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# ETHYL 4-(DIETHOXYPHOSPHINYL)-3-OXOBUTANOATE: SELECTIVE SYNTHESIS OF $\beta$ -KETO PHOSPHONATES

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#### SYNTHETIC COMMUNICATIONS, 32(2), 305-314 (2002)

## ETHYL 4-(DIETHOXYPHOSPHINYL)-3-OXOBUTANOATE: SELECTIVE SYNTHESIS OF β-KETO PHOSPHONATES

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#### ABSTRACT

The selective synthesis of ethyl 4-(diethoxyphosphinyl)-3oxobutanoate (7) and the utilization of its trimethylsilyl enolether (14) in a tandem desilylation Horner-Wittig condensation is illustrated.

 $\beta$ -Keto phosphonates (1)<sup>1-7</sup> in general are utilized as versatile starting materials for the synthesis of a wide array of  $\alpha$ , $\beta$ -unsaturated carbonyl compounds,  $\beta$ -hydroxy derivatives and for liquid–liquid extraction of metal ions. Consequently, the development of reliable methods for the selective synthesis of  $\beta$ -keto phosphonates (1), i.e. devoid of the concomitant formation of undesired enol phosphates (2),<sup>5</sup> were actively pursued by various laboratories during recent years.<sup>4-7</sup>

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Our laboratory is especially interested in the synthetic potential of phosphonates (3) derived from 3-oxobutanoates, since the corresponding phosphinyl stabilized carbanions (4) are ambident nucleophiles that may react as  $\alpha$ - or  $\gamma$ -anions with appropriate electrophiles, e.g.  $\alpha$ , $\beta$ -unsaturated carbonyl compounds.<sup>1,2</sup> Furthermore, successive treatment of the phosphonates (3) with sodium hydride and butyllithium easily generates the corresponding dianions (5) which are nucleophiles with substantially enhanced reactivity, and may be regarded as promising candidates for the annulation of  $\alpha$ , $\beta$ -unsaturated carbonyl compounds.<sup>1–3</sup>



Direct condensation between triethyl phosphite and ethyl 4-bromo-3-oxobutanoate (6) produces a mixture of the phosphonate (7) (Arbusov reaction product) and the enol phosphate (8) (Perkow reaction product).<sup>8</sup> In our hands this condensation yielded a *ca* 1:1 mixture of the phosphonate (7) and enol phosphate (8) in a combined yield of 90% when the reaction was performed at  $110^{\circ}$ C.<sup>1,2</sup>



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Various methods for the selective synthesis of phosphonates of type (3) were consequently developed during recent years, but these methods generally necessitate the use of excessive amounts of strong bases<sup>9,10</sup> and the implementation of a rather cumbersome deprotection step.<sup>11–13</sup> Although the masked  $\beta$ -ketophosphonate (9) could be utilized in Horner-Wittig condensations,<sup>11</sup> deprotection of the reaction products was still an inevitable manipulation.



Although condensation of the 4-halo-3-alkoxy-2-butenoates (10) with trialkyl phosphates yielded the corresponding phosphonates (11), acidcatalysed hydrolysis, either before or after Horner-Wittig condensation, is an essential and critical step in this procedure.<sup>14,15</sup>

In our endeavour to develop a selective synthesis for the phosphonate (7), the dianion of ethyl acetoacetate was treated with diethyl phosphochloridite followed by air oxidation.<sup>16</sup> The phosphonate (7) was indeed produced selectively under these conditions but a yield of only 35% could be realized.



In order to achieve a higher yield of (7), eliminate the use of strong bases but still maintain the desired selectivity, we decided to protect the carbonyl group of the bromoester (6) as an enolether which must be stable under Arbusov conditions, but on the other hand be labile enough to allow selective removal of the protecting group under mild conditions without affecting the ester group. With these prerequisites in mind we elected to apply the trimethylsilyl group as the protecting substituent.<sup>17</sup>



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Silylation of the bromoester (6) with hexamethyldisilazane (HMDS) and a catalytic amount of imidazole<sup>17</sup> yielded an 82:18 mixture of the desired (*E*)- and (*Z*)-silyl enolethers (12) and (13) in high yield. The mixture of enolethers (12) and (13) could be distilled under vacuum but was generally utilized without the need for further purification.



