Preparation of Diethyl 3-Hydroxy-1-alkenylphosphonates by the Reaction of Diethyl (Arylsulfinylmethyl)phosphonate with Aldehydes under the Knoevenagel Conditions

Junzo Nokami,* Akito Taniguchi, Masayuki Honda, and Satoshi Fukutake
Department of Applied Chemistry, Faculty of Engineering, Okayama University of Science, Ridai, Okayama 700

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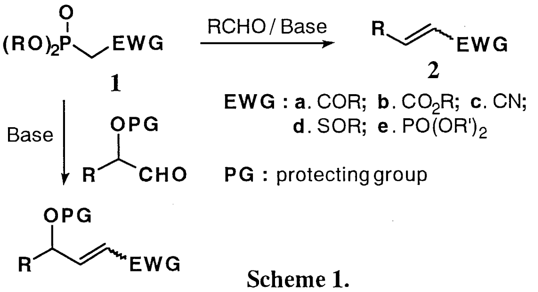
The title compounds were prepared by the reaction of diethyl (arylsulfinylmethyl)phosphonate with aldehydes in the presence of piperidine in aceto(or propio)nitrile.

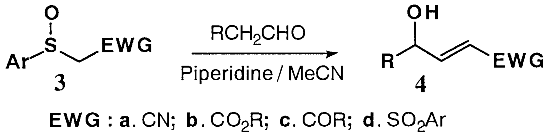
Reaction of phosphonate carbanions with carbonyls (ketones or aldehydes) is well known to result in the Wittig-type olefin formation called Wittig-Horner reaction.[1] Moreover, the reaction of dialkyl (substituted-methyl)phosphonate (**1**), having another electron-withdrawing group (EWG) as a substituent on the methyl group, with carbonyls is the best method to give the corresponding α,β-unsaturated ketones **2a**, esters **2b**, nitriles **2c**, sulfoxides **2d**,[2] etc **2e**.[3] and we are calling the reaction Horner-Wadsworth-Emmons (HWE) reaction.[4]

Horner-Wadsworth-Emmons reaction



Scheme 1.

On the other hand, we have found out that the reaction of sulfinyl activated-methylene compounds **3** with aldehydes (and ketones) gave γ-hydroxy-α,β-unsaturated-EWG compounds **4**,[5] in which the α-carbon of the starting carbonyls was functionalized into the γ-hydroxy carbon of the product **4** *via* the following three-step reaction, (1) Knoevenagel (or aldol) reaction of **3** with carbonyls to give α-arylsulfinyl-α,β-unsaturated-EWG compounds, (2) migration of the α,β-double bond to β,γ-double bond, and (3) Mislow-Evans rearrangement of the allylic sulfoxide to give sulfur-free allylic alcohols **4**. This reaction seems to be more useful, when we require γ-hydroxy-α,β-unsaturated-EWG compounds **4**, than HWE reaction of **1** with α-hydroxycarbonyls which are somewhat more difficult to prepare than simple carbonyls used in our reaction (Scheme 2).



Scheme 2.

Mikolajczyk *et al.*[2a] have first reported the preparation of α,β-unsaturated sulfoxides **2d** by HWE reaction of **1d** with carbonyls. Since then, there are a few works on the application of the reaction of **1d** for synthesis of some α,β-unsaturated sulfoxides.[2] However, there is no report on a reaction of **1d** with aldehydes under our reaction conditions to give dialkyl γ-hydroxy-α,β-unsaturated phosphonate **5**. Herein, we describe the reaction of diethyl (arylsulfinylmethyl)phosphonate **1d** with aldehydes under Knoevenagel reaction conditions to give **5** which is expected to play an important role in organic synthesis as one of the useful vinylphosphonates reviewed by Minami *et al.*[6]

At first, we tried to allow to react **1d** (Ar=XC_6H_4; X=H) with hexanal to give **5a** as shown in Table 1, and made it clear that treatment under the moderate heating (at 40 °C) gave a better yield in a shorter reaction time than that of the cases at room temperature. Next, we examined the substituent effect of the aryl group (*p*-XC_6H_4) of **1d**, and we could obtain the desired products **5** by using *p*-ClC_6H_4 (X=Cl) derivative more effectively than C_6H_5 (X=H). The typical procedure is representable as follows; diethyl (*p*-chlorophenylsulfinylmethyl)phosphonate **1d** (X=Cl, 311 mg, 1 mmol), hexanal (0.09 ml, 1.5 mmol), and piperidine (0.5 ml, 5 mmol) were dissolved in acetonitrile (3.5 ml), and the solution was stirred at 40 °C for 12 h.[7] The reaction mixture was acidified with diluted hydrochloric acid (1N) and extracted with chloroform twice, and then usual work-up gave **5a**[8] as a single product.

