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PROCESS IMPROVED PREPARATION OF A VERSATILE α-KETOESTER ACYL ANION SYNTHON

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ABSTRACT: An improved scalable procedure for preparation of an α-ketoester acyl anion synthon is described.

Recently, we required kilogram quantities of the phosphonate based, α-ketoester acyl anion equivalent **5**. Although the preparation of related compounds differing in the ester and protected hydroxyl functionalities has been described[1] these procedures did not satisfy our requirements for a procedure amenable to large-scale work and, ideally, that the intermediates be crystalline. In attempting to adapt the known approaches to suit our needs, it became apparent that we could not achieve the level of purity or physical state required for our purposes. Therefore, we initiated a process improvement effort resulting in a very scalable four-step approach giving high purity, crystalline intermediates. The details of this work are described herein.

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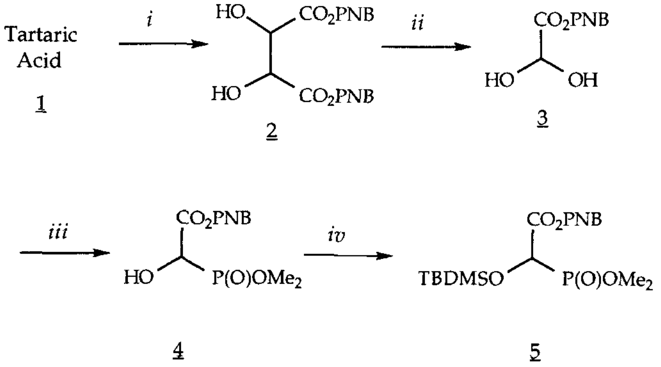
As indicated in the scheme, our process begins with the diesterificaton of tartaric acid (**1**). We found that slow, sequential addition of triethylamine and a p-nitrobenzylbromide/DMF solution followed by an ice-water quench produced a solid filterable product (**2**) in high yield. Careful control of the temperature was maintained during these additions. The product could be slurried in ethanol to effect a final purification.

Scheme



i : p-nitrobenzylbromide, DMF, Et_3N, 0-5°C; *ii* : H_5IO_6, THF, RT;
iii : $H(O)P(OMe)_2$, EtOAc, Δ; *iv* : TBDMS-CL, imidazole, DMF.

Oxidation of the 1,2-diol moiety proved to be challenging with regard to reaction throughput. This transformation has been described in the literature using various oxidants including lead tetraacetate[2a,b,c] and ozone[2d], however, for practical reasons and ease of handling, we opted to use a periodate based oxidant[2e]. Because of the insolubility of periodic acid in tetrahydrofuran, it was not immediately clear how concentrated we could perform this reaction. However, we found that by operating at concentrations consistent with desireable throughput levels (i.e. 18% w/w tartrate-THF), the reaction proceeded smoothly. Removal of the inorganic salts was easily accomplished by filtration.

After addition of water, it was possible to effect crystalization of the desired glyoxalate intermediate (**3**)[2a].

The most common protocols for driving reversible additions to aldehyde moities to completion involve some form of water removal and/or acid catalysis. Indeed, the literature procedures described for similar compounds use both of these approaches[1]. Also noteworthy is a method involving adsorption of the aldehyde and phosphite onto basic alumina followed by heating[3]. In our hands, condensation between **3** and dimethylphosphite was observed using p-toluenesulfonic acid catalysis and water removal *via* benzene azeotrope. However, it was clear that side reactions were occurring and therefore, it was never possible to obtain the product in a pure, crystalline form. After examining temperature and stoichiometry variations without any significant improvement, we began studying the reaction exclusive of acid catalysis or water removal. Other solvents were considered with the requirement that they be amenable to large-scale processing. From this resulted the procedure of refluxing the reactants in ethyl acetate, concentrating the reaction mixture and dissolving the residue in an ethyl acetate-hexane mixture to precipitate pure **4**. In light of the hydrated nature of **3**, it was pleasing that the condensation occurred so well without the aid of acid catalysis or water removal. This approach has proven to be highly reproducible.

