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Reactions of Chloroalkyl-*gem*-dichlorocyclopropanes with Amines

E. K. Aminova, A. N. Kazakova, N. N. Mikhailova, and S. S. Zlotskii

Ufa State Oil Technical University, ul. Kosmonavtov 1, Ufa, 450062 Russia
e-mail: K.elmira.k@yandex.ru

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Abstract—*N*-Alkylation of primary and secondary amines with monochloroalkyl-*gem*-dichlorocyclopropanes under conditions of thermal and microwave heating results in the corresponding amino-*gem*-dichlorocyclopropanes. With microwave irradiation heating, the reaction time has been decreased to 1 h, the yields of the amines containing *gem*-dichlorocyclopropane moiety being the same. Formation of the bicyclic amine in reaction of *cis*-2,3-dichloromethyl-*gem*-dichlorocyclopropane with primary amines under conditions of phase-transfer catalysis has been studied.

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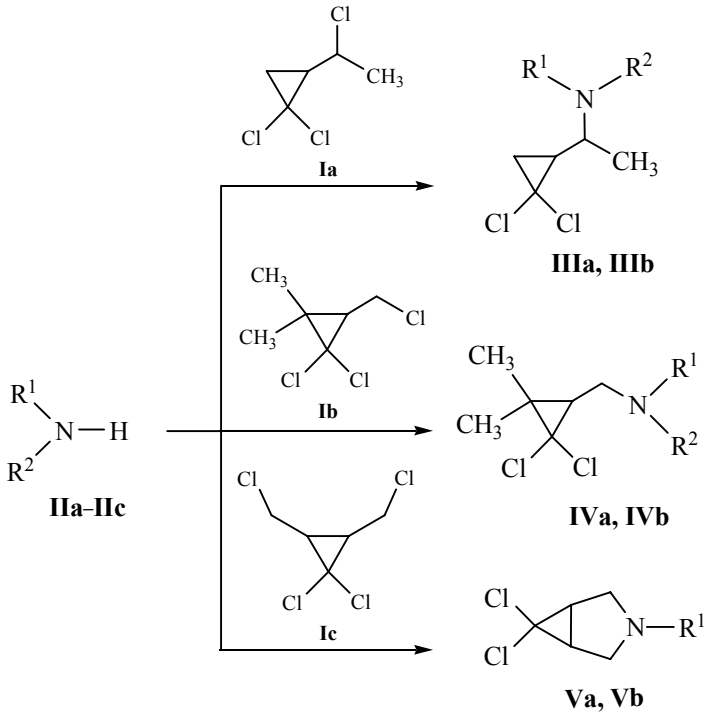
Monochlorinated butenes and pentenes, easily prepared from the industrial dienes (isoprene and butadiene), are widely used as (co-)monomers as well as in fine organic synthesis [1]. In particular, their dichlorocarbenylation by the Makosza method affords the corresponding *gem*- substituted dichlorocyclopropanes with quantitative yield [2, 3]. The so prepared monochloroalkyl- and *cis*-2,3-dichloromethyl-*gem*-dichlorocyclopropanes **Ia–Ic** can be used for *N*-alkylation of the primary and secondary amines **IIa–IIc**.



R^1 = Bu, R^2 = H (**IIa, IIIa, IVa, Va**); R^1 = Bn, R^2 = H (**IIb, Vb**); $R^1 = R^2 = C_2H_5$ (**IIc, IIIb, IVb**).

2-Chloroethyl-*gem*-dichlorocyclopropane **Ia** and 2,2-dimethyl-3-chloromethyl-*gem*-dichlorocyclopropane **Ib** reacted with *n*-butylamine **IIa** to give the corresponding secondary amines **IIIa** and **IVa** with 93–95% yield.

The reactions with diethylamine **IIc** were slower, giving tertiary amines **IIIb** and **IVb** (see table). The yield of the **IVb** tertiary amine from **Ib** was below 50% even after 20 h.

Under conditions of microwave irradiation, **IIc** alkylation led to the same yields of **IIIb** and **IVb** within only 1 h (see table).

cis-2,3-Dichloromethyl-*gem*-dichlorocyclopropane **Ic** reacted with the primary amines **IIa** and **IIc** to yield the bicyclic tertiary amines **Va** and **Vb** (see table).

