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# A CONVENIENT METHOD FOR THE SYNTHESIS OF α-KETOESTERS FROM ALDEHYDES

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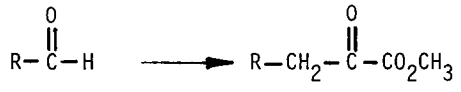
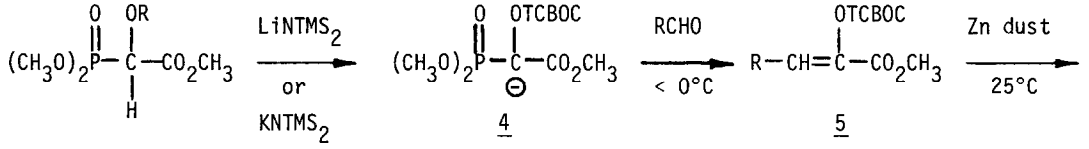
Summary: An efficient two step, two carbon homologation of aldehydes to α-ketoesters is described.

In connection with a program directed at the synthesis of rationally designed analogues of the tremorgenic mycotoxins, we required a general method for the preparation of monosubstituted α-ketoesters (2), where the substitutent R contained remote sites of unsaturated and acid sensitive functionality. While a number of synthetic equivalents for the acyl anion of glyoxalate esters have been reported,[1] none of these were generally useful for this type of transformation.[2]

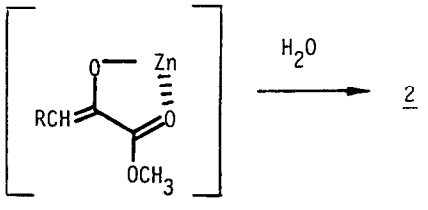


1 2

We report here a very convenient solution to this problem. The crystalline trichloro-t-butyloxy carbonate (TCBOC) protected phosphonoglycolate ester 3b[3] is quantitatively converted to the enolate anion 4 at low temperature (lithium or potassium hexamethyldisilylamide in THF). Solutions of the stabilized enolate 4 undergo facile Horner-Emmons reaction with a variety of aldehydes at or below 0°C.[8]



3a, R = H
3b, R = $CO_2C(CH_3)_2CCl_3$



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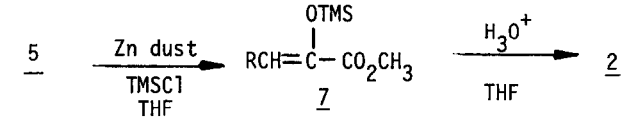
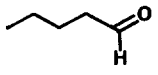
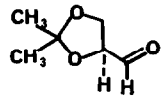
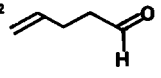
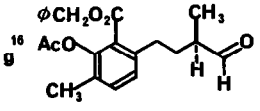
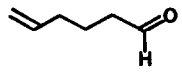
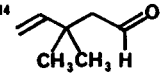
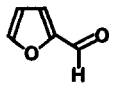
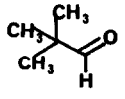
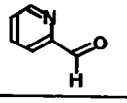
The non-basic nature of the enolate 4 allows the preparation of α-ketoesters 2f and 2g from chiral aldehydes 1f and 1g without racemization. Conversion of the Horner-Emmons products 5 into the α-ketoesters could be effected by reductive elimination of the TCBOC protecting group with zinc dust[9] (20 equivalents) in a dilute ethereal solution (5% v/v) of glacial acetic acid. It was noted that in some cases the intermediate zinc enolate (6) was remarkably stable to the mild conditions of the reaction and workup. In those cases the α-ketoesters could be obtained after purification by flash chromatography[6] on silica gel. If aldol type dimerization was observed as was the case for ketoesters 2d and 2e, the deprotection was carried out in the presence of 2 equivalents of trimethylsilyl chloride (TMSCl). The resultant labile silylenolether (7) underwent clean conversion to the α-ketoester on aqueous workup.[9]




The utility of the α-ketoester 2d for the synthesis of a rationally designed analogue of the mycotoxin marcfortine is currently under investigation.

