Stereochemistry in the Knoevenagel Reaction of Methyl Arylsulphinylacetate and Aldehydes

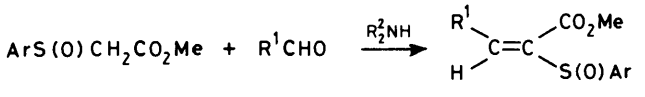
Rikuhei Tanikaga,* Naoto Konya, Tadashi Tamura, and Aritsune Kaji
Department of Chemistry, Faculty of Science, Kyoto University, Kitashirakawa, Sakyo-ku, Kyoto 606, Japan

The stereochemistry of the mechanism of the amine-catalyzed Knoevenagel reaction has been studied. Simple treatment of methyl arylsulphinylacetate (**1**) and aldehydes (**2**) with a catalytic amount of a secondary amine produced thermodynamically stable *E*-alkenes (*E*)-(**3**), and the intermediary diastereoisomeric amino compounds (**8**) were isolated. In acetic acid (**8**) underwent *anti*-elimination to yield (*E*)-(**3**) and (*Z*)-(**3**), while under the Knoevenagel reaction conditions only compounds (*E*)-(**3**) were obtained from (**8**). Both condensation and elimination were found to be reversible, and the stereochemistry of products was determined in the elimination step *via* stable planar carbanions (**9**), in which the small difference in the steric requirements of sulphinyl and carbonyl group is effective for the formation of (*E*)-(**3**).

One of the most useful reactions for the formation of carbon–carbon bonds is the amine-catalyzed aldol condensation referred to as the Knoevenagel reaction. The main advantage of this reaction is that it takes place easily under mildly basic conditions.[1–4] In practice, the reaction has proved to be of great utility in the condensation of aldehydes and ketones with readily enolizable compounds usually containing two activating groups (Y and Z). With regard to the stereochemistry of the condensation products only a few examples have been reported. The condensation of cyanoacetic esters or methylsulphonylacetic esters with aldehydes gives alkenes, in which the β-aryl or the β-alkyl group is *Z* to a small cyano group,[5,6] or *E* to a large methylsulphonyl group.[7] However, the stereochemistry of the reaction has remained obscure when the two groups Y and Z are comparable in their steric requirements.

$$YCH_2Z + RCHO \longrightarrow RCH{=}CYZ$$

Although α-sulphinylated carbanions find wide application in carbon–carbon bond formation, the sodium and the lithium enolates of arylsulphinylacetic esters (**1**) are too stable to react with aldehydes (**2**) and it is necessary to use the magnesium or the zinc salt to drive the equilibrium of the condensation towards products.[8–10] Recently we found that the simple treatment of (**2**) with methyl arylsulphinylacetate (**1**) and a catalytic amount of piperidine produced stereoselectively, (*E*)-methyl 2-arylsulphinylalk-2-enoate (*E*)-(**3**),[11] but the detailed reaction mechanisms were not described. Here we elucidate the stereochemical course of the Knoevenagel reaction starting with compound (**1**).

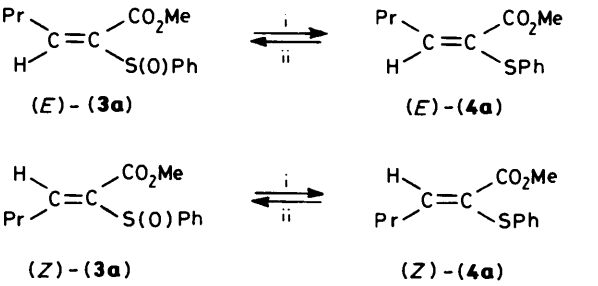


(**1**) (**2**) (*E*)-(**3**)

