Asian Journal of Chemistry Vol. 15, Nos. 3 & 4 (2003), 1744–1748

Reactions of Some 1,1,2-Trihalocycloalkanes with Morpholine

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The five to eight membered 1,1,2-trihalocycloalkanes **1** to **5** react with greater than seven equivalents of morpholine under reflux conditions to yield single clean elimination-substitution products: the 2-halo-3-morpholinyl-1-cycloalkenes **7-9.**

Key Words: 1,1,2-Trihalocycloalkanes; Elimination-substitution reactions; 2-Halo-3-morpholinyl-1-cycloalkenes

INTRODUCTION

Halogenated cycloalkanes are known to undergo dehydrohalogenation with a wide variety of bases such as potassium *tert*-butoxide, alcoholic potash, pyridine, quinoline or morpholine to form the corresponding cycloalkenes[1,2]. More specifically, 1,1,2-trihalocyclo-alkanes yield 1,2-dihalocycloalkenes.

During the course of studies for the synthesis of some cyclic vinylsilanes[3–6], a number of 1,1,2-trihalocycloalkanes were prepared through well established routes[7–11].

EXPERIMENTAL

The 1,1,2-trihalocycloalkanes **1–5** were reacted with morpholine as base and benzene-DMSO mixture as solvent. Refluxing **1–5** with 1–6 molar equivalents of morpholine in benzene/DMSO solvent at 80–90°C oil bath temperature, the gas chromatograms showed formation of varying amounts of 1,2-dihalocycloalkenes and a product with high retention time. Separation of these mixtures by distillation alone or through column chromatographic methods proved difficult.

However, when the proportion of morpholine was raised to 7–8 equivalents or greater, a single product with high retention time was indicated in the gas chromatograms. A typical example is given for the synthesis of **7**.

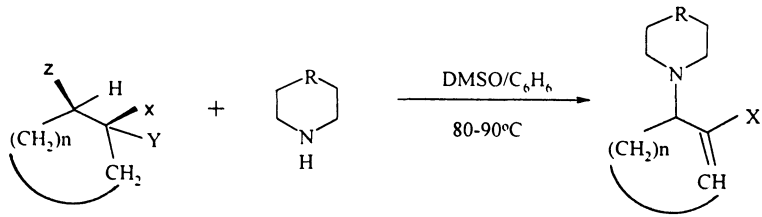
3-(N-morpholinyl)-2-chloro-1-cyclopentene (7): A mixture of 2.1 g (8.0 mmol) of 1,2-dibromo-1-chlorocyclopentene[7] (**1**) and 4.96 g (56.9 mmol) of morpholine in 6 mL of benzene and 4 mL of DMSO was refluxed on an oil bath at 90°C for 60 h. The GC analysis indicated complete conversion of **1** and the formation of only one product (**7**) with high retention time. The reaction mixture was cooled, filtered to remove the solid morpholine hydrobromide and washed with $CHCl_3$ (50 mL). The organic extract was washed successively with saturated

$NaHCO_3$ solution (30 mL), water (10 mL), saturated NaCl solution (30 mL) and dried $MgSO_4$. The extract was concentrated and finally distilled under reduced pressure to isolate 1.08 g (72%) of **7**, b.p. 98–100°C/2.5 torr.

The reaction was extended to the other 1,1,2-trihalocycloalkanes **2–5 (Scheme 1)**. The results, reaction conditions and yields are given in Table-1. The best yield was obtained from **3**,[9] followed by decreasing yields in case of **1**,[7] **2**,[4] **4**[8] and **5**[10] respectively. 1,2-Dibromo-1-chlorocyclododecane **6**[11] failed to give any product.

TABLE-1

	Reactant	Product	Yield (%)	Morpholine	DMSO (mL)	Benzene (mL)	Time (h)	b.p. (°C) (found)	b.p. (°C) (reported)
1	2.1 g (8.0 mmol)	**7**	1.08 g (72)	4.96 mL (56.9 mmol)	4	6	60	98–100/ 2.5 torr	—
2	2.32 g (12.75 mmol)	7	1.23 g (52)	8.99 g (103.3 mmol)	4	6	40	98–100/ 2.5 torr	—
3	3.12 g (11.2 mmol)	8	2.12 g (93)	8.06 g (92.52 mmol)	4.5	7	20	110–115/ 1.75 torr	130/ 4 torr[13]
4	4.5 g (23.8 mmol)	8	1.63 g (34)	19.98 g (229.6 mmol)	10	16	70	110–115/ 1.75 torr	130/ 4 torr[13]
5	6.26 g (20.55 mmol)	9	0.57 g (11.6)	15.24 g (174.9 mmol)	1	20	45	175–180/ 1 torr	73–74/ 13 torr[10]
			Piperidine						
1	5.28 g (20.1 mmol)	10	2.24 g (60)	13.77 g (161.7 mmol)	15	20	50	72–75/ 4 torr	—
3	11.8 g (42.6 mmol)	11	3.60 g (42.2)	25.83 g (303.4 mmol)	20	30	70	115/ 1 torr	—



