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Carbomethoxypropionyl Cyanide: A Regioselective C-Acylation Reagent for the Preparation of β-Dicarbonyl Compounds.

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Abstract: Carbomethoxypropionyl cyanide reacts regioselectively with a variety of enolates to provide C-acylation products in high yield.

The preparation of 1,3-diketones and 1,3-ketoesters by the C-acylation of ketone enolates is an important synthetic method which has been well studied and summarized in several reviews.[1] A variety of factors play a role in the efficient preparation of β-dicarbonyl compounds, including the regioselectivity of C-acylation (using asymmetric ketone precursors), the generation of diacylation products, proton exchange between starting material enolate and the more acidic 1,3-diketone products, and the generation of both O-acylation and C-acylation materials. Numerous carboxylic acid derivatives including anhydrides, acid chlorides, dialkyl carbonates, dialkyl oxalates, and methyl methoxymagnesium carbonate have been used as acylating agents;[2] however, these reagents can produce either low product yields or a mixture of O- and C-acylation products which are often difficult to separate from one another because of their similar polarity.[3] In contrast, several reports have suggested that acyl cyanides are effective acylating agents, reacting with ketone enolates almost exclusively at the carbanion center.[4] Despite their potential utility in the construction of β-dicarbonyl compounds and their synthetic accessibility through a variety of methods,[5] acyl cyanides are not commonly used as acylating reagents in organic synthesis.

In an effort to prepare antigen precursor **2**, for use in the development of an antibody-catalyzed herbicide degradation system, we required the introduction of a β-ketoester functionality into decalone derivative **1**. Traditional acylation methods using succinic anhydride failed to give either C- or O- acylation products when reacted with the enolate of **1**, due to steric hindrance caused by the *cis*-methyl fusion of the bicyclic ring system. Reaction of the enolate of **1** with 3-carbomethoxypropionyl chloride afforded almost exclusively the corresponding enol ester, even when reverse addition was performed. Other acylating reagents, including dimethyl carbonate, dimethyl oxalate and methyl methoxymagnesium carbonate, also failed to provide significant quantities of β-ketoester product.

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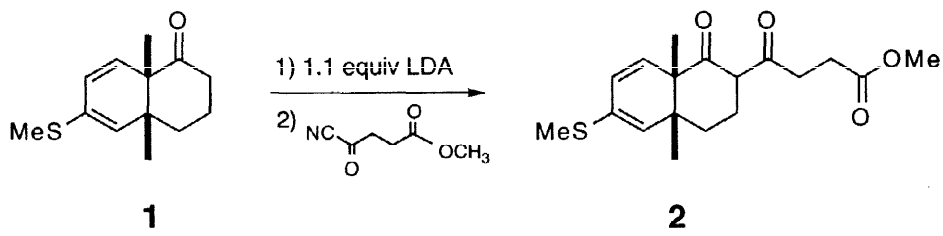


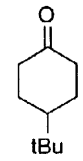
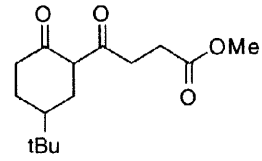
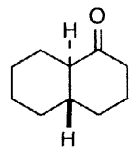
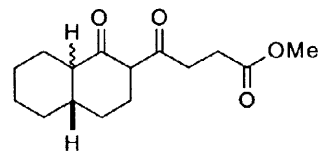
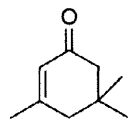
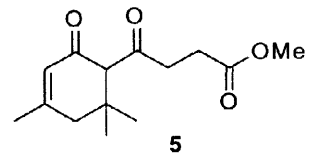
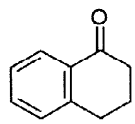
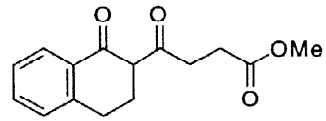
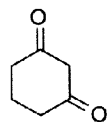
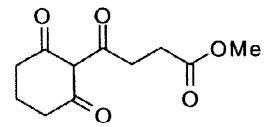
1 2

