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SOLVENT EFFECT ON THE REACTION OF 2,6-DIBROMOCYCLOHEXANONE WITH MORPHOLINE

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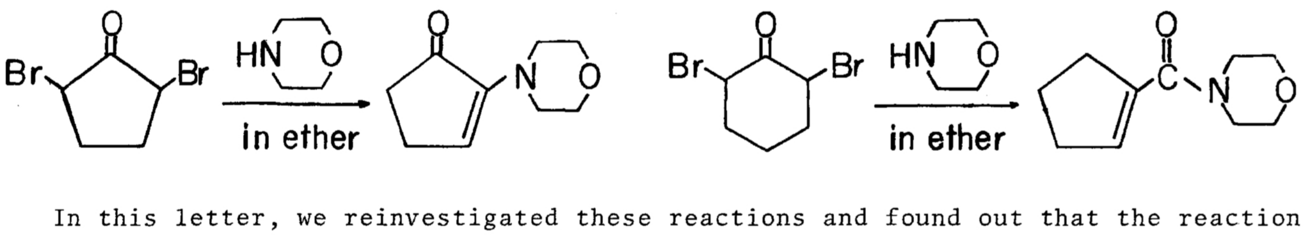
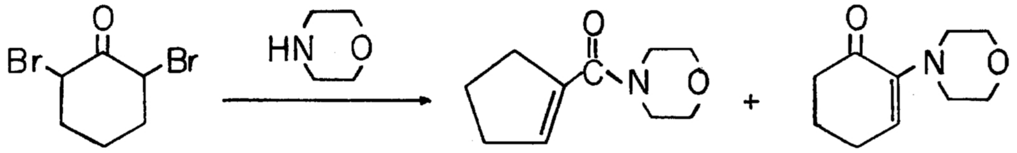
The reaction of 2,6-dibromocyclohexanone (1) with morpholine gives 1-cyclopentenecarboxymorpholide (2) and 2-morpholino-2-cyclohexenone (3). The ratio of 2 : 3 is remarkably affected by the reaction solvent, and the amide 2 or the enaminoketone 3 is obtained selectively when chloroform or HMPA was used, respectively.

It has been known as Favorskii rearrangement that α-haloketones react with bases to afford carboxylic acid derivatives[1]. 2,6-Dibromocyclohexanone was shown[2] to give methyl 1-cyclopentenecarboxylate by the treatment with sodium methoxide.

Previously, in the course of the study of the synthesis of cyclic α-diketones, we reported[3] that the treatment of 2,5-dibromocyclopentanone with morpholine in ether afforded 2-morpholino-2-cyclopentenone (yield; 57.5%) without any formation of the Favorskii rearrangement product. On the other hand, the similar treatment of 2,6-dibromocyclohexanone with morpholine furnished the Favorskii rearrangement product, 1-cyclopentenecarboxymorpholide, in 25.5% yield.

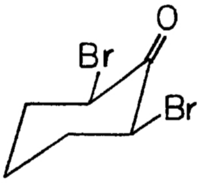


In this letter, we reinvestigated these reactions and found out that the reaction of 2,6-dibromocyclohexanone (1) with morpholine in ether provided 1-cyclopentenecarboxymorpholide (2) together with a minor amount of 2-morpholino-2-cyclohexenone (3), and that the ratio of the formation of the amide 2 and the enaminoketone 3 was remarkably affected by the reaction solvent.

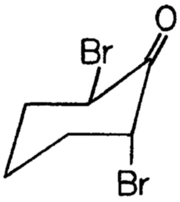


1 **2** **3**

Thus, 10.5 g (0.12 mol) of morpholine in 20 ml of *N,N*-dimethylformamide (DMF) was added over 30 min into 5.12 g (0.02 mol) of *cis*-dibromoketone **1a** in 30 ml of DMF with stirring at 0°C and the mixture was stirred for further 7 hr at 0°C. The precipitated morpholine hydrobromide was filtered off, and filtrate was distilled (bp 100-105°C/0.75 mmHg) to give the amide **2** and the enaminoketone **3** as a mixture (2.77 g, 76.0%; **2** : **3** = 25.9 : 74.1 by glc), which could be separated by silica gel column chromatography with benzene as eluent. The structures of the amide **2** and the enaminoketone **3** was assigned by ir, nmr, and ms spectra. The similar treatment of *trans*-dibromoketone **1b** gave the same result.



cis-dibromoketone, **1a**



trans-dibromoketone, **1b**

The above results suggest that the reaction of dibromoketone **1** with a base is affected by the reaction solvent. Then the reaction was carried out in several solvents. The results are shown in Table 1.

