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REACTION OF α-CHLOROKETONES WITH 1,4-DIANION OF ACETOPHENONE N-ETHOXYCARBONYLHYDRAZONE

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Abstract: 1,4-Dianion of acetophenone N-ethoxycarbonylhydrazone (2) reacts with α-chloroketones such as phenacyl chloride, 1-chloroacetone, 3-chloro-2-butanone, and 1,3-dichloroacetone to give pyrazoline derivatives in good yields. In the reactions of 2-chlorocyclohexanone and 3-chloro-2-norbornanone with 2, cis-chlorohydrin and exo-chlorohydrin were selectively obtained, respectively.

We have recently reported$^{1)}$ that 1,4-dianion of acetophenone N-ethoxycarbonylhydrazone (2) reacts with carbonyl compounds such as ester, amide, acyl chloride, and alkyl carbonate to give pyrazole derivatives. In our continuing study on the reaction behavior of 2, we have found that 2 reacts with α-chloroketones to give pyrazoline derivatives in good yields. Although a number of synthetic methods of pyrazoline derivatives have been reported$^{2)}$ so far, this reaction newly provides a convenient synthetic method of the 2-pyrazoline having various functional groups at the 5 position.

We now wish to report the reaction of mono- and di-α-chloroketones with 2. In the reaction of α-chloroketones such as phenacyl chloride, 1-chloroacetone, 3-chloro-2-butanone, and 1,3-dichloroacetone with 2, pyrazoline derivatives were obtained in good yields. Whereas, when cyclic α-chloroketones, 2-chlorocyclohexanone and 3-chloro-2-norbornanone, were reacted with 2, the chlorohydrin derivatives, (5) and (6), were obtained as addition products. On the other hand, in the reaction of α-dichloroketones (1,1-dichloroacetophenone and 1,1-dichloroacetone) with 2, γ-dichloro-β-hydroxyketone derivatives (8) and dibenzoylethane (10) were obtained.

A typical procedure for the reaction of α-chloroketone with 2 is as follows: To a cooled THF solution (-78°C) of acetophenone N-ethoxycarbonylhydrazone (1, 2.42 mmol) was added a hexane solution of butyllithium (5.32 mmol) with stirring at -78°C under argon. To the resulting yellowish brown colored solution was added dropwise a THF solution of α-chloroketone (2.18 mmol). After a complete fading of the color, the reaction mixture was stirred for additional 2h at -78°C, and THF was removed in vacuo. To the residual mixture was added water, conc. HCl, acetic acid, and methanol (10 ml each), and stirred for 2h at room temperature. After methanol was evaporated, the residue was extracted with ether, and the extract was washed with water, dried over anhydrous $MgSO_4$, and condensed under reduced pressure. The residue was chromatographed on a silicagel column or preparative TLC to give pyrazoline derivatives (4). The yields are given in Table 1.

Scheme 1 shows a possible pathway for the reaction. The regiospecific attack of the nitrogen atom at the epoxy ring carbon in the intermediate 3′ should be a key step in the pyrazoline formation reaction.