1: X=Cl, Y=Z=Br, n=2
2: X=Y=Cl, Z=Br, n=2
3: X=Cl, Y=Z=Br, n=3
4: X=Y=Z=Cl, n=3
5: X=Cl, Y=Z=Br, n=5
6: X=Cl, Y=Z=Br, n=9

7: R=O, X=Cl, n=2
8: R=O, X=Cl, n=3
9: R=O, X=Cl, n=5
10: R=CH_2, X=Cl, n=2
11: R=CH_2, X=Cl, n=3

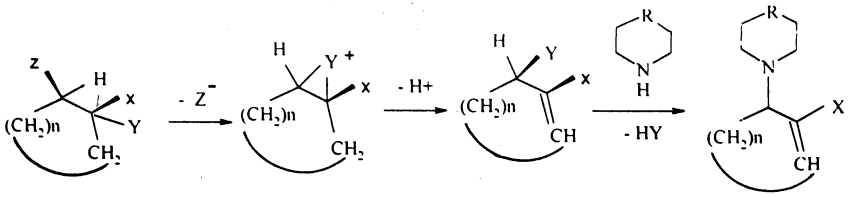
Scheme-1

GC was carried out with Vista Varian 6000 instrument with 10% OV-101 and 15% FFAP columns with temperature programme 80°C (2 min hold)—5°C/min—160°C (hold 32 min). NMR spectra were recorded on JEOL FX-90Q and Bruker AC-250 spectrophotometers. IR spectra were run on Beckmann IR 4260 and Carl-Zeiss Specord 75 spectrometers with films of liquid samples between NaCl plates. GC-MS were obtained on Hewlett Packard 5985 B system attached to a HP 5840 A GC.

RESULTS AND DISCUSSION

Allylic amines are an important class of compounds not only as intermediates in organic synthesis, but also because of their physiological properties and occurence in natural products[12]. Further, the formation of the 2-bromo/chloro-3-morpholinyl-1-cycloalkenes with 6–9 carbons is known by the ring opening of *gem*-dihalocyclopropanes[13–14]

In our reactions, the formation of the elimination-substitution products **7–9** is unusual. The base rather than forming the 1,2-dihalocycloalkene after dehydrohalogenation[7–11], gives the elimination substitution products **7–9.** Therefore, the mechanism for the formation of the 2-halo-3-morpholinyl-1-cycloalkene appears to be proceeding through an E1cB mechanistic pathway. The most probable mechanism for the 1,1,2-trihalocycloalkanes first undergoes a β-elimination to form a bridged halonium[16] ion as shown in **Scheme-2.**



Scheme-2

The halonium ion next loses a proton to form a 2,3-dihalocycloalkene, which undergoes a rapid allylic substitution to form the 2-halo-3-morpholinyl-1-cycloalkenes.

Literature survey shows the formation of a 2,3-dihalocycloalkene with the use of an organic base. 1,2-Dibromo-1-fluoro-cyclohexane is known to give 3-bromo-2-fluoro-1-cyclohexene upon reflux with eight equivalents of collidine[15]. Collidine apparently being an aromatic tertiary base cannot displace the allylic bromine to form substitution products in this reaction.

However, in our case, morpholine being a secondary amino heterocycle, and with the reflux conditions employed, the allylic halogen is likely to undergo fast allylic substitution to form the products **7–9.** With the use of lesser proportions of base, allylic substitution may become less important leading to more complex products as seen in the gas chromatograms.

In this context it was further observed that the gas chromatograms did not indicate any peak corresponding to the formation of 2,3-dihalocycloalkene, further indicating that the substitution of the allylic position is very rapid.

The reactions were also carried out with piperidine (pKa = 11.1), a stronger base than morpholine (pKa = 8.5). In this case also **1** gave 60% of **10** and **3** gave 42% of **11** respectively (Table-1). The yields indicate the subtle difference between using a strong base and a comparatively weak base.

