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A General Procedure for the Preparation of β-Ketophosphonates

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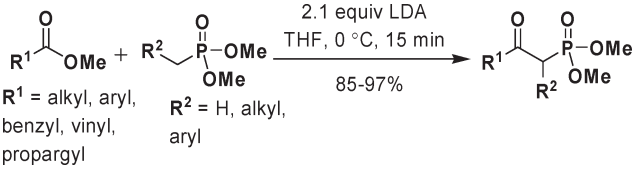
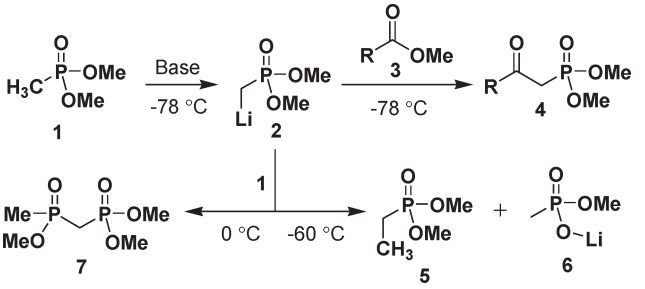


A mild, high-yielding procedure for the preparation of β-ketophosphonates is described. The condensation is general with respect to the ester and phosphonate, and the products are obtained in high yields within minutes at 0 °C. The reaction procedure is operationally simple and amenable to large-scale preparations.

β-Ketophosphonates are versatile intermediates for the synthesis of α,β-unsaturated carbonyl compounds via the Horner−Wadsworth−Emmons (HWEs) reaction[1] and for liquid−liquid extraction of metal ions.[2] Consequently, the development of a reliable and scalable method for the synthesis of β-ketophosphonates has been actively pursued by several laboratories.[3] Several methods exist for the preparation of β-ketophosphonates, and the most common method involves the condensation of methyl dialkylphosphonates with esters. The condensation of dimethyl methylphosphonate (**1**) with esters typically involves the deprotonation of **1** with *n*-BuLi,[4] LDA,[5] or LiHMDS[6] at −78 °C followed by the addition of an ester as shown in Scheme 1. As expected, a second equivalent of phosphonate anion (**2**) or base is required to deprotonate the more acidic β-ketophosphonate product (**4**). Though the reaction has been used on several occasions for the large-scale synthesis of β-ketophosphonates,[7] the cryogenic conditions (−78 °C) and the tendency of **2** to dimerize[8] (**2** → **7**) or undergo an intermolecular alkyl transfer[9] (**2** → **5** + **6**) severely limits this synthetic route for large-scale preparations (Scheme 1). During the preparation of this manuscript, a report was published by Milburn and co-workers at Amgen detailing the development of a mild preparation of aryl β-ketophosphonates.[10] While this reaction procedure is an improvement over previous methodologies, the reaction conditions could not be extended to aliphatic esters and esters with active α-protons. In this Note, we wish to report the development of a general, mild, high-yielding procedure for the preparation of β-ketophosphonates.

SCHEME 1. Condensation of $LiCH_2PO(OMe)_2$ with Esters



The key to the preparation of β-ketophosphonates under noncryogenic conditions is the elimination of side reactions associated with phosphonate anion **2** (Scheme 1). We envisioned that generating anion **2** in the presence of ester **3** would lead to the instantaneous formation of β-ketophosphonate **4** and the elimination of side reactions. In order to test this hypothesis, we began with the synthesis of β-ketophosphonate **9**. We discovered that simply adding a solution of LDA to a mixture of **1** and **8** at 0 °C afforded **9** in 90% yield. Only 1 equiv of phosphonate **1** was needed for complete conversion, indicating that the decomposition of **2** was completely suppressed. Attempts to use other bases including *n*-BuLi and LiHMDS were complicated by competing side reactions such as the Claisen condensation of **8**.

Having identified mild conditions for the preparation of β-ketophosphonate **9**, the scope and generality of the procedure was examined. As shown in Table 1, the condensation of several electronically and structurally diverse esters with

(1) (a) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738. (b) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87–99. (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927. (d) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp 729−818 and references therein.

(2) (a) Cotton, F. A.; Schunn, R. A. *J. Am. Chem. Soc.* **1963**, *85*, 2394–2402. (b) Sturtz, G.; Clement, J. C.; Daniel, A.; Molinier, J.; Lenzi, M. *Bull. Soc. Chim. Fr.* **1981**, 167–171. (c) McCabe, D. J.; Duesler, E. N.; Paine, R. T. *Inorg. Chem.* **1985**, *24*, 4626–4629.