However, an even higher yield of the silyl enolethers (12) and (13) was achieved when the catalytic amount of imidazole was omitted from the reaction mixture. The intermediate formation of 1-(trimethylsilyl)imidazole as the active silylating agent is, contrary to general belief,<sup>17,18</sup> not an essential element for the successful outcome of these silylation processes. It was furthermore found that the above mixture of silyl enolethers (12) and (13) was effectively desilylated at room temperature upon treatment with a suspension of protonated imidazole, or the precipetate that was formed during the silylation of the bromoester (6) with HMDS/imidazole.

When the mixture of silvl enolethers (12) and (13) was treated with triethylphosphite, the Arbusov reaction proceeded selectively to yield a product mixture which consisted of the silvlated phosphonate (14, 82%), the phosphonate (7, 8%) and the enol phosphate (8, 10%) according to NMR analysis. The formation of small amounts of enol phosphate (8) and phosphonate (7) indicated that some desilylation of the enol ethers (12) and (13) took place under the reaction conditions, while limited desilylation of the phosphonate (14) could also have contributed to the formation of the phosphonate (7). We eventually found that the silvlated phosphonate (14) can conveniently be synthesized as the sole reaction product in a one-pot procedure by successive treatment of the bromoester (6) with HMDS and triethyl phosphite. The silvlated phosphonate (14) could not be distilled due to extensive desilylation but was sufficiently pure for further utilization. Removal of HMDS prior to the addition of triethyl phosphite to the reaction mixture was essential for the successful outcome of the one-pot procedure, since the Arbusov reaction appeared to be





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inhibited by the presence of HMDS. Desilylation of the phosphonate (14) was almost instantly and cleanly effected by treatment with silica gel.



In order to establish whether the silylated phosphonate (14) could as such be utilized in a Horner-Wittig condensation, it was consecutively treated with one molar equivalent each of sodium *bis*(trimethylsilyl)amide (NaHMDS) and benzaldehyde. No Horner-Wittig condensation took place but complete desilylation of the phosphonate (14) was effected instead. Horner-Wittig condensation of the silylated phosphonate (14), which was pretreated with two molar equivalents of NaHMDS, proceeded smoothly to yield of 3:1 mixture of the keto- and enolesters (15) and (16) in good yield.<sup>19</sup> The desilylation that accompanied the Horner-Wittig condensation most probably resulted from interaction of the silylated phosphonate (14) with the first molar equivalent of base to generate the intermediate phosphonoenolate (17) and *tris*(trimethylsilyl)amine (18).<sup>20</sup> This was followed by



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deprotonation and Horner-Wittig condensation of the resultant phosphonate dianion (19) with the carbonyl compound. The total failure of the Horner-Wittig condensation when the silylated phosphonate (14) was treated with one molar equivalent of base is, therefore, not surprising.



To summarise we conclude that our results illustrate that the silylated phosphonate (14) can now be synthesized in high yield according to a very convenient one-pot procedure and utilized directly in tandem desilylation/ Horner-Wittig condensations. Desilylation of the phosphonate (14) can be achieved in a few minutes at room temperature in the presence of silica gel to produce the phosphonate (7) in quantitative yield.

#### **EXPERIMENTAL**

All operations were carried out in an argon atmosphere. Merck silica gel 60 (particle size 0.063–0.200 mm) was used for column chromatography. NMR spectra were recorded for solution in deuteriochloroform on a Varian VXR 300 instrument, while mass spectra were taken on a Varian 311A spectrometer. Multiplicities were confirmed by APT and SFORD experiments and HETCOR experiments were performed to interpret the more complex NMR spectra.

