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A CONVENIENT METHOD FOR THE PREPARATION OF ENOL ACETATES OF α-KETO ESTERS BY THE ALKYLATION OF CYANOHYDRIN SILYL ETHERS DERIVED FROM GLYOXYLIC ESTERS WITH BENZYL AND ALLYL HALIDES

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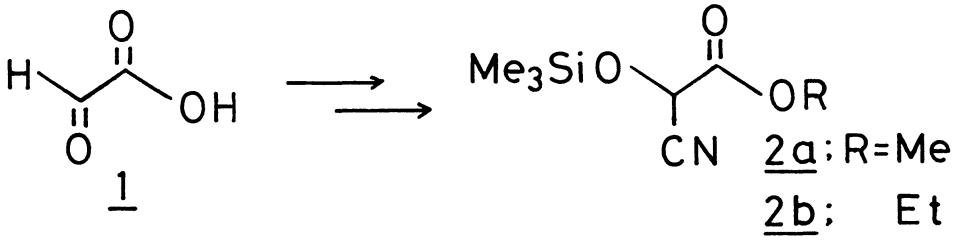
Cyanohydrin silyl ethers, prepared by trimethylsilylcyanation of glyoxylic esters, smoothly react with LDA (lithium diisopropylamide) to yield the lithium salts, which in turn react with alkyl halides such as allyl bromide to give, after acetylation, the corresponding enol acetates of α-keto esters in good yields.

Glyoxylic acid (1) is the simplest α-keto acid and exists in plants and some microorganisms as an important metabolic intermediate of the glyoxylate cycle. However, this acid is unstable except in water and has not often been used in organic synthesis. From the standpoint of synthetic chemistry, glyoxylic acid could be a stable and useful intermediate by transforming formyl group of 1 into cyanohydrin silyl ether,[1,2] since cyanohydrin silyl ethers are distinguished from free cyanohydrins both in their ease of preparation and isolation, and in their reluctance to undergo cleavage and reversion to the parent carbonyl compounds under basic or nucleophilic conditions.

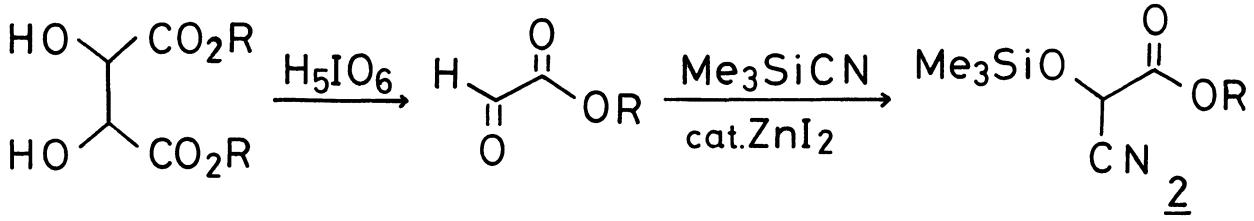
In this communication, we wish to report a convenient method for the preparation of enol acetates of α-keto esters from cyanohydrin silyl ethers derived from glyoxylic esters (2) and alkylating reagents such as benzyl bromide and allyl bromide.

Scheme I



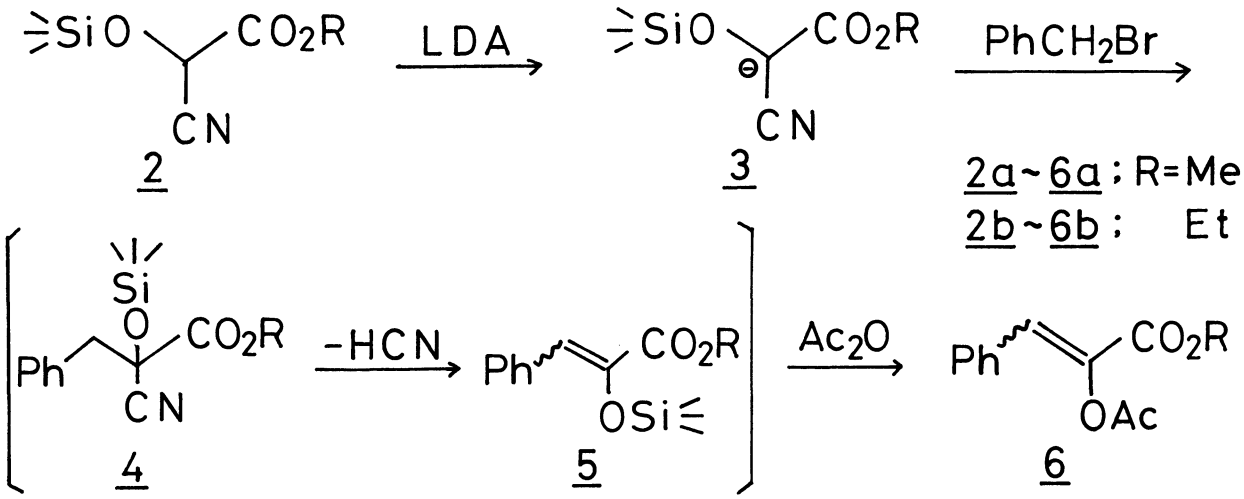
In the first place, methyl (ethyl) glyoxylate,[3] prepared by oxidative cleavage of dimethyl (diethyl) tartrate with periodic acid, was successively converted to the corresponding cyanohydrin silyl ether (2)[4] by treatment with trimethylsilylcyanide in the presence of zinc iodide[1c,1d] as a catalyst (Scheme II).

