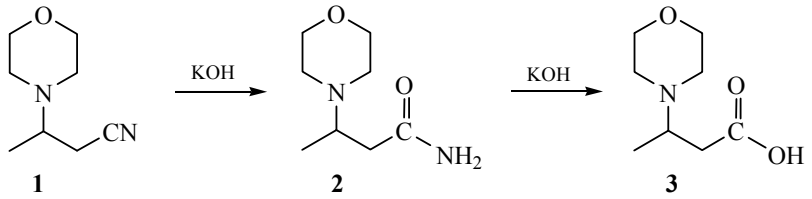
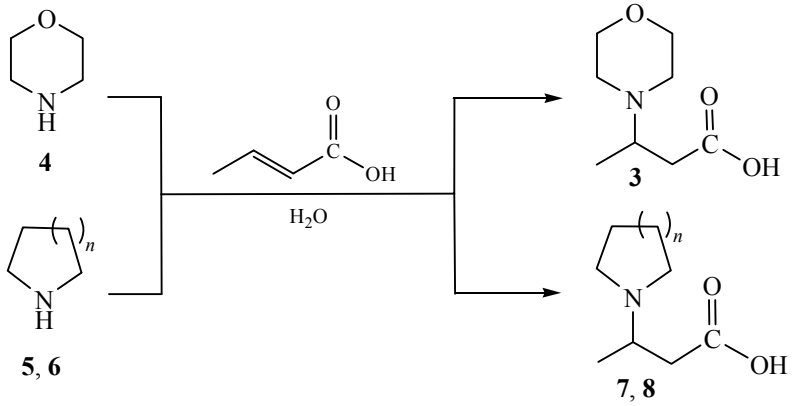
It has been earlier shown that cyclic amines (morpholine, piperidine, and pyrrolidine) react on heating with but-2-enonitrile with the formation of butanenitriles in 65–78% yield [1]. In this work we performed partial and full hydrolysis of 3-(morpholin-4-yl)butanenitrile **1**. When using an equimolar amount of KOH, the reactions stopped at the stage of amide **2** formation, while acid **3** was formed in an excess of KOH.



1 **2** **3**

The synthesis of 3-morpholine- (**3**); 3-piperidine- (**7**), and 3-pyrrolidinebutanoic acids (**8**) via the reaction of amines addition to α,β-unsaturated esters, followed by hydrolysis has been reported [2]. Amines **4**–**6** reacted with crotonic acid in the absence of solvent to form the reaction products in low yields

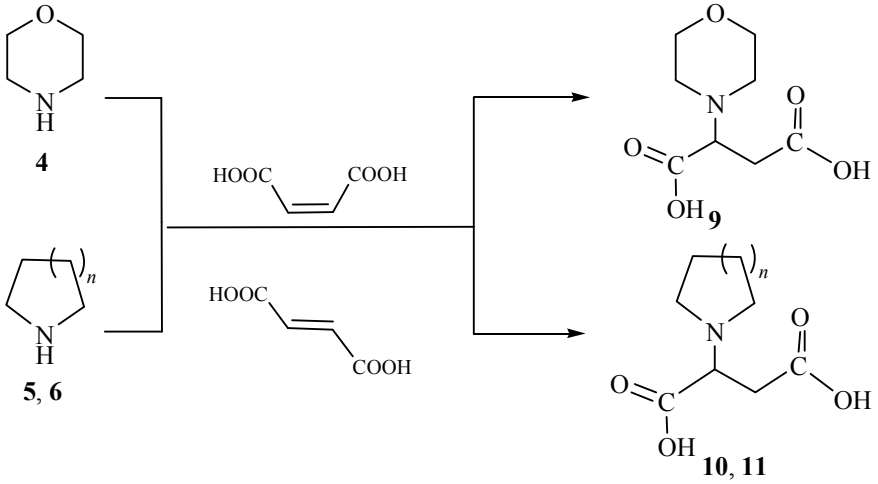
Scheme 1.



4 **5**, **6** **3** **7**, **8**

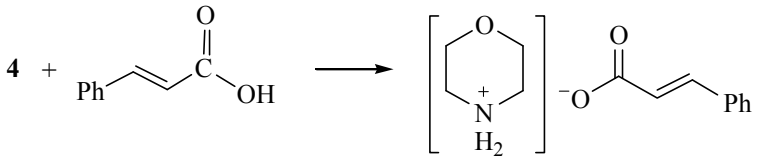
n = 2 (**5**, **7**), 1 (**6**, **8**).