a; Ar = Ph
b; Ar = *p*-ClC$_6$H$_4$
c; Ar = *p*-O$_2$NC$_6$H$_4$

Results and Discussion

A solution of (**1a**) (10 mmol), butanal (12 mmol), and piperidine (1 mmol) in MeCN (50 ml) was allowed to stand at 0 °C for 24 h. Column chromatography on silica gel gave (*E*)-methyl 2-phenylsulphinylhex-2-enoate (*E*)-(**3a**) as the sole product in 57% yield, and (**1a**) in 37% recovery. The configuration of (*E*)-(**3a**) was determined in the following way. The product (*E*)-(**3a**) was instantaneously reduced with $(CF_3CO)_2O$–Me_2S[12] to give (*E*)-methyl 2-phenylthiohex-2-enoate (*E*)-(**4a**) in quantitative yield, and (*E*)-(**4a**) was oxidized quantitatively into (*E*)-(**3a**) with *m*-chloroperbenzoic acid (MCPBA). The same oxidation–reduction procedure was carried out using (*Z*)-methyl 2-phenylthiohex-2-enoate (*Z*)-(**4a**) and (*Z*)-methyl 2-phenylsulphinylhex-2-enoate (*Z*)-(**3a**). Although no marked difference could be detected in the ^{1}H n.m.r. spectra of (*E*)- and (*Z*)-(**3a**), the spectrum of (*Z*)-(**4a**) revealed the vinylic proton to be much lower field (δ 7.43) than that of (*E*)-(**4a**) (δ 6.47), hence the signal at δ 7.43 can reasonably be assigned to a hydrogen *cis* to a carbonyl group. This assignment was also confirmed by the findings that (*Z*)-(**4a**) had a longer retention time on g.l.c. and a smaller R_F value on t.l.c. than (*E*)-(**4a**).



Scheme 1. *Reagents:* i, $(CF_3CO)_2O$, Me_2S; ii, MCPBA

Similar treatment of compounds (**1b**,**c**) and (**2**) with a catalytic amount of piperidine in MeCN also led to the stereoselective formation of (*E*)-alkenes (*E*)-(**3**), the results of which are shown in Table 1. In these reactions neither dry solvent nor inert atmosphere was required, and MeCN could be replaced by solvents such as $CHCl_3$, benzene, and EtOH. Other secondary amines such as dimethylamine or pyrrolidine could now be employed, but neither primary nor tertiary amines were effective. When an excess of the amine was used, the subsequent [2,3]-sigmatropic rearrangement occurred easily with formation of (*E*)-methyl 4-hydroxyalk-2-enoates.[13] Consequently, butanal or heptanal could not always be employed to elucidate the reaction mechanism.

The Knoevenagel reaction was once considered to proceed by the mechanism (1) in which the amine served only as a base to generate an enolate anion, followed by condensation and dehydration *via* an intermediate alcohol (**5**).[14] However, this possibility was excluded by the finding that the alcohol (**5a**

Table 1. Preparation of compound (*E*)-(**3**) by the Knoevenagel reaction

(3)	Ar	R^1	Temp. (°C)	Time (h)	Yield (%)[a]	*E*:*Z*[b]
(**3a**)	Ph	Pr	0	24	57	98:2
(**3b**)	*p*-ClC_6H_4	Pr	0	24	70	98:2
(**3c**)	*p*-$O_2NC_6H_4$	Pr	0	24	74	98:2
(**3d**)	*p*-ClC_6H_4	$Me(CH_2)_5$	0	24	75	98:2
(**3e**)	*p*-ClC_6H_4	Pr^i	20	24	90	99:1
(**3f**)	*p*-ClC_6H_4	$-CH_2CH=CH(CH_2)_2-$	20	48	83	99:1
(**3g**)	*p*-ClC_6H_4	Ph	60	6	88	99:1

[a] Isolated yield. [b] Determined by g.l.c. after reduction of (**3**) to the sulphide (**4**).