2-Chloro-3-(N-morpholinyl)-1-cyclopentene (7): **IR** ν_{max} (cm^{-1}): 3070, 2950, 2850, 1660, 1620, 1430, 1360, 1260, 1120, 1080, 1020, 930, 880, 855, 800, 580, 505 and 495; **^{1}H NMR**: ($CDCl_3$) (δ) (ppm) 2.02 (dt, 2H), 2.25 (m, 2H), 2.60 (m, 4H), 3.75 (m, under which a short peak, 5H), and 5.92 (v narrow q, 1H); **^{13}C NMR**: ($CDCl_3$): (δ) 22.4, 29.65, 48.30, 67.28, 71.76, 130.22, 132.20; **MS** m/e (relative intensity): 189 (29.3), 188 (14.7), 187 (93.3), (M^+), 152 (30.3), (M^+—Cl), 122 (100), (C_4H_8NOCl) 103 (23.2), (M^+—C_4H_8NO), 101 (69.3), (C_5H_5Cl), 86 (58.4), (C_4H_8NO), 65 (54.3), and 56 (30.9). **Elemental analysis**: Found C: 57.83, H: 7.80; $C_9H_{14}NOCl$ requires C: 57.60, H: 7.52.

2-Chloro-3-(N-piperidinyl)-1-cyclopentene (10): **IR** ν_{max} (cm^{-1}): 3010, 2990, 2970, 1645, 1470, 1360, 1235, 1195, 1130, 1040, 1025, 940 and 880 cm^{-1}; **^{1}H NMR**: ($CDCl_3$) (δ) 1.98 (m, 4H), 2.22 (m, 4H), 2.51 (m, 6H), 3.79 (m, 1H), 5.8 (m, 1H); **^{13}C NMR**: ($CDCl_3$): (δ) (ppm) 22.88, 24.78, 26.44, 29.61, 49.29, 72.23, 129.39, 133.70; **MS** m/e (relative intensity): 187 (8.3), 186 (11.4), 185 (25.0), 184 (26.5) (M^+), 156 (16.2), 150 (33.9), (M^+—Cl), 134 (4.0), 122 (8.9), 103 (6.2), 101 (18.6) (M^+—$C_5H_{10}N$), 84 (100), ($C_5H_{10}N$), 67 (15.9), 66 (11.3), 65 (72.9), (C_5H_5), 55 (30.8), 39 (68.6), 28 (35.4). **Elemental analysis**: Found C: 64.46, H; 8.62; $C_{10}H_{16}NCl$ requires C: 64.68, H: 8.69.

2-Chloro-3-(N-piperidinyl)-1-cyclohexene (11): **IR** ν_{max} (cm^{-1}): 3010, 2980, 2970, 1700, 1665, 1470, 1385, 1340, 1240, 1185, 1130, 1060, 1030, 1010, 940, 920, 880, 860, 830, 790 and 740 ; **^{1}H NMR**: ($CDCl_3$) (δ) (ppm) 1.70 (m. 10H), 2.06 (m, 2H), 2.52 (m, 4H), 3.25 (m, 1H), 6.0 (m, 1H); **MS** m/e (relative intensity): 201 (8.1), 200 (6.8), 199 (26.5), 198 (12.2) (M^+), 184 (0.6), 173 (17.6), 171 (53.7), 164 (12.6), ($C_{11}H_{18}N^+$), 158 (31.2), 156 (100), 136 (57.4), 124 (48.1), 115 (11.0) ($C_6H_8Cl^+$), 106 (4.7), 94 (6.8), 86 (12.7), 85 (41.9), ($C_5H_{11}N$), 84 (56.3) ($C_5H_{10}N^+$), 80 (11.7), (C6H8$^+$), 79 (38), 78 (6.3), 77 (33.1), 55 (5.7) and 41 (6.1). **Elemental analysis**: Found C: 66.08, H: 9.13; $C_{11}H_{18}NCl$ requires C: 66.15, H: 9.08.

ACKNOWLEDGEMENTS

We thank the DST and UGC for financial assistance. We are also grateful to the Chairman, Department of Organic Chemistry, IISc, Bangalore and Prof. K. Griesbaum, Karlsruhe University, Karlsruhe, Germany, for furnishing spectral and analytical data. Thanks are placed on record to the Alexander von Humboldt Foundation, Germany, for providing some instruments used in this study.

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(*Received*: 24 February 2003; *Accepted*: 12 May 2003) AJC-3095