Tetrahedron Letters 50 (2009) 870–872

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A practical preparation of aryl β-ketophosphonates

Robert R. Milburn *, Ken McRae, Johann Chan, Jason Tedrow, Robert Larsen, Margaret Faul

Small Molecule Process Chemistry, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799, USA

ARTICLE INFO

Article history:
Received 29 October 2008
Revised 25 November 2008
Accepted 26 November 2008
Available online 3 December 2008

ABSTRACT

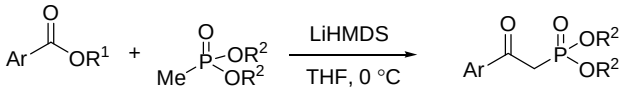
The condensation of alkyl phosphonates with aryl esters to give β-ketophosphonates may be carried out at elevated temperatures mediated by LiHMDS under Barbier type conditions. The reaction is scalable, does not require specialized cryogenic equipment, and is general for all aryl and heteroaryl esters examined.

Ketophosphonates are extremely valuable synthetic intermediates owing to their application in the Horner–Wadsworth–Emmons (HWEs) reaction.[1] Some notable features of the HWE reaction that make it both general and scalable include the inexpensive and widespread availability of methyl dialkylphosphonates, the mild reaction conditions, and byproducts (phosphate salts) that are benign, water soluble and therefore easily removed. In addition, the esters used to make the ketophosphonates are typically stable and readily accessible. Although the condensation of methyl dialkylphosphonates with esters has been used on a number of occasions for the large-scale preparation of ketophosphonates,[2] the very low temperatures required (e.g., −78 °C), and the tendency of methyl dimethylphosphonate to undergo an intermolecular alkyl transfer can be a significant barrier to carrying out these reactions on large scale.[3,4]

Condensation reactions of esters and methyl dialkylphosphonates to form ketophosphonates are typically carried out via deprotonation of methyl dialkylphosphates with one equivalent of *n*-BuLi,[5] LDA,[6] or LiHMDS[7,8] at −78 °C followed by treatment of the resulting anion with either esters and anhydrides or acid chlorides. As with the Claisen condensation, a second equivalent of base/alkylphosphonate anion is required to deprotonate the acidic ketophosphonate product. For the large-scale synthesis of a HWE adduct, a non-cryogenic aryl ketophosphonate synthesis was desired. Based on a patent by Harada et al.[9] which demonstrated the use of LiHMDS for the condensation of methyl dimethylphosphonate with aromatic anhydrides at −20 °C, we attempted the reaction of aryl esters with methyl dimethylphosphonate mediated by LiHMDS, and found that this reaction could also be carried out at elevated temperatures in very high yield (Table 1, entry 1).[10] Further study of the reaction showed that steric hindrance in the dialkyl portion of the $MePO(OR)_2$ or the alkyl portion of the aryl ester has little influence on the yield of ketophosphonate, as dialkylphosphonates (Table 1, alkyl = methyl, ethyl, and isopropyl) along with isopropyl arylesters are uniformly compatible with the reaction. However, diphenyl methyl- (entry 4) and bis(trifluoroethyl) methylphosphonates (entry 5), which would give access to valuable substrates for the Still-Gennari-modified HWE reaction,[11] are not tolerated under these reaction conditions.[12]

The reaction is remarkably general for aryl esters (Table 2), and tolerates both steric and electronic deactivation of the ester without significant loss in yield. For extremely deactivated esters (entry 9), the reaction rate is significantly reduced, and these substrates tend to give incomplete conversion under standard conditions due to reagent ($MePO(OMe)_2$/LiHMDS) decomposition. These reactions can, however, proceed to completion using either additional reagent (entry 9) or portionwise addition of reagent. Both π-deficient (entries 12 and 13) and π-excessive (entries 10 and 11) heteroaryl esters participate in the reaction, giving clean 1,2-addition products. Aliphatic esters and esters with active α-protons are incompatible with the reaction conditions and instead undergo Claisen condensations.

