Chemistry of Heterocyclic Compounds, Vol. 44, No. 6, 2008

BASE CATALYZED INTRAMOLECULAR CYCLIZATION OF DIALKYCROTYL(3-ALKENYL-PROPYN-2-YL)AMMONIUM SALTS AND AQUEOUS BASE FISSION OF 2,2-DIALKYL-4-METHYL- AND 2,2-DIALKYL-4,6-DIMETHYL-2,6,7,7a-TETRAHYDRO-1H-ISOINDOLIUM BROMIDES

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Cyclization of dimethylcrotyl(3-vinyl- or -3-isopropenylpropyn-2-yl)ammonium bromides in the presence of base gave a mixture of the isomeric 2,2-dialkyl-4-methyl- and 2,2-dialkyl-4,6-dimethyl-2,6,7,7a-tetrahydro-1H-isoindolium bromides. Basic fission of the salts obtained at increased temperature gave a mixture of the isomeric N,N- disubstituted di- and trimethylbenzylamines whose structures were confirmed by their IR, ^{1}H NMR, and ^{13}C NMR spectra.

Keywords: 2,2-dialkyl-4-methyl- and -4,6-dimethyl-2,6,7,7a-tetrahydro-1H-isoindolium bromides, isomeric N,N-dialkylmethyl- and -trimethylbenzylamines, intramolecular cyclization, aqueous base fission, basic catalysis.

It is known that 2,2-dialkyl-3a,4-dihydroisoindolinium and 2,2-dialkyl-6-methyl-3a,4-dihydroisoindolinium bromides, obtained by the cyclization of dialkylallyl(3-vinyl- or 3-isopropenylpropyn-2-yl)ammonium salts in aqueous base, isomerize to 2,2-dialkyl-2,6,7,7a-tetrahydro-1H-isoindolium and 2,2-dialkyl-5-methyl-2,6,7,7a-tetrahydro-1H-isoindolium bromides [1].

In order to study the general nature of the isomerization observed by us for a series of dialkyl-3a,4-dihydroisoindolinium salts and the preparation of novel bioactive tetrahydroisoindolinium derivatives we have carried out the intramolecular cyclization of the bromides **1a-f** in the presence of alkali.

It was found that the cyclization of these salts, in contrast to the allyl analogs [1], occurs even in a molar ratio of salt to base of 5:1as a moderately exothermic reaction to give a mixture of the bromides **2a-f** and **3a-f** in 72-76% yields. According to their ^{1}H NMR spectra the mixture contains 82-88% of the salt **3a-f**. When a solution of KOH (molar ratio of salt to base 12:1) is added to an aqueous solution of this mixture at room temperature the salts **2a-f** fully isomerize to the stable forms **3a-f** [1].

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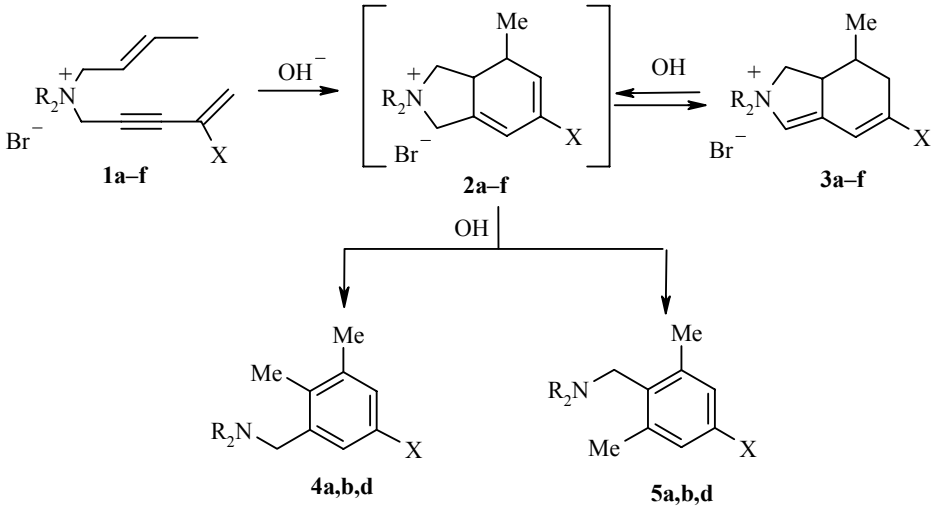
TABLE 1. ^{13}C Spectra of Compounds **3a-f**