1. Condensation of the Dianion of Ethyl Acetoacetate with Diethyl Phosphochloridite Followed by Air Oxidation: Ethyl acetoacetate (1.81 g, 13.9 mmol) in THF ( $20 \text{ cm}^3$ ) was added dropwise to an oil-free suspension of sodium hydride (0.37 g, 15.4 mmol) in THF ( $20 \text{ cm}^3$ ) at 0°C and the



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resulting mixture stirred for an additional 5 min. Butyllithium (16.9 mmol) in hexane was then added dropwise to the reaction mixture at  $-15^{\circ}$ C and stirring was maintained for 30 min before diethyl phosphochloridite (13 g, 20 mmol) was slowly added and the temperature of the reaction mixture was allowed to reach room temperature during the course of 30 min. Air was bubbled through the reaction mixture overnight, saturated aqueous ammonium chloride (20 cm<sup>3</sup>) was added followed by extraction with ether. The residue from the dried (MgSO<sub>4</sub>) ether extract was chromatographed on silica gel and the ether eluate yielded *ethyl* 4-(*diethoxyphosphinyl*)-3-oxobutanoate (7)<sup>1,2</sup> (1.13 g, 35%), b.p. 130°C (air-bath temp.)/0.05 mm Hg;  $\delta_{\rm H}$  1.27 (t, J 7.0 Hz, 3H), 1.31 (t, J 7.0 Hz, 6H), 3.25 (d, J<sub>PH</sub> 23.0 Hz, 2H), 3.65 (s, 2H), 4.12 (dq, J<sub>HH</sub> 7.0 and J<sub>PH</sub> 7.0 Hz, 4H).

2. (E)- and (Z)-Ethyl-4-Bromo-3-trimethylsiloxy-2-butenoate (12) and (13): Ethyl 4-bromo-3-oxobutanoate (6) (10.79 g, 51.6 mmol) was added dropwise to hexamethyldisilazane (HMDS) (28.19 g, 174.0 mmol) at room temperature and the resulting mixture was stirred for 6 h at room temperature before ether  $(20 \text{ cm}^3)$  was added. The mixture was then filtered through a 0.45 µm Teflon filter via a syringe and the ether and HMDS removed under reduced pressure at 30°C. The residue consisted of an 82:18 mixture of pure (E)-ethyl 4-bromo-3-trimethylsiloxy-2-butenoate (12) and (Z)-ethyl 4-bromo-3-trimethylsiloxy-2-butenoate (13) in quantitative yield (14.4 g. 99%) which was directly utilized without the need for further purification; δ<sub>H</sub> (E-12) 0.31 (s, 9H), 1.28 (t, J 7.2 Hz, 3H), 4.15 (s, 2H), 4.16 (q, J 7.0 Hz, 2H), 5.16 (s, 1H); δ<sub>C</sub> (E-12) 0.70 (SiMe<sub>3</sub>), 14.30 (CH<sub>3</sub>), 28.33 (CH<sub>2</sub>Br), 60.0 (CH<sub>2</sub>), 101.25 (=CH), 165.20 and 166.53 (=C < and >C=O);  $\delta_{\rm H}$  (Z-13) 0.31 (s, 9H), 1.26 (t, J 7.2 Hz, 3H), 3.78 (s, 2H), 4.14 (q, J 7.0 Hz, 2H), 5.39 (s, 1H); δ<sub>C</sub> (Z-13) 0.70 (SiMe<sub>3</sub>), 14.30 (CH<sub>3</sub>), 28.33 (CH<sub>2</sub>Br), 60.0 (CH<sub>2</sub>), 101.25 (=CH), 165.20 and 166.53 (=C < and >C=O). Partial desilylation followed by dimerization took place during distillation at 60°C(air-bath temp.)/ $7.5 \times 10^{-4}$  mm Hg.

3. Condensation of Triethyl Phosphite with a Mixture of (*E*)- and (*Z*)-Ethyl 4-Bromo-3-trimethylsiloxy-2-butenoate (12) and (13): Triethyl phosphite (6.21 g, 37.4 mmol) was added dropwise to an 82:18 mixture of (*E*)- and (*Z*)-ethyl 4-bromo-3-trimethylsiloxy-2-butenoate (12) and (13) (9.52 g, 33.9 mmol) at room temperature, the resulting yellow reaction mixture stirred for 15 min at room temperature and for an additional 17 h at 50°C, before the excess of triethyl phosphite was removed and reduced pressure at 30°C. <sup>1</sup>H NMR analysis of the residue established that it consisted of an 8:10:82 mixture of *ethyl 4-(diethoxyphosphinyl)-3-oxobutanoate* (7)<sup>1.2</sup> (8%), *ethyl 3-(diethoxyphosphinyloxy)-3-butenoate* (8)<sup>1.2</sup> (10%), b.p. 100°C (air-bath temp.)/0.08 mm Hg;  $\delta_{\rm H}$  1.25 (t, J 7.0 Hz, 3H), 1.33 (dt, J<sub>PH</sub> 7.0 and J<sub>HH</sub> 7.0 Hz, 6H), 3.22 (s, 2H), 4.17 (dq, J<sub>PH</sub> 6.5 and J<sub>HH</sub> 7.0 Hz, 4H),