The final conversion to **5** was accomplished using standard Corey conditions[4] for preparation of silyl ethers. The *tert*-butyldimethylsilyl ether was a highly crystalline solid which could be crystallized from an ethyl acetate/ heptane mixture to afford pure **5** as a free flowing solid which is stable to storage for extended periods of time[5].

In summary, a four-step process has been described to prepare the versatile α-ketoester acyl anion equivalent **5**. The overall yield of this approach is 40%. Significant process improvements were introduced which resulted in crystalline intermediates and a crystalline final product. All aspects of reaction design were such that large-scale production can be easily achieved.

Experimental Section

bis-p-Nitrobenzyl tartrate (2). To a 22-L vessel was charged DMF (3.4 L) and L-tartaric acid (900.5 g, 6.0 mol). This solution was cooled to 0-5°C and triethylamine (1275 g, 1756 ml, 12.6 mol) was added over a 2-h period with mechanical stirring while maintaining the temperature at 0-5°C. A solution of p-nitrobenzylbromide (2592 g, 12.0 mol) in DMF (5.6 L) was added to the vessel over a 5-h period maintaining the temperature at 5-10°C. After addition was complete the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with water (6 L) and ice (4.0 kg) and the resultant suspension was stirred for 2-h. The product was collected by filtration washed with water (4x1.5 L) and air-dried. A final slurry of the product in ethanol (9 L) followed by filtration washing with ethanol (3x1.5 L) and drying gave 2.14 kg (85%) of **2** : mp 163 - 164°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.23 (d, 4H, J = 8.76 Hz), 7.68 (d, 4H, J = 8.6 Hz), 5.86 (d, 2H, J = 8.1 Hz), 5.34 (s, 4H), 4.68 (d, 2H, J = 9.0 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 171.10, 147.05, 143.84, 128.30, 123.49, 72.64, 64.78. Anal. Calcd for $C_{18}H_{16}N_2O_{10}$: C, 51.44; H, 3.84; N, 6.66. Found: C, 51.24; H, 3.95; N, 6.68. MS (CI, NH_3): m/z 438 $(M+NH_4)^+$.

p-Nitrobenzyl glyoxalate Hydrate (3). To a 22-L vessel was charged THF (12.6 L) and **2** (2101.5 g, 5 mol). The resulting solution was stirred for 10 min. In a portionwise manner was added periodic acid (1367.6 g, 6 mol) over 1h so as not to allow the temperature to exceed 30°C and the resulting suspension was stirred for 2.5-h. The inorganic salts were removed by filtration, the filter cake was washed with THF (3x1L) and water (43.75 L) was added to the filtrate. The solution was cooled to 5°C and a seed crystal of **3** was added. The resulting mixture was allowed to stand for 24-h at 5°C whereupon the product was collected *via* filtration. The solid product was washed sequentially with water (3x3 L) and heptane (3x2.5 L) to produce 1673 g (74%) of **3** : mp 100 - 102°C (lit. 80-88°C)[2a]; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.25 (d, 2H, J = 8.9 Hz), 7.66 (d, 2H, J = 8.9 Hz), 6.82 (d, 2H, J = 7.5 Hz), 5.30 (s, 2H), 5.13 (t, 1H, j = 7.6 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 170.16, 147.08, 143.75, 128.39, 123.53, 86.84, 64.27. Anal. Calcd for $C_9H_9NO_6$: C, 47.58; H, 3.99; N, 6.17. Found: C, 47.60; H, 3.94; N, 6.34. MS (CI, NH_3): m/z 210 (M - H_2O + H)$^+$.