(3) (a) Arbuzov, B. A. *Pure Appl. Chem.* **1964**, *9*, 307–353. (b) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654–5656. (c) Corbel, B.; L'Hostis-Kervella, I.; Haelters, J.-P. *Synth. Commun.* **1996**, *26*, 2561–2568. (d) Kim, D. Y.; Kong, M. S.; Kim, T. H. *Synth. Commun.* **1999**, *29*, 1271–1274. (e) Du-Pisani, C.; Schneider, D. F.; Venter, P. C. R. *Synth. Commun.* **2002**, *32*, 305–314.

(4) For a recent example, see: Somu, R. V.; Boshoff, J.; Quao, C.; Bennett, E. M.; Barry, C. E.; Aldrich, C. C. *J. Med. Chem.* **2006**, *49*, 31–34.

(5) For a recent example, see: Palacios, F.; Ochoa de Retanam, A. M.; Alonso, J. M. *J. Org. Chem.* **2006**, *71*, 6141–6148.

(6) For a recent example, see: Westermann, J.; Schneider, M.; Platzek, J.; Petrov, O. *Org. Proc. Res. Dev.* **2007**, *11*, 200–205.

(7) For the preparation of a ketophosphonate on 20 kg scale, see: Zhi-Jiang Hisun Pharmaceutical Co. Ltd. The process and intermediates for the selective synthesis of fluvastatin. WO Patent 2006021326, 2006.

(8) Tuelade, M.-P.; Savignac, P.; Aboujaoude, E. E.; Collignon, N. *J. Organomet. Chem.* **1986**, *312*, 283.

(9) Yasuda, N.; Hsiao, Y.; Jensen, M. S.; Rivera, N. R.; Yang, C.; Wells, K. M.; Yau, J.; Palucki, M.; Tan, L.; Dormer, P. G.; Volante, R. P.; Hughes, D. L.; Reider, P. J. *J. Org. Chem.* **2004**, *69*, 1959–1966.

(10) Milburn, R. R.; McRae, K.; Chan, J.; Tedrow, J.; Larsen, R.; Faul, M. *Tetrahedron Lett.* **2009**, *50*, 870–872.

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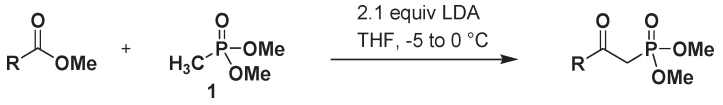
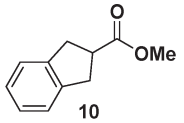
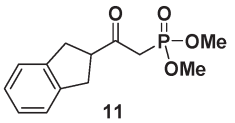
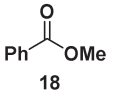
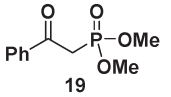
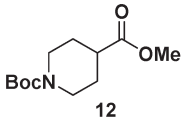
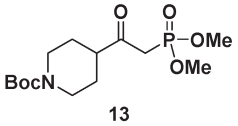
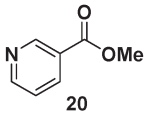
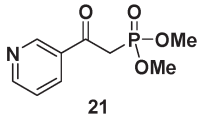
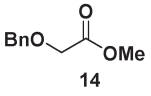
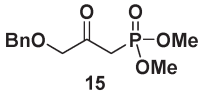
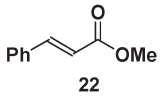
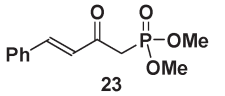
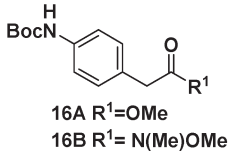
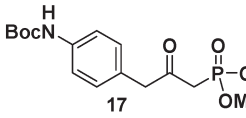
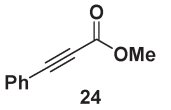
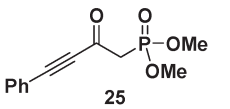
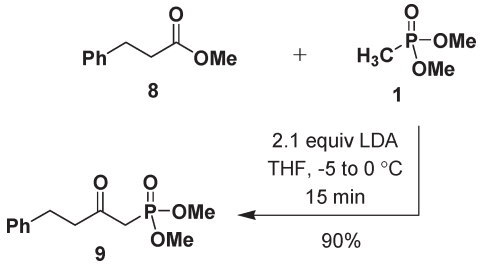
TABLE 1. LDA-Mediated Condensation of Various Esters with Phosphonate 1



Entry	Substrate	Product	yield (%)[a]	Entry	Substrate	Product	yield (%)[a]
1			93	5			90
2			96	6			92
3			96	7			90
4			77 92	8			94

[a]Isolated yields.

