Tetrahedron Letters,Vol.24,No.31,pp 3239-3242,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

# 1,4-DIANION OF ACETOPHENONE N-ETHOXYCARBONYLHYDRAZONE AS A SYNTHETIC INTERMEDIATE

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Abstract: Various β-hydroxyketones and α,β-unsaturated ketones were prepared by the reaction of aldehydes and ketones with 1,4-dianion (2) which is derived from acetophenone N-ethoxycarbonylhydrazone (1) with butyllithium. In the reaction of 2 with carbonyl compounds such as ester, amide, acid anhydride, acyl chloride, and alkyl carbonate, pyrazole derivatives were obtained in good yields.

1,4-Dianion of N-monosubstituted hydrazones[1)] have received much attention as synthetic intermediates owing to their interesting reactivities and preparative significance. However, their application in organic synthesis has been limited because of the considerable difficulty[2)] in converting a hydrazone to carbonyl compound by hydrolysis. In our preceding study[3)] on the synthesis of 5-substituted 2-alkoxy-1,3,4-oxadiazoles, it was observed that acetophenone N-ethoxycarbonylhydrazone (1) underwent facile acidic hydrolysis under mild conditions. This finding led us to apply the anion 1 to synthetic organic reactions. The reaction behavior of N-alkoxycarbonylhydrazono-ketones has not been well investigated[4)] so far.

We now wish to report the reaction of various carbonyl compounds with 1,4-dianion (2) which is readily derived from 1 with butyllithium. In the reaction of aldehydes and ketones with 2, β-hydroxyketones and/or α,β-unsaturated ketones were obtained in good yields. On the other hand, when the carbonyl compounds such as ester, amide, acid anhydride, acyl chloride, alkyl chloroformate and alkyl carbonate were reacted with 2, pyrazole derivatives were obtained in good yields by the cyclization of the reaction intermediates.

A typical procedure is descrived for the preparation of β-hydroxyketones and α,β-unsaturated ketones: To a cooled THF solution (-78 °C) of 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 a carbonyl compound (2.18 mmol). After a complete fading of the color, the reaction mixture was stirred for additional 2h at -78 °C, and the solvent was removed in vacuo. The residual mixture was treated with conc. HCl, acetic acid, water, 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 ($CHCl_3$) or preparative TLC ($CHCl_3$) to give $\beta$-hydroxyketone (3) and/or $\alpha,\beta$-unsaturated ketone (4) (Scheme 1). The yields are shown in Table 1.

Scheme 1

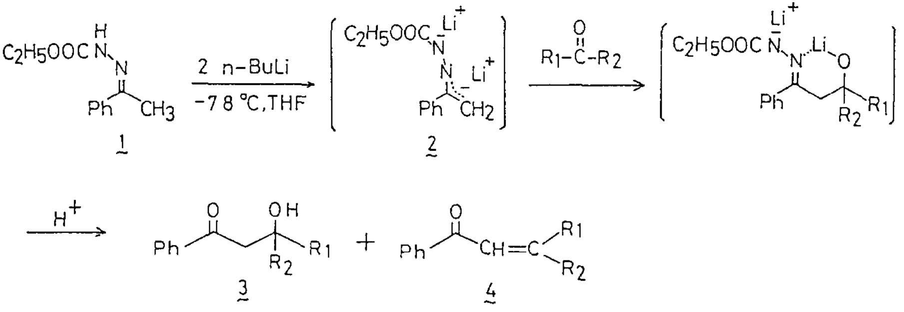
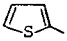


Table 1. Reaction of Aldehydes and Ketones with 2[a)]

| Entry | Carbonyl Compound | | Yield[b)] (%) | |
|---|---|---|---|---|
| | $R_1$ | $R_2$ | 3 | 4 |
| a | Ph | H | 68 (0)[c)] | 10 (86)[c)] |
| b | $CH_3CH_2CH_2CH_2CH_2$ | H | 64 | 13 |
| c |  | H | - | 90 |
| d | Ph | Ph | 61 (0)[c)] | 23 (94)[c)] |
| e | $CH_3CH_2CH_2$ | $CH_3CH_2CH_2$ | 24 | 42 |
| f | $-(CH_2)_5-$ | | 46 | 14 |

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

b) Isolated yields by column chromatography and preparative TLC.

c) Yields when the hydrolyses were carried out at 50 °C.