Scheme II



Next, cyanohydrin silyl ether (2b) was treated with LDA in THF solution and so formed anion (3b) was allowed to react with benzyl bromide. Then, acetic anhydride was added to the resulting solution and after usual work-up, ethyl 2-acetoxycinnamate (6b) was isolated in 32% yield (Scheme III). The reaction is considered to proceed with the acetylation of silyl enol ether (5b) formed by the α,β-elimination of hydrogen cyanide from (4b).

Scheme III



A screening of the reaction conditions using benzyl bromide as an alkylating reagent revealed that THF-HMPA (hexamethylphosphoric triamide) mixed solvent raised the yield of the enol acetate (6b) to 66%. In addition, it was found that the use of 1.2 equivalents of LDA to silyl ether (2) and a small excess of diisopropylamine gave the best result as shown in Table 1.

Table 1. The Effect of Reaction Conditions

R	Molar Ratio of LDA per 2	Solv.	Temp	Time (h)	Yield of 6 (%)[b,c]
Et	1.2	THF	refulx	2	32
"	"	THF-HMPA (5:1)	-78°C	3	23
"	"	"	0°C	3	66
"	" [a]	"	"	1.5	79
Me	1.0[a]	"	"	"	66
"	1.2[a]	"	"	"	82
"	1.5[a]	"	"	"	73

a) Molar ratio of BuLi : diisopropylamine = 1 : 1.6∿2.0
b) Molar ratio of cyanohydrin silyl ether (2) : benzyl bromide = 1 : 0.7
c) Isolated yield. Yields are based on benzyl bromide.

The anion (3a), prepared from cyanohydrin silyl ether, was treated with various alkyl halides such as allyl bromide, and after the acetylation, the corresponding enol acetates (7) were obtained in good yields as summarized in Table 2.

Scheme IV

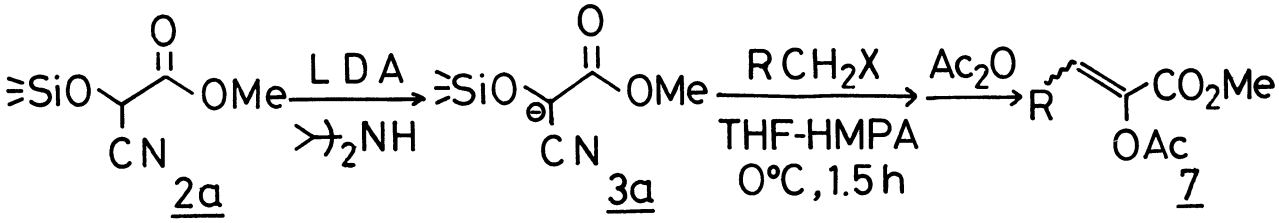
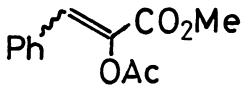
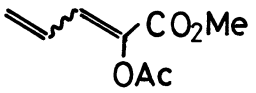
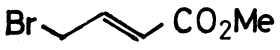
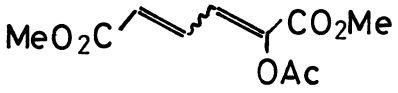
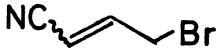
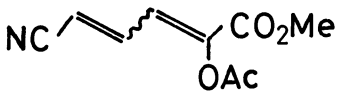
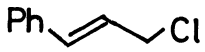
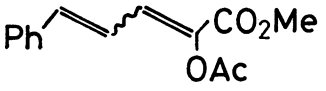
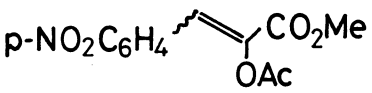
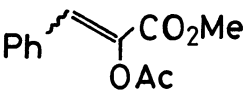