Ar = Ph, R^1 = Pr), which was prepared by an alternative route,[9] was unreactive towards piperidine. In several cases, it has been established that an imine does not function as a simple base but instead is involved in a prior reaction with (**2**) to form an iminium salt (**6**) (Scheme 2).[14] This salt will be considerably more electrophilic than (**2**), and subsequent reaction with an enolate anion produces an intermediate amino compound (**8**).[14] This is supported by the fact that a secondary amine was found to be effective as a catalyst. On the basis of the latter reaction mechanism (2), we are able to clarify the stereochemical aspects in the Knoevenagel reaction of (**1b**) (Scheme 2).

$$(1) + (2) \longrightarrow \underset{(5)}{R^1CH(OH)CH(CO_2Me)[S(O)Ar]} \quad (1)$$

$$(5) \longrightarrow (E)\text{-}(3) + H_2O$$

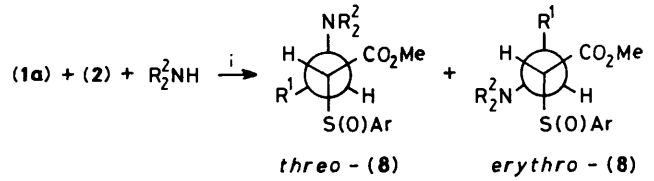
$$(2) + 2(R_2^2NH) \rightleftharpoons \underset{(6)}{[R^1CH{=}\overset{+}{N}R_2^2]} \rightleftharpoons \underset{(7)}{R^1CH(NR_2^2)_2}$$

$$(6) + (1) \longrightarrow \underset{(8)}{R^1CH(NR_2^2)CH(CO_2Me)[S(O)Ar]} \quad (2)$$

$$(8) \longrightarrow (E)\text{-}(3) + R_2^2NH$$

Scheme 2.

Phenyldipiperidinomethane [**7a**; R^1 = Ph, $R_2^2 = -(CH_2)_5-$] was readily obtained by mixing benzaldehyde and piperidine. From a solution of (**1b**) and (**7a**) in a small quantity of dry MeCN, methyl 2-(*p*-chlorophenylsulphinyl)-3-phenyl-3-piperidinopropanoate (**8c**) crystallized directly with time at 0 °C. Purification was achieved by filtration and washing with cold MeCN. The *threo*:*erythro* ratio was determined by ^{1}H n.m.r. spectroscopy from the OMe and R^1CH (3-*H*) signals of *threo*-(**8c**) which resonated at lower field than the corresponding signals of *erythro*-(**8c**) (Tables 2 and 3). From a solution of (**1b**), benzaldehyde, and piperidine in MeCN, compound (**8c**) was also obtained with the same *threo*:*erythro* ratio and in a similar chemical yield. This implies that the iminium ion (**6**) is involved in the condensation reaction. Similarly, some amino compounds (**8a**,**b**,**d**—**j**) were isolated as a crystalline solids; these results are shown in Tables 2 and 3.



Scheme 3. *Reagents*: i, MeCN, 0 °C

Table 2. Preparation of compound (**8**)

(8)	R^1	R_2^2	Yield (%)[a]	*threo*:*erythro*[b]
(**8a**)	Ph	Me, Me	78	0:100
(**8b**)	Ph	$-(CH_2)_4-$	67	0:100
(**8c**)	Ph	$-(CH_2)_5-$	82	15:85
(**8d**)	Ph	$-CHMe(CH_2)_4-$	29	30:70
(**8e**)	Ph	$-CH_2CHMe(CH_2)_3-$	79	25:75
(**8f**)	Ph	$-(CH_2)_6-$	80	8:92
(**8g**)	*p*-$MeOC_6H_4$	$-(CH_2)_5-$	84	0:100
(**8h**)	Pr^i	$-(CH_2)_5-$	73	60:40
(**8i**)	Pr^i	$-CHMe(CH_2)_4-$	39	70:30
(**8j**)	Pr^i	$-(CH_2)_2CHMe(CH_2)_2-$	68	55:45

[a] Isolated yield. [b] Determined by ^{1}H n.m.r. spectroscopy.

