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CONJUGATE NUCLEOPHILIC AROYLATION OF α,β-UNSATURATED ESTERS

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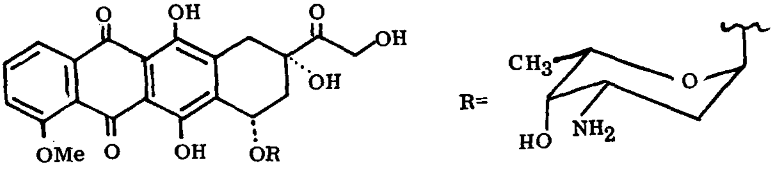
As a key step in a regiospecific approach to the synthesis of anthracyclinone antibiotics, in particular Adriamycin (1)[1], we envisioned the conjugate addition of a masked acyl anion[2] to an α,β-unsaturated ester (Eq. 1).



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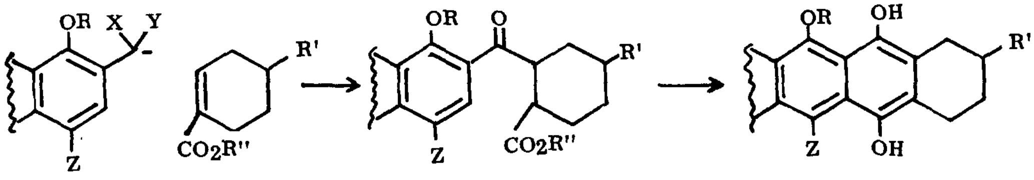
(1)

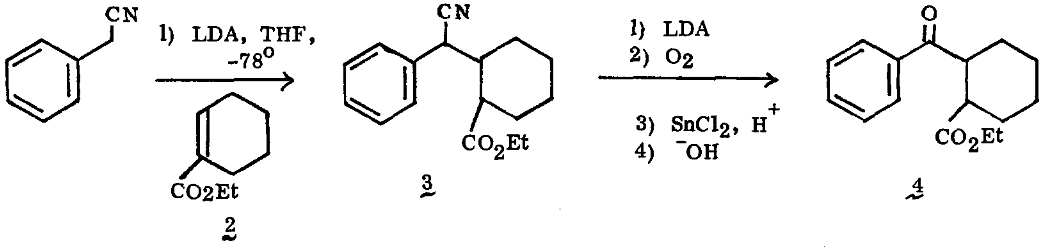


Although a number of workers have reported 1,4-addition of acyl anion equivalents to enones[2], few examples of the analogous conjugate addition to α,β-unsaturated esters have appeared[3]. We describe here a new and versatile method for conjugate nucleophilic aroylation of α,β-unsaturated esters.

Nitrile enolates add conjugatively to enones[4] and acrylates[5]. In view of the numerous methods for the oxidative conversion of α,α-disubstituted nitriles to ketones[6] we felt that addition of a nitrile enolate to an α,β-unsaturated ester followed by oxidation might provide a simple entry to the desired γ-ketoesters.

In a model study, addition of a THF solution of ester 2 to the lithium enolate of phenyl acetonitrile gave the Michael adduct 3[9] in 73% yield. Neither adding HMPA to the reaction mixture nor increasing the reaction time had an observable effect on the yield. Oxidative decyanation[8] gave aroyl ester 4[9](Eq. 2).

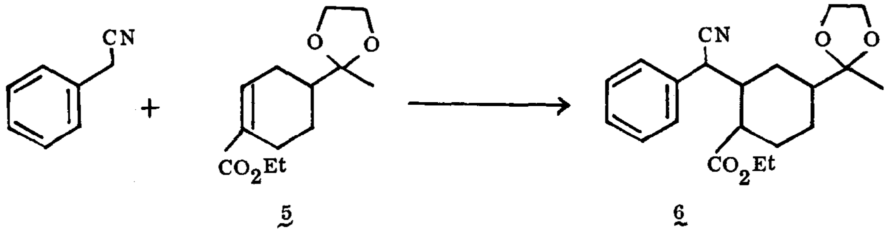
(2)



The addition/oxidation sequence is amenable to a variety of nitrile-ester systems (Table 1). In a typical experimental procedure, 1.87 g of phenylacetonitrile in 4 ml THF was added to a solution of LDA (1.3 equiv.) in THF (10 ml, -78°, N_2 or argon). After stirring 1/2 hr, 2.49 g of ester 2 was added dropwise in 5 ml THF. The reaction mixture was stirred for 3 hr at -78°, warmed to 0° over 1 hr and quenched with 5 ml of H_2O. Chromatography of the crude product on silica gel, followed by distillation, gave 3.15 g (73%) of the 1,4-adduct 3 as a pale, viscous oil. Oxidation by the method of Watt[6a] afforded ketoester 4 in 70% yield.