In general, the solvent of the high polarity results in higher proportion of the enaminoketone **3**. In the case of using hexamethylphosphortriamide (HMPA) as a solvent the enaminoketone **3** was obtained selectively, and when chloroform or dichloromethane was used, the amide **2** was obtained exclusively.

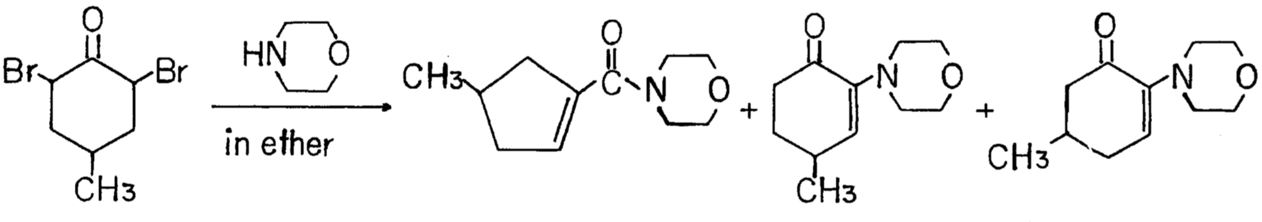
As to the reaction mechanism, the formation of the enaminoketone **3** can tentatively be explained by the monosubstitution followed by 1,4-elimination[3] (Scheme 1-A).

Table 1. The reaction of 2,6-dibromocyclohexanone with morpholine.[a)]

Solvent	Substrate	Reaction time (hr)	Yield (%)	2 : 3
HMPA	1a	7.0	75.1	2.6 : 97.4
DMF	1a	6.5	76.0	25.9 : 74.1
	1b	7.0	66.3	25.6 : 74.4
Pyridine	1a	5.5	80.3	29.4 : 70.6
Methanol	1a	4.5	85.6	53.5 : 46.5
Acetone	1a	8.0	53.5	56.1 : 43.9
Ethyl ether	1a	4.5	79.9	61.1 : 38.9
	1b	7.5	70.5	60.9 : 39.1
Benzene	1a	10.0	65.7	67.0 : 33.0
	1b	8.5	56.6	63.8 : 36.2
Ethanol	1a	9.5	87.4	81.9 : 18.1
Dichloromethane	1a	7.5	87.8	94.5 : 5.5
Chloroform	1a	5.5	83.1	96.1 : 3.9

a) The reactions were carried out at 0°C.

