Bis-Wittig Reactions of 1,2-Diketones; a Useful Way of Preparing 3,4-Disubstituted Muconates

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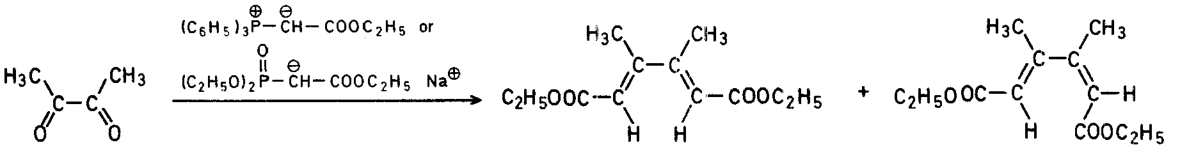
In connection with another study, we required a straightforward way of preparing diethyl (*E,E*)- and (*E,Z*)-3,4-dimethylmuconate. The methods currently available for the preparation of substituted muconates were unsuitable since they either required several synthetic steps[1,2,3] or led to products with the (*Z,Z*)-stereochemistry[4].

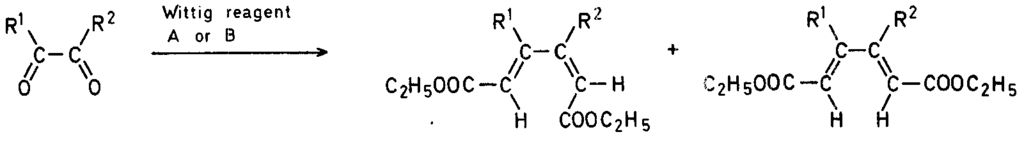
A review of the literature revealed that, with one exception[5], such bis-Wittig reactions have only been successful with 1,2-diketones that cannot undergo enolisation [6]. Attempts have been made to employ butane-2,3-dione in bis-Wittig reactions but they were unsuccessful; reaction with benzylidenetriphenylphosphorane was reported to give an intractable tar[7] and treatment with diethyl α-ethoxycarbonyl-α-sodiomethanephosphonate gave alkene formation at only one of the carbonyl groups[8]. However, we decided to carry out a more extensive study of the bis-Wittig reactions of 1,2-diketones in the hope that a method could be devised for the preparation of (*E,E*)- and (*E,Z*)-3,4-dimethylmuconates. The results of this study are summarised in Table 1.



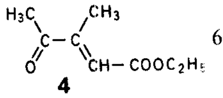
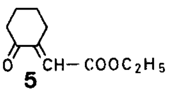
One of the most direct ways of preparing these compounds appeared to be the reaction of butane-2,3-dione with stabilised Wittig reagents such as ethoxycarbonylmethylenetriphenylphosphorane or diethyl α-ethoxycarbonyl-α-sodiomethanephosphonate.

Diphenylcyclobutadiene-1,2-dione (**1a**) and cyclobutane-1,2-dione (**1b**) both reacted with ethoxycarbonylmethylenetriphenylphosphorane to give good yields of the substituted muconates (Table 1) as expected[9] whereas butane-2,3-dione (**1c**) and cyclohexane-1,2-dione (**1d**) both underwent alkene

