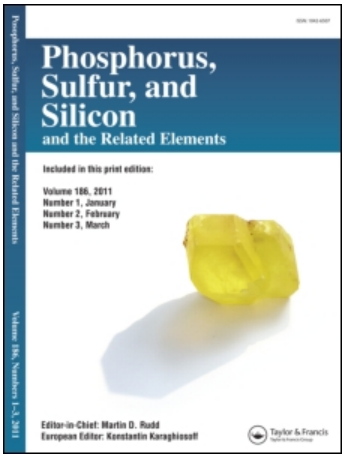

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A Comparison of Wittig and Wittig Horner (Wadsworth Emmons) Reagents in Reactions with Some α-Dicarbonyl Compounds

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A COMPARISON OF WITTIG AND WITTIG HORNER (WADSWORTH EMMONS) REAGENTS IN REACTIONS WITH SOME α-DICARBONYL COMPOUNDS

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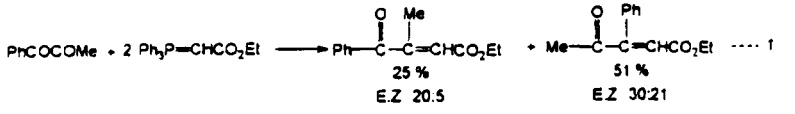
For the α-dicarbonyl compounds RCOCHO studied where R=H, Me or Ph it was found that the use of Wittig reagents resulted in higher overall yields of the expected products and that with neither type of reagent could the product $OCHCH{=}CHCO_2Et$ from glyoxal be isolated.

Keywords: Wittig reagents; Wittig-Horner reagents

Some work has been done on the reactions of α-dicarbonyl compounds with Wittig and Wittig Horner (Wadsworth Emmons) reagents. On the whole the reactions followed the predicted routes, although surprisingly in one case the Wittig reagent reacted as follows[1]:



REACTION 1

Even though a 1:2 molar ratio of dicarbonyl compound to Wittig reagent was always used reaction at both ketonic groups to give a dienediester was

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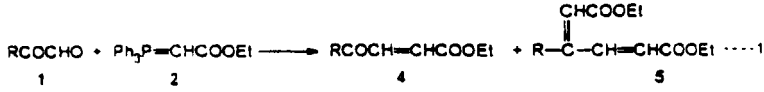
not observed. In other studies reaction at the less sterically hindered carbonyl group yielded the only or greatly predominating, products.[2–4]

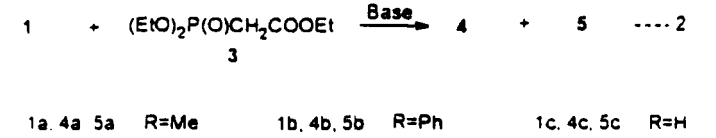
In the case of the muconaldehyde $OCH(CH{=}CH)_2CHO$ reaction with one equivalent of $Ph_3P{=}CHR$ gave only $OCH(CH{=}CH)_2CH{=}CHR$ and no $R(CH{=}CH)_4R$.[3] Similarly reactions of $OCH(CH_2)_nCHO$ (n=2 or 3) with triethylphosphonoacetate resulted in reaction at one carbonyl group only and the product was the E isomer.[5] In another case where geometrical isomerism was noted, it was found that RCOCHO yielded predominantly trans $RCOCH{=}CHR'$.[6] However glyoxal reacted with replacement of both oxygen atoms yielding EE and EZ isomers,[7] the ratio of EE:EZ being 68:32.

Acid hydrolysis of α, β unsaturated ester products sometimes resulted in isomerization, the cis acid being produced from the trans ester.[6] On treatment with iodine isomerization of an EZ product to its EE isomer was recorded,[7] and various dimerizations[7] and cyclizations [4,6,7] have also been observed.

In our present work we varied the experimental conditions, namely solvent, ylide and molar ratio of reactants in order to establish the optimum conditions for preparation of the desired α, β-unsaturated ketoesters or dienediesters. Schemes (1) and (2) summarise the reactions studied and table I summarises the results.