Scheme 1

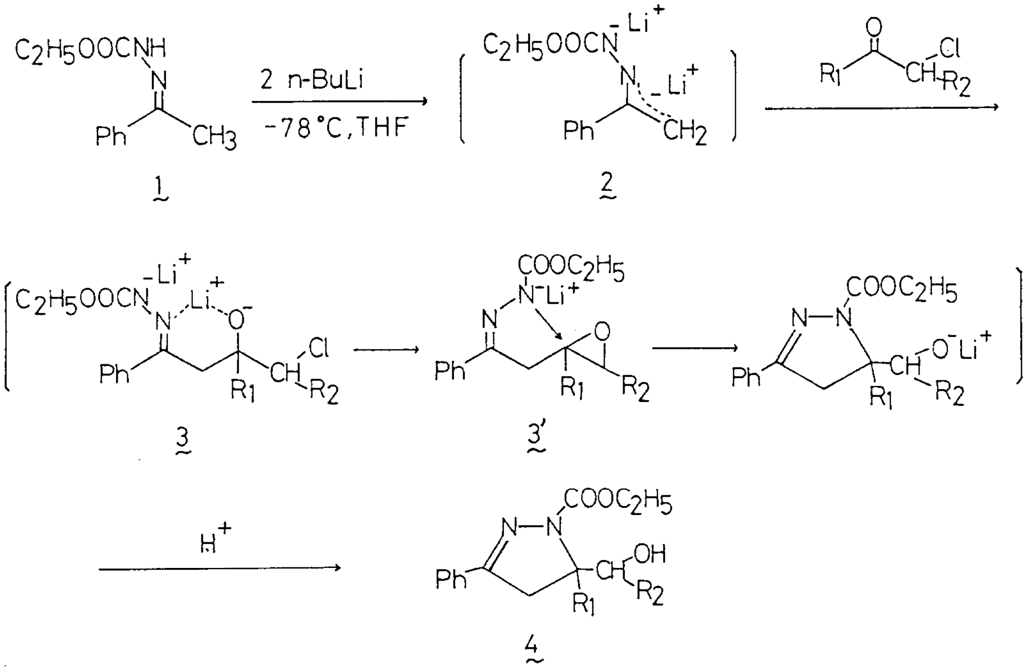


Table 1. Reaction of α-chloroketone with 2[a)]

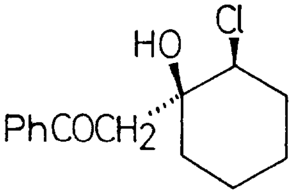
	α-Chloroketone		Product[b)]
Entry	R_1	R_2	Yield[c)], %
1	C_6H_5	H	61
2	CH_3	H	39
3	CH_3	CH_3	62
4	$ClCH_2$	H	43

a) The reactions were carried out for 2h at -78°C in THF

b) All products gave satisfactory ir, mass, nmr and elementary analyses

c) Isolated yields by column chromatography and preparative TLC

Next, the reactions of α-chloroketones such as 2-chlorocyclohexanone and 3-chloro-2-norbornanone with 2 were carried out under same conditions, which gave no pyrazoline derivatives, but cis-chlorohydrin (5) and exo-chlorohydrin (6) in 68% and 65% yields, respectively. This result strongly suggests[3)] that the hydroxy anion and the chlorine atom of intermediate 3 (Scheme 1) have a cis form.



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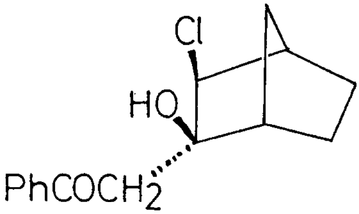

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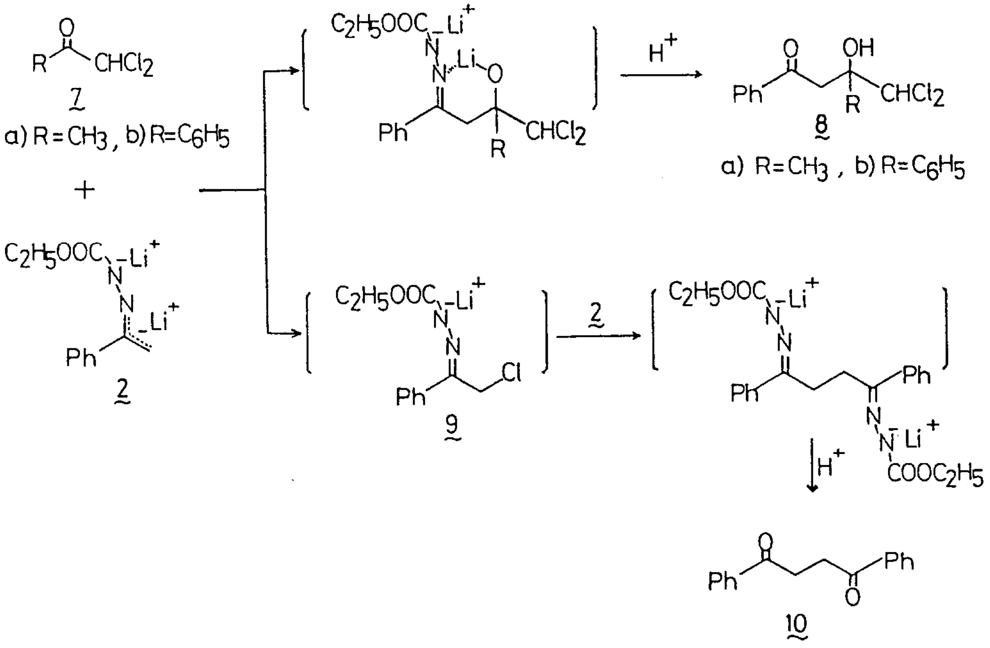
The reaction of 1,1-dichloroacetone (7a) with 2 gave γ-dichloro-β-hydroxyketone (8a) and 1,2-dibenzoylethane (10) in 62% and 8% yields, respectively. Our mechanistic interpretation is outlined in Scheme 2. The formation of 10 can be explained via intermediate (9) followed by the reaction with the other 1,4-dianion, 2.

Scheme 2



We are further investigating the synthetic and mechanistic ramifications.

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