Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Organometallic Chemistry 690 (2005) 2688–2691
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Note

Preparation of α-ketophosphonates by a [3,3]-sigmatropoic shift of enolphosphonates

Kamyar Afarinkia *, Andrew J. Twist, Hiu-wan Yu

Department of Chemistry, King's College London, Strand, London WC2R 2LS, UK

Received 29 July 2004; accepted 7 October 2004

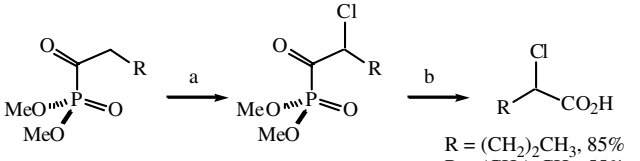
Abstract

α-Ketophosphonates are prepared by a [3,3]-sigmatropic shift of enolphosphonates.

Keywords: α-Ketophosphonate; [3,3]-Sigmatropic shift; Enolphosphonate

α-Ketophosphonates are one of the most interesting and versatile classes of organophosphorus compounds. α-Ketophosphonates undergo a diverse range of reactions and therefore, have found many useful synthetic applications both towards the preparation of other organophosphorus compounds as well as the synthesis of non-phosphorus containing molecules [1]. For instance, the reduction of α-ketophosphonates affords the corresponding α-hydroxyphosphonates [2]; treatment of α-ketophosphonates with a Wittig reagent affords the corresponding vinylphosphonates [3]; the corresponding oximes [4] and hydrazones [5] can be obtained from the reactions of α-ketophosphonates with hydroxylamine and hydrazine; β,γ-unsaturated-α-ketophosphonates can be epoxidized [6] and also undergo a very facile Diels–Alder cycloaddition both as diene [7] and hetero-dienophile [8]. Finally, C–P bond in α-ketophosphonates is susceptible to facile cleavage under nucleophilic attack, for instance during acidic and basic hydrolysis [9] and therefore, α-ketophosphonates can be considered as synthetic equivalents to acid chlorides. More recently, asymmetric α-ketophosphonates containing a chiral phosphorus atom are prepared which provide exciting opportunities for introducing an asymmetric dimension in one or all of these reactions [10].

One of the reactions of α-ketophosphonates which has as yet remained unexplored is their *C*-alkylation at the adjacent position to the C=O. Indeed, there are very few examples in the literature pertaining to derivatization at the β-carbon of α-ketophosphonates. Two examples of halogenation of α-ketophosphonates are reported using either elemental bromine or chlorine [11], or sulfuryl chloride (Scheme 1) [12]. No base is required for either reaction and it is not certain if the reactions proceed through enolization of α-ketophos-



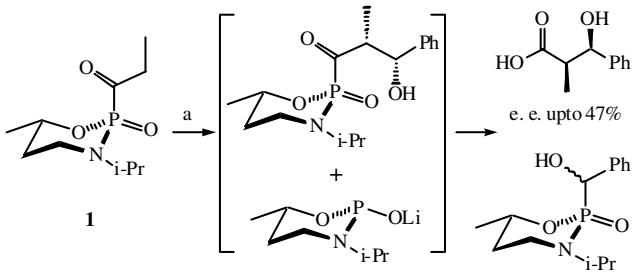
R = $(CH_2)_2CH_3$, 85%
R = $(CH_2)_6CH_3$, 55%
R = $(CH_2)_{10}CH_3$, 65%
R = $(CH_2)_{14}CH_3$, 75%

a) SO_2Cl_2 (1.3 eq.), 7h, dark, rt; b) H_2O_2 (4 eq.), $NaHCO_3$ (4 eq.), CH_2Cl_2

Scheme 1.

* Corresponding author. Tel.: +44 2078482422; fax: +44 2078482810.
E-mail address: kamyar.afarinkia@kcl.ac.uk (K. Afarinkia).

0022-328X/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2004.10.016

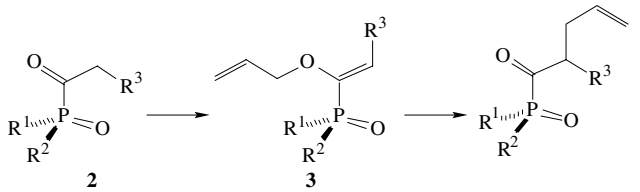


Scheme 2.