Table 1
LiHMDS-mediated condensation of $MePO(OR)_2$ with alkyl benzoates

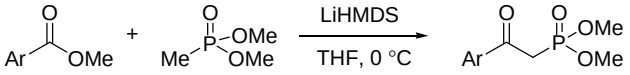


Entry	Ar	R^1	R^2	Product	Isolated yield, % (HPLC yield, %)
1	Ph	Me	Me	**1a**	92 (96)
2			Et	**1b**	91 (99)
3			*i*Pr	**1c**	91 (95)
4			Ph	**1d**	—
5	Ph	*i*Pr	CH_2CF_3	**1e**	—
5			Me	**2a**	87 (99)
6			Et	**2b**	93 (99)
7			*i*Pr	**2c**	91 (95)

* Corresponding author.
E-mail address: rmilburn@amgen.com (R.R. Milburn).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.11.112

Table 2
LiHMDS-mediated condensation of MePO(OMe)2 with aryl esters

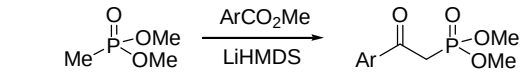


Entry	Ar	Product	Isolated yield, % (HPLC yield, %)
1	Ph	**1a**	92 (96)
2	2-MeC_6H_4	**2**	95 (99)
3	4-MeC_6H_4	**3**	94 (99)
4	2-IC_6H_4	**4**	80 (99)
5	4-IC_6H_4	**5**	99 (99)[a]
6	2-$CF_3C_6H_4$	**6**	78 (99)
7	4-$CF_3C_6H_4$	**7**	92 (99)
8	2-$OMeC_6H_4$	**8**	97 (98)
9	2,6-$OMeC_6H_3$	**9**	72 (—)[b]
10	2-Furan	**10**	66 (94)
11	2-Thiophene	**11**	91 (99)
12	Nicoinate	**12**	99 (—)[a]
13	5-Br 2-methoxy nicotinate	**13**	84 (92)

LiHMDS required to give complete conversion.
[a] Isolated as Li salts.
[b] 2 equiv $MePO(OMe)^2$ and 4 equiv.

Although the aryl ketophosphonates are usually oils, their lithio salts are typically non-hygroscopic and bench-stable solids, which provide an effective control point and allow for purity upgrade through recrystallization. In some cases (Table 2, entries 5 and 12), the lithio-ketophosphonate salt precipitated from solution during the reaction and could be isolated directly by filtration. In the case where direct isolation was not possible, we have shown that the lithio-ketophosphonates can be accessed via treatment of the ketophosphonate with LiO*i*-Pr/*i*-PrOH. These isolated salts have a shelf life of upwards of six months without apparent decomposition, and may be engaged directly in HWE reactions to afford the corresponding enones in high yield (Fig. 1).

There are several notable features of the reaction that deserve attention. The reaction is mildly exothermic upon addition of the phosphonate to the cooled solution of LiHMDS, a sizable exotherm is observed upon addition of the aryl ester to the mixture of $MePO(OR)_2$/LiHMDS, and a single equivalent of the $MePO(OR)_2$ and two equivalents of LiHMDS are sufficient to drive the reaction to completion. The reaction can also be run at much higher temperatures than with either LDA or *n*-BuLi, which makes it much more amenable to large-scale application than existing approaches. Recent work by Yasuda et al.[3] demonstrated the instability of the $MePO(OR)_2$/LDA mixture through trapping experiments, and showed that above −60 °C $EtPO(OMe)OLi$ is formed through a methyl transfer reaction. To assess the stability of the combination of $MePO(OR)_2$/LiHMDS system at elevated temperatures, we chose to take advantage of the rapid reaction of the $LiCH_2PO(OMe)_2$ with methyl benzoate. Thus, we incubated the $MePO(OMe)_2$/LiHMDS mixture at 0 °C, and then treated this mixture with methyl 2-methylbenzoate at various times (Fig. 2). The experiment highlights the remarkable stability of this mixture, which decomposes only



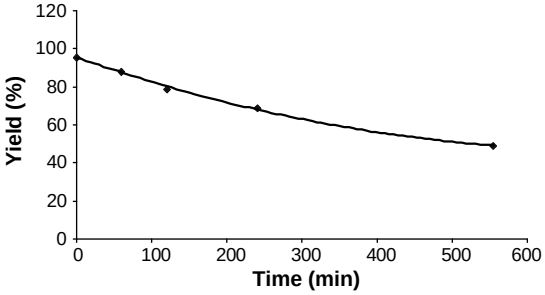


Figure 2. Decomposition of $MePO(OMe)^2$/LiHMDS mixture at 0 °C.

slowly ($t_{1/2}$ = 8 h) at 0 °C. Similar to observations using LDA,[3] the addition order in the preparation of the reagent is important, presumably due to reaction of the $LiCH_2PO(OMe)_2$ with the excess of free $MePO(OMe)_2$.

