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REGIOSELECTIVE SYNTHESIS OF β-KETOESTERS FROM LITHIUM ENOLATES AND METHYL CYANOFORMATE

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Summary: C-acylation of lithium enolates by methyl cyanoformate provides high yields of β-keto esters under mild conditions and with 100% regioselectivity.

There has been a pressing need in the organic synthesis repertoire for a reliable and general procedure which would allow C-acylation of ketones in a regio-controlled process to give β-keto ester derivatives. Methods based on the use of dialkyl carbonates[1], dialkyl oxalates[2], and methyl methoxymagnesium carbonate[3] do not permit the required control, while reaction with acyl halides or anhydrides[4,5] usually leads to mixtures of O- and C-alkylated products[6]. The quenching of lithium enolates by CO_2 does provide a general approach to the preparation of a specific regio-isomer, but the yields are frequently poor . This may be a consequence of the instability of the intermediate β-keto acids, but could also be due to the formation of unstable enol carbonates which decompose on work-up to return starting material[7].

In this Letter we report the development of a very efficient method which appears to be completely general for the regiocontrolled preparation of β-keto esters from the parent ketone. The method is based on the reaction of preformed lithium enolates with methyl cyanoformate[8] as indicated in the following scheme:

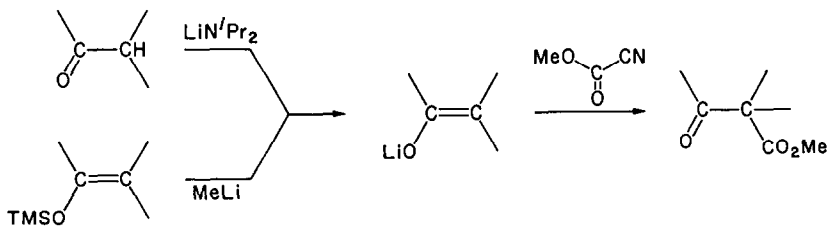
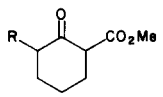
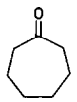
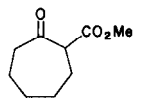
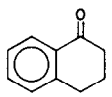
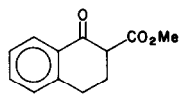
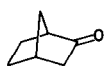
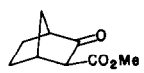
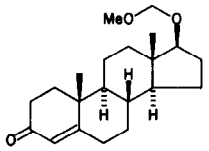
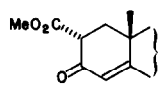
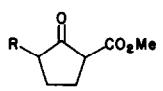
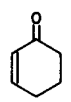
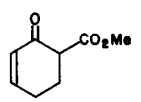
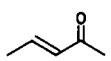
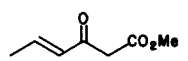
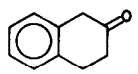
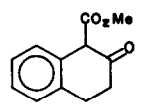
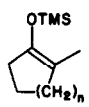
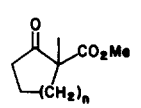


Table: Methoxycarbonylation of ketones *via* Lithium Enolates.

entry	substrate	product	yield (%)[a,b]	ref.
1,2	$CH_3(CH_2)_nCOCH_3$	$CH_3(CH_2)_nCOCH_2CO_2Me$	n = 2 84 n = 5 86	10 11
3,4			R = H 86 R = Me 86	12 13
5			96	14
6			92	15
7			85	16
8			96	17
9,10			R = H 71 R = Me 75	18 19
11			84	20
12			65	21
13			92	22
14,15			n = 1 72 n = 2 68	19 23

[a] Products characterised by ^{1}H-NMR and HRMS.

[b] Yields of isolated, chromatographically homogeneous products.

Procedure:

n-Butyl lithium (1.6 ml, 1.5M in hexane) was added to a stirred solution of diisopropylamine (336 μℓ, 2.4 mmole) in THF (5 ml) at -20°C under an atmosphere of nitrogen. After 30 min the temperature was lowered to -78°C, a solution of ketone (2.0 mmole) in THF (2.0 ml) was added through a double tipped needle, and then stirring continued at 0°C for 1h. The temperature was lowered again to -78°C, HMPA (204 μℓ, 2.0 mmole) added, followed by methyl cyanoformate (204 mg, 2.4 mmole). After stirring for 10 min the mixture was poured into cold water (20 ml) and the product extracted into ether (2x20 ml), dried (Na_2SO_4), concentrated, and chromatographed on silica gel. The simple β-keto esters were eluted with 2-10% ethyl acetate in hexane (up to 10% ethyl acetate was necessary with the more highly functionalized derivatives); acidification during the work-up procedure was not necessary.

Worthy of note is the use of nearly stoichiometric quantities of reagents and the stability of the cyanoformate towards the liberated amine.[9] Lithium enolates reacted rapidly at -78°C but no reaction was observed with either sodium or potassium derivatives, even at 20°C. Essentially no variation in yield was observed with a range of lithium bases, i.e. lithium diisopropylamide, lithium 2,2,6,6-tetramethylpiperidide and lithium hexamethyl disilazide. The results obtained with a wide range of substrates have been consistently very good to excellent and are summarized in the Table. The regioselectivity in all cases was 100%, reflecting the specificity of enolization.

With straightforward examples (entries 1-8) the yields were often considerably superior to those obtained from other procedures, and even with base sensitive substrates (entries 9-13) the results were very satisfactory. The last two examples (entries 14,15) are especially important in that they establish the first direct syntheses of non-enolizable β-keto esters from C-acylation of ketones. Moreover, by demonstrating the possibility of reversing traditional acylation-alkylation sequences, they furnish important implications for stereochemical control in chiral substrates. Studies on such compounds are in progress, as well as an examination of the utilization of benzyl, trichloroethyl and other cyanoformate esters[8] which would allow selective deesterification at a later stage.

References and Footnotes

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6. The problem of controlling C- versus O-alkylation with enolate anions has been thoroughly reviewed.[4,5] The partition of products from reaction with acyl halides and acid anhydrides is highly dependent upon some or all of the following factors: temperature, stoichiometry, solvent, the metal cation, the nucleofugal group in the reagent and steric congestion in the substrate. High yields of β-diketones have been obtained from the reaction of lithium enolates with alkanoyl or aroyl nitriles (A.S. Howard, C.A. Meerholz and J.P. Michael, *Tetrahedron Lett.*, 1979, 1339).

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17. M.p. 139-141°C; IR 1740,1670,1608cm^{-1}; ^{1}H NMR (270MHz) δ0.80,1.18,3.28(s, 3H) 3.47(dd J5, 15Hz, H2) 3.53(t, J8Hz, H17) 3.72(s,3H) 4.62,4.63(ABq, J 7Hz, 2H) 5.76(s,H4). Calcd. for $C_{23}H_{34}O_5$: C,70.7; H,8.8. Found: C,71.0; H,9.2%.

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20. B.p. 70°C/15mm(kugelrohr,bath temp.); IR 1740,1675,1618cm^{-1}; ^{1}HNMR(270MHz) δ3.4(m,H1)3.75(s,3H)6.06(dt,J10,2Hz,H3)7.04(dt,J10,3Hz,H4). Calcd for $C_8H_{10}O_3$: C,62.3; H,6.5. Found: C,62.3; H,6.7%.

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