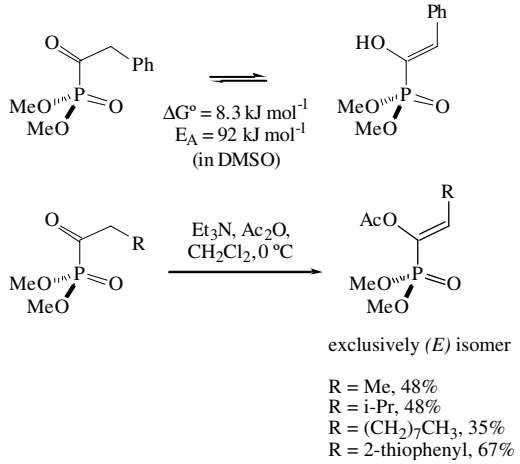
phonates or whether they are radical initiated. Gordon and Evans [10] reported isolation of an aldol product from the reaction of α-ketophosphonates **1** (Scheme 2) although the reaction affords substantial quantities of a by-product and its mechanism is unclear.

Here, we report on a methodology for the *C*-alkylation of α-ketophosphonates **2** via a [3,3]-sigmatropic shift of the corresponding allylenolphosphonates, **3** (Scheme 3). Furthermore, we will show that asymmetric α-ketophosphonates undergo this reaction with diastereoselectivity and that the selectivity in these reactions is influenced by chirality at the phosphorus.

We had previously demonstrated that the enol tautomers of α-ketophosphonates are thermodynamically quite stable. Indeed, simple α-ketophosphonates undergo very facile tautomerization to the extent that at room temperature in polar solvents, significant quantities of the enol tautomer can be spectroscopically observed (Scheme 4) [13]. The enol tautomers can be "trapped" as vinylacetates [13], silylenolethers [13], and sulfonates [14] which have in all cases been isolated as the *E* isomer. Although a study of the relative stability of the enolate anions of α-ketophosphonates has not been carried out, it can be assumed that they are also thermodynamically quite stable and that their formation is facile. Therefore, it was doubtful from the outset if the enolates derived from α-ketophosphonates would be reactive enough to undergo *C*-alkylation. Indeed, enolate formation by treatment of α-ketophosphonates **4a** and **4b** with organolithium bases such as LDA and BuLi and attempted *C*-alkylation with various electrophiles failed to give any desired product, affording instead mainly unreacted α-ketophosphonates. During the subsequent extensive studies using various additives and reaction conditions, we failed to obtain any *C*-alkylation prod-



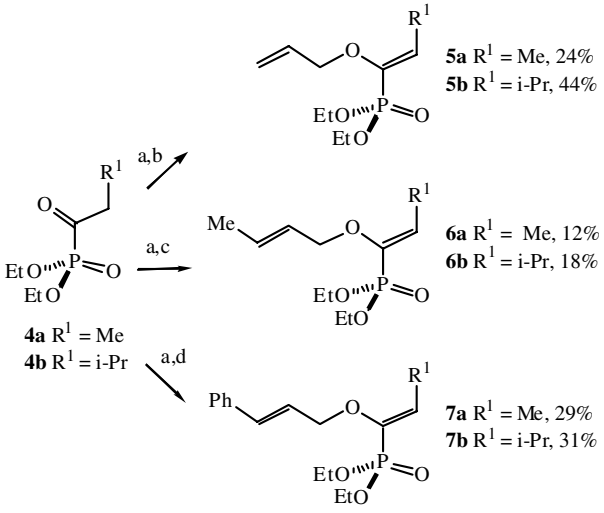
Scheme 3.



Scheme 4.

ucts. Careful examination of some reaction mixtures however, revealed the presence of small quantities of *O*-alkylation products. After further exploration, it became possible to isolate phosphoenols **5a**–**7a** and **5b**–**7b** by treatment of α-ketophosphonates **4a** and **4b** with organopotassium bases such as *t*-BuOK and KHMDS, followed by an excess of electrophiles such as allyl bromide, crotyl chloride and cinnamyl bromide (Scheme 5) [15]. The enol configuration in all compounds was found to be exclusively *trans* as determined by large [3] J_{PH} couplings of 10–12 Hz, indicative of a *cis* arrangement between the phosphorus atom and the olefinic hydrogen. This is consistent with the previous observations on the *O*-acylation, *O*-silylation and *O*-sulfonation of enolphosphonates [13,14].