Table 1. Reactions of 1,2-Diketones with Stabilised Wittig Reagents



1a-d **2a-d** **3a-d**

Substrate No.	R¹	R²	Wittig Reagent[a]	Reaction Conditions solvent/temp./time	Product	Yield [%]	m.p.[b]	Molecular formula[c]	¹H-N.M.R. (CDCl₃, 60 MHz) δ [ppm] (vinylic protons)
1a	$C_6H_5-C=C-C_6H_5$		A	C_6H_6/reflux/7 h	**2a**	84	96–98°	$C_{24}H_{22}O_4$ (374.4)	7.07 (s, 1 H); 6.02 (s, 1 H)
					3a	10	oil	—[d]	5.73 (s, 2 H)
1b	$-(CH_2)_2-$		A	C_6H_6/r.t./17 h	**2b**	28	46°	$C_{12}H_{16}O_4$ (224.3)	5.73 (m, 1 H); 7.08 (m, 1 H)
					3b	46	86°	$C_{12}H_{16}O_4$ (224.3)	6.03 (s, 2 H)
1c[e,f]	CH_3	CH_3	A	C_6H_6/r.t./17 h	 **4**	66	20–21°	$C_8H_{12}O_3$ (156.2)	6.58 (m, 1 H)
1c	CH_3	CH_3	B	C_6H_6/r.t./15 min	**2c**	2	oil	$C_{12}H_{14}O_4$ (222.2)	5.62 (m, 1 H); 5.54 (m, 1 H)
					3c	6	42–44°	$C_{12}H_{14}O_4$ (222.2)	6.03 (d, 2 H, $J = \sim 1$ Hz)
1d[e,f]	$-(CH_2)_4-$		A	C_6H_6/reflux/7 h	 **5**	76	oil	$C_{10}H_{14}O_3$ (182.2)	6.42 (t, 1 H, $J = 2$ Hz)

[a] A = ethoxycarbonylmethylenetriphenylphosphorane; B = diethyl α-ethoxycarbonyl-α-sodiomethanephosphonate.

[b] Uncorrected.

[c] All products except where stated gave satisfactory microanalyses (C ±0.26%; H ±0.09%).

[d] Analysis not obtained due to instability of compound.

[e] Small amounts of substituted muconates were observed but the quantity did not appear to increase even after the addition of excess phosphorane and prolonged refluxing.

[f] The α,β-unsaturated ketones were formed as a mixture of isomers although butane-2,3-dione gave a crystalline product which on recrystallisation gave a single compound according to ¹H-N.M.R. spectroscopy.

Table 2. Reactions of α,β-Unsaturated Ketones **4** and **5** with Diethyl α-Ethoxycarbonyl-α-sodiomethanephosphonate

Substrate	Reaction Conditions solvent/temp./time	Product	Yield [%]	m.p.[a]	Molecular formular[b]	^{1}H-N.M.R. (CDCl$_3$, 60 MHz) δ [ppm] (vinylic protons)
4	C_6H_6/r.t./1 h	**2c**	46	see Table 1		
		3c	6			
5	C_6H_6/r.t./0.5 h	**2d**	11	oil	$C_{14}H_{20}O_4$ (252.3)	5.67 (m, 2H)[c]
		3c	41	33–35°	$C_{14}H_{20}O_4$ (252.3)	5.87 (s, 2H)

[a] Uncorrected.

[b] All products gave satisfactory microanalyses (C ±0.08%; H ±0.14%).

[c] Although only one set of vinyl hydrogens was present, the ethyl ester absorptions clearly indicated the (E,Z)-structure: δ=4.18 and 4.13 (q, 2H each, J=7Hz), 1.27 and 1.22 (t, 3H each, J=7Hz).

formation at only one carbonyl group (Table 1; products **4** and **5**). However, on treatment with diethyl α-ethoxycarbonyl-α-sodiomethanephosphonate, butane-2,3-dione (**1c**) gave the desired compounds (**2c** and **3c**), albeit in low yields (Table 1). This result encouraged us to look into the possibility of subjecting the α,β-unsaturated ketones (**4** and **5**) to a second Wittig reaction using the more nucleophilic[10] phosphonate reagent. When these reactions were carried out the desired 3,4-disubstituted muconates (**2c,d** and **3c,d**) were prepared in reasonable yields, as can be seen from Table 2.

It is interesting that only two of the three possible isomeric muconates were obtained from each 1,2-diketone whether the direct or the two-step Wittig procedure was used. The structures were assigned mainly by ^{1}H-N.M.R. spectroscopy, the unsymmetrical (E,Z)-isomers showing many more resonances than the symmetrial isomers (often two sets of vinyl resonances were observed for the (E,Z)-isomers as can be seen from Table 1). The symmetrical isomers could either possess the (E,E)- or the (Z,Z)-structure and the (E,E)-structure was allocated for the following reasons:

(a) the relative chemical shifts of the vinyl hydrogens of isomeric muconates correspond to those of similar examples in the literature[1,2,3,11];

(b) as expected from the literature[1], the allylic hydrogens of diethyl (E,E)-3,4-dimethylmuconate (**3c**) are deshielded by the presence of the *cis*- ethoxycarbonyl group (2.33 ppm) whereas the (E,Z)-isomer (**2c**) shows one set of allylic protons at significantly higher field (2,3 and 1.97 ppm);

(c) molecular models show that the (Z,Z)-muconates derived from cyclic 1,2-diketones are unlikely to be formed because of severe steric congestion.