Compound	Chemical shifts, δ, ppm										
	CH_3	$\underline{C}H–CH_3$	CH_2	$\underline{C}H–CH_2N$	$N–CH_2$	=CH	=CH–N	$=\underline{C}–CH$	=C–X	X	R
3a	18.9*	32.9	33.5	45.2	66.3	117.9	126.2	137.6	138.3	–	21.3, 21.6, 64.7, 66.3
3b	18.9	33.0	33.5	44.4	64.7	117.9	126.8	137.5	138.2	–	20.2, 20.4, 20.9, 60.2, 62.4
3c	18.8	33.1	38.9	44.2	64.5	113.7	125.1	138.1	147.5	23.2	20.0, 20.6, 21.0 60.1, 62.5
3d	18.7	33.0	38.7	44.1	64.3	113.4	124.6	139.0	148.5	23.3	59.0, 61.1, (2C), 61.6
3e	18.9	32.9	33.5	44.4	64.6	117.8	126.5	138.5	138.5	–	58.9, 61.0, (2C), 61.5
3f	18.8	33.5	38.8	45.8	63.5	113.5	122.6	138.75	147.1	23.1	10.2 (2C), 15.9, 16.1, 64.3, 64.7

* Values given relative to the signal for internal TMS.

Under aqueous alkali conditions the salts **3a-c**, probably again isomerizing to the corresponding 3a,4-dihydroisoindolinium salts **2a-c**, undergo fission upon heating in two directions, i.e. with breaking of the C(1)–N(2) or the N(2)–C(3) bond to give a mixture of the isomeric benzylamines **4a-c** and **5a-c** in 60-65% overall yield.



1–5 a, b, d $R_2 = (CH_2)_4$, X = H; **b** $R_2 = (CH_2)_5$, X = H; **d** $R_2 = (CH_2)_2O(CH_2)_2$, X = Me;
1–3 c $R_2 = (CH_2)_5$, X = Me; **e** $R_2 = (CH_2)_2O(CH_2)_2$, X = H; **f** R = Pr, X = Me

According to ^{1}H NMR spectroscopic data and gas liquid chromatography the content of amines **4a-c** in the mixture is 75-85%. The mixtures of isomeric amines **4a-c** and **5a-c** were separated by vacuum distillation in 60-65% yields.

The structures of the salts **1a-f, 3a-f** and amines **4a,b,d** and **5a,b,d** were in agreement with their IR spectra. The structures of salts **3a-f** and amines **4a,b,d,** and **5a,b,d** were also shown on the basis of their ^{1}H NMR spectra and of the salts **3a-f** from their ^{13}C NMR spectra (Table 1). For confirmation of the structure of salts **3a-f** and assignment of the signals in the ^{1}H and ^{13}C NMR spectra we have used COSY, NOESY, DEPT, and HMQC double resonance and 2D correlation spectroscopic methods.

EXPERIMENTAL

IR Spectra were taken on a UR-20 spectrometer for KBr tablets or in vaseline oil. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury-300 (300 and 75 MHz respectively) at 303ºK using a mixture of DMSO-d_6 and CCl_4 (1:3) and with TMS as internal standard. The purity of the salts was established by TLC on Silufol UV-254 plates in the system *n*-butanol-ethanol-water-acetic acid (10:2:1:5) and revealed using iodine vapor. The ratio of amines **4a,b,d** and **5a,b,d** was shown by GLC on an LXM-8MD chromatograph, column 1.5 m×4 mm filled with Inerton AW-HMDS coated with 10% Carbowax-20M, gas carrier helium (40 ml/min), and temperature 230ºC. The composition of the compounds obtained was proved by elemental analysis.

The starting dialkyl(3-isopropenylpropyn-2-yl)amines were synthesized *via* a Mannich reaction [1-3].