Scheme 2.



n = 2 (**5**, **10**), 1 (**6**, **11**).

Scheme 3.



(20–30%). Taking into account that the addition of amines to unsaturated systems readily occurs in aqueous media [3, 4], we performed the reaction of amines **4**–**6** with crotonic acid in water. Under those conditions, the yields of compounds **2**, **7**, and **8** were up to 45–90% (Scheme 1).

Under similar conditions, amines **4**–**6** reacted with maleic (the product yield was lower) and fumaric acids to form the corresponding aminosuccinic acids **9**–**11** (Scheme 2).

Unlike the reactions with the above-mentioned α,β-unsaturated acids, the reaction of morpholine with cinnamic acid did not lead to either of the two possible aza-Michael products, but gave salt **12** in quantitative yield. Apparently, that was due to steric hindrance from the phenyl group, preventing the addition (Scheme 3).

Amide of 3-morpholinobutanoic acid (2). A solution of 3.4 g (0.06 mol) of KOH in 30 mL of water was added to 7.7 g (0.05 mol) of 3-(morpholin-4-yl)-butanonitrile **(1)**; the mixture was heated until evolution of ammonia ceased (24 h), extracted with chloroform, and dried over $MgSO_4$. After removal of chloroform, the residue was crystallized from benzene. Yield 2.5 g (29.0%), mp 98–99°C. IR spectrum, ν, cm^{-1}: 1680 (C=O), 3100–3500 (COOH). ^{1}H NMR spectrum, δ, ppm: 1.00 d (3H, CHC$\underline{H}_3$, J = 6.6 Hz), 1.95 d.d (1H, CH_2-CO, J = 14.2, 7.6 Hz), 2.30 d.d (1H, CH_2-CO, J = 14.2, 6.2 Hz) 2.40–2.53 m (4H, $2CH_2$), 2.89–3.01 m (1H, C$\underline{H}$CH$_3$), 3.57 t (4H, $2CH_2$, J = 4.6 Hz), 6.41 br.s (1H, NH_2), 7.21 br.s (1H, NH_2). ^{13}C NMR spectrum, δ, ppm: 14.3 (CH_3), 38.3, 48.1, 55.9, 66.4, 172.5 (CO). Found, %: C 55.48; H 8.99; N 16.51. $C_8H_{16}N_2O_2$. Calculated, %: C 55.79; H 9.36; N 16.27.

3-Morpholinobutanoic acid (3). *a.* A solution of 6.7 g (0.12 mol) of KOH in 30 mL of water was added to 7.7 g (0.05 mol) of 3-(morpholin-4-yl)butan-4-nitrile **(1)**; the mixture was heated until evolution of ammonia ceased (24 h) and then extracted with diethyl ether. The formed solution of 3-morpholinobutanoic acid potassium salt was neutralized with HCl solution; water was removed in vacuum; the residue was dissolved in ethanol and filtered. The filtrate was evaporated, and the residue was dried in vacuum. Yield 3.5 g (40%), mp 119–120°C. IR spectrum, ν, cm^{-1}: 1680 (C=O), 3100–3500 (COOH). ^{1}H NMR spectrum, δ, ppm: 1.04 d (3H, C$\underline{H}_3$CH, J = 6.6 Hz), 2.11 d.d (1H,

CHC$\underline{H}_2$, J = 14.9, 7.5 Hz), 2.42 d.d (1H, CHC$\underline{H}_2$, J = 14.9, 6.8 Hz), 2.43–2.56 m [4H, N(CH_2)$_2$], 2.93–3.06 m (1H, $\underline{CH}$-CH_3), 3.53–3.64 m [4H, O(CH_2)$_2$], 12.23 br.s (1H, COOH). Found, %: C 56.85; H 8.43; N 8.26. $C_8H_{15}NO_3$. Calculated, %: C 56.47; H 8.73; N 8.09.

b. 11.3 g (0.13 mol) of morpholine **4** was added dropwise in the course of 1 h to a mixture of 8.6 g (0.1 mol) of crotonic acid and 20 mL of water, at stirring and heating to 70–75°C. The mixture was stirred for 10 h, cooled down, and extracted with chloroform. The aqueous layer was separated and concentrated in vacuum. The formed crystals were crystallized from dioxane. Yield 11.5 g (66%).