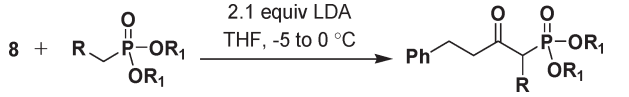
SCHEME 2. LDA-Mediated Condensation of $MePO(OMe)_2$ with Ester 8

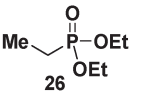
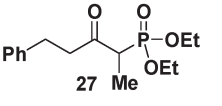
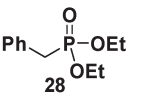
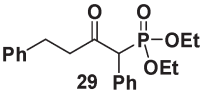
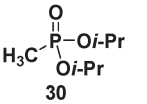
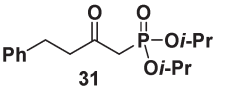
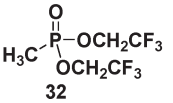
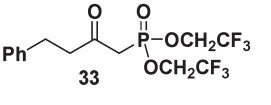


phosphonate **1** afforded the desired β-ketophosphonates in excellent yield. The reaction procedure worked well with esters having active α-protons as shown in entries 3 and 4. It is noteworthy that substrate **16** having an acidic BocN-H proton is tolerated under the reaction conditions by using an extra equivalent of LDA (total of 3 equiv). Interestingly, we discovered that the Weinreb amide derivative **16B** afforded **17** in higher yield than the corresponding methyl ester derivative **16A** (92% versus 77%). Unfortunately, this was not a general trend as methyl esters tend to give higher yields than the corresponding Weinreb derivatives. In general, the condensations were instantaneous at 0 °C and the β-ketophosphonates were typically isolated in high purities (> 90%) after a simple aqueous workup. Also, we found that commercial LDA solutions[11] worked as well as prepared LDA solutions further simplifying the procedure.

(11) 2.0 M solution of LDA purchased from Sigma Aldrich.

TABLE 2. LDA-Mediated Condensation of Various Phosphonates with Ester 8



Entry	Phosphonate[a]	Product	yield(%)[b]
1			97
2			85
3			90
4			0

[a]Used 1.1 equiv of phosphonate. [b]Isolated yields.

Next, we set out to explore the reactivity of different phosphonates with ester **8** using our standard procedure

(Table 2). As shown in entries 1 and 2, α-substitued phosphonates **26** and **28** afforded the desired β-ketophosphonates **27** and **29** in 97% and 85% yield, respectively. In addition, phosphonate **30** reacted with ester **8** under our standard conditions to give **31** in 90% yield. This clearly demonstrates that steric differences in the phosphonate have little influence on the yield and rate of the condensation reaction. Unfortunately, we were unable to extend the reaction conditions to the preparation of trifluoroethyl-substituted β-ketophoshponates such as **33**, which are key reagents for the Still−Gennari-modified HWE reaction[12] (entry 4). Presumably, the electron-withdrawing trifluoroethyl groups make the dimerization of **32** more favorable than the competing condensation reaction (see Scheme 1).

In conclusion, we have developed a mild, noncryogenic procedure for the synthesis of β-ketophosphonates. The condensation is general with respect to the ester and phosphonate and the products are obtained in high yields within minutes at 0 °C. The mild conditions and the operational simplicity of the procedure make it amenable to large-scale applications. In addition, the condensation works with commercial LDA solutions further simplifying the procedure.

Experimental Section

Representative Procedure. Preparation of (2-Oxo-4-phenylbutyl)-phosphonic Acid Dimethyl Ester (9). A 1-L, three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, addition funnel, thermocouple, and mechanical stirrer was charged with ester **8** (20 g, 122 mmol), dimethyl methylphosphonate **1** (14.5 mL, 16.6 g, 134 mmol), and 200 mL of THF. The reaction mixture was cooled at −5 °C while a 2.0 M solution of LDA (128 mL, 256 mmol) was added dropwise via addition funnel keeping the internal temperature below 0 °C. After complete addition, the reaction mixture was stirred at 0 °C until complete consumption of **8** as determined by HPLC analysis (typically < 5 min). The reaction mixture was then carefully quenched with 5 M HCl to adjust the pH to ca. 4 and diluted with EtOAc. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to yield 32.0 g of β-ketophosphonate **9** (ca. 90% pure as judged by HPLC and NMR analysis). Purification by column chromatography afforded 28.1 g (90% yield) of **9** as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.27 (m, 2 H), 7.14−7.18 (m, 3H), 3.72 (d, J = 11.2 Hz, 6 H), 3.05 (d, J = 22.7 Hz, 2 H), 2.86−2.95 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9 (d, J_{CP} = 6.3 Hz), 140.6, 128.5, 128.4, 126.1, 53.0 (d, J_{CP} = 6.5 Hz), 45.5, 41.4 (d, J_{CP} = 128.1 Hz), 29.4; HRMS (m/z) $[M + H]^+$ calcd for $C_{12}H_{18}O_4P$, 257.0943; found, 257.0946.

Supporting Information Available: Detailed experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Still, W. C.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405–4408.