Synthesis of salts 1a-f (General Method). Crotyl bromide (25 mmol) was added to a solution of the corresponding amine (17 mmol) in a mixture of ether (15 ml) and acetonitrile (5 ml). The reaction occurs with a moderate exotherm. The precipitated salts **1a-f** were washed with absolute ether (2×25 ml).

Crotyl(3-vinylpropyn-2-yl)pyrrolidinium Bromide (1a). Yield 4.4 g (96%) as a hygroscopic salt. IR spectrum, ν, cm^{-1}: 870, 920, 980, 1600, 1660, 2230, 3100. Found, %: Br 29.31; N 5.44. $C_{13}H_{20}BrN$. Calculated, %: Br 29.63; N 5.19.

Crotyl(3-vinylpropyn-2-yl)piperidinium Bromide (1b). Yield 4.5 g (97%); mp 120ºC. IR spectrum, ν, cm^{-1}: 870, 930, 970, 1600, 1660, 2230, 3100. Found, %: Br 28.49; N 5.21. $C_{14}H_{22}BrN$. Calculated, %: Br 28.17; N 4.93.

Crotyl(3-isopropenylpropyn-2-yl)piperidinium Bromide (1c). Yield 4.8 g (96%) as a hygroscopic salt. IR spectrum, ν, cm^{-1}: 870, 1600, 1660, 2230, 3100. Found, %: Br 26.56; N 4.92. $C_{15}H_{24}BrN$. Calculated, %: Br 26.85; N 4.70.

Crotyl(3-isopropenylpropyn-2-yl)morpholinium Bromide (1d). Yield 4.98 g (98%); mp 152ºC. IR spectrum, ν, cm^{-1}: 870, 890, 1600, 1660, 2240, 3100. Found, %: Br 26.96; N 4.46. $C_{14}H_{22}BrNO$. Calculated, %: Br 26.67; N 4.67.

Crotyl(3-isopropenyl-2-yl)morpholinium Bromide (1e). Yield 4.75 g (98%); mp 155ºC. IR spectrum, ν, cm^{-1}: 870, 890, 1580, 1670, 2240, 3100. Found, %: Br 28.30; N 4.63. $C_{13}H_{20}BrNO$. Calculated, %: Br 27.97; N 4.90.

Dipropylcrotyl(3-isopropenylpropyn-2-yl)ammonium Bromide (1f). Yield 5.25 g (98%) as a hygroscopic salt. IR spectrum, ν, cm^{-1}: 870, 1600, 1670, 2230, 3100. Found, %: Br 25.79; N 4.67. $C_{16}H_{30}BrN$. Calculated, %: Br 25.48; N 4.46.

Cyclization of salts 1a-f (General Method). KOH solution (2N, 1 ml) (molar ratio of salt to base 5:1) was added to a solution of salt **1** (10 mmol) in water (3.5-4 ml). After 5-10 min an exotherm was observed and the temperature of the reaction mixture increased from 25ºC to 60-65ºC. The reaction mixture was cooled externally using cold water. After 10-15 min the mixture was extracted with ether (2×30 ml) to remove possible neutral side products. When the alkaline medium stood at room temperature or in the fridge crystals of the salts **2a-f** and **3a-f** precipitated from the solution in 72-76% overall yield and these were removed from the aqueous solution by filtration. Addition of 2N KOH solution (0.3 ml) to a solution of this mixture (7.4 mmol) in water (2 ml) caused a total conversion of salts **2a-f** to **3a-f** which were separated from the reaction mixture by filtration.