| 1, RCHO | 5, yield[a,b] | 2, yield[a] | 1, RCHO | 5, yield[a,b] | 2, yield[a] |
|---|---|---|---|---|---|
| a  | 82 | 81[c] | f[15]  | 80 | 85[c] |
| b[12]  | 85 | 80[c] | g[16]  | 74 | 78[c] |
| c[13]  | 79 | 82[c] | | | |
| d[14]  | 82 | 80[d] | h  | 79 | 41[c] |
| e  | 76 | 64[d] | i  | 86 | 35[c] 83[20] |

[a] isolated yields of pure products.[8-11,17]

[b] mixtures of E and Z isomers were obtained.

[c] method a: Zn dust ; 5% AcOH in ether.[9]

[d] method b: Zn dust ; TMSCl in THF.[9]

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References and Notes:

1) For a review of methods for the preparation of α-keto acid derivatives see A.J.L. Cooper, J.Z. Ginos and A. Meister, Chem. Rev., 1983, 83, 321-58.

2) For recent glyoxalate derived acyl anion equivalents see M.T. Reetz, H. Heimbach and K. Schwellnus, Tetrahedron Lett., 1984, 25, 511-4; W.J. Thompson and C.A. Buhr, J. Org. Chem., 1983, 48, 2769-72; and references cited therein.

3) The α-hydroxyphosphonate 3a and its utility for the synthesis of 2-alkoxyacrylates was first reported by: E. Nakamura, Tetrahedron Lett., 1981, 22, 663-6. For large scale preparation of 3, we found the modified procedure described below to be more convenient.[4] For the synthesis of α-ketoesters, we found the TCBOC protected[5] reagent 3b to be more generally convenient and efficient than the silyl or alkyl ether protected reagents. This carbonate (3b) is an air stable, non-hygroscopic, white crystalline solid.[7]

4) Preparation of 3a: To a rapidly stirred solution of dimethyl tartrate (60.6g, 0.34 mole) in 500 mL of 35% THF in ether cooled in an ice bath was added 74g (0.32 mole) of finely pulverized $H_5IO_6$. After stirring for 1 hr at 0°C, it was allowed to warm and stir at 25°C until TLC (5% MeOH/E)[19] indicated complete consumption of tartrate. The mixture was diluted with ether (500 mL), filtered and dried ($MgSO_4$ and $K_2CO_3$). Concentration and distillation through a 10 cm Vigreux column afforded 47.4g (83%) of a clear, colorless oil (b.p. 50-55°C, 30mm). The methyl glyoxalate,[18] freshly distilled dimethylphosphite (50g, 0.44 mole) and p-toluenesulfonic acid (0.25g) were dissolved in 400 mL of benzene and heated to reflux under a Dean-Stark water separator for 2 hrs. More dimethylphosphite was added (4.4g) and the reflux was continued until the reaction was complete (TLC; 60% acetone/H;[19] 12 hrs). After concentration, the product crystallized from ethyl acetate (60 mL) and ether (20 mL). Ether was added in 20 mL portions until the supernatant remained clear. After drying the first crop weighed 68g. A second crop was obtained in a similiar manner from the mother liquor (4.5g, 82% combined yield). m.p. 59-61°C.

5) H. Eckert, M. Listl, and I. Ugi, Angew. Chem. Int. Ed. Engl., 1978, 17, 361-2.

6) W.C. Still, M. Kahn and A. Mitra, J. Org. Chem., 1978, 43, 2923-5.

7) Preparation of 3b: To a stirred, ice cooled solution of 3a (16g) and 10 mL of pyridine in 50 mL of $CH_2Cl_2$ was added 25g of TCBOC-Cl in 10 mL $CH_2Cl_2$ over 20 min. After 15 min, no 3a could be detected by TLC (1:4:5 MeOH/EA/D).[19] The mixture was washed with 10% HCl; sat. $NaHCO_3$ and dried ($MgSO_4$). After filtration through 50 mL of silica gel with 200 mL of ether (Rf 0.4 in E)[19] and concentration, the product crystallized on addition of hexane. After drying the product weighed 26.7g. A second crop was obtained from the mother liquor (2.2g, 92% combined yield). m.p. 79-80°C; $^1$H-NMR ($CDCl_3$) δ 2.0 (s, 6H), 3.9 (s, 3H), 3.9 (d, 6H, J = 11 Hz), 5.35 (d, 1H, J = 18 Hz); IR ($CHCl_3$) 1790-1740, 1460, 1440 $cm^{-1}$.