Table 2. Synthesis of Enol Acetates[a)]

RCH_2X[b)]	Product	Yield of 7 (%)[c)]
$PhCH_2Br$		74
		71
		72
		69
		61[d)]
$p\text{-}NO_2C_6H_4CH_2Br$		70
$PhCH_2Cl$		45[d)]

a) All the products gave satisfactory NMR and IR spectra.
b) Molar ratio of cyanohydrin silyl ether (2a) : BuLi : diisopropylamine : alkyl halide = 1 : 1.2 : 2 : 1.1∿1.4
c) Isolated yield. Yields are based on cyanohydrin silyl ether (2a).
d) Reactions were carried out at 0°C for 1 h and at room temperature for 0.5 h.

A typical procedure is described for the synthesis of methyl 2-acetoxycinnamate; under an argon atmosphere, to a THF (1.5 ml) solution of diisopropylamine (106 mg, 1.1 mmol) was added dropwise a hexane (0.37 ml) solution of butyllithium (0.55 mmol) at -78°C. Then a THF (1.5 ml) solution of methyl 2-cyano-2-trimethylsilyloxyacetate (86 mg, 0.46 mmol) was added dropwise at -78°C and the pale yellow solution was stirred for 0.5 h at this temperature. After hexamethylphosphoric triamide (1 ml) was added, the temperature was allowed to warm up to 0°C, and a THF (1.5 ml) solution of benzyl bromide (89 mg, 0.52 mmol) was added and stirred for 1.5 h at this temperature. The reaction was quenched by the addition of a THF (1.5 ml) solution of excess acetic anhydride (150 mg, 1.5 mmol) at 0°C and was allowed to warm up to room temperature. The organic materials were extracted with ether, and combined extracts were washed with water and dried over $MgSO_4$. Methyl 2-acetoxycinnamate (74 mg, 74%) was isolated by thin layer chromatography on silica gel. ^1H NMR (CCl_4) δ 2.19 (3H, s), 3.73 (3H, s), 7.1 - 7.6 (6H, m); IR (neat) 1765, 1725, 1650 cm^{-1}.

The present procedure provides a convenient one-pot synthesis of enol acetates of α-keto esters, starting from the cyanohydrin silyl ether of glyoxylic ester and alkylating reagents such as benzyl and allyl halides. The adduct (7), which has an α,β-unsaturated carbonyl function and an enol acetate moiety, is a useful synthetic intermediate. Further synthetic investigations using this intermediate (7) are now in progress.

References

1) For preparations of cyanohydrin silyl ethers by trimethylsilylcyanation of carbonyl compounds, see for instance: a) W. Lidy and W. Sundermeyer, Chem. Ber., 106, 587 (1973); b) D. A. Evans, J. M. Hoffman, and L. K. Truesdale, J. Am. Chem. Soc., 95, 5822 (1973); c) D. A. Evans, L. K. Truesdale, and G. L. Carroll, J. Chem. Soc., Chem. Commun., 1973, 55; d) D. A. Evans and L. K. Truesdale, Tetrahedron Lett., 1973, 4929.

2) For representative reactions of cyanohydrin silyl ethers with electrophiles, see: a) K. Deuchert, U. Hertenstein, and S. Hünig, Synthesis, 1973, 777; b) S. Hünig and G. Wehner, ibid., 1975, 180; c) S. Hünig and G. Wehner, ibid., 1975, 391; d) U. Hertenstein, S. Hünig, and M. Öller, ibid., 1976, 416.

3) T. R. Kelly, T. E. Schmidt, and J. G. Haggerty, Synthesis, 1972, 544.

4) 2a: bp 69°C/1.8 mmHg; ^1H NMR (CCl_4) δ 0.12 (9H, s), 3.68 (3H, s), 4.78 (1H, s); IR (neat) 1770 cm^{-1}. 2b: bp 71°C/3 mmHg; ^1H NMR (CCl_4) δ 0.15 (9H, s), 1.23 (3H, t, J = 7 Hz), 4.17 (2H, q, J = 7 Hz), 4.87 (1H, s); IR (neat) 1765 cm^{-1}.

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