Under conditions of thermal heating, the benzylamine derivative **Vb** was produced with yield of 60% within 18 hours, whereas the use of microwave radiation gave the same yield within 1 h.

Comparison the chlorinated derivatives **Ia** and **Ib** reactivity towards primary amine **IIa** showed that the presence of geminal dimethyl groups in cyclopropane ring reduced the rate of the exocyclic chlorine substitution by 2.5 times. In all the cases, the endocyclic chlorine atoms did not participate in the reaction with the amines.

N-Alkylation of amines with monochloroalkyl- and *cis*-2,3-dichloromethyl-*gem*-dichlorocyclopropanes **Ia–Ic**[a]

Reactants		Product	Reaction time, h	Yield, %
Ia	**IIa**	**IIIa**	4	95
	IIc	**IIIb**	15	93
			1[b]	95
Ib	**IIa**	**IVa**	12	93
	IIc	**IVb**	20	40
			1[b]	42
Ic	**IIa**	**Va**	8	90
	IIb	**Vb**	18	55
			1[b]	58

[a] Molar ratio **II** : **Ia, Ib** = 3 : 1, DMSO, T = 75–80°C; **II** : **Ic** : KOH = 2 : 1 : 0.3, DMSO, phase transfer catalyst: triethylbenzylammonium chloride, T = 75–80°C. [b] Microwave irradiation (240 W).

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra of the solutions in $CDCl_3$ were recorded with Bruker AM-300 spectrometer (500 and 75.47 MHz, respectively) relative to internal Me_4Si standard. GC-MS traces were recorded with Focus instrument equipped with Finnigan DSQ II MS detector (ion source temperature of 200°C, direct injection temperature of 50–270°C, heating rate of 10 deg min^{-1}, column: Thermo TR-5MS 50×2.5×10^{-4} m, helium flow rate 0.7 mL min^{-1}). GLC analysis was performed with Kristal-2000M chromatograph equipped with thermal conductivity detector (helium as carrier gas at flow rate of 1.5 L h^{-1}, column: h = 2 m, filled with 5% SE-30 on Chromaton N-AW).

Dihalocarbenylation of chloroalkenes Ia–Ic. 320 g of NaOH aqueous solution (50 wt %) was added dropwise to a vigorously stirred mixture of 0.1 mol of the corresponding chloroalkene **Ia–Ic** and 0.2 g of phase transfer catalyst catamine AB in 300 mL of chloroform during 2 h under cooling to 10°C (or under heating up to 40°C in the case of **Ic**). Then the mixture was stirred during another 1–6 h at 20°C (or 40°C in the case of **Ic**) and was washed with water. The extract was dried over calcined $MgSO_4$. After the solvent evaporation, the residue was distilled in vacuum.

1,1-Dichloro-2-chloroethylcyclopropane (Ia). Yield 90%, colorless liquid, bp 56°C (3 mm Hg). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.32 d (3H, C$^{2'}$H$_3$), 1.47 d.d (1H, C^{2}H$_a$, ^2J 7.6, ^3J 6.7), 1.58 d.d (1H, C^{2}H$_b$, ^2J 7.6, ^3J 15.2), 1.76 d.d.d (1H, C^{1}H, ^3J 6.7, ^3J 7.6, ^3J 15.2), 3.68 d.d (1H, C$^{1'}$H, ^3J 7.6). ^{13}C NMR spectrum, δ_C, ppm: 25.26 (C$^{2'}$H$_3$), 27.74 (C^{2}H$_2$), 37.99 (C^{1}H), 58.18 (C$^{1'}$H), 60.49 (C^{3}Cl$_2$). Mass spectrum, m/z, (I_{rel}, %): 170/172/174 (<1) $[M]^{\bullet+}$, 135/137/139 (10/9/3) $[M - {}^{\bullet}Cl]^+$, 156/158/160 (55/53/15), 143/145/147 (33/28/10), 134/136/138 (1/4/2), 111 (14), 109 (23), 101 (6), 78 (32), 76 (100), 65 (29), 63 (16).