SCHEME 1



SCHEME 2

As can be seen from table **1** higher yields were generally obtained from ylide **2** than from ylide **3**. **1a** and **1b** readily yielded good to fair yields of their α, β-unsaturated ketoesters **4a** and **4b**, and in addition **1a** could readily be made to yield the dienediester **5a** by changing molar ratios but this was not observed for preparation of **5b** from **1b**, only very poor yields being obtained.

TABLE 1 Dienediesters and α,β-unsaturated ketoesters prepared according to schemes 1 and 2

α-dicarbonyl compound (1a-c)[a]	*Ylide (2 or 3)*	*Molar ratio of 1:2 or of 1:3*	*Solvent (base)*	*α,β-unsaturated ketoesters ratio of E & Z isomers (4)*		*Dienediester products (5)*	*Overall % isolated yield*
				E	*Z*		
1a	2	1:1	MeOH	71	29	0	94.5
1a	2	1:2	MeOH	14	25	52	34[b]
1a	2	1:3	MeOH	5	5	90[c]	58
1a	2	1:1	$CHCl_3$	79	19	0	88[d]
1a	2	1:2	$CHCl_3$	(91)[e]		1	92
1a	3	1:1	EtOH (EtO^-)	70	30	0	18[f]
1b[g]	2	1:1	Benzene	92	8	0	52
1b	2	1:1	DMF	99	1	0	73
1b	2	1:1	DMF	96	4	0	66
1b	2	1:2.5	CH_2Cl_2	0	0	100	8
1b	3	1:1	EtOH (EtO^-)	90	10	0	43[f]
1c[h]	2	1:2	Pyridine	0	0	73%EE. 27%EZ	26
1c	3	1:2	H_2O, $CO_3^=$	0	0	100% EE	24
1c	3	1:2	EtOH (EtO^-)	0	0	100% EE	22

a. Based on the limiting agent.
b. 9% unidentified bye-product.
c. A mixture of 4 isomers: E_1Z_2, E_1E_2, Z_1E_2 and Z_1Z_2.
d. 2% unidentified bye-product.
e. E:Z ratio not determined.
f. Other solvents and bases gave even lower yields.
g. Phenylglyoxal monohydrate.
h. Triglyoxal dihydrate.