Since selective C-acylation of a variety of ketone enolates had been demonstrated with the use of methyl cyanoformate,[6] we prepared carbomethoxypropionyl cyanide from 3-carbomethoxypropionyl chloride by reaction with copper cyanide.[7] Condensation of the enolate of **1** with carbomethoxypropionyl cyanide provided **2** as the exclusive product in 88% isolated yield. Based on this remarkable result, we decided to investigate the scope of the method, by reacting carbomethoxypropionyl cyanide with several other ketone substrates (Table). In all cases, good to excellent yields were achieved. A general procedure follows (Method A):

A solution of the ketone **1** (0.2 mmol) in THF (1 mL) was added dropwise to lithium diisopropylamide (0.22 mmol) in THF (4 mL) at -78 °C. The resulting mixture was stirred for 1 h at -78 °C to ensure complete enolate formation. Carbomethoxypropionyl cyanide (0.22 mmol) was then added in one portion at -78 °C. After stirring for another 10 min, the reaction mixture was quenched by the addition of water. The mixture was extracted with Et_2O (2 x 15 mL) and the combined organic layers were washed with water (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (20% CH_2Cl_2 in hexane) to provide **2** (88% yield).[8]

According to both NMR and GC analysis of the reaction mixtures of Entries 1-5 (Table),[9-11] neither O-acylation nor diacylation occurred. Although a more complicated product distribution can potentially arise with unsaturated ketone **5a**, due to γ–deprotonation, only the kinetically favored C-acylation product **5** was obtained. Similarly, we found that when *trans* decalone was used as substrate, ester **4** was selectively formed as a result of kinetic enolization.[12] Excess base, which is typically required when other acylating agents are used, was not necessary; thus, the reaction occurred efficiently with only stoichiometric amounts of LDA. Interestingly, unlike the corresponding reactions with acyl chloride or anhydride electrophiles, acylation with carbomethoxypropionyl cyanide was a facile reaction, occurring rapidly even at -78 °C.

To examine the feasibility of this method for enolates generated under thermodynamic control, reaction of carbomethoxypropionyl cyanide with 1,3-cyclohexanedione was examined (Entry 5). Using a one-pot method (Method B), the diketone was treated with 1.2 equivalents of triethyl amine and 1.1 equivalents of acyl cyanide at 0 °C for 0.5 h. No starting material remained after 0.5 h and analysis of the recovered material indicated that C-acylation had preferentially occurred to yield **7** as the sole product.[13] This method is a clear advantage over the alternative two-step synthesis involving enolate acylation with 3-carbomethoxypropionyl chloride followed by subsequent treatment of the crude enol ester with triethyl amine and acetone cyanohydrin.[14]

Entry	Substrate	Product[a]	Method	Yield (%)[b]
1		 **3**	A	73
2		 **4**	A	75[c]
3	 **5a**	 **5**	A	92
4		 **6**	A	81
5		 **7**	B	95

[a] All products were recovered exclusively in the enol form (as determined by ^{1}H NMR), except **4** (3:2 keto/enol tautomers) and **5** (keto form). [b] Isolated yield after column chromatography. [c] Acylation occurred exclusively at the carbon center, as determined by comparison with authentic enol ester obtained by treatment with 3-carbomethoxypropionyl chloride.[15]

TABLE

In conclusion, carbomethoxypropionyl cyanide is a useful acylating reagent for the generation of 1,3-diketone systems. The reaction appears to be of general utility for a variety of ketone enolates, being highly selective for the formation of C-acylation products in high yields.