2,2-Tetramethylene-4-methyl-2,6,7,7a-tetrahydro-1H-isoindolium Bromide (3a). Yield 2.05 g (76%); mp 261-262ºC. IR spectrum, ν, cm^{-1}: 1600, 1650, 3070. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.02 (3H, d, *J* = 6.5, CH_3); 1.73 (1H, tqd, *J* = 11.3, 6.5, 4.7, C<u>H</u>CH_3); 1.98 (1H, dd, *J* = 18.6, 4.7, =CHC<u>H</u>$_2$); 2.12-2.28 (4H, m, $NCH_2C\underline{H}_2$ pyrrolidine); 2.35 (1H, dt, *J* = 18.6, 5.1, =CHC<u>H</u>$_2$); 3.02 (1H, m, $NCH_2C\underline{H}$); 3.45 (1H, m, NCH_2 pyrrolidine); 3.47 (1H, t, *J* = 10.8, CH_2 pyrrolidine); 3.69 (1H, m, NCH_2 pyrrolidine); 3.79-3.88 (2H, m, NCH_2 pyrrolidine); 4.28 (1H, dd, *J* = 11.2, 7.1, NCH_2); 6.25 (1H, ddd, *J* = 9.8, 5.6, 2.1 =C<u>H</u>CH_2); 6.35 (1H, dd, *J* = 9.8, 2.7, =CH); 6.45 (1H, br, NCH=). Found, %: Br 29.34; N 5.42. $C_{13}H_{20}BrN$. Calculated, %: Br 29.63; N 5.19.

2,2-Pentamethylene-4-methyl-2,6,7,7a-tetrahydro-1H-isoindolium Bromide (3b). Yield 2.05 g (72%); mp 283-284ºC. IR spectrum, ν, cm^{-1}: 1605, 1650, 3080. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.04 (3H, d, *J* = 6.5, CH_3); 1.54-1.96 (7H, m, CH_2 piperidine, $NCH_2C\underline{H}_2$ piperidine and C<u>H</u>CH_3); 1.98 (1H, m, =CHC<u>H</u>$_2$); 2.34 (1H, dt, *J* = 18.7, 5.1, =CHC<u>H</u>$_2$); 3.00 (1H, m, $NCH_2C\underline{H}_2$); 3.38 (1H, dd, *J* = 11.5, 10.6, NCH_2); 4.40 (1H, dd, *J* = 11.5, 7.2, NCH_2); 3.46-3.66 (4H, m, NCH_2 piperidine); 6.26 (1H, ddd, *J* = 9.8, 5.5, 2.0, =C<u>H</u>CH_2); 6.34 (1H, dd, *J* = 9.8, 2.6, =CH); 6.58 (1H, br, NCH=). Found, %: Br 28.46; N 4.62. $C_{14}H_{22}BrN$. Calculated, %: Br 28.17; N 4.93.

2,2-Pentamethylene-4,6-dimethyl-2,6,7,7a-tetrahydro-1H-isoindolium Bromide (3c). Yield 2.18 g (73%); mp 267-268ºC. IR spectrum, ν, cm^{-1}: 1600, 1650, 3070. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.07 (3H, d, *J* = 6.5, C<u>H</u>$_3$CH); 1.61-1.86 (6H, m, CH_2 piperidine and $NCH_2C\underline{H}_2$ piperidine); 1.7 (1H, m, C<u>H</u>CH_3); 1.89 (3H, s, =CC<u>H</u>$_3$); 2.00 (1H, m, =CC<u>H</u>$_2$); 2.19 (1H, dd, *J* = 18.1, 4.9, =CC<u>H</u>$_2$); 2.96 (1H, m, C<u>H</u>$CHCH_3$); 3.39 (1H, dd,

J = 11.5, 10.5) and 4.48 (1H, dd, *J* = 11.5, 7.2, NCH_2); 3.50-3.66 (3H, m) and 3.78 (1H, ddd, *J* = 12.4, 8.9, 4.2, NCH_2 piperidine); 6.11 (1H, br, =CH); 6.58 (1H, br, NCH=). Found, %: Br 27.17; N 4.43. $C_{15}H_{24}BrN$. Calculated, %: Br 26.85; N 4.70.