8) General procedure for enol carbonates 5: To a stirred solution of $LiNTMS_2$ (28.2 mmol) in 30 mL of THF cooled to -78°C was added the phosphonate 3b (25 mmol) in 30 mL THF, dropwise. After stirring for 10 min, the aldehyde was rapidly added. After 5 min. the reaction was alloed to warm to 0°C and stir 20 min. The mixture was poured into ether (200 mL) and washed with 10% HCl; sat. $NaHCO_3$ and dried ($MgSO_4$). Concentration and evaporative distillation at 0.02mm afforded the pure enol-carbonate.[10,17]

9) General procedure for the α-ketoesters 2: (Method a) A solution of 1 mmol of the enol-carbonate 5 in 20 mL of 5% glacial AcOH in ether (v/v) was stirred with 20 mmol zinc dust for 1 hr at 25°C. The mixture was filtered, washed with sat. $NaHCO_3$ and dried ($MgSO_4$). Concentration and flash chromatography[6] afforded pure α-ketoesters.[11,17] (Method b) A solution of 1 mmol of the enol carbonate 5 in 20 mL THF containing 2 mmol TMSCl and 20 mmol zinc dust was stirred for 3 hrs at 25°C. The mixture was filtered, washed with 10% HCl and dried ($MgSO_4$). Concentration and evaporative distillation affored the pure α-ketoesters.[11,17]

10) Characteristics of enol-carbonates.[17,19] **5a**: Rf .3 (5% E/PE); H-NMR ($CDCl_3$) δ 0.9 (t, 3H, J = 6 Hz), 1.45 (m, 4H), 1.95 (s, 6H), 2.7 (m, 2H), 3.8 (s, 3H), 6.2, 6.5 (2t, 2H, J = 7 Hz); IR ($CHCl_3$) 1770, 1740 $cm^{-1}$. **5b**: Rf .35 (5% E/PE); H-NMR ($CDCl_3$) δ 2.0 (s, 6H), 2.3 (t, 2H, J = 8 Hz), 2.7 (t, 2H, J = 7 Hz), 3.8 (s, 3H), 4.9-5.2 (m, 2H), 5.5-5.9 (m, 1H), 6.25, 6.5 (2t, 2H, J = 9 Hz); IR ($CHCl_3$), 1770, 1740 cm-1. **5c**: Rf .4 (5% E/PE); H-NMR ($CDCl_3$) δ 1.2-1.8 (m, 2H), 2.0 (s, 6H), 2.0-2.4 (m, 2H), 2.5-2.8 (m, 2H), 3.8 (s, 3H), 4.8-5.2 (m, 2H), 5.6-5.9