TABLE II IR and ^{1}H NMR data of products

Compound	*IR νmax cm^{-1} (assignments)*	*^{1}H NMR δ (J assignments)*
E isomer of **4a**	3080(w, =C-H), 1730(s, ester C=O), 1690(s, ketonic C=O), 1645(w, C=C), 1300–1160(s, br, ester C-O), 985(m-w, trans C-H)	90 MHz in CCl_4: 1.19(t J~7 $C\underline{H}_3CH_2O$), 2.32(s $C\underline{H}_3CO$), 4.26 (q J~7 $CH_3C\underline{H}_2O$), 6.81(d J=22 $CH{=}C\underline{H}CO_2Et$), 7.25(d J=22 $C\underline{H}{=}CHCO_2Et$
Z isomer of **4a**	3080w, 1730, 1690, 1645, 1300–1160, 815 and 710(cis C-H deformation)	90 MHz in CCl_4: 1.16(t J~7 $C\underline{H}_3CH_2O$), 2.30(s CH_3CO), 4.18 (q J~7 $CH_3C\underline{H}_2O$), 5.97(d J~11 $CH{=}C\underline{H}CO_2Et$), 6.43(d J~11 $C\underline{H}{=}CHCO_2Et$)
5a 51% E_1Z_2 isomer, 49% other isomers	3090 and 3060(w =C-H), 1720(vs ester C=O), 1635 and 1610(s C=C), 1310- 1150(s br ester C-O), 990 (m-s trans C-H), 815 and 710(w cis C-H)	90 MHz in CCl_4: 1.24 and 1.26(overlapping triplets due to $C\underline{H}_3CH_2O$), 2.03(s CH_3 trans to CO_2Et, Z), 2.25(s CH_3 cis to CO_2Et, E), 4–4.3(overlapping quartets due to $CH_3C\underline{H}_2O$), 5.83 (s E and Z CH_3-$C{=}C\underline{H}CO_2Et$), 6.05(d J~15.5 E $CH{=}C\underline{H}CO_2Et$), 6.14(d J~15.5 Z $CH{=}C\underline{H}CO_2Et$), 7.25(d J~15.5 Z $C\underline{H}{=}CHCO_2Et$), 8.57(d J~16 E $C\underline{H}{=}CHCO_2Et$)
E isomer of **4b**	3060(w =C-H), 1725(s ester C=O), 1675(s ketonic C=O), $C\underline{H}_3CH_2O$), 1635(m C=C), 1600 and 1580 (aromatic C=C), 1300- 1175(3 m-s sharp bands ester C-O), 985(m trans C- H), 730 and 690	90 MHz in CCl_4: 1.42(t J=7 4.33 $C\underline{H}_3CH_2O$(q J=7 $CH_3C\underline{H}_2O$), 6.75(d J=15 $CH{=}C\underline{H}CO_2Et$), 7.75(d J=15 bands, $C\underline{H}{=}CHCO_2Et$), 7.3–8(m aromatic)
Z isomer of **4b**	3060 w, 1725 s, 1675 s, 1640 w, 1600 m, 1580 m, 1290-1170 s br, 760 and 690, 710(cis C-H)	90 MHz in CCl_4: 1.1(t J=7 $C\underline{H}_3CH_2O$), 4.06(q J=7 $CH_3C\underline{H}_2O$), 6.15(d J~11 $CH{=}C\underline{H}CO_2Et$), 7.9(d J~11 $C\underline{H}{=}CHCO_2Et$), 7.3–8(m aromatic)
A mixture of isomers of **5b**	3060(w =C-H), 1720(vs ester C=O), 1630(m trans C=C), 1615(w cis C=C), 1600 and 1575(aromatic C=C), 1290- 1170(vs ester C-O), 980(mw trans C-H), 775 mw and 700 m (aromatic), 720 (w cis C-H)	80 MHz in $CDCl_3$: 1.25(overlapping triplets of $C\underline{H}_3CH_2O$), 4.2(overlapping quartets of ($CH_3C\underline{H}_2O$), 5.85(d J=16 E $CH{=}C\underline{H}CO_2Et$), 5.92(s Z $PhC{=}C\underline{H}CO_2Et$), 6.19(s E $PhC{=}C\underline{H}CO_2Et$), 6.8- 7.4(overlapping aromatic and vinyl H signals), 8.66(d J=16 E $C\underline{H}{=}CHO_2Et$)

Compound	*IR νmax cm^{-1} (assignments)*	*^1H NMR δ (J assignments)*
EE isomer of **5c**	3070(w =C-H), 1725(vs ester C=O), 1640(m C=C), 1620(m C=C), 1305–1155(several strong bands, ester C-O), 975(w trans C-H)	80 MHz in $CDCl_3$: 1.31(t J~7 $C\underline{H}_3CH_2O$), 4.24(q J~7 $CH_3C\underline{H}_2O$), 6.19(dd J=11.5 and 3.2 $CH{=}C\underline{H}CO_2Et$), 7.31(dd J=11.4 and 3.2 $C\underline{H}{=}CHCO_2Et$)
EZ isomer of **5c**	3070(m =C-H), 1710 s, 1640, 1620, 1310–1170 (broads, ester C-O), 980, 670 (w cis C-H)	200 MHz in $CDCl_3$: 1.32(t J=7 $C\underline{H}_3CH_2O$), 4.24(q J=7 $CH_3C\underline{H}_2O$), 5.95(doublet with shoulders J=11.3 and very small Z $CH{=}C\underline{H}CO_2Et$), 6.09(d J=15.6 E $CH{=}C\underline{H}CO_2Et$), 6.63(t J~11.5 Z $C\underline{H}{=}CHCO_2Et$), 8.39(ddd J=15.6, ~11.6 and 1 E $C\underline{H}{=}CHCO_2Et$)

