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THE SYNTHESIS OF SELECTIVELY PROTECTED β-DIKETONES AND β-KETOALDEHYDES

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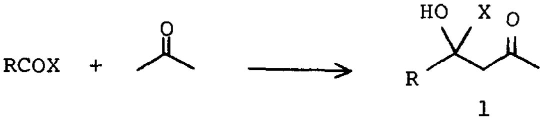
Summary: The reaction of acyl cyanides with enol silyl ethers produces β-cyano, β-hydroxy carbonyl compounds.

As part of our synthetic efforts, the preparation of a selectively protected β-diketone was desirable. Although several carbonyl protecting groups have been developed,[1] few exhibit any selectivity in the case of β-diketones.[2] The selective protection of β-ketoaldehydes, however, has been reported.[3] In view of these difficulties, we sought to introduce the protected carbonyl group directly by means of an aldol or alkylation reaction. A general plan is depicted in equation 1.



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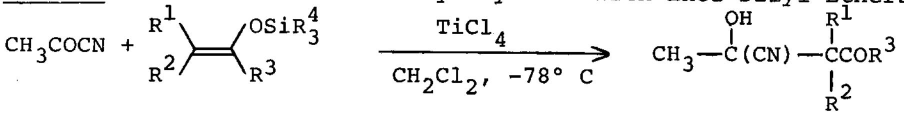
Since the use of carbanion chemistry would afford the deprotonated β-diketone, the Lewis acid mediated reactions of enol silyl ethers[4] was investigated. The reactions of acid chlorides and anhydrides had been reported[5] to provide β-diketones in good yield. However, the reaction with acyl cyanides, which can be conveniently prepared from acid chlorides in one step,[6,7] had not been described. In this Letter, we report that acyl cyanides react with enol silyl ethers at -78° C to afford 1 (X = CN) in modest to excellent yields. The resulting cyanohydrins can be protected,[8] decomposed with dilute base to the β-dicarbonyl compounds or dehydrated under acidic conditions to the unsaturated ketonitrile. The results are illustrated in Table I.

A low temperature is vital for a successful reaction. If the reaction is conducted at ambient temperature or at 0° C, no recognizable products can be isolated. From the results of Table I, it is clear that enol silyl ethers of ketones react effectively, while aldehyde enol silyl ethers afford low yields. Interestingly, the chemistry of aldehyde enol silyl ethers has been little studied.[9] Although the reduced yields for entries 6 and 7 may be due to the

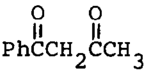
Table I - The Reaction of Acetyl Cyanide With Enol Silyl Ethers



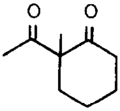
Entry	R^1	R^2	R^3	R^4	% Yield[a]
1	H	H	Ph	CH_3	81
2	H	H	Pr	CH_3	92
3	H	CH_2CH_2	CH_2CH_2	CH_3	67[b]
4	CH_3	H	Et	CH_3	85
5	CH_3	CH_2CH_2	CH_2CH_2	CH_3	93.5
6	H	$PhCH_2$	H	Et	31
7	H	C_5H_{11}	H	CH_3	37

[a] Isolated, chromatographed yields. Entries 3-7 were mixtures of diastereomers.
[b] Crude yield. The product dehydrated on silica gel chromatography.

instability of the cyanohydrin aldehyde, other factors such as a change of solvent or Lewis acid might improve the yields. Entries 1 and 5 were converted in high yield to the known β-diketones 2[10] and 3[11], respectively, by stirring with cold, dilute aqueous base. The spectra were identical to those


$PhC(=O)CH_2C(=O)CH_3$

2



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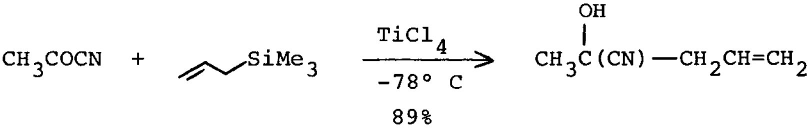
of the diketones prepared by the literature methods. The reaction with allyl trimethyl silane was also investigated. At -78° C with acetyl cyanide an 89% yield of cyanohydrin 4 was obtained.



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In a typical experiment, titanium tetrachloride (1.6 mmol) was added to a stirred solution of acetyl cyanide (1.5 mmol) in 6 mL CH_2Cl_2 at -78° C. To the above solution was added cyclohexanone enol silyl ether (1.5 mmol) in 2 mL CH_2Cl_2. After 2 hrs at -78° C, water as added and the reaction was allowed to warm to 10° C. The aqueous layer was extracted twice with ether. The combined organic extracts were dried and concentrated in vacuo to afford a 67% yield of crude product.

NMR data for entries 1-7 can be found in reference 12.

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12. Entry 1: NMR ($CDCl_3$) δ 1.70 (s, 3H), 3.4 (AB quartet, 2H), 5.05 (bs, 1H), 7.1-8.05 (m, 5H).
Entry 2: NMR ($CDCl_3$) δ 0.93 (t, J = 7 Hz, 3H), 1.59 (s, 3H), 1.4-1.9 (m, 2H), 2.25-2.7 (m, 2H), 2.9 (AB quartet, 2H), 4.95 (bs, 1H).
Entry 3: NMR ($CDCl_3$) δ 1.2-2.8 (m, 9H), 1.58 (s, 3H), 4.8 (bs, 1H).
Entry 4: NMR ($CDCl_3$) δ 1.0-1.4 (m, 6H), 1.52 and 1.60 (s, 3H), 2.3-3.0 (m, 3H).
Entry 5: NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.46 and 1.53 (s, 3H).
Entry 6: NMR ($CDCl_3$) δ 1.64 (s, 3H), 7.23 (bs, 5H), 9.62 (bs, 1H).
Entry 7: NMR ($CDCl_3$) δ 0.75-1.7 (m, 11H), 1.60 and 1.63 (s, 3H), 9.70 (t, J = 2Hz, 1H).

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