(m, 1H), 6.15, 6.5 (2t, 1H, J = 7 Hz); IR ($CHCl_3$) 1770, 1740 $cm^{-1}$. **5d**: Rf .5 (10% E/PE); H-NMR ($CDCl_3$) δ 1.1 (s, 6H), 2.0 (s, 6H), 2.2, 2.6 (2d, 0.3H and 0.7H, J = 4 Hz), 3.8 (s, 3H), 4.8 (dd, 1H, $J_1$ = 10 Hz, $J_2$ = 2 Hz), 5.1 (dd, 1H, $J_1$ = 18 Hz, $J_2$ = 2 Hz), 5.8 (dd, 1H, $J_1$ = 18, $J_2$ = 10), 6.6, 6.1 (2t, 0.3H and 0.7H, J = 8 Hz); IR ($CHCl_3$), 1770, 1740 $cm^{-1}$. **5e**: Rf .5 (20% EA/H); H-NMR ($CCl_4$) δ 1.3 (s, 9H), 1.95 (s, 6H), 3.7 (s, 3H), 6.0, 6.1, (2s, 1H); IR ($CHCl_3$) 1770, 1740 $cm^{-1}$. **5f**: Rf .5 (30% E/PE); $[\alpha]_D^{23}$ = +42.5 (C = 0.01, $CHCl_3$); H-NMR ($CDCl_3$) δ 1.48, 1.50 (2s, 6H), 2.0 (s, 6H), 3.9 (s, 3H), 3.8-4.2 (m, 2H), 5.45 (q, 1H, J = 8 Hz), 6.3, 6.6 (2d, 1H, J = 7 Hz); IR ($CHCl_3$) 1770, 1740 $cm^{-1}$. **5g**: Rf .35 (20% EA/H); $[\alpha]_D^{23}$ = +15.2 (C = 0.014, $CHCl_3$); H-NMR ($CDCl_3$) δ 1.0 (d, 3H, J = 7 Hz), 1.25-1.9 (m, 2H), 1.95, 2.0 (2s, 6H), 2.1 (s, 3H), 2.4-2.8 (m, 3H), 3.8 (s, 3H), 5.4 (s, 2H), 5.8, 6.4 (2t, 2H, J = 9 Hz), 7.0, 7.25 (2d, 2H, J = 7 Hz), 7.4 (s, 5H); IR ($CHCl_3$) 1775, 1735 $cm^{-1}$. **5h**: Rf .4 (20% EA/H); H-NMR ($CCl_4$) 1.95 (s, 6H), 3.8 (s, 3H), 6.4-6.6 (m, 1H), 6.8, 7.1, (2s, 1H), 7.4-7.6 (m, 2H); IR ($CHCl_3$) 1770, 1735 $cm^{-1}$. **5i**: Rf .5, .35 (20% EA/H); H-NMR ($CCl_4$) δ 2.0 (s, 6H), 3.7, 3.8 (2s, 3H), 6.8, 7.3 (2s, 1H), 7.0-7.3 (m, 1H), 7.5-7.7 (m, 2H), 8.4-8.7 (m, 1H); IR ($CCl_4$) 1770, 1740 $cm^{-1}$.

11) Characteristics of the α-ketoesters.[17,19] **6a**: Rf .23 (10% E/PE); H-NMR ($CDCl_3$) δ 0.7-2.8 (m, 9H), 2.8 (t, 2H, J = 7 Hz), 3.9 (s, 3H); IR ($CHCl_3$) 1740 $cm^{-1}$. **6b**: Rf .25 (10% E/PE); H-NMR ($CDCl_3$) δ 1.6-2.4 (m, 4H), 3.8 (s, 3H), 4.9, 5.1 (2d, 2H, J = 4 Hz), 5.5-6.0 (m, 1H); IR ($CHCl_3$) 1740 $cm^{-1}$. **6c**: Rf .3 (10% E/PE); H-NMR ($CDCl_3$) δ 1.1-1.8 (m, 4H), 2.2 (m, 2H), 3.9 (s, 3H), 4.8-5.2, 5.4-6.2 (m, 3H); IR ($CHCl_3$) 1740 $cm^{-1}$. **6d**: Rf .45 (20% EA/H); H-NMR ($CCl_4$) δ 1.0 (s, 6H), 1.6 (t, 2H, J = 8 Hz), 2.7 (t, 2H, J = 8 Hz), 3.8 (s, 3H), 4.8 (dd, 1H, $J_1$ = 10 Hz, $J_2$ = 2 Hz), 5.1 (dd, 1H, $J_1$ = 18 Hz, $J_2$ = 2 Hz), 5.8 (dd, 1H, $J_2$ = 18 Hz, $J_2$ = 10 Hz); IR ($CHCl_3$) 1740 $cm^{-1}$. **6e**: (volatile), H-NMR ($CCl_4$) δ 1.0 (s, 9H), 2.6 (s, 2H), 3.8 (s, 3H); IR ($CHCl_3$) 1740 $cm^{-1}$. **6f**: Rf .25 (35% E/PE); H-NMR ($CDCl_3$) δ 1.4, 1.45 (2s, 6H), 3.2 (t, 2H, J = 6 Hz), 3.5 (m, 1H), 3.9 (s, 3H), 4.1 (m, 1H), 4.6 (t, 1H, J = 6 Hz); IR ($CHCl_3$) 1740 $cm^{-1}$; $[\alpha]_D^{23}$ = +12.4 (C = 0.012, $CHCl_3$). **6g**: Rf .25 (25% EA.H); H-NMR ($CDCl_3$) δ 0.8 (d, 3H, J = 6 Hz), 1.4-1.8 (m, 1H), 2.2, 2.3 (2s, 6H), 2.7 (t, 2H, J = 8 Hz), 3.8 (s, 3H), 5.4 (s, 2H), 6.8, 7.1 (2d, 2H, J = 7 Hz), 7.4 (s, 5H); IR ($CHCl_3$) 1760, 1740 $cm^{-1}$; $[\alpha]_D^{23}$ = + 7.0 (C = 0.005, $CHCl_3$). **6h**: Rf .35 (20% E/PE); m.p. 99-100°C; H-NMR($CDCl_3$) δ 3.9 (s, 3H), 6.4 (m, 1H), 6.4-6.6 (m, 2H), 6.9 (d, 1H, J = 2.0 Hz), 7.5 (d, 1H, J = 3.0 Hz; IR ($CHCl_3$) 1700-1720 $cm^{-1}$. **6i**: Rf .5 (E); H-NMR ($CCl_4$) δ 3.6 (s, 3H), 6.5 (s, 1H), 6.9-7.3 (m, 2H), 7.5 (m, 1H), 8.4 (m, 1H); IR ($CHCl_3$) 1740 $cm^{-1}$.