TABLE III ^{13}C NMR data of products

Compound	*^{13}C NMR δ (Multiplicity for partially decoupled samples, assignments)*
4b (E and Z isomers have identical spectra)	200 MHz in $CDCl_3$ (decoupled): 14.17 ($\underline{C}H_3$), 61.40 ($O\underline{C}H_2$), 136.60 (aromatic $\underline{C}$ attached to C=O), 128.7–136.4 (other aromatic C atoms), 165.6 ($O\underline{C}$=O), 189.5 (ketonic $\underline{C}$=O)
EE isomer of **5c**	50 MHz in $CDCl_3$, partially coupled: 14.20 (q $\underline{C}H_3$ of OEt), 60.85 (t $\underline{C}H_2$of OEt), 128.4 (d CH=$\underline{C}$HCO$_2$Et), 140.8 (dd $\underline{C}$H=CHCO$_2$Et), 165.86 (s O$\underline{C}$=O)
EZ isomer of **5c**	50 MHz in $CDCl_3$, partially coupled: 14.2 (q $\underline{C}H_3$ of E and Z OEt), 60.85 (t $\underline{C}H_2$ of E and Z OEt), 124.68 (d Z CH=$\underline{C}$HCO$_2$Et), 129.04 (d E CH=$\underline{C}$HCO$_2$Et), 138.53 (dd Z $\underline{C}$H=CHCO$_2$Et), 140.45 (dd E $\underline{C}$H=CHCO$_2$Et), 165.39 (s probably Z O$\underline{C}$=O), 165.86 (s probably E O$\underline{C}$=O)

TABLE IV Physical properties of products

Compound	*Retention time in mins. (conditions)*	*R_f values (solvent system)*	*m.p*	*n_D^t*
E isomer of **4a**	3.20–3.40 (3% SE 30); 2.8 (OV17)	0.27–0.28 (A); 0.62 (B)	–	1.459[28a]
Z isomer of **4a**	3.05–3.15 (3% SE 30); 2.45 (OV17)	0.27 (A); 0.62 (B)	–	–
The 4 isomers of **5a**	6.55, 7.30, 7.75, 8.45 (OV17)	0.38 (A)	–	–
E isomer of **4b**	9.9–10.3 (OV17)	0.42–0.44 (A)	–	1.547[31]
Z isomer of **4b**	9.7–10.0 (OV17)	0.23–0.28 (A)	–	–
Isomeric **5b**	–	0.4 and 0.5 (A)	–	–
EE isomer of **5c**	10.0 (3% SE 30)	0.4–0.44 (A)	60°	–
EZ isomer of **5c**	9.5 (3% SE 30)	0.4 (A)	27°	–

a. Contained Z isomer also

1c gave completely different results. Even on using a tenfold molar excess of **1c** the product **4c** was not isolated and indeed was not even detected during monitoring of the reaction; the products **4a** and **4b** were easily detected by TLC analysis using 2,4-dinitrophenylhydrazine spray reagent.

Whether the ylide used was **2** or **3** approximately the same E:Z ratios of α, β-unsaturated ketoesters were isolated if none of the product **5** was formed. These ratios depended on the dicarbonyl compound only and were also independent of solvent used. However directly dienediester formation accompanied formation of product **4a** the residual quantity of E isomer of **4a** decreased more rapidly then the Z isomer. This is in keeping with analysis of PMR spectra obtained from the isomeric **5a** products which indicated that the predominant isomer was $EtO_2CCH^2 = C(Me)\text{-}CH^1 = CHCO_2Et(E_1Z_2)$ but all four isomers E_1Z_2, E_1E_2, Z_1E_2 and Z_1Z_2 were formed. GLC combined with NMR analysis indicated that 51% of the mixture of these four isomers was the E_1Z_2 product and probably 20% was E_1E_2.

In the case of glyoxal, **1c**, which reacted to give only **5c** and no **4c**, a solvent effect was observed and indeed in our laboratory we have noticed a similar solvent effect in other reactions. Pyridine increased the amount of EZ isomer **5c** at the expense of the EE isomer. In the absence of pyridine the only isomer obtained, as established from GLC and NMR analysis was the EE isomer. The lack of detection of the product **4c** could be understood when one considers the fact that **1c** was used in the form of triglyoxal dihydrate, solutions of which showed only very weak bands due to the carbonyl group in their IR spectra. It appears that the small amount of free glyoxal and presumably of product **4c**, react very rapidly with the ylide present.