Table 3. ^{1}H N.m.r. data[a] for *threo*-(**8**) and *erythro*-(**8**)

Compound	2-H (1 H, d, *J* 12)	3-H (1 H, d, *J* 12)	MeO (3 H, s)
erythro-(**8a**)	4.18	4.59	3.16
erythro-(**8b**)	4.24	4.85	3.09
threo-(**8c**)	4.20	4.57	3.56
erythro-(**8c**)	4.17	4.46	3.08
threo-(**8d**)	4.20	5.14	3.80
erythro-(**8d**)	4.18	5.02	3.68
threo-(**8e**)	4.14	4.54	3.51
erythro-(**8e**)	4.12	4.42	3.05
threo-(**8f**)	4.09	4.66	3.52
erythro-(**8f**)	4.09	4.54	3.06
erythro-(**8g**)	4.15	4.49	3.08
threo-(**8h**)	*b*	3.58	3.23
erythro-(**8h**)		3.26	3.23
threo-(**8i**)		3.93	3.28
erythro-(**8i**)		3.90	3.28
threo-(**8j**)		3.61	3.27
erythro-(**8j**)		3.29	3.27

[a] δ (100 MHz; $CDCl_3$; standard Me_4Si). [b] Assignment was impossible owing to overlap with R^2-H signals.

Compound (**8**) in the solid state was stable at room temperature for several months, but decomposed slowly in solution. The *threo*:*erythro* ratio was not appreciably affected by the reaction conditions used, and there was no interconversion of the *threo*- and the *erythro*-isomers. This ratio can be explained rationally by the relative bulkiness of the groups CO_2Me, S(O)Ar, R^1, and R_2^2N which increase in the order CO_2Me < S(O)Ar; Pr^i < Ph; Me_2N, $\overline{CH_2(CH_2)_3N}$ < $\overline{CH_2(CH_2)_5N}$ < $\overline{CH_2(CH_2)_5N}$ < $\overline{CHMeCH_2)_4N}$.

In AcOH:

$$\textit{threo}\text{-}(8) \longrightarrow (E)\text{-}(3)$$
$$\textit{erythro}\text{-}(8) \longrightarrow (Z)\text{-}(3)$$

In MeCN or $CDCl_3$:

$$(1b) \longleftarrow \textit{threo}\text{-}(8) + \textit{erythro}\text{-}(8) \longrightarrow (E)\text{-}(3)$$

Scheme 4.

Even under mildly acidic conditions compound (**8**) was susceptible to elimination. For example, silica-gel column chromatography of (**8**) afforded (*E*)- and (*Z*)-alkenes [(*E*)- and (*Z*)-(**3**)] in high yields. Dissolution of (**8c**) in AcOH at 20 °C caused *anti*-elimination within 10 min to afford the corresponding (*E*)-(**3g**) and (*Z*)-(**3g**) (*E*:*Z* 13:87) in 87% yield. Acetic acid may accelerate expulsion of the leaving group $R_2^2\overset{+}{N}H$. Some

Table 4. Formation of (3) from (8) in AcOH or MeCN

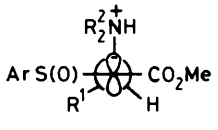
Transformation (8) ⟶ (3)	AcOH[a] Yield[c]	AcOH[a] $E:Z$[d]	MeCN[b] Yield (3)[c]	MeCN[b] $E:Z$[d]	MeCN[b] Yield (1b)[c]
(8a) ⟶ (3g)	78	6:94	69	100:0	29
(8b) ⟶ (3g)	71	8:92	63	100:0	27
(8c) ⟶ (3g)	81	13:87	58	97:3	26
(8d) ⟶ (3g)	77	31:69	51	100:0	38
(8e) ⟶ (3g)	81	20:80	60	100:0	24
(8f) ⟶ (3g)	97	13:87	65	100:0	20
(8g) ⟶ (3h)[e]	77	10:90	40	88:12	58
(8h) ⟶ (3e)	95	60:40	60	100:0	27
(8i) ⟶ (3e)	90	73:27	62	100:0	24
(8j) ⟶ (3e)	70	57:43	55	100:0	30

[a] (8) in AcOH at 20 °C for 10 min. [b] (8a—g) in MeCN at 60 °C for 6 h, or (8h—j) at 20 °C for 24 h. [c] Isolated yield (%). [d] Determined by g.l.c. after reduction of (3) to the sulphide (4). [e] (3h; Ar = p-ClC_6H_4, R^1 = p-$MeOC_4H_4$).