To summarise, certain enolisable 1,2-diketones[12] can be considered to be synthetic precursors of 3,4-disubstituted muconates although it may be necessary to carry out the transformation by a two-step procedure.

Bis-Wittig Reaction of Cyclobutane-1,2-dione (1b); Typical One-Step Procedure:

To a solution of the diketone (3.61 g, 43 mmol) in dry benzene (250 ml) is added ethoxycarbonylmethylenetriphenylphosphorane (33 g, 94 mmol) and the reaction is stirred under nitrogen at room temperature for 17 h. The solution is then passed through a short silica column to remove phosphorus-containing material and the solvent is evaporated under reduced pressure. Chromatography of the resultant white crystalline material on silica using ether/hexane (1:19) as eluent gives the symmetrical isomer **3b** (4.40 g, 46%) followed by the unsymmetrical isomer **2b** (2.71 g, 28%).

Bis-Wittig Reaction of Butane-2,3-dione (1c); Typical Two-Step Procedure:

Step A: To a solution of the diketone (0.493 g, 5.7 mmol) in dichloromethane (25 ml) is added ethoxycarbonylmethylenetriphenylphosphorane (2 g, 5.7 mmol) and the reaction is stirred under nitrogen for 17 h. Evaporation of the solvent under reduced pressure and chromatography on a silica column using ether/hexane (1:3) as eluent gives the α,β-unsaturated ketone **4**: yield: 0.59 g (66%).

Step B: Diethyl α-ethoxycarbonylmethanephosphonate (1.7 g, 7.5 mmol) is added to sodium hydride (80% in oil, 222 mg, 7.4 mmol) in dry benzene (15 ml) under nitrogen. After gas evolution has ceased, the α,β-unsaturated ketone (**4**; 0.59 g, 3.8 mmol) in benzene (2 ml) is added in one portion. After 30 min the now yellow solution is poured into water and extracted with ether. The ether solution is dried and evaporated under reduced pressure. Chromatography of the resultant oil on silica using ether/hexane (1:19) as eluent gives the symmetrical isomer **3c** (444 mg, 46%) followed by the unsymmetrical isomer **2c** (60 mg, 6%).

I would like to thank Professor F. Sondheimer for his advice and University College London for the provision of bench space and elemental and spectral analyses.

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[1] E. Gil-av, J. H. Leftin, A. Mandelbaum, S. Weinstein, *Org. Mass Spectrom.* **4**, 475 (1970).

[2] J. A. Elvidge, *J. Chem. Soc.* **1959**, 474.

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R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. V. Daeniker, K. Schenker, *Tetrahedron* **19**, 247 (1963).

[5] P. J. Garratt, D. N. Nicolaides, *J. Org. Chem.* **39**, 222 (1974).

[6] For examples see M. P. Cava, M. J. Mitchell, *Cyclobutadiene and Related Compounds*, Academic Press, 1967 p. 227.
K. P. C. Vollhardt, *Synthesis* **1975**, 765.

[7] J. Parrick, *Can. J. Chem.* **42**, 190 (1964).

[8] B. G. Kovalev, E. M. Al'tmark, E. S. Lavrinenko, *Zh. Org. Khim.* **56**, 2187 (1970). On repeating this work under both the original and modified conditions (see Table 1) small quantities of **2c** and **3c** were obtained.

[9] Both of these compounds have been previously employed in bis-Wittig reactions; see reference 4 and P. J. Garratt, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **94**, 1022 (1972).