When heated at reflux in toluene, phosphoenols **5a**–**7a** and **5b**–**7b** underwent a clean and facile [3,3]-sigma-



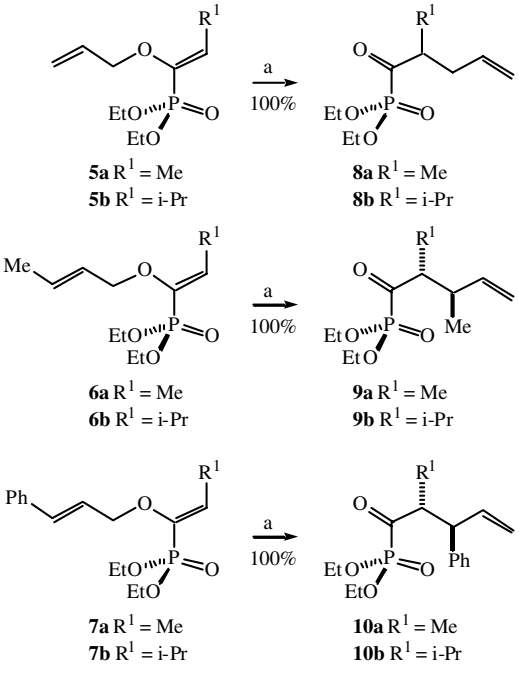
Scheme 5.

tropic rearrangement to the corresponding α-ketophosphonates **8a–10a** and **8b–10b** (Scheme 6) [16]. Interestingly, all six phosphoenols showed trace amounts of the corresponding rearranged α-ketophosphonates when stored at room temperature for period of days suggesting the rearrangement is a facile reaction.

Compounds **9a–10a** and **9a–10b** were obtained as a single diastereomer as determined by NMR spectroscopy. The relative configuration of the rearranged products was assumed from a proposed chair transition state for the sigmatropic shift (Scheme 7).

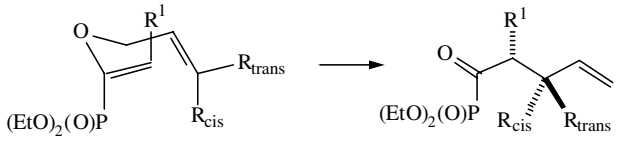
As expected, α-ketophosphonates **8–10** undergo efficient nucleophilic displacement reactions with a variety of nucleophiles with a concomitant loss diethyl phosphite (Scheme 8) [17].

In summary, we have shown that α-ketophosphonates can be alkylated at the position adjacent to the C=O function through a two step process of *O*-allylation followed by a [3,3]-sigmatropic shift. The reaction is stereospecific affording exclusively the anti (*threo*) product.

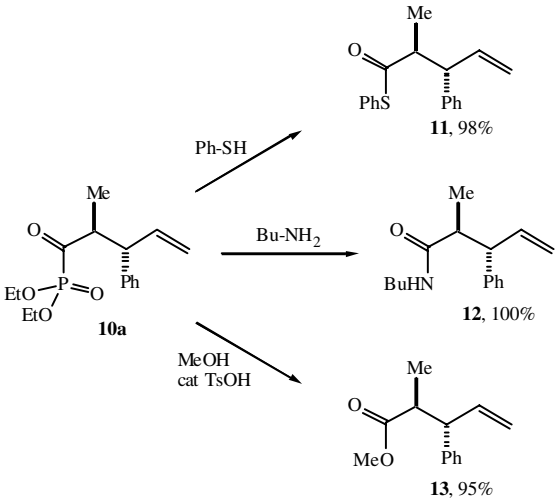


a) Toluene, reflux, 4hours

Scheme 6.



Scheme 7.



Scheme 8.

Acknowledgments

We thank EPSRC and SmithKline Beecham for financial support to A.J.T. and Garlick Foundation for financial support to H.Y.

References

[1] (a) K. Afarinkia, M.V. Vinader, in: C.J. Moody (Ed.), Comprehensive Organic Functional Group Transformations, vol. 5, Pergamon, London, 1995, p. 393;
(b) P. Savignac, B. Igora, in: Modern Phosphonate Chemistry, CRC Press, New York, 2003, p. 319;
(c) K. Afarinkia, in: R.C.F. Jones (Ed.), Comprehensive Organic Functional Group Transformations II, vol. 5, Elsevier, London, 2004 (in press).
[2] (a) T. Oshikawa, M. Yamashita, Bull. Chem. Soc. Jpn 63 (1990) 2728;
(b) R. Karaman, A. Goldblum, E. Breuer, H.J. Leader, Chem. Soc., Perkin Trans. 1 (1989) 765.
[3] M. Yamashita, M. Kojima, H. Yoshida, T. Ogata, S. Inokawa, Bull. Chem. Soc. Jpn 53 (1980) 1625.
[4] (a) E. Breuer, A. Schlossman, M. Safadi, D. Gibson, M. Chorev, H.J. Leader, Chem. Soc., Perkin Trans. 1 (1990) 3263;
(b) E. Breuer, H. Zaher, Z. Tashma, Tetrahedron Lett. (1992) 2067.
[5] H. Scherer, A. Hartmann, M. Regitz, B.D. Tunggal, H. Günther, Chem. Ber. 105 (1972) 3357.
[6] (a) E. Öhler, E. Zbiral, M. El-Badawi, Tetrahedron Lett. 24 (1983) 5599;
(b) F. Hammerschmidt, E. Zbiral, Ann. Chem. (1979) 492.
[7] (a) D.A. Evans, J.S. Johnson, E.J. Olhava, J. Am. Chem. Soc. 122 (2000) 1635;
(b) L.A. Telan, C.-D. Poon, S.A. Evans Jr., J. Org. Chem. 61 (1996) 7455.
[8] S. Hanessian, P. Compain, Tetrahedron 58 (2002) 6521.
[9] (a) A. Kume, M. Fujii, M. Sekine, T. Hata, J. Org. Chem. 49 (1984) 2139;
(b) M. Sekine, M. Satoh, H. Yamagata, T. Hata, J. Org. Chem. 45 (1980) 4162;