Next, the reaction of esters, amides, acid anhydrides, acyl chlorides with 2 were carried out under similar reaction conditions. In these cases, 5-substituted 1-ethoxycarbonyl-3-phenyl pyrazoles 5 were obtained in good yields by the cyclization of the reaction intermediate A and the following dehydration of B. The yields of 5 are shown in Table 2.

Scheme 2

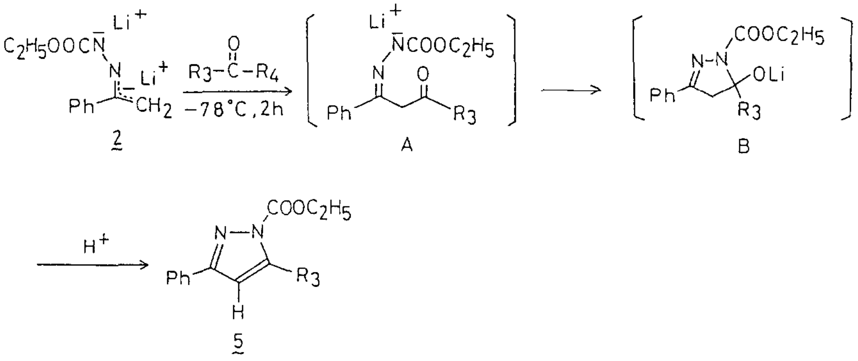


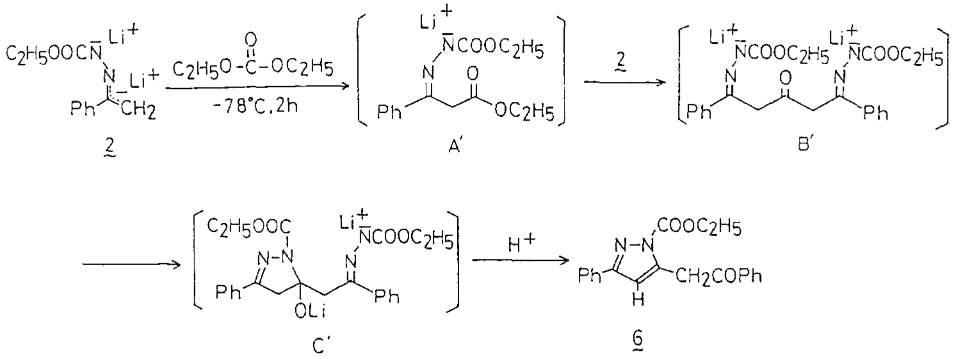
Table 2. Reaction of Esters, Amides, Acid Anhydrides and Acyl Chlorides with 2

| Entry | Carbonyl Compound | | Yield (%) |
|---|---|---|---|
| | $R_3$ | $R_4$ | $5^{a)}$ |
| g | Ph | $CH_3O$ | 74 |
| h | $CH_3$ | n-$C_4H_9O$ | 36 |
| i | H | n-$C_4H_9O$ | 77 |
| j | $CH_3$ | $(CH_3)_2N$ | 37 |
| k | H | $(CH_3)_2N$ | 38 |
| l | Ph | PhCOO | 43 |
| m | $CH_3$ | $CH_3COO$ | 25 |
| n | Ph | Cl | 49 |
| o | $CH_3$ | Cl | 32 |

a) All products gave satisfactory ir, mass, nmr and elemental analyses.

The reaction of diethyl carbonate with 2 gave pyrazole having $PhCOCH_2$-group at the 5 position in 22% yield. The mechanistic interpretation is outlined in Scheme 3. In a similar manner as seen in Scheme 2, the reaction would be initiated by the C-C bond formation to give intermediate A′. The intermediate A′, in this case, would undergo nucleophilic attack by 2 to afford intermediate B′. Subsequent ring closure would give C′ and result in the formation of 6 by hydrolysis and dehydration. The reaction of methyl chloroformate with 2 also gave 6 in 42% yield.

Scheme 3



Work is in progress to explore the applicability of 2 to other organic syntheses.

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(Received in Japan 29 March 1983)