3-(Piperidin-1-yl)butanoic acid (7) was prepared similarly via procedure *b* from 8.6 g (0.1 mol) of crotonic acid and 12.7 g (0.15 mol) of piperidine **5**. Yield 7.7 g **(**45%), mp 153°C (from dioxane). IR spectrum, ν, cm^{-1}: 1680 (C=O), 3000–3400 (COOH); ^{1}H NMR spectrum, δ, ppm: 1.03 d (3H, CHC$\underline{H}_3$, J = 6.7 Hz), 1.45–1.70 m (6H, (CH_2)$_3$,), 2.09 d.d (1H, CHC$\underline{H}_2$, J = 15.9, 5.9 Hz), 2.37 d.d (1H, CHC$\underline{H}_2$, J = 15.9, 9.3 Hz), 2.45–2.54 m (2H, NCH_2), 2.62–2.71 m (2H, NCH_2), 2.99-3.11 m (1H, C$\underline{H}$CH$_3$), 11.48 br.s (1H, COOH). Found, %: C 63.31; H 10.35; N 8.41. $C_9H_{17}NO_2$. Calculated, %: C 63.13; H 10.01; N 8.18.

3-(Pyrrolidin-1-yl)butanoic acid (8). A mixture of 8.6 g (0.1 mol) of crotonic acid, 20 mL of water, and 10.7 g (0.15 mol) of pyrrolidine was refluxed for 6 h. Water and excess of pyrrolidine were removed in vacuum, the formed crystals were filtered and washed with diethyl ether. Yield 14.1 g (90%), mp 134–135°C. IR spectrum, ν, cm^{-1}: 1670 (C=O), 3000–3400 (COOH). ^{1}H NMR spectrum, δ, ppm: 1.11 d (3H, CHC$\underline{H}_3$, J = 6.5 Hz), 1.73–1.85 m (4H, (CH_2)$_2$,), 2.19 d.d (1H, CHC$\underline{H}_2$, J = 15.5, 6.9 Hz), 2.35 d.d (1H, CHC$\underline{H}_2$, J = 15.5, 6.1 Hz), 2.61–2.72 m (4H, N(CH_2)$_2$), 2.90–3.01 m (1H, C$\underline{H}$CH$_2$), 9.81 br.s (1H, COOH). Found, %: C 61.45; H 9.85; N 8.58. $C_8H_{15}NO_2$. Calculated, %: C 61.12; H 9.62; N 8.91.

2-Morpholinosuccinic acid (9). *a.* A mixture of 5.8 g (0.05 mol) of maleic acid, 5.3 g (0.06 mol) of morpholine, and 25 mL of water was refluxed for 7 h and then concentrated in vacuum. The residue was crystallized from a 1 : 1 dioxane–water mixture. Yield 6.6 g (65%), mp 210–215°C. IR spectrum, ν, cm^{-1}: 1680 (COOH). ^{1}H NMR spectrum, δ, ppm: 2.39 d.d (1H, CH_2, J=16.0, 6.0 Hz), 2.44–2.52 m (2H**)** and 2.64–2.72 m [2H, N(CH_2)$_2$], 2.66 d.d (1H, CH_2, J = 16.0, 8.7 Hz), 3.48 d.d (1H, CH, 8.7, 6.0 Hz), 3.50–3.61 m [4H, O(CH_2)$_2$], 10.60 br.s (2H, COOH). Found, %: C 47.09; H 6.71; N 6.95. $C_8H_{15}NO_5$. Calculated, %: C 47.29; H 6.45; N 6.89.

b. Prepared similarly from 5.8 g (0.05 mol) of fumaric acid and 5.3 g (0.06 mol) of morpholine in 25 mL of water. Yield 3.5 g (35%).