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4.17 (q, J 7.0 Hz, 2H), 4.69 (dd,  $J_{PH}$  2.3 and  $J_{HH}$  1.8 Hz, 1H), 5.01 (dd,  $J_{PH}$  2.4 and  $J_{HH}$  1.8 Hz, 1H) and (*E*)-ethyl 4-(diethoxyphosphinyl)-3-trimethyl-siloxy-2-butenoate (14) (82%).

4. One-pot Synthesis of (E)-Ethyl 4-(Diethoxyphosphinyl)-3-trimethylsiloxy-2-butenoate (14): Ethyl 4-bromo-3-oxobutanoate (6) (1.34 g, 6.4 mmol) and HMDS (3.53 g, 21.9 mmol) were stirred for 6 h at room temperature, the reaction mixture diluted with ether (20 cm<sup>3</sup>), filtered through a pad of celite on a sintered glass filter under argon pressure and the excess of HMDS and ether evaporated under reduced pressure at 30°C. Triethyl phosphite (1.22 g, 7.3 mmol) was added to the clear residue at room temperature and the reaction mixture stirred for 15 min at room temperature and 7.5 h at 55°C. The unreacted triethyl phosphite was removed under reduced pressure at 30°C and NMR analysis of the residue established that (E)-ethyl 4-(diethoxyphosphinyl)-3-trimethylsiloxy-2-butenoate (14) (1.80 g, 83%);  $\delta_{\rm H}$  0.31 (s, 9H), 1.27 (t, J 7.1 Hz, 3H), 1.35 (dt, J<sub>PH</sub> 1.6 and J<sub>HH</sub> 7.0 Hz, 6H), 3.55 (d, J<sub>PH</sub> 22.9 Hz, 2H), 4.12 (dq, J<sub>PH</sub> 7.3 and J<sub>HH</sub> 7.3 Hz, 4H), 4.13 (q, J 7.0 Hz, 2H), 5.17 (d,  $J_{PH}$  3.3 Hz, 1H);  $\delta_{C}$  - 0.01 (SiMe<sub>3</sub>), 14.36 (CH<sub>3</sub>), 16.34 ( $J_{PC}$  6.7 Hz, CH<sub>3</sub>), 31.92 ( $J_{PC}$  134.3 Hz, CH<sub>2</sub>), 59.61 (CH<sub>2</sub>), 61.96 (J<sub>PC</sub> 6.1 Hz, CH<sub>2</sub>), 100.67 (J<sub>PC</sub> 9.3 Hz, =CH), 163.24 (J<sub>PC</sub> 12.1 Hz, =C <), 167.24 (J<sub>PC</sub> 2.7 Hz, > C=O), was formed exclusively in this one-pot procedure. The phosphonate (14) could not be distilled due to extensive desilylation but was sufficiently pure for further utilization.

5. Condensation of (E)-Ethyl 4-(Diethoxyphosphinyl)-3-trimethylsiloxy-2-butenoate (14) with Benzaldehyde in the Presence of Two Molar Equivalents of NaHMDS: HMDS (0.615 g, 4.0 mmol) was added to sodium amide (0.48 g, 1.2 mmol) and the mixture stirred for 30 min at 50°C followed by 2 h at  $80^{\circ}$ C. THF (9 cm<sup>3</sup>) was added to the reaction mixture, the resulting solution of NaHMDS cooled  $(0^{\circ}C)$  and the silvlated phosphonate (14) (0.162 g, 0.5 mmol) in THF  $(11 \text{ cm}^3)$  added dropwise at 0°C. Stirring was maintained for 15 min at 0°C before benzaldehyde (0.104 g, 1.0 mmol) was added at  $0^{\circ}$ C. The reaction mixture was stirred for an additional 2 h at  $0^{\circ}$ C before the solvent was evaporated under reduced pressure at  $30^{\circ}$ C, the residue treated with saturated aqueous sodium chloride  $(80 \text{ cm}^3)$ , and the aqueous mixture extracted with ether. The residue from the dried  $(MgSO_4)$ ether extract was chromatographed on silica gel with ether-petroleum ether (9:1) as eluent. <sup>1</sup>H NMR<sup>19</sup> analysis of the solid eluate established that it consisted of a 3:1 mixture of (E)-ethyl 5-phenyl-3-oxo-4-pentenoate (15)<sup>19</sup> and (2E, 4E)-ethyl 3-hydroxy-5-phenyl-2,4-pentadienoate (16)<sup>19</sup> (0.774 g, 71%), m.p. (from hexane)  $46^{\circ}$ C (lit., <sup>19</sup> m.p.  $46^{\circ}$ C).