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6. Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
7. a) Pfaltz, A.; Anwar, S. *Tetrahedron Lett.* **1984**, *25*, 2977. b) Normant, J. F.; Piechucki, C. *Bull. Soc. Chim. Fr.* **1972**, 2402. c) Carbomethoxypropionyl cyanide was prepared as follows: To a solution of CuCN (1.79 g, 20 mmol) in CH_3CN (10 mL) was added carbomethoxypropionyl chloride (1.5 g, 10 mmol). The reaction mixture was refluxed for 0.5 h, then cooled to rt, and the solvent was removed under reduced pressure. The CuCl byproduct was removed by filtration after redissolving the residue in ether. Removal of the solvent followed by distillation gave carbomethoxypropionyl cyanide as a slightly yellow oil (0.95 g, 67%): IR (cm^{-1}) 2225, 1727; ^1H NMR ($CDCl_3$) δ 3.72 (s, 3H); 3.07 (t, J = 6.6 Hz, 2H), 2.74 (t, J = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 175.2, 171.3, 113.0, 52.3, 39.8, 27.0.
8. **2**: ^1H NMR ($CDCl_3$) δ 15.70 (s, 1H), 5.72 (m, 2H), 5.01 (s, 1H), 3.70 (s, 3H), 2.78 (t, J = 6.6 Hz, 2H), 2.72-2.61 (m, 2H), 2.30 (t, J = 6.6 Hz, 2H), 2.25 (s, 3H), 1.88-1.76 (m, 1H), 1.49-1.39 (m, 1H), 1.21 (s, 3H), 1.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 201.3, 181.7, 173.4, 133.5, 129.9, 126.9, 122.3, 105.0, 51.8, 44.8, 38.0, 32.5, 29.9, 27.8, 21.1, 20.2, 17.8, 14.5.
9. **3**: ^1H NMR ($CDCl_3$) δ 15.36 (s, 1H), 3.70 (s, 3H), 2.92-2.74 (m, 2H), 2.63 (t, J = 6.2 Hz, 2H), 2.45-2.30 (m, 3H), 2.10-1.97 (m, 1H), 1.90-1.80 (m, 1H), 1.32-1.20 (m, 2H), 0.92 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 200.7, 179.0, 173.5, 106.4, 51.8, 44.4, 32.3, 31.4, 27.7, 27.3, 24.8, 22.7.
10. **5**: ^1H NMR ($CDCl_3$) δ 5.82 (s, 1H), 3.65 (s, 3H), 3.38 (s, 1H), 3.00-2.38 (m, 5H), 1.95 (s, 3H), 1.99-1.93 (m, 1H), 1.09 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 204.9, 194.7, 172.8, 162.5, 123.4, 69.9, 51.7, 43.4, 40.2, 36.1, 28.6, 27.4, 25.9, 24.5.
11. **6**: ^1H NMR ($CDCl_3$) δ 15.91 (s, 1H); 7.90 (d, J = 7.4 Hz, 1H); 7.39-7.18 (m, 3H); 3.71 (s, 3H), 2.88 (two overlapping t, J = 6.6 Hz, 4H), 2.72-2.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 197.3, 173.3, 173.2, 140.3, 131.6, 130.6, 127.5, 126.8, 125.6, 105.6, 51.8, 32.0, 28.2, 28.0, 21.9.
12. Compound **4** was a complex mixture of *cis* and *trans* fused bicycles, in enol and keto forms: ^1H NMR ($CDCl_3$) δ 15.87 (s, 0.7H, enol H), 3.69 and 3.66 (s, 3:2 ratio, 3H), 3.57 and 3.52 (d, J = 5.9, 3:2 ratio, 0.3H, diketone H), 2.90- 2.50 (m, 4 H), 2.48-0.88 (m, 14H); ^{13}C NMR ($CDCl_3$, peaks assigned to *trans* fused enolic form) δ 199.5, 182.5, 173.5, 105.5, 51.8, 46.6, 39.3, 33.6, 32.1, 29.7, 27.9, 27.0, 26.4, 25.9, 23.5.
13. **7**: ^1H NMR ($CDCl_3$) δ 17.60 (br s, 1H), 3.72 (s, 3H), 3.38 (t, J = 5.9 Hz, 2H), 2.63 (t, J = 5.9 Hz, 2H), 2.82-2.35 (m, 4H), 1.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 204.4, 196.8, 195.3; 173.2, 113.2, 51.7, 38.5, 36.4, 32.4, 27.8, 19.1.
14. Montes, I. F.; Burger, U. *Tetrahedron Lett.* **1996**, *37*, 1007. *Note*: This reaction is presumed to occur through an acyl cyanide intermediate.
15. Enol ester: ^1H NMR ($CDCl_3$) δ 5.30 (m, 1H), 3.69 (s, 3H), 2.77-2.62 (m, 4H), 2.18-2.05 (m, 3H), 1.76-1.56 (m, 4H), 1.53-0.85 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 172.5, 170.8, 150.4, 113.9, 51.8, 43.1, 41.3, 33.1, 29.3, 29.0, 28.9, 28.0, 26.3, 23.7.