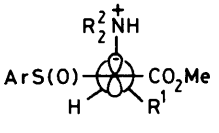
other results are shown in Table 4. The *threo*:*erythro* ratios of compound (8), even if not determined by ^1H n.m.r. spectroscopy can be roughly estimated from the $E:Z$ ratio of the elimination products (3) due to stereoselective elimination under these conditions.

When a solution of compound (8) in MeCN was allowed to stand under the reaction conditions similar to those in the piperidine-catalyzed Knoevenagel reaction of (1b) and (2), another type of elimination took place to give a thermodynamically stable alkene (*E*)-(3) in the so-called stereoconvergent manner,[15] as well as (1b) (Table 4). These findings suggest that (8) is an intermediate compound along the reaction path from (1b) to (*E*)-(3). These elimination reactions could be followed by n.m.r. measurements using CD_3CN or $CDCl_3$, and thereby both *threo*-(8) and *erythro*-(8) were found to disappear simultaneously, forming only the *E*-isomer.

The initial stage of elimination of MeCN would be the removal of an α-proton with the formation of a planar carbanion (9)[16] stabilized by two electron-withdrawing groups CO_2Me and S(O)Ar. For elimination of an ammonium ion to occur, the preferred orientation of the p-orbital of the carbanion and of the C–N bond is periplanar. The formation of (*E*)-(3) may be controlled mainly by the steric requirements of the functions CO_2Me, S(O)Ar, R^1, and H. A similar mechanism has already been proposed in the base-catalyzed elimination of sulphones.[17–19] and the nucleophilic addition–elimination of vinylic compounds.[20,21]



(9a)



(9b)

In these planar carbanion (9) involving a fairly large leaving group, the two groups S(O)Ar and R^1, or CO_2Me and R^1 are brought close together, and hence affect to a great extent the stereochemistry of the reaction. The carbanion (9b) leading to the formation of (*E*)-(3) must be the more stable of the two alternatives as the aryl- or alkyl-sulphinyl interaction is avoided. Although no conclusive proof has been provided, an electronic effect. is not likely to be an important factor because no differences were observed in the cases of R^1 = Ph and Pr^i.

In MeCN, (1b) as well as (*E*)-(3g) were obtained from (8c), which was also generated by treatment of (*E*)-(3g) with piperidine at 0 °C for a few days. That is to say, both condensation and elimination in the Knoevenagel reaction of (1) are reversible.

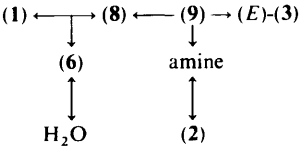
When activated by carbanion-stabilizing groups, base-catalyzed eliminations and nucleophilic additions on vinylic systems are known to proceed *via* the same planar carbanionic intermediate.[20] A solution of methyl 2-(*p*-chlorophenylsulphinyl)-4-methyl-3-piperidinopentanoate (8h) in $CDCl_3$ afforded (*E*)-methyl 2-(*p*-chlorophenylsulphinyl)-4-methylpent-2-enoate (*E*)-(3e) in 40% when allowed to stand at 20 °C for 1 h, and ^1H n.m.r. spectroscopic examination during the period of the reaction showed no formation of the *Z*-isomer under conditions in which concentrations as little as 0.5% would easily have been detected. Treatment of (*Z*)-(3e) with piperidine under similar conditions resulted in *E*–*Z* isomerization affording (*E*)-(3e) in 5% yield. On the basis of these results we conclude that the stereochemistry of the products is controlled primarily in the elimination step, although *E*–*Z* isomerization may be marginally operative.