Acetic acid, (dimethoxyphosphinyl)hydroxy-, (4-nitrophenyl)methyl ester (4). To a 22-L vessel was charged ethyl acetate (7.4 L), **3** (1476.5 g, 6.5 mol) and dimethyl phosphite (1073 g, 894 mL, 9.75 mol). The solution was brought to reflux and stirred for 4-h. After cooling to room temperature water (1.5 L) was added, the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (3x1 L), brine (2x1 L) and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* , the resulting solid material was taken up in ethyl acetate/heptane (1:2, 6 L) and stirred at -10°C for 1-h. The resulting solid was filtered and washed with ethyl acetate/ heptane (1:2) to produce 1427 g (69%) of **4** : mp 83.5 - 84.5 °C; ^{1}H-NMR (300 MHz, $CDCL_3$) δ 8.25 (d, 2H, J = 8.8 Hz), 7.59 (d, 2H, J = 8.8 Hz), 5.41 (dd, 2H, J = 13.3 Hz), 4.70 (d, 1H, $J_{P\text{-}C\text{-}H}$ = 16.52 Hz), 3.86 (d, 3H, $J_{P\text{-}O\text{-}CH}$ = 10.6 Hz), 3.83 (d, 3H, $J_{P\text{-}O\text{-}CH}$ = 10.8 Hz), 3.61 (br s,1H); ^{13}C NMR (75.5 MHz, $CDCL_3$) δ 168.59, 147.74, 141.88, 128.33, 123.59, 68.52 (d, $J_{P\text{-}C}$ = 155.4 Hz), 66.31, 54.50 (d, $J_{P\text{-}O\text{-}C}$ = 7.1 Hz), 54.17 (d, $J_{P\text{-}O\text{-}C}$ = 6.8 Hz). Anal. Calcd for $C_{11}H_{14}NPO_8$: C, 41.39; H, 4.42; N, 4.39; P, 9.70. Found: C, 41.24; H, 4.27; N, 4.39; P, 9.54. MS (CI, NH_3): m/z 320 (M + H)$^+$.

Acetic acid, (dimethoxyphosphinyl)[[1,1-dimethylethyl)dimethylsilyl]oxy]-, (4-nitrophenyl)methyl ester (5). To a 22-L vessel was charged DMF (5.83 L) and **4** (1436.4 g, 4.5 mol) followed by t-butyldimethylsilyl chloride (847.85 g, 5.625 mol) and imidazole (842.5 g, 12.4 mol). This reaction mixture was stirred for 2-h and ethyl acetate (10 L) and water (5 L) was added. The organic layer was seperated and washed with water (5 L), saturated aqueous $NaHCO_3$ (5 L) and brine (5 L). *After drying* over anhydrous Na_2SO_4, the solvent was removed *in* *vacuo* to produce 2275 g of crude material which was slurried with ethyl acetate (2 L) and heptane (6 L) and filtered to yield 1407 g of **5** as a faint yellow crystalline solid. Final purification was achieved by taking the product up in ethyl acetate/heptane (1:1, 10 L), heating the mixture to 50° C and filtering through a pad (1440 g) of Magnesol. The pad was washed with ethyl acetate/heptane (1:1, 3x2 L) and the solvent was removed *in vacuo* to provide pure **5** (1321.0 g, 68%) as a crystalline solid: mp 93.5 - 94.5 °C; ^{1}H-NMR (300 MHz, $CDCL_3$) δ 8.24 (d, 2H, J = 6.9 Hz), 7.60 (d, 2H, J = 8.8 Hz), 5.35 (dd, 2H, J = 13.3 Hz), 4.72 (d, 1H, $J_{P\text{-}C\text{-}H}$ = 18.7 Hz), 3.84 (d, 3H, $J_{P\text{-}O\text{-}CH}$ = 10.9 Hz), 3.81 (d, 3H, $J_{P\text{-}O\text{-}CH}$ = 10.8 Hz), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCL_3$) δ 167.71, 147.36, 142.17, 128.14, 123.31, 70.11 (d, $J_{P\text{-}C}$ = 161.8 Hz), 53.82 (d, $J_{P\text{-}O\text{-}C}$ = 7.1 Hz), 53.67 (d, $J_{P\text{-}O\text{-}C}$ = 6.7 Hz), 25.12, 17.92. Anal. Calcd for $C_{17}H_{28}NPSiO_8$: C, 47.11; H, 6.51; N, 3.23; P, 7.15. Found: C, 47.02; H, 6.40; N, 3.15; P, 7.03. MS (CI, NH_3): m/z 451 $(M + NH_4)^+$.

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5. The product has been stored without special handling at 4°C for more than one year without noticable decomposition.

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