Remote Control of Double Bond Stereochemistry in the Wadsworth–Emmons Reaction

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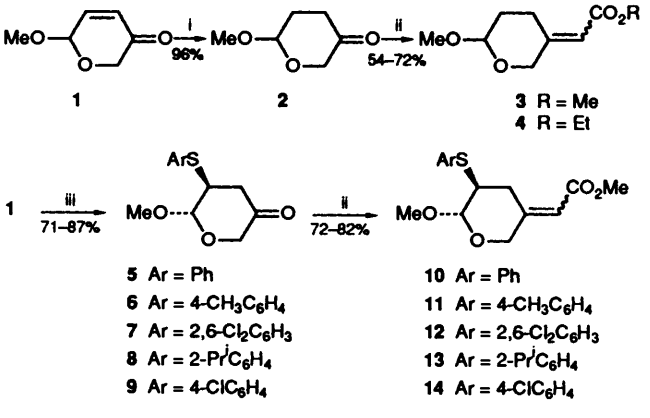
Wadsworth–Emmons reactions of 6-methoxytetrahydropyran-3-one **2** and 5-arylthio-6-methoxytetrahydropyran-3-ones **5–9** have been investigated and the ratio of (*E*)- and (*Z*)-α,β-unsaturated esters formed has been shown to be affected by the presence and type of arylthio substituent.

The synthesis of trisubstituted carbon/carbon double bonds is complicated by the attendant problem of stereocontrol. Although the Wittig and related reactions are among the most useful methods for double bond synthesis, they usually show poor stereoselectivity for trisubstituted double bonds.[1] Indeed, several methods now exist which allow such stereocontrol[2] although they are not always compatible with a wide range of functionalities or are sometimes inconvenient to use on a large scale. Consequently, the factors which affect the stereochemical outcome of the Wittig and Wadsworth–Emmons reactions are of considerable interest. In connection with this, we have recently discovered an unusual, remote stereocontrol feature in the Wadsworth–Emmons synthesis of an exocyclic, trisubstituted double bond.

6-Methoxy-2,6-dihydropyran-3-one **1** was prepared by standard literature methods[3] from furfuryl alcohol. Hydrogenation of **1** gave 6-methoxytetrahydropyran-3-one **2** in 96% yield whilst treatment of **1** with an arenethiol and a catalytic amount of cinchonine in toluene, gave the arylthiotetrahydropyranones **5–9** in yields in the range 71–87% (see Scheme 1). The methoxy



Scheme 1 *Reagents and conditions:* i, H_2, Pd; ii, Wadsworth–Emmons; iii, ArSH, cinchonine, toluene

group and the arylthio group in **5–9** were found to adopt axial positions as judged by the absence of any large *trans*-diaxial coupling for either 5-H or 6-H in the ^{1}H NMR spectra. Although it was expected that the arylthio group and the methoxy group would be *trans* to one another, their diaxial disposition indicates that the anomeric effect is sufficient to overcome the extra energy of the axial arylthio group.

Two series of experiments were carried out. In the first, the 5-unsubstituted tetrahydropyranone **2** was treated with a variety of phosphonates to give an inseparable mixture of the (*E*)- and (*Z*)-α,β-unsaturated esters **3** and **4**. The results of these reactions are shown in Table 1. In every case the base used to generate the phosphonate anion was potassium hexamethyldisilazide (KHMDS) and all reactions were performed in the same manner. The reactions in toluene were not homogeneous but, nevertheless, gave comparable yields. The stereochemistry of the resultant alkenes **3** and **4** was assigned on the basis of the downfield shift of the 2-H resonance in the ^{1}H NMR spectrum of the (*Z*)-isomer compared to the (*E*)-isomer.[4] The ^{13}C NMR spectra of these isomers showed exactly the opposite effect with the C-2 resonance of the (*Z*)-isomer being *ca.* 4 ppm upfield of the same signal in the (*E*)-isomer.

Table 1 Reactions of the phosphonates with **2** to give **3**

Phosphonate	Solvent	Product	Yield (%)	(*E*:*Z*)*
1 $(MeO)_2P(O)CH_2CO_2Me$	THF	**3**	60	57:43
2 $(MeO)_2P(O)CH_2CO_2Me$	Toluene	**3**	54	57:43
3 $(EtO)_2P(O)CH_2CO_2Et$	THF	**4**	60	55:45
4 $(EtO)_2P(O)CH_2CO_2Et$	Toluene	**4**	72	50:50
5 $(TFEO)_2P(O)CH_2CO_2Me$ †	THF	**3**	70	50:50
6 $(TFEO)_2P(O)CH_2CO_2Me$ †	Toluene	**3**	62	37:63
7 $(TFEO)_2P(O)CH_2CO_2Et$ †	THF	**4**	65	50:50
8 $(TFEO)_2P(O)CH_2CO_2Et$ †	Toluene	**4**	54	41:59

* Ratio determined by ^{1}H NMR spectroscopy. † TFEO = CF_3CH_2O.

Table 2 Olefination of 5-arylthiotetrahydropyranones **4** to give **5**[8]

Aryl group	Solvent	Product	Yield (%)	(*E*:*Z*)*
1 Ph	Toluene	**10**	75	50:50
2 Ph	THF	**10**	78	80:20
3 4-MeC_6H_4	THF	**11**	77	78:22
4 2,6-$Cl_2C_6H_3$	THF	**12**	72	82:18
5 2-PriC_6H_4	THF	**13**	80	72:28
6 4-ClC_6H_4	THF	**14**	82	67:33

* Ratios were determined by separation of the isomers by flash chromatography.