2,2-Dimethyl-3-chloromethyl-*gem*-dichlorocyclopropane (Ib). Yield 95%, colorless liquid, bp 58°C (3 mm Hg). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.29 s (3H, C$^{1'}$H$_3$), 1.42 s (3H, C$^{2'}$H$_3$), 1.66 d.d (1H, C^{3}H, ^3J 7.4, ^3J 8.2), 3.55 d.d (1H, C^{4}H$_a$, ^2J 11.8, ^3J 8.2), 3.75 d.d (1H, C$^{4'}$H$_b$, ^2J 11.8, ^3J 7.4). ^{13}C NMR spectrum, δ_C, ppm: 16.89 (C$^{1'}$H$_3$), 24.65 (C$^{2'}$H$_3$), 30.63 (C^2), 39.31 (C^{3}H), 41.13 (C^{4}H$_2$), 70.28 (C^{1}Cl$_2$). Mass spectrum, m/z, (I_{rel}, %): 186 (1) $[M]^{+\bullet}$, 151/153/155 (20/14/2) $[M - {}^{\bullet}Cl]^+$, 137 (100), 109 (22), 101 (11), 79 (30), 65 (29), 53 (10), 39 (32), 76 (100), 65 (29).

2,3-Bis(chloromethyl)-*gem*-dichlorocyclopropane (Ic). Yield 92%, colorless liquid, bp 100°C (3 mm Hg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25–2.28 m (2H, C^2H, C^3H), 3.70–3.72 m (4H, C^1H_2, C^4H_2). Mass spectrum, *m*/*z*, (I_{rel}, %): 205 (1) $[M]^+$, 170/172/174 (10/9/3) $[M - {}^{\bullet}Cl]^+$, 156/158/160 (55/53/15), 143/145/147 (33/28/10), 134/136/138 (37/23/4), 120/122/124 (34/22/5), 109/111/113 (100/63/10), 99/101 (34/13), 85/87/89 (32/21/15), 73/75 (24/22), 65 (18), 51 (21).

***N*-Alkylation of butyl- and diethylamine with *gem*-dichlorocyclopropanes Ia, Ib.** A mixture of 15 mmol of amine and 5 mmol of *gem*-dichlorocyclopropane in 5 mL of DMSO was stirred during 4–20 h at 75–80°C. After cooling, the reaction mixture was washed with 20% aqueous NaOH, and the product was extracted with diethyl ether. The extract was washed with water and dried over K_2CO_3. After the solvent evaporation, the residue was distilled under reduced pressure and under nitrogen stream.

Butyl[1-(2,2-dichlorocyclopropyl)ethyl]amine (IIIa). Colorless liquid, bp 109°C (5 mm Hg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.92 t (3H, $C^{4''}H_3$, ^3J 7.2), 1.28–1.32 m (3H, $C^{2'}H_3$), 1.29–1.41 м (4H, $C^{3''}H_2$, C^3H_2), 1.43–1.55 m (3H, $C^{2''}H_2$, C^2H), 1.58 s (1H, NH), 2.61–2.68 m (2H, $C^{1''}H_2$), 2.87 d.d (1H, $C^{1'}H$, ^3J 5.3, ^3J 12.9). Mass spectrum, *m*/*z*, (I_{rel}, %): 210/212 $[M]^{\bullet+}$ (<0.1), 166/168/170 $[M - {}^{\bullet}C_3H_7]^+$ (21/17/2), 137 (7), 101 (11), 86 (12), 69 (20), 65 (40), 44 (51), 41 (100), 40(10).

[1-(2,2-Dichlorocyclopropyl)ethyl]diethylamine (IIIb). Colorless liquid, bp 97°C (5 mm Hg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.04 t (6H, $C^{2'''}H_3$, $C^{2''''}H_3$, ^3J 7.2), 1.21–1.25 m (2H, C^3H_2), 1.28–1.32 m (3H, $C^{2'}H_3$), 2.52–2.65 m (5H, $C^{1''}H_2$, $C^{1'''}H_2$, C^1H), 2.82 d.d (1H, $C^{1'}H$, ^3J 5.1, ^3J 13.8). Mass spectrum, *m*/*z*, (I_{rel}, %): 207/209/211 $[M]^+$ (<1), 194/196/198 $[M - {}^{\bullet}CH_3]^+$ (10/8/2), 137 (3), 101 (13), 86 (100), 75 (7), 65 (38), 58 (42), 42 (52), 41(25).