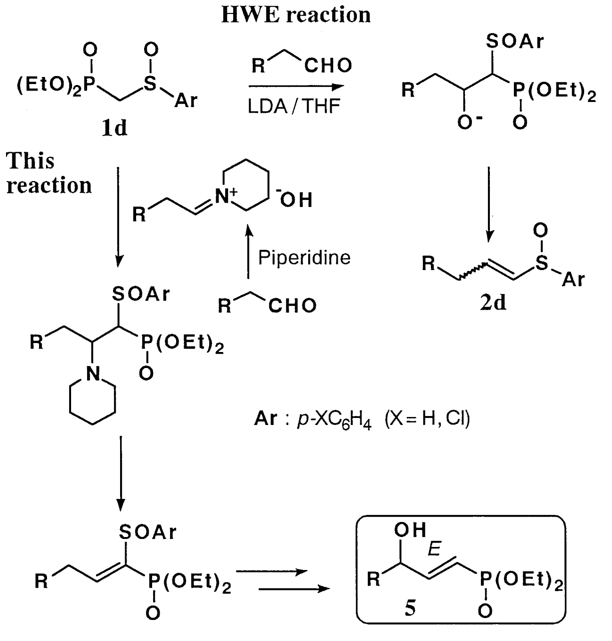
The difference of the products between this reaction and HWE reaction due to the reaction condition would be explained as shown in Scheme 3. That is, our reaction condition seems to be similar to that of the Knoevenagel reaction in which the

Table 1. Reaction of Diethyl (arylsulfinyl)phosphonate with Aldehydes (RCH_2CHO)

X[a]	aldehyde (R)	solvent	Reaction temp/°C	time/h	5	Yield[b] /%
H	$CH_3(CH_2)_3$	MeCN	r.t.	12	a	33
H	$CH_3(CH_2)_3$	MeCN	r.t.	24	a	56
H	$CH_3(CH_2)_3$	MeCN	40	12	a	57
H	$CH_3(CH_2)_3$	MeCN	40	24	a	89
H	$CH_3(CH_2)_3$	MeCN-THF (2/1)	40	24	a	86
H	$CH_3(CH_2)_3$	THF	40	24	a	38
Cl	$CH_3(CH_2)_3$	MeCN	40	6	a	70
Cl	$CH_3(CH_2)_3$	MeCN	40	12	a	86
Cl	citroneral[c]	MeCN	40	13	b	90
Cl	$i\text{-}PrO_2C(CH_2)_2$	MeCN	40	12	c	57[d]
Cl	$i\text{-}PrO_2C(CH_2)_2$	MeCN	40	24	c	59[d]
Cl	$i\text{-}PrO_2C(CH_2)_2$	EtCN	40	12	c	63[d]
Cl	$THPO(CH_2)_3$	EtCN	40	12	d	71
Cl	$PhS(CH_2)_3$	EtCN	40	12	e	77
Cl	$c\text{-}C_6H_{11}CHO$	MeCN	40	20	f	< 25

[a] Substituent(X) in *p*-$XC_6H_4SOCH_2PO(OEt)_2$ (**1d**).
[b] After column chromatography on silica gel.
[c] $(CH_3)_2C{=}CHCH_2CH_2CH(CH_3)CH_2CHO$
[d] Isolated as the corresponding γ-butyrolactone.[10]

condensation reaction of an active methylene compound with aldehyde is accelerated *via* the initial formation of the iminium salt from an aldehyde and a secondary amine.[9] Therefore, in this reaction, the Knoevenagel-type condensation reaction proceeds advantageously rather than the HWE reaction which proceeds *via* an oxyanion intermediate from the phosphonate carbanion and carbonyls.[2] Then the migration of the double bond followed by Mislow-Evans allylic rearrangement of the sulfinyl group should give the allylic alcohol **5**.



R= **a**: $CH_3(CH_2)_3$; **b**: $(CH_3)_2C{=}CHCH_2CH_2CH(CH_3)$;
c: i-$PrO_2C(CH_2)_2$; **d**: $THPO(CH_2)_3$; **e**: $PhS(CH_2)_3$

Scheme 3.

The geometry of **5** was perfectly *E*,[8] and **1d**, as well as **3b**, **3c**, and **3d**, did not react with ketone (cyclohexanone), though **3a** reacted with ketones and aldehydes.[5a-c]

Synthetic application of dialkyl 3-hydroxy-1-alkenylphosphonates is now in progress.

References and Notes

1 L. Horner, H. Hoffmann, H. G. Wippel, and G. Klahre, *Chem. Ber.*, **92**, 2499 (1959); W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).

2 a) M. Mikolajczyk, S. Grzejszczak, and A. Zatorski, *J. Org. Chem.*, **40**, 1979 (1975); b) M. Mikolajczyk, W. Midura, S. Grzejszczak, A. Zatorski, and A. Chefczynska, *J. Org. Chem.*, **43**, 473 (1978); c) B. E. de Jong, H. de Koning, and H. O. Huisman, *J. Roy. Neth. Chem. Soc.*, **100**, 410 (1981); d) G. Solladie and G. Moine, *J. Am. Chem. Soc.*, **106**, 6097 (1984); e) G. Solladie, *Synthesis*, **1981**, 185; f) R. A. Holton and H.-B. Kim, *Tetrhaedron Lett.*, **27**, 2191 (1986).