2-(Piperidin-1-yl)succinic acid (10). *a.* Prepared similarly from 5.8 g (0.05 mol) of maleic acid and 5.1 g (0.06 mol) of piperidine. Yield 6.1 g (60%), mp 199–200°C. IR spectrum, ν, cm^{-1}: 1690 (COOH). ^{1}H NMR spectrum, δ, ppm: 1.41–1.69 m [6H, (CH_2)$_3$], 2.43 d.d (2H, NCHC$\underline{H}_2$, J = 16.0, 5.6 Hz), 2.54–2.79 m (4H, NCH_2), 3.55 d.d (1H, NC$\underline{H}$, J = 9.0, 5.6 Hz), 8.0–13.0 br.s (2H, COOH). Found, %: C 53.43; H 7.65; N 6.75. $C_9H_{17}NO_4$. Calculated, %: C 53.72; H 7.51; N 6.96.

b. Prepared similarly from 5.8 g (0.05 mol) of fumaric acid and 5.1 g (0.06 mol) of piperidine in 25 mL of water. Yield 4.0 g (40%).

2-(Pyrrolidin-1-yl)succinic acid (11). A mixture of 5.8 g (0.05 mol) of maleic acid and 4.3 g (0.06 mol) pyrrolidine in 25 mL of water was heated to reflux for 6 h; water was removed in vacuum; the residue was crystallized from isopropanol. Yield 4.1 g (44%), mp 200°C. IR spectrum, ν, cm^{-1}: 1680 (COOH). ^{1}H NMR spectrum, δ, ppm: 1.80–1.87 m (4H, 2CH_2), 2.44–2.63 m (1H^a, CH$\underline{CH_2}$CH$_2$), 2.72 d.d (1H^b, CH$\underline{CH_2}$CH$_2$, J = 15.8, 9.1 Hz), 2.80–3.02 m (4H, 2NCH_2), 3.79 d.d (1H, NCH, J = 9.1, 4.8 Hz), 1.0–5.0 br.s (2H, 2COOH). Found, %: C 51.53; H 6.78; N 7.65. $C_8H_{13}NO_4$. Calculated, %: 51.33; H 7.00; N 7.48.

b. Prepared similarly from 5.8 g (0.05 mol) of fumaric acid and 4.3 g (0.06 mol) of pyrrolidine in 25 mL of water. Yield 2.9 g (30.8%).

Morpholine cinnamate (12). A Mixture of 7.4 g (0.05 mol) of cinnamic acid and 5.3 g (0.06 mol) of morpholine in 25 mL of water was refluxed for 2.5 h and then concentrated in vacuum. The residue was crystallized from isopropanol. Yield 10.3 g (87.5%), mp 160–162°C. IR spectrum, ν, cm^{-1}: 1530 (Ph), 1640 (C=C), 2000–2800 (NH_2^+). ^{1}H NMR spectrum, δ, ppm: 2.74–2.78 m (4H, 2CH_2O), 3.63–3.67 m (4H, 2HHCH_2O), 6.37 d (1H, =CH, J = 16.0 Hz), 6.68 br.s (2H, NH_2), 7.2–7.40 m (3H, Ph), 7.52–7.56 m (2H, Ph), 7.51 d (1H, =CH, J = 16.0 Hz). Found, %: C 66.51; H 7.08; N 5.78. $C_{13}H_{17}NO_3$. Calculated, %: 66.38; H 7.29; N 5.95.

IR spectra were recorded using a Nexus spectrophotometer (Thermo Nicolet Corporation, USA). ^{1}H NMR spectra were registered using a Varian Mercury spectrometer (300 MHz) in DMSO–CCl_4, 1 : 3. Elemental analysis was performed using a Korshun–Klimova instrument.

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REFERENCES

1. Hayotsyan, S.S., Khachatryan, H.N., Attaryan, O.S., and Asratyan, G.V., *Russ. J. Gen. Chem*., 2015, vol. 85, no. 10, p. 2408. doi 10.1134/S1070363215100291.
2. Essawi, M.Y.H., *Pharmazie*, 1999, vol. 54, no. 8, p. 575.
3. Ranu, B.C. and Banerjee, S., *Tetrahedron Lett*., 2007, vol. 48, no. 1, p. 141. doi 10.1016/j.tetlet.2006.10.142.
4. Surendra, K., Srilakshmi Krishnaveni, N., Sridhar, R., and Rama Rao, K., *Tetrahedron Lett*., 2006, vol. 47, no. 13, p. 2125. doi 10.1016/j.tetlet.2006.01.124.