6. Desilylation of (*E*)-Ethyl 4-(Diethoxyphosphinyl)-3-trimethylsiloxy-2-butenoate (14): A suspension of silica gel (20 g) in a solution of the silylated phosphonate (14) (3.32 g, 10 mmol) in ether (40 cm<sup>3</sup>) was stirred for 5 min at



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room temperature, the suspension filtered and the silica gel washed on the filter with ethanol. The combined filtrates were evaporated under reduced pressure at  $30^{\circ}$ C to give an almost quantitative yield of pure 4-(*diethoxy-phosphinyl*)-3-oxobutanoate (7)<sup>1,2</sup> (2.63 g, 99%).

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#### REFERENCES

- 1. Moorhoff, C.M.; Schneider, D.F. Tetrahedron Lett. 1987, 28, 559.
- 2. Moorhoff, C.M.; Schneider, D.F. Tetrahedron 1998, 54, 3279.
- Pietrusiewics, K.M.; Monkiewicz, J.; Bodalski, R. J. Org. Chem. 1983, 48, 783.
- 4. Corbel, B.; L'Hostis-Kervella, I.; Haelters, J.-P. Synth. Commun. **2000**, *30*, 609 and references cited therein.
- 5. Corbel, B.; L'Hostis-Kervella, I.; Haelters, J.-P. Synth. Commun. 1996, 26, 2561 and references cited therein.
- 6. Kim, D.Y.; Suh, K.H. Synth. Commun. **1999**, *29*, 1271 and references cited therein.
- 7. Kim, D.Y.; Kong, M.S.; Kim, T.H. Synth. Commun. **1996**, *26*, 2487 and references cited therein.
- 8. Jagodic, V. Croat. Chem. Acta 1977, 49, 487.
- 9. Fouqué, D.; About-Joudet, E.; Collignon, N. Synth. Commun. 1992, 22, 219.
- Bodalski, R.; Pietrusiewicz, K.M.; Koszuk, J. Tetrahedron Lett. 1980, 21, 2287.
- Boeckman, R.K.; Thomas, A.J. J. Org. Chem. 1982, 47, 2823; Boekman, R.K.; Perni, R.B.; Macdonald, J.E. Synthesis 1987, 66, 194; Boekmman, R.K.; Kamenecka, T.M.; Nelson, S.G. Tetrahedron Lett. 1991, 32, 2581.
- 12. Moore, M.C.; Cox, R.J.; Duffin, G.R.; O'Hagan, D. Tetrahedron 1998, 54, 9195.
- 13. Ley, S.V.; Smith, S.C.; Woodward, P.T. Tetrahedron 1992, 48, 1145.
- 14. Natsias, K.; Hopf, H. Liebiegs Ann. Chem. 1988, 705.
- 15. Duc, L.; McGarrity, J.F.; Meul, T.; Warm, A. Synthesis 1992, 391.

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- 16. Lee, K.; Wiemer, D.F. J. Org. Chem. 1991, 56, 5556.
- 17. Ainsworth, C.; Torkelson, S. Synthesis 1976, 722; Peterson, D.J. J. Org. Chem. 1968, 33, 780.
- Ritter, A.; Birkofer, L.; Richter, P. Chem. Ber. 1960, 93, 2804. 18.
- 19. Padwa, A.; Kline, D.N.; Norman, B.H. J. Org. Chem. 1989, 54, 810.
- 20. Schumann-Ruidisch, I.; Kalk, W.; Brüning, R. Z. Naturforsch. 1968, *23b*, 307.

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