3 W. Waszkuc, T. Janecki, and R. Bodalski, *Synthesis*, **1984**, 1025.

4 J. Boutagy and R. Thomas, *Chem. Rev.*, **74**, 87 (1974); B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, **89**, 863 (1989); S. E. Denmark and I. Rivera, *J. Org. Chem.*, **59**, 6887 (1994), references cited therein.

5 *EWG=CN* : a) J. Nokami, T. Mandai, Y. Imakura, K. Nishiuchi, M. Kawada, and S. Wakabayashi, *Tetrahedron Lett.*, **22**, 4489 (1981); b) T. Ono, T. Tamaoka, Y. Yuasa, T. Matsuda, J. Nokami, and S. Wakabayashi, *J. Am. Chem. Soc.*, **106**, 7890 (1984); c) J. Nokami, T. Mandai, A. Nishimura, T. Takeda, and S. Wakabayashi, *Tetrahedron Lett.*, **27**, 5109 (1986); d) R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi, and A. Restelli, *Gaz. Chim. Ital.*, **115**, 637 (1985); e) B. M. Trost and G. B. Tometzki, *Synthesis*, **1991**, 1235. *EWG=CO$_2$R* : f) Q. B. Cass, A. A. Jaxa-Chamiec, and P. G. Sammes, *J. C. S., Chem. Commun.*, **1981**, 1248; g) R. Tanikaga, Y. Nozaki, K. Tanaka, and A. Kaji, *Chem. Lett.*, **1982**, 1703; h) R. Tanikaga, Y. Nozaki, T. Tamura, and A. Kaji, *Synthesis*, **1983**, 134; i) H. Kosugi, M. Kitaoka, A. Takahashi, and H. Uda, *J. C. S., Chem. Commun.*, **1986**, 1268; j) K. Burgess and I. Henderson, *Tetrahedron Asym.*, **1**, 57 (1990); k) E. J. Corey and P. Carpino, *Tetrahedron Lett.*, **31**, 7555 (1990); l) J. Nokami, M. Ohkura, Y. Dan-oh, and Y. Sakamoto, *Tetrahedron Lett.*, **32**, 2409 (1991); m) B. M. Trost and S. Mallart, *Tetrahedron Lett.*, **34**, 8025 (1993); n) J. Nokami, T. Taniguchi, S. Gomyo, and T. Kakihara, *Chem. Lett.*, **1994**, 1103. *EWG=COR* : o) J. Nokami, A. Nishimura, M. Sunami, and S. Wakabayashi, *Tetrahedron Lett.*, **28**, 649 (1987); p) J. Nokami, T. Taniguchi, and Y. Ogawa, *Chem. Lett.*, **1995**, 43. *EWG=SO$_2$Ph* : q) E. Dominguez and J. C. Carretero, *Tetrahedron Lett.*, **31**, 2487 (1990); r) C. Alcaraz, J. C. Carretero, and E. Dominguez, *Tetrahedron Lett.*, **32**, 1385 (1991); s) B. M. Trost and T. A. Grese, *J. Org. Chem.*, **56**, 3189 (1991); t) J. C. Carretero and E. Dominguez, *J. Org. Chem.*, **57**, 3867 (1992).

6 For review: T. Minami and J. Motoyoshiya, *Synthesis*, **1992**, 333.

7 When we used pyrrolidine as a base, we could obtain the same result.

8 The single isomer **5** was determined to be *E*, as well as **4**, formed by the reaction of **3** with carbonyls, in which the single isomer (**4**) was determined to be *E*. See Ref. 5.

5a: Rf 0.35 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.80 (1H, ddd, J=22.4, 17.2, and 4.4 Hz, H-2), 5.93 (1H, ddd, J=18.7, 17.2, and 1.8 Hz, H-1), 4.28 (1H, m, H-3), 4.09, 4.07 (each 2H, q, J=7.0 Hz, $O\text{-}C\underline{H}_2CH_3$), 2.35 (1H, m, O-H), 1.58 (1H, m, H-4), 1.2-1.5 (4H, m, H-5 and 6), 1.33 (6H, t, J=7.0 Hz, $O\text{-}CH_2C\underline{H}_3$), 0.91 (3H, t, J=7.2 Hz, H-7).

9 Knoevenagel reaction of triethyl phosphonoacetate with aldehyde gave the corresponding condensation product: T. Minami, T. Utsunomiya, S. Nakamura, M. Okubo, N. Kitamura, Y. Okada, and J. Ichikawa, *J. Org. Chem.*, **59**, 6717 (1994), references cited therein.

10 In this case, it was difficult to purify **5c** which was not detectable on silica gel TLC (Merck, Kieselgel 60 F_{254}), though the progress of the reaction was clearly detected by consumption of the sulfoxide and increase of disulfide $(ArS)_2$ by the TLC monitorring. Then, we obtained the correct result after conversion of **5c** into TLC detectable derivatives such as the corresponding lactone or acetate. The conversion was estimated >90% by using partially isolated **5c**.