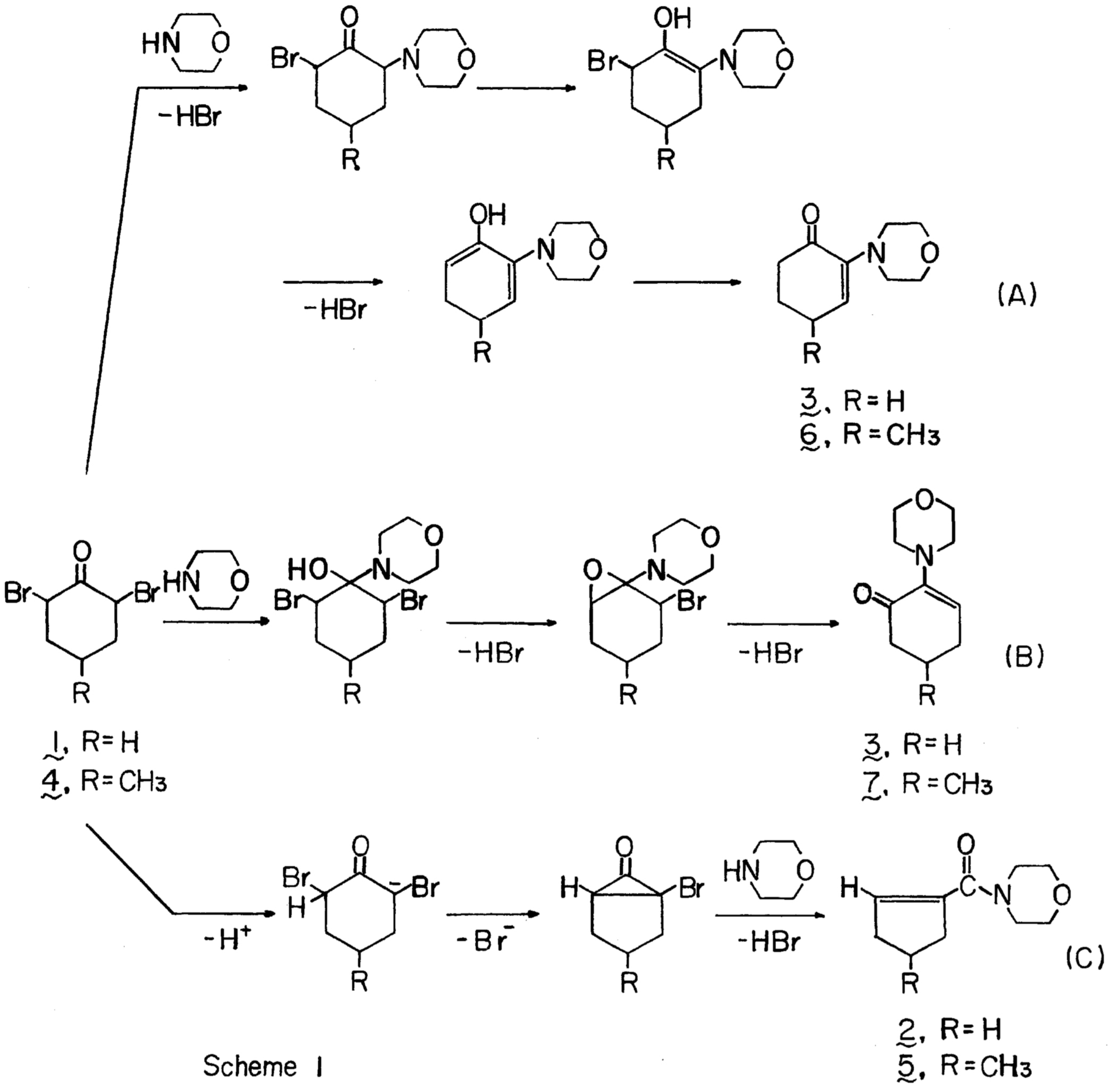
In order to make this reaction mechanism clear, we examined the reaction of 2,6-dibromo-4-methylcyclohexanone (4) with morpholine in ether, and obtained the Favorskii rearrangement product, 4-methyl-1-cyclopentenecarboxymorpholide (5), and two kinds of enaminoketones, the expected 4-methyl-2-morpholino-2-cyclohexenone (6) and the entirely unexpected 5-methyl-2-morpholino-2-cyclohexenone (7), in 72.5% yield (5 : 6 : 7 = 73.4 : 18.2 : 8.4 by glc).



4 5 6 7

The mutual isomerization between enaminoketones 6 and 7 under these reaction conditions was not observed.

Judging from these results, there should be two reaction paths for the formation of the enaminoketone(s). The formation of the enaminoketone 7 can be postulated as shown in Scheme 1-B: the nucleophilic addition of morpholine to the carbonyl followed by the elimination of hydrogen bromide to form an epoxide[4)] which produces the enaminoketone 7 by the subsequent elimination of hydrogen bromide.



Scheme I

Investigations are continuing for the mechanism of this reaction.

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