[10] W. S. Wadsworth, W. D. Emmons, *J. Am. Chem. Soc.* **83**, 1733 (1961).
L. Horner, W. Klink, H. Hoffmann, *Chem. Ber.* **96**, 3133 (1963).

[11] J. A. Elvidge, P. D. Ralph, *J. Chem. Soc. [C]* **1966**, 387.

[12] Preliminary experiments indicated that benzil and hexane-3,4-dione gave alkene formation at only one carbonyl group with ethoxycarbonylmethylenetriphenylphosphorane, but that muconate derivatives were not formed on treatment of these α,β-unsaturated ketones with the phosphonate reagent.

Errata:

S. A. DiBiase, G. W. Gokel, *Synthesis* **1977**, 629; the following acknowledgement was omitted:

We thank the Donors of the Petroleum Research Fund, Administered by the American Chemical Society, for support of this work.

R. J. K. Taylor, *Synthesis* **1977**, 564; Table 2 should be as follows:

Table 2. Reactions of α,β-Unsaturated Ketones **4** and **5** with Diethyl α-Ethoxycarbonyl-α-sodiomethanephosphonate

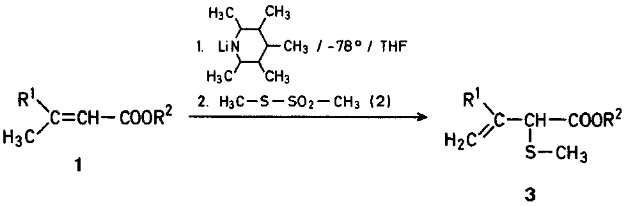
Substrate	Reaction Conditions solvent/temp./time	Product	Yield [%]	m.p.[a]	Molecular formular[b]	^{1}H-N.M.R. ($CDCl_3$, 60 MHz) δ [ppm] (vinylic protons)
4	C_6H_6/r.t./1 h	**2c**	6	see Table 1		
		3c	46			
5	C_6H_6/r.t./0.5 h	**2d**	11	oil	$C_{14}H_{20}O_4$ (252.3)	5.67 (m, 2H)[c]
		3d	41	33–35°	$C_{14}H_{20}O_4$ (252.3)	5.87 (s, 2H)

R. J. K. Taylor, *Synthesis* **1977**, 564–565.
Table 2 should be as follows:

Table 2. Reactions of α,β-Unsaturated Ketones **4** and **5** with Diethyl α-Ethoxycarbonyl-α-sodiomethanephosphonate

Sub-strate	Reaction Conditions solvent/temp./time	Product	Yield [%]	m.p.[a]	Molecular formula[b]	^{1}H-N.M.R. ($CDCl_3$, 60 MHz) δ [ppm] (vinylic protons)
4	C_6H_6/r.t./1 h	**2c**	6	see Table 1		
		3c	46			
5	C_6H_6/r.t./0.5 h	**2d**	11	oil	$C_{14}H_{20}O_4$ (252.3)	5.67 (m, 2H)[c]
		3d	41	33–35°	$C_{14}H_{20}O_4$ (252.3)	5.87 (s, 2H)

Abstract No. 5000, *Synthesis* **1977**, 657.
The formula scheme for the conversion **1**→**3** should be:



J. T. Wr6bel, J. Cybulski, Z. Dabrowski, *Synthesis* **1977** (10), 686–688.

The second paragraph (p. 686) should begin:
2-Methylglutarimide (**1a**)[2] and the *N*-benzyl derivative (**1b**) react readily with phenyllithium (**2d**) and 3-furyllithium (**2c**)[3]...

In footnoote of the Table (p. 687) the maximum deviations should be:
C ±0.32%, H ±0.12%, N ±0.21%.

In the second experimental procedure (p. 687) the first line should be:
A solution of 3-furyllithium[3] (**2c**; 0.01 mol) or phenyllithium (**2d**;

K. Yamamoto, O. Nunokawa, J. Tsuji, *Synthesis* **1977**, 721–722.
The heading for the last experimental procedure (p. 721, right-hand column) should be:
(*E*)-2-Octenal; Typical Procedure for the Preparation of 2-Alkenals.