In the case of hindered esters, more vigorous conditions are required to effect conjugate addition. Thus, at -78° ester 5 failed to react with phenylacetonitrile enolate; however, upon warming to 0° for 3 hr, adduct 6[7] was isolated in 76% yield (Eq. 3). Similarly nitrile 7 failed to react with 5 at -78°; upon warming to -20°, 8[7](64%) and 9[9] (18%) were isolated[10](Eq. 4).

(3)



(4)

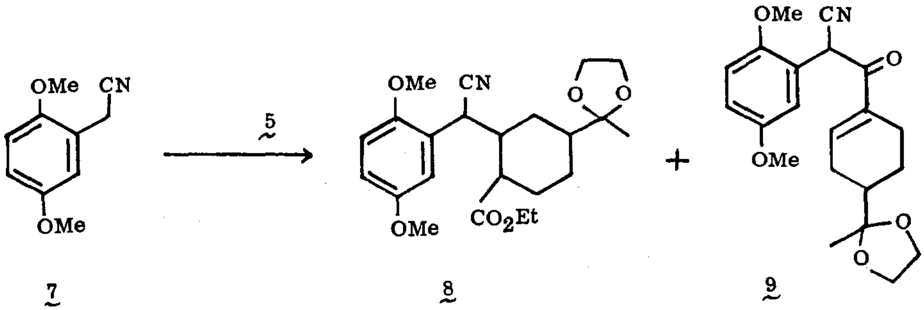
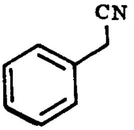
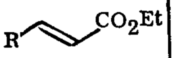
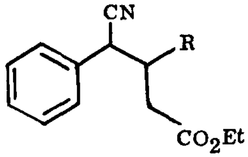
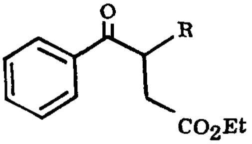
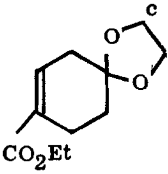
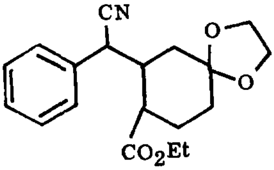
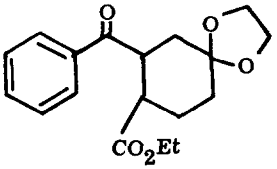
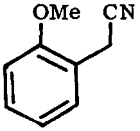
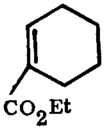
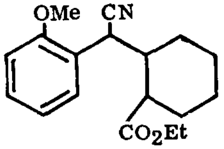
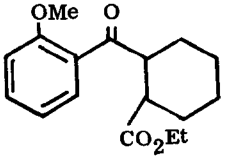


TABLE 1 AROYLATION OF UNSATURATED ESTERS

NITRILE	ESTER[a]	1,4 ADDUCT[9]	YIELD	KETOESTER[9]	YIELD
	 H R = Me Ph		50%[b] 89 74		— 72% 74
	[c] 		73[d]		84
			76		85

a) Methyl esters gave lower yields of 1,4-adducts.

b) All yields are for chromatographed and distilled or recrystallized material.

c) From cycloaddition of ethyl acrylate and trans-1-methoxy-3-trimethylsilyloxybutadiene. See S. Danishefsky and T. Kitahara, J. Org. Chem., 40, 538 (1975).

d) Based on recovered nitrile.

Application of the conjugate aroylation sequence to the synthesis of anthracyclinones is in progress.

Acknowledgment

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References

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2. See O. W. Lever, Tetrahedron, 32, 1943 (1976) for a review.

3. (a)H. Stetter and M. Schreckenberg, Angew. Chem., Int. Ed. Engl., 12, 81 (1973);(b) J. L. Herrmann, J. E. Richman, and R. L. Schlessinger, Tetrahedron Letters, 3271 (1973); (c) E. J. Corey, K. Narasaka, and M. Shibasaki, J. Am. Chem. Soc., 98, 6417 (1976); (d) M. P. Cooke and R. M. Parkman, J. Am. Chem. Soc., 99, 5222 (1977).

4. See, for example, R. Sauvetre and J. Seyden-Penne, Tetrahedron Letters, 3949 (1976).

5. D. E. Green, A. R. Martin, and A. I. White, J. Pharm. Sci., 59, 526 (1970).

6. (a) See S. J. Selikson and D. S. Watt, J. Org. Chem., 40, 267 (1975) and references therein; (b) E. Vedejs and J. E. Telschow, J. Org. Chem., 41, 740 (1976).

7. Infrared and nmr spectra were in accord with the assigned structure.

8. The Watt procedure is compatible with other functionality, at least in the case of benzyl nitriles; no α-hydroxy ester was observed as a result of the oxidation sequence.

9. Infrared and nmr spectra were in accord with the assigned structure. A satisfactory elemental analysis was obtained.

10. The ratio of 8 to 9 is extremely sensitive to temperature. When a solution of 5 and the enolate of 7 was warmed quickly from -78° to 0°, 8 and 9 were recovered in a ratio of 3:2.