These reactions gave little or no *E*/*Z* selectivity. Changing the nature of the carboxylic ester group has no effect and changing the phosphonate ester has little effect. Even the trifluoroethyl phosphonate (entries 5, 6, 7 and 8) which is reported to favour formation of the (*Z*)-olefin in both di- and tri-substituted olefin synthesis[5] has only a limited effect. Additionally, the solvent effect is small. These results are not surprising since there appears to be little steric difference between the C-2 and C-4 sites in the starting ketone.

We next turned to the reaction of the 5-arylthio substituted substrates **5–9**. These reactions were carried out in the same way but in every case, the phosphonate used was the bistrifluoroethyl phosphonate [$(CF_3CH_2O)_2P(O)CH_2CO_2Me$]. The results are shown in Table 2.

In toluene (entry 1), the reaction is again unselective. However, in tetrahydrofuran (THF) with the 5-phenylthio group (entry 2) a 4:1 selectively is observed favouring the (*E*)-isomer. The *E*:*Z* ratio was found to vary depending on the aryl group and we briefly explored this effect. Use of the *p*-tolyl derivative **6** gave virtually the same ratio as **5** whereas the 4-chlorophenyl derivative **9** gave a significantly reduced *E*:*Z* ratio. We felt this could arise from an electronic effect, making the sulfur less electron-rich. However, the 2,6-dichlorophenyl derivative **7** gave the highest *E*:*Z* ratio contradicting this hypothesis. In order to test whether some steric effect was operating *via* a change in conformation of the tetrahydropyranone ring, we used the 2-isopropylphenyl derivative **8**. This gave a lower *E*:*Z* ratio than either **5** or **7** which implies that there is no simple steric/conformational effect operating.

The reason for the large effect on the *E*:*Z* ratio on introducing a 5-arylthio substituent into the tetrahydropyranone ring is not easy to determine. It is known that introduction of electron-withdrawing 3-substituents into cyclohexanones affects the ratio of axial *vs.* equatorial attack[6] and this has been extended to 4-substituents and interpreted in terms of an electrostatic effect.[7] However, in these Wadsworth–Emmons reactions, both axial and equatorial attack can lead to either stereoisomer depending on the stereochemistry at the phosphorus-bearing carbon. In addition, the presence of the oxygen in the ring removes a potential 1,3-diaxial interaction further complicating the comparison with cyclohexanones. Finally, there is evidence in such reactions that the initial attack by the phosphonate-stabilised carbanion is reversible and it is not possible to say whether this stereochemically-important step is under kinetic or thermodynamic control.

Although the reasons for the observed stereoselectivity are unclear, the α,β-unsaturated esters **10–14** are useful synthetic intermediates as the three substituents on the double bond can be selectively reacted and extended.

Experimental

General Procedure for Wadsworth–Emmons Reactions.—A solution of potassium hexamethyldisilazide in toluene (0.5 mol dm^3; 4 cm^3) was added by syringe to a stirred solution of the phosphonate (2 mmol) in dry tetrahydrofuran (15 cm^3) at 0 °C under nitrogen. After 15 min, the reaction mixture was cooled to −78 °C (solid CO_2–acetone bath) and ketone **5** (2 mmol) added in dry solvent (5 cm^3). After 15 min at −78 °C the solution was warmed to 0 °C for 1 h and then warmed to room temperature for 2 h. The reaction mixture was poured into saturated aqueous ammonium chloride (30 cm^3), extracted with ether (2 × 30 cm^3) and the combined extracts were dried and purified by flash chromatography to give *trans*-(3*Z*)-6-methoxy-3-methoxycarbonylmethylene-5-phenylthiotetrahydropyran (*Z*)-**10** (92 mg, 15.6%) as an oil (Found: *M*, 294.0932. $C_{15}H_{18}O_4S$ requires *M*, 294.0921); ν_{max}/cm^{-1} 1715 (C=O) and 1652 (C=C); δ_H(360 MHz, $CDCl_3$) 2.44 (1 H, dd, *J* 14.5 and 8.4, 4-H), 2.79 (1 H, dd, *J* 14.5 and 4.6, 4-H), 3.28 (1 H, ddd, *J* 8.4, 4.6 and 3.6, 5-H), 3.40 (3 H, s, OMe), 3.69 (3 H, s, CO_2Me), 4.57, 4.96 (2 H, ABq, *J* 16.5, 2-H_2), 4.72 (1 H, d, *J* 3.6, 6-H), 5.67 (1 H, br s, C=CH) and 7.24–7.46 (5 H, m, Ph); δ_C(90 MHz, $CDCl_3$) 34.82, 47.89, 51.24, 55.60, 60.50, 101.68, 115.15 and 127.51–133.53 (ArC), 155.35, 166.02; and *trans*-(3*E*)-6-methoxy-3-methoxycarbonylmethylene-5-phenylthiotetrahydropyran (*E*)-**10** (368 mg, 62.4%) as an oil (Found: M^+, 294.0934. $C_{15}H_{18}O_4S$ requires *M*, 294.0921); ν_{max}/cm^{-1} 1716 (C=O) and 1659 (C=C); δ_H(360 MHz, $CDCl_3$) 3.20 (1 H, dd, *J* 16.1 and 3.8, 4-H), 3.37 (1 H, ddd, *J* 5.4, 3.8 and 3, 5-H), 3.42 (3 H, s, OMe), 3.47 (1 H, dd, *J* 16.1 and 5.4, 4-H), 3.68 (3 H, s, CO_2Me), 3.95, 4.35 (2 H, ABq, *J* 13.5, 2-H_2), 4.67 (1 H, d, *J* 3, 6-H), 5.79 (1 H, br s, C=CH) and 7.25–7.45 (5 H, m, Ph); δ_C(90 MHz, $CDCl_3$) 28.35, 47.91, 51.12, 55.43, 64.87, 100.7, 116.04, 127.41–133.79 (ArC), 151.97 and 166.16.

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