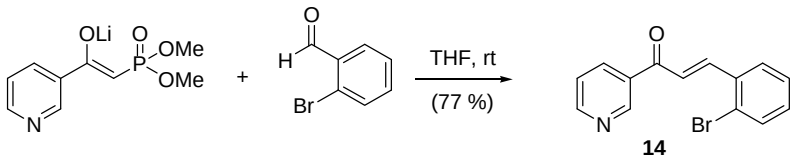
In summary, we have found that $MePO(OR)_2$/LiHMDS mixtures have unusual stability at elevated temperatures, allowing for their reaction with aromatic esters without the need for cryogenics. Methyl dialkylphosphonates in general are compatible with these conditions, but the diaryl- and di(trifluoroethyl)-phosphonates used in Still-Gennari-modified HWE reactions[11] are not accessible using this methodology. The background decomposition of this mixture is sufficiently slow at 0 °C ($t_{1/2}$ = 8 h) to allow for complete reaction of most aryl esters, but for less reactive systems where reagent decomposition competes with the desired condensation reaction, incomplete conversions may be overcome by using additional reagent. In many cases, the lithio-ketophosphonates may be isolated directly to give stable, non-hygroscopic salts, which have been successfully used directly in subsequent HWE reactions with aldehydes.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.112.

References and notes

1. Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738; Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87–99; Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927; Kelly, S. E.. In *Comp. Org. Synth.*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp 729–818.
2. For the preparation of a ketophosphonate on 20 kg scale, see: Zhe-Jiang Hisun Pharmaceutical Co. Ltd (2006) *The Process and Intermediates for the Selective Synthesis of Fluvastatin*. WO Patent: 2006021326.
3. 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, and references therein.
4. Boute, A.; Kelly, J.; Hsiao, Y.; Yasuda, N.; Antonucci, V. *J. Chromatogr., A* **2002**, *978*, 177–183.
5. 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.



14

Figure 1. HWE reaction of isolated lithio-ketophosphonate salt with 2-bromobenzaldehyde.

6. For a recent example, see: Palacios, F.; Ochoa de Retanam, A. M.; Alonso, J. M. *J. Org. Chem.* **2006**, *71*, 6141–6148.
7. Westermann, J.; Schneider, M.; Platzek, J.; Petrov, O. *Org. Proc. Res. Dev.* **2007**, *11*, 200–205.
8. Paterson, I.; Lyothier, I. *Org. Lett.* **2004**, *6*, 4933–4936.
9. UBE Ind. Ltd, 1996. Production of Beta-Ketophosphonate Derivative, Jpn Patent: 08099982 A.
10. Typical procedure (demonstrated on 14 mol scale): To a solution of LiHMDS (2.2 equiv) in THF (1.0 M), cooled in an ice bath, was added methyl dimethylphosphonate (1.1 equiv). No significant exotherm was observed during the addition. To this mixture was added the ester (either neat or dissolved in a minimal amount of THF) drop-wise, maintaining the internal temperature of the reaction below 5 °C. The addition of the ester was exothermic to varying extents depending on the reactivity of the aryl ester. The reaction was stirred at 0 °C until complete consumption of the ester as determined by HPLC. The mixture was partitioned between satd NH_4Cl (aq) and EtOAc, and the aqueous layer was extracted with EtOAc (1×). The combined organic layer was washed with water (1×), brine (1×), dried (Na_2SO_4), and the solvent removed in vacuo.
11. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
12. The condensation of bis(trifluoroethyl) methylphosphonates with esters mediated by LiHMDS has been demonstrated at −98 °C, see Ref. 8.