(c) M. Fujii, K. Ozaki, M. Sekine, T. Hata, Tetrahedron 43 (1987) 3395;
(d) E. Breuer, R. Karaman, A. Goldblum, H. Leader, J. Chem. Soc., Perkin Trans. 2 (1988) 2029;
(e) R. Karaman, A. Goldblum, E. Breuer, H. Leader, J. Chem. Soc., Perkin Trans. 1 (1989) 765.

[10] (a) N.J. Gordon, S.A. Evans, J. Org. Chem. 58 (1993) 5293;
(b) N.J. Gordon, S.A. Evans, Phosphorus, Sulfur Silicon Relat. Elements 75 (1–4) (1995) 47.

[11] E. Öhler, M. El-Badawi, E. Zbiral, Chem. Ber. 117 (1984) 3034.

[12] C. Stevens, L. De Buyck, N. De Kimpe, Tetrahedron Lett. 39 (1998) 8739.

[13] K. Afarinkia, J. Echenique, S.C. Nyburg, Tetrahedron Lett. 38 (1997) 1663.

[14] T. Okauchi, T. Yano, T. Fukomachi, J. Ichikawa, T. Minami, Tetrahedron Lett. 40 (1999) 5337.

[15] Typical experimental procedure: The corresponding alkyl bromide (4.84 g, 40 mmol) was added to a stirred solution of diethyl 1-oxopropyl phosphonate **4a** (1.94 g, 10 mmol) in THF (25 ml) maintained under an argon atmosphere at a temperature of −78 °C. A 0.5 M solution of KHMDS in toluene (40 ml, 20 mmol) was added and the resulting solution was stirred at −78 °C for 3 h. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction was quenched by addition of 10% aqueous ammonium acetate (10 ml) and the organic products were extracted with diethyl ether (3×20 ml). The combined organic extracts were washed with brine (20 ml) and water (20 ml) and were dried over $MgSO_4$. The solvent was removed in vacuo to give the crude product. The product was purified by column chromatography using 40% ethyl acetate in petroleum ether as eluent to afford diethyl 1-(*trans*-3-phenyl prop-2-enyloxy)-prop-1-ene phosphonate, **7a** as a colourless oil (0.89 g, 29%). δ_H ($CDCl_3$, 400 MHz) 1.36 (6H, t, $J_H = 7$ Hz, $2 \times OCH_2CH_3$), 1.80 (3H, dd, $J_H = 7$ Hz, $J_P = 3$ Hz, C=CHCH_3), 4.13 (4H, m, $2 \times OCH_2$), 4.56 (2H, d, $J_H = 7$ Hz, OCH_2CH), 6.16 (2H, m, PhC=C*H*), 6.37 (1H, m, PC=C*H*), 6.66 (1H, d, $J_H = 16$ Hz, CH=C*H*Ph), 7.24–7.41 (5H, m, aromatic *H*); δ_C {H}($CDCl_3$, 100 MHz) 11.8 (d, $J_P = 13$ Hz, C=CH*C*H$_3$), 16.8 (d, $J_P = 6$ Hz, OCH$_2$*C*H$_3$), 62.6 (d, $J_P = 5$ Hz, O*C*H$_2$), 73.3 (d, $J_P = 2$ Hz, O*C*H$_2$CH=), 125.2 (=*C*HPh), 126.9 (Aromatic C), 128.3 (Aromatic C), 129.0 (Aromatic C), 129.2 (d, $J_P = 34$ Hz, OC=*C*H), 133.6 (CH$_2$*C*H=), 136.9 (Aromatic C), 146.4 (d, $J_P = 216$ Hz, P*C*=CH); δ_P {H}($CDCl_3$, 162 MHz) 8.2; IR (liquid) 2980, 2933 (C–H str), 1736, 1639 (C=C str), 1251 (P=O str), 1055, 1027 (P–O str), 966 (P–O bnd) cm^{-1}; *m/z* 310 (M^+, 11), 281 (21), 253 (22), 172 (33), 117 (100). Calc. for $C_{16}H_{23}O_4PNa$: 333.1232. Found: $[M + Na]^+$ 333.1232.