12) L.K. Montgomery, J.W. Matt, J. Am. Chem. Soc., 1967, 89, 6556-64.

13) N.A. LeBel, M.E. Post, J.J. Whang, J. Am. Chem. Soc., 1964, 86, 3759-67.

14) R.K. Boeckman, Jr., S.S. Ko, J. Am. Chem. Soc., 1982, 104, 1033-41.

15) E. Baer and O.L. Fischer, J. Biol. Chem., 1939, 128, 463-73.

16) This aldehyde[17] was prepared by acetylation ($Ac_2O$, pyridine Rf .42, 15% EA/H)[19] of the phenolic aldehyde reported by R.E. Ireland, R.C. Anderson, R. Badoud, B.J. Fitzsimmons, G.J. McGarvey, S. Thaisrivongs and C.S. Wilcox, J. Am. Chem. Soc., 1983, 105, 1988-2006. $[\alpha]_D^{23}$ = -6.4 (C = 0.009, $CHCl_3$); $^1$HNMR ($CDCl_3$) δ 1.00 (d, 3H, J = 7 Hz), 1.95 (s, 6H), 2.17 (s, 6H), 2.62 (t, 2H, J = 8 Hz), 5.37 (s, 2H), 6.83,7.14 (2d, 2H, J = 8 Hz), 7.40 (s, 5H), 9.35 (d, 1H, 1 Hz); IR ($CHCl_3$) 1780, 1740 $cm^{-1}$.

17) All new compounds described in this communication gave correct C,H analysis.

18) Methyl glyoxalate prepared by the ozonation of dimethyl maleate (M.E. Jung, K. Shisido and L.H. Davis, J. Org. Chem., 1982, 47, 891-2) was not suitable for this procedure. Only complex mixtures of products were obtained after repeated attempts to employ it for the preparation of phosphonate 3a.

19) Solvents used for TLC are abbreviated as follows: ether = E; ethylacetate = EA; hexane = H; petroleum ether (20-40) = PE; dichloromethane = D. Analytical (0.05mm) E. Merck silica gel G plates were used in all cases.

20) Deprotection of the pyridyl-ketoester 2i was best effected using 3 equivalents of methanol and 0.1 equivalent of 4-dimethylaminopyridine catalyst in refluxing dichloromethane (12 h). This α-ketoester is > 95% enolic.

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