The Pummerer rearrangement is known to proceed *via* a carbocation stabilized by an adjacent sulphur atom.[22] When a solution of methyl 2-phenylsulphinylhexanoate (10a) in CH_2Cl_2 was stirred with $(CF_3CO)_2O$ at room temperature, methyl 2-phenylthiohex-2-enoate [(*E*)-(4a) and (*Z*)-(4a)] was formed in 81% yield, probably *via* an intermediary carbocation (11a),[23] but the $E:Z$ ratio was found to be quite low ($E:Z$ = 20:80). In contrast with the elimination *via* a stable carbanion as described above, deprotonation from (11a) was not greatly affected by the groups CO_2Me and SPh, though the steric effects are considerably different (Scheme 5).

$$\underset{(10a)}{PrCH_2CH(CO_2Me)[S(O)Ph]} \xrightarrow{(CF_3CO)_2O} PrCH_2CH(CO_2Me)[\overset{+}{S}(OCOCF_3)Ph] \xrightarrow{-CF_3CO_2H} \underset{(11a)}{PrCH_2\overset{+}{C}(CO_2Me)(SPh)} \xrightarrow{-H^+} (E)(4a) + (Z)\text{-}(4a)$$

Scheme 5.

In conclusion, the amine-catalyzed Knoevenagel reaction involves many reversible steps, and usage of a catalytic amount of an amine forces this thermodynamically-controlled reaction to completion to give the most stable product (Scheme 6).



Scheme 6.

Experimental

^1H N.m.r. spectra were recorded with a JEOL JNM-PS-100 (100 MHz) spectrometer, using Me_4Si as an internal standard. I.r. spectra were taken on a Hitachi 215 spectrometer, and mass spectra were determined with a JEOL JMS-DX300 instrument. G.l.c. analysis was carried out with a Varian 920 instrument using a glass column (1 m × 6 mm) packed with 20% silicone DS-550. Column chromatography and t.l.c. were performed, using Wakogel 200 silica gel and Merck plastic sheets silica gel 60 F_{254}, respectively.

Methyl arylsulphinylacetates (1a—c) were prepared by the method previously described.[13] The aldehydes (2) and secondary amines were commercially available and were

purified by distillation before use. Commercial MeCN, AcOH, Me_2S, and $(CF_3CO)_2O$ were used without further purification.

Knoevenagel Reaction of Compounds (**1**) *and* (**2**).—A solution of the sulphinyl ester (**1**) (10 mmol), the aldehyde (**2**) (12 mmol), and piperidine (1 mmol) in MeCN (50 ml) was kept under the conditions (reaction time and temperature) given in Table 1. T.l.c. of the reaction mixture revealed the presence of compound (**1**) and a product which was subsequently identified as the (**3**). After having removed the MeCN under reduced pressure a minimum quantity of the reaction mixture was withdrawn to determine the *E*:*Z* ratio of the product (**3**) prior to isolation. The residue was chromatographed on silica-gel column using hexane–EtOAc (4:1 v/v) as the eluant, to give the *E*-isomer (*E*)-(**3**) and compound (**1**) in the yields as shown in Table 1. The products (*E*)-(**3**) were unable to be distilled owing to its thermolability.[24] A by-product (2*E*)-2-ethylhex-2-enal was also obtained by the competitive bimolecular condensation of butanal when Ar = Ph.

By this route the following compounds were obtained. (E)-*Methyl 2-phenylsulphinylhex-2-enoate* (*E*)-(**3a**): liquid; $\nu_{max.}$(neat) 1 720 (C=O) and 1 050 cm^{-1} (S→O); δ_H (100 MHz; $CDCl_3$) 0.96 (3 H, t, *J* 7 Hz, Me), 1.60 (2 H, sextet, *J* 7 Hz CH_2), 2.73 (2 H, q, *J* 7 Hz, CH_2), 3.64 (3 H, s, MeO), 7.12 (1 H, t, *J* 7 Hz, 3-H), and 7.4—7.8 (5 H, m, ArH); *m*/*z* 252 (M^+, 45%).

(E)-*Methyl* 2-(p-*chlorophenylsulphinyl*)*hex-2-enoate* (*E*)-(**3b**): liquid; $\nu_{max.}$(neat) 1 725 and 1 055 cm^{-1}; δ_H 0.96 (3 H, t, *J* 7 Hz), 1.59 (2 H, sextet, *J* 7 Hz), 2.73 (2 H, q, *J* 7 Hz), 3.65 (3 H, s), 7.15 (1 H, t, *J* 7 Hz), 7.36 (2 H, d, *J* 7 Hz, ArH), and 7.56 (2 H, d, ArH); *m*/*z* 286 (M^+, 38%).