[16] Typical experimental procedure: A solution of **7a** in toluene (5 ml) was refluxed for 4 h under an atmosphere of argon. The solvent was removed in vacuo to give diethyl (1-oxo-2-methyl-3-phenyl-pent-4-enyl)phosphonate, **10a** as a colourless oil in quantitative yield. δ_H ($CDCl_3$, 400 MHz) 1.17 (3H, t, $J_H = 7$ Hz, CHCH_3), 1.26 (6H, t, $J_H = 7$ Hz, $2 \times OCH_2CH_3$), 3.67–4.07 (6H, overlapping m, $2 \times OCH_2$ and C*H*C*H*Ph), 5.11 (2H, m, CH=CH_2), 5.91 (1H, m. C*H*=CH$_2$), 7.13–7.36 (5H, m, aromatic *H*); δ_C {H}($CDCl_3$, 100 MHz) 15.1 [C(O)CH*C*H$_3$], 16.6 ($2 \times CH_2CH_3$), 51.3 [d, $J_P = 52$ Hz, C(O)*C*HMe], 51.8 (*C*HCH=CH$_2$), 63.9 (d, $J_P = 7$ Hz, O*C*H$_2$), 117.4 (CH=*C*H$_2$), 127.0 (aromatic CH), 128.3 (aromatic CH), 128.9 (aromatic CH), 138.6 (*C*H=CH$_2$), 142.6 (aromatic C), 214.3 (d, $J_P = 159$ Hz, C=O); δ_P {H}($CDCl_3$, 162 MHz) −2.8; IR (liquid) 2981, 2932 (C–H str), 1691 (C=O str), 1636 (C=C str), 1256 (P=O str), 1054, 1022 (P–O str), 971 (P–O bnd); *m/z* 310 (M^+, 5), 173 (45), 137 (100), 131 (57). Calc. for $C_{16}H_{23}O_4PNa$: 333.1232. Found: $[M+Na]^+$ 333.1221.

[17] Typical experimental procedure: Butylamine (625 mg, 85 mmol) was added to a solution of **10a** (530 mg, 17 mmol) in dichlroromethane (5 ml) at room temperature under a dry atmosphere of argon. After 15 h, the solvent was removed in vacuo to give *N*-butyl 2-methyl-3-phenylpent-4-enamide, **12** as a gum in quantitative yield (416 mg). δ_H ($CDCl_3$, 400 MHz) 1.00 (3H, d, $J = 7$ Hz, CH_3CH), 1.06 (3H, t, $J_H = 7$ Hz, CH_3CH$_2$), 1.38 (4H, m, $2 \times (CH_2)_2$], 2.84 (1H, d, $J = 7$ Hz, C*H*Me), 3.22 (2H, m, NCH_2), 3.45 (1H, dm, $J = 8$, C*H*Ph), 5.10 (2H, m, CH=CH_2), 6.00 (1H, ddd, $J = 16$, 10, 8 Hz, CH$_2$=C*H*), 7.15–7.38 (5H, m, aromatic H); δ_C {H}($CDCl_3$, 100 MHz) 14.5 (*C*H$_3$CH$_2$), 16.0 (*C*H$_3$CH), 19.0 (Et*C*H$_2$), 21.0 (Pr*C*H$_2$), 39.3 (N*C*H$_2$), 51.3 (*C*HMe), 53.8 (*C*HPh), 116.5 (CH=*C*H$_2$), 127.0 (aromatic CH), 128.3 (aromatic CH), 128.9 (aromatic CH), 139.5 (*C*H=CH$_2$), 141.6 (aromatic C), 177.6 (C=O); IR (liquid) 2977, 2923 (C–H str), 1657 (C=O str), 1640 (C=C str) cm^{-1}; *m/z* 245 (M^+, 77), 173 (16), 73 (100). Calc. for $C_{16}H_{23}NONa$: 268.1677. Found: $[M + Na]^+$ 268.1676.