Butyl[(2,2-dichloro-3,3-dimethylcyclopropyl)-methyl]amine (IVa). Colorless liquid, bp 113°C (5 mm Hg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.95 t (3H, $C^{4''}H_3$, ^3J 7.2), 1.18 s (3H, $C^{2'''}H_3$), 1.31–1.53 m (9H, $C^{2''}H_2$, $C^{1'''}H_3$, NH, $C^{3''}H_2$, C^1H), 2.58–2.63 m (2H, $C^{1'}H_2$), 2.72 d (1H, $C^{1'}H$, ^3J 6.8). ^{13}C NMR spectrum, δ_C, ppm: 13.97 ($C^{4''}H_3$), 17.24 ($C^{2'''}H_3$), 20.41 ($C^{3''}H_2$), 24.82 ($C^{1'''}H_3$), 28.62 (C^3), 32.19 ($C^{2''}H_2$), 38.33 (C^1H), 46.17 ($C^{1'}H_2$), 49.35 ($C^{1''}H_2$), 70.99 (C^2Cl_2). Mass spectrum, *m*/*z*, (I_{rel}, %): 223/225/227 $[M]^{\bullet+}$ (<1), 190 (27), 180 (100), 166 (2), 151 (33), 114 (81), 86 (83), 79 (66), 57 (18), 44 (41), 41 (25), 30 (13).

[(2,2-Dichloro-3,3-dimethylcyclopropyl)methyl]-diethylamine (IVb). Colorless liquid, bp 103°C (5 mm Hg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.02 t (6H, $C^{2''}H_3$, $C^{2'''}H_3$, ^3J 7.1), 1.15 s (3H, $C^{2''''}H_3$), 1.37 s (3H, $C^{1''''}H_3$), 1.45 m (1H, C^1H), 2.51–2.54 m (6H, $C^{1''}H_2$, $C^{2''}H_2$, $C^{1'}H_2$). Mass spectrum, *m*/*z*, (I_{rel}, %): 223/225/227 $[M]^{\bullet+}$ (<0.1), 208 (8), 188 (10), 115 (9), 86 (100), 79 (21), 58 (32), 41 (8).

***N*-Alkylation of butyl- and benzylamine with *gem*-dichlorocyclopropane Ic.** A mixture of 5 mmol of amine, 2.5 mmol of *gem*-dichlorocyclopropane **Ic**, 0.75 mmol of solid KOH, and 0.02 g of phase transfer catalyst (triethylbenzylammonium chloride) in 6.2 mL of DMSO was stirred during 4–20 h at 75–80°C. After cooling down, the reaction mixture was washed with 20% aqueous NaOH, and the product was extracted with diethyl ether. The extract was washed with water and dried over K_2CO_3. After the solvent evaporation, the residue was distilled under reduced pressure and under nitrogen stream.

3-Butyl-6,6-dichloro-3-azabicyclo[3.1.0]hexane (Va). Colorless liquid, bp 108°C (5 mm Hg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.95 t (3H, $C^{4''}H_3$, ^3J 7.1), 1.25–1.41 m (4H, $C^{3''}H_2$, $C^{2''}H_2$), 2.29 s (2H, C^2H, C^3H), 2.40–2.43 m (2H, $C^{2'}H_a$, $C^{1'}H_a$,), 2.78–2.82 m (2H, $C^{1''}H_2$), 3.12–3.15 m (2H, $C^{2'}H_b$, $C^{1'}H_b$). Mass spectrum, *m*/*z*, (I_{rel}, %): 207/209/211 $[M]^{\bullet+}$ (<1), 192/194/196 $[M - {}^{\bullet}CH_3]^+$ (6/4/1), 114 (4), 86 (14), 79 (19), 57 (16), 44 (100), 41(81), 40(6).

3-Benzyl-6,6-dichloro-3-azabicyclo[3.1.0]hexane (Vb). Colorless liquid, bp 157°C (5 mm Hg). Physicochemical constants, NMR, and mass spectra parameters coincided with the literature data [4].

Competitive interaction of *n*-butylamine with monochloroalkyl-*gem*-dichlorocyclopropanes Ia and Ib. A mixture of 15 mmol of *n*-butylamine **IIa** and *gem*-dichlorocyclopropanes **Ia** and **Ib** (2.5 mmol each) in 5 mL of DMSO was stirred at 75–80°C. The reaction mixture was sampled every 30 min and analyzed by GLC. Relative reactivity of the amine was estimated from the rate of the final products accumulation; conversion of the starting compounds being below 25–35%.

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