[4,6-Dimethyl-2,6,7,7a-tetrahydrospiro-1H-isoindole-2,4'-morpholinium] Bromide (3d). Yield 2.25 g (75%); mp 275-276ºC. IR spectrum, ν, cm^{-1}: 1600, 1650, 3080. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.08 (3H, d, *J* = 6.5, $CHCH_3$); 1.81 (1H, m, $CHCH_3$); 1.89 (3H, s, $=CCH_3$); 2.01 (1H, dd, *J* = 18.0, 10.1) and 2.20 (1H, dd, *J* = 18.0, 4.8, $=CCH_2$); 3.03 (1H, m, $CHCHCH_3$); 3.58 (1H, dd, *J* = 11.5, 10.5) and 4.70 (1H, dd, *J* = 11.5, 7.3, NCH_2); 3.56-3.71 (3H, m) and 3.82-4.14 (5H, m, CH_2 morpholine); 6.12 (1H, br, =CH); 6.55 (1H, br, NCH=). Found, %: Br 26.98; N 4.44. $C_{14}H_{22}BrNO$. Calculated, %: Br 26.67; N 4.67.

[4-Methyl-2,6,7,7a-tetrahydrospiro-1H-isoindole-2,4'-morpholinium] Bromide (3e). Yield 2.06 g (72%); mp 291-292ºC. IR spectrum, ν, cm^{-1}: 1595, 1650, 3070. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.06 (3H, d, *J* = 6.5, CH_3); 1.78 (1H, tqd, *J* = 11.2, 6.5, 4.7, $CHCH_3$); 2.00 (1H, dd, *J* = 18.7, 5.3) and 2.36 (1H, dt, *J* = 18.7, 5.3, $=CHCH_2$); 3.06 (1H, m, NCH_2CH); 3.50-3.67 (4H, m, NCH_2 morpholine); 3.80 (1H, ddd, *J* = 12.5, 8.4, 3.6) and 4.63 (1H, dd, *J* = 11.5, 7.3, NCH_2); 3.91-4.11 (4H, m, OCH_2); 6.28 (1H, ddd, *J* = 9.9, 5.3, 2.0, $=CHCH_2$); 6.35 (1H, dd, *J* = 9.9, 2.7, =CH); 6.69 (1H, br, NCH=). Found, %: Br 28.26; N 4.63. $C_{13}H_{20}BrNO$. Calculated, %: Br 27.97; H 4.90.

2,2-Dipropyl-4,6-dimethyl-2,6,7,7a-tetrahydro-1H-isoindolium Bromide (3f). Yield 2.3 g (72%); mp 260-262ºC. IR spectrum, ν, cm^{-1}: 1610, 1650, 3070. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.98 (3H, t, *J* = 7.2, CH_3CH_2); 1.01 (3H, t, *J* = 7.2, CH_3CH_2); 1.04 (3H, d, *J* = 6.5, $CHCH_3$); 1.67 (1H, m, $CHCH_3$); 1.65-1.79 (4H, m, CH_2CH_3); 1.86 (3H, s, $=CCH_3$); 1.97 (1H, dd, *J* = 18.1, 10.2, $=CCH_2$); 2.17 (1H, dd, *J* = 18.1, 4.9, $=CCH_2$); 2.83 (1H, m, $CHCHCH_3$); 3.45 (1H, m) and 4.28 (1H, dd, *J* = 12.2, 7.7, NCH_2); 3.41-3.65 (4H, m, NCH_2); 6.10 (1H, t, *J* = 1.6, =CH); 6.31 (1H, d, *J* = 2,2, NCH=). Found, %: Br 25.77; N 4.67. $C_{16}H_{28}BrN$. Calculated, %: Br 25.48; N 4.46.

Aqueous Alkali Fission of Salts 3a-c (General Method). 25% KOH solution (6.8 g) was added to the salt **3** (13 mmol) in water (5 ml), water was distilled off, and from time to time, water was added to the reaction mixture via a dropping funnel. During the fission the reaction mixture temperature was held at 110-120ºC. At the end the temperature of the reaction mixture was raised to 140-150ºC to ensure completion of the process. The reaction mixture and the distilled fraction were extracted with ether (3×40 ml). The combined ether extracts were washed with 15% HCl solution. The hydrochloric acid layer was separated from the ether solution, basified, and extracted with ether to remove the amine products. The ether extract was washed with water and dried over $MgSO_4$. Distillation of the ether and vacuum distillation gave a mixture of the isomeric amines **4a-c** and **5a-c** respectively.