The spectral data for products are listed in tables II and III. Physical properties, retention times and R_f values are listed in table IV. One interesting observation is that for the ^1H NMR spectrum of EZ $EtO_2C\text{-}C_aH{=}C_bH\text{-}C_cH{=}C_dHCO_2Et$ allylic coupling occurred for the Z branch (J_{bd}~1) but not for the E branch (J_{ac}=0). The vinyl pattern consisted of a dd, d, t ($J_{bc}=J_{cd}$) and a ddd. In the corresponding EE isomer allylic coupling does however occur and is more pronounced (J=3.2).

EXPERIMENTAL

General

All melting points are uncorrected and were determined on a Fisher Johns apparatus. For NMR spectra, chemical shifts are reported in ppm downfield from tetramethylsilane and J values are in hertz. IR spectra of liquids were recorded from thin films and of solids from nujol mulls. GLC analyses were recorded on Pye-Unicam GCD chromatograph using the packing indicated in table IV, a N_2 flow rate of 30 cm^3per minute, initial column temperature of 120° for two minutes followed by a heating programme for the column of 8° per minute. TLC analyses were carried out on Merck silica gel plates using either (A) petroleum ether : ether 3:1 or (B) petroleum ether : ether 1:6

Solvents were purified where necessary and all reactions were carried out at room temperature unless otherwise stated, and under N_2 gas. Reactions of Wittig reagents were monitored by titration using bromophenol blue as indicator and neutralised methanol as solvent. Reactions of Wadsworth-Emmons reagents were monitored using TLC.

Products were quantitatively analysed for C and H and gave satisfactory results; analyses were carried out at the University of North London. Ketonic products were converted to their 2,4-dinitrophenylhydrazones and satisfactory melting points were observed. The refractive indices of liquid products agreed with literature values. E:Z ratios were determined from combination of GLC and NMR analyses.

Typical Procedures

1. Using a Wittig reagent

reaction of **2** with **1b** to give **4b. 2** (3.64g, 95.8% pure, 10.0 mmoles) dissolved in DMF (13 cm^3) was added to 1b (1.65g, 97% pure, 10.5 mmoles) in DMF (25cm^3). Titration indicated 100% consumption of **2** after 3.5 hours. Solvent was evaporated using a rotary evaporator, petroleum ether was added, solid was triturated and the mixture filtered through a fine filter paper. This procedure was repeated until TLC indicated no product left in the residual triphenylphosphine oxide. Extracts were placed in the freezer overnight to ppt. out dissolved TPPO, which was filtered off. Evaporation of solvent yielded crude product which was chromatographed on a silica

gel column yielding pure **4b** (1.49g, 73%). The fractions obtained were (a) 1.46g, 100% E isomer, (b) 0.020g (20.3% E and 79.7% Z) and (c) 0.006g (100% Z isomer). Thus the overall E:Z ratio was 98.5:1.5. Using solvent system A, R_f values were (a) 0.42 (b) 0.42 and 0.23 and (c) 0.23. Fraction (a) had n_D^{31} 1.540, lit. n_D^{20} 1.549. the 2,4-dinitrophenylhydrazone of fraction (a) was prepared, m.p. (from EtOAc) 165°, lit. m.p. 167.5 – 169°.[8] All fractions gave satisfactory analyses and spectra.

2. Using a Wadsworth-Emmons reagent

Reaction of **3** with **1c** to give **5c**. Sodium metal (0.69g, 30.0 mmoles) was dissolved in 20 cm^3 of absolute ethanol; to this solution was added **3** (6.79g, 30.0 mmoles). This resulting solution was then added to **1c**, triglyoxal dihydrate (1.05g ≡ 14.99 mmoles of $C_2H_2O_2$) in 40 cm^3 of absolute ethanol. TLC monitoring showed reaction was complete after 4 days. Solvent was evaporated and the crude product was chromatographed on a column using petroleum ether : ether mixtures to elute. This yielded a solid, 1.25g, R_f values 0.38 and 0.27 using solvent system A. Recrystallization of this solid from hexane yielded E, E-diethyl 2,4-hexadienedioate (0.67g, 22.4%), m.p. 60°, lit. m.p. 60–61°. R_f values using solvent system A, 0.40. This product gave satisfactory C, H analyses and its spectral properties are listed in tables II and III.

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