1-(2,3-Dimethylbenzyl)pyrrolidine (4a) and **1-(2,6-Dimethylbenzyl)pyrrolidine (5a)**. Overall yield 1.47 g (60%); bp 94-95ºC (2-3 mm Hg), n_D^{20} 1.5286. IR spectrum, ν, cm^{-1}: 720, 760 (1,2,3-substituted benzene ring), 1580, 3030, 3070 (arom. ring). ^1H NMR spectrum of a mixture of **4a** (75%) and **5a** (25%), δ, ppm (*J*, Hz): 1.68-1.76 (4H, m, NCH_2CH_2); 2.24 (2.25H, s, CH_3); 2.27 (2.25H, s, CH_3); 2.37 (1.5H, s, CH_3); 2.41-2.49 (4H, m, NCH_2CH_2); 3.52 (1.5H, s, CH_2); 3.56 (0.5H, s, CH_2); 6.87-7.02 (3H, m, HAr). Found, %: C 82.05; H 10.36; N 7.80. $C_{13}H_{19}N$. Calculated, %: C 82.54; H 10.11; N 7.41.

1-(2,3-Dimethylbenzyl)piperidine (4b) and **1-(2,6-Dimethylbenzyl)piperidine (5b)**. Overall yield 1.66 g (63%); bp 92-94ºC (1-2 mm Hg), n_D^{20} 1.5260. IR spectrum, ν, cm^{-1}: 710, 770 (1,2,3-sub benzene ring), 1570, 3030, 3080 (arom. ring). ^1H NMR spectrum of a mixture of **4b** (75%) and **5b** (25%) δ, ppm: 1.39-1.56 (6H, m, β,γ-CH_2 piperidine); 2.22 (2.25H, s, CH_3); 2.26 (3H, s, CH_3); 2.35 (1.5H, s, CH_3); 2.29-2.35 (4H, α-CH_2 piperidine); 3.33 (1.5H, s, CH_2); 3.37 (0.5H, s. CH_2); 6.86-6.98 (3H, m, HAr). Found, %: C 82.27; H 10.67; N 6.55. $C_{14}H_{21}N$. Calculated, %: C 82.76; H 10.34; N 6.90.

4-(2,3,5-Trimethylbenzyl)morpholine (4d) and **4-(2,4,6-trimethylbenzyl)morpholine (5d)**. Overall yield 1.85 g (65%); bp 96-97ºC (2-3 mm Hg), n_D^{20} 1.5320. IR spectrum, ν, cm^{-1}: 870 (1,2,3,5- substituted benzene ring), 1570, 3030, 3080 (arom. ring). ^1H NMR spectrum of a mixture of **4d** (85%) and **5d** (15%), δ,

ppm: 2.19 (2.55H, s, CH_3); 2.22 (0.45H, s, CH_3); 2.22 (2.55H, s, CH_3); 2.23 (2.55H, s, CH_3); 2.31 (0.9H, s, CH_3); 2.33-2.38 (4H, m, $N(CH_2)_2$); 3.35 (1.7H, s, CH_2); 3.40 (0.3H, s, CH_2); 3.51-3.60 (4H, m, $(OCH_2)_2$); 6.71 (0.3H, s, H_{Ar}); 6.77 (0.85H, d, *J* = 1.8, HAr); 6.79 (1H, d, *J* = 1.8, HAr). Found, %: C 76.30; H 9.88; N 6.67. $C_{14}H_{21}NO$. Calculated, %: C 76.71; H 9.95; N 6.39.

REFERENCES

1. E. H. Chukhajian, M. K. Nalbandyan, H. G. Gevorkyan, E. H. Chukhajian, H. A. Panosyan, A. G. Ayvazyan, and R. A. Tamazyan, *J. Heterocyclic. Chem.*, **45**, 687 (2008).
2. C. Mannich, *Chem. Ber.*, **66**, 418 (1933).
3. E. O. Chukhadzhyan, A. R. Gevorkyan, and M. K. Nalbandyan, *Zh. Org. Khim.*, **42**, 1784 (2006).