(E)-*Methyl* 2-(p-*nitrophenylsulphinyl*)*hex-2-enoate* (*E*)-(**3c**): liquid; $\nu_{max.}$(neat) 1 723 and 1 055 cm^{-1}; δ_H 0.96 (3 H, t, *J* 7 Hz), 1.59 (2 H, sextet, *J* 7 Hz), 2.72 (2 H, q, *J* 7 Hz), 3.75 (3 H, s), 7.20 (1 H, t, *J* 7 Hz), 7.86 (2 H, d, *J* 9 Hz), and 8.26 (2 H, d, *J* 9 Hz); *m*/*z* 297 (M^+, 20%).

(E)-*Methyl* 2-(p-*chlorophenylsulphinyl*)*non-2-enoate* (*E*)-(**3d**): liquid; $\nu_{max.}$(neat) 1 730 and 1 055 cm^{-1}; δ_H 0.87 (3 H, t, *J* 7 Hz), 1.0—1.8 (10 H, m, 5 × CH_2), 2.73 (2 H, m, CH_2), 3.68 (3 H, s), 7.12 (1 H, t, *J* 7 Hz), 7.41 (2 H, d, *J* 7 Hz), and 7.61 (2 H, d); *m*/*z* 328 (M^+, 33%).

(E)-*Methyl* 2-(p-*chlorophenylsulphinyl*)-4-*methylpent-2-enoate* (*E*)-(**3e**): m.p. 72 °C; $\nu_{max.}$(Nujol) 1 710 and 1 055 cm^{-1}; δ_H 1.10 (3 H, d, *J* 6 Hz, Me), 1.12 (3 H, d, *J* 6 Hz, Me), 3.3—3.8 (1 H, m, CH), 3.70 (3 H, s), 6.98 (1 H, d, *J* 11 Hz), 7.40 (2 H, d, *J* 7 Hz), and 7.58 (2 H, d); *m*/*z* 286 (M^+, 100%).

(E)-*Methyl* 2-(p-*chlorophenylsulphinyl*)-3-*cyclohex-3-enylprop-2-enoate* (*E*)-(**3f**): liquid; $\nu_{max.}$(neat) 1 720 and 1 050 cm^{-1}; δ_H 1.5—2.4 (7 H, m, 3 × CH_2 + CH), 3.68 (3 H, s), 5.70 (2 H, br, 2 × CH=), 7.09 (1 H, d, *J* 10 Hz), 7.40 (2 H, d, *J* 7 Hz), and 7.62 (2 H, d); *m*/*z* 324 (M^+, 90%).

(E)-*Methyl* 2-(p-*chlorophenylsulphinyl*)-3-*phenylprop-2-enoate* (*E*)-(**3g**): m.p. 120 °C; $\nu_{max.}$(Nujol) 1 700 and 1 050 cm^{-1}; δ_H 3.68 (3 H, s) and 7.2—7.7 (10 H, m, 3-H + Ph + ArH); *m*/*z* 320 (M^+, 30%).

The elemental analyses found were in good agreement with the calculated values throughout: they have been treated as a Supplementary publication (SUP. No. 56671 (2 pp.)] *.

Reduction of Sulphoxides (**3**) *to Sulphides* (**4**) *with* $(CF_3CO)_2O$ *and* Me_2S.—To a stirred solution of (*E*)-(**3a**) (505 mg, 2 mmol) and Me_2S (189 mg, 3 mmol) in CH_2Cl_2 (30 ml) was added $(CF_3CO)_2O$ (630 mg, 3 mmol) at 0 °C, and after having been stirred for 10 min, the resulting solution was washed successively with water, aqueous $NaHCO_3$, and water. The organic phase was dried (anhydrous Na_2SO_4) and the solvent was removed under reduced pressure. Column chromatography on silica gel eluting with hexane–EtOAc (5:1 v/v) gave (E)-*methyl 2-phenylthiohex-2-enoate* (*E*)-(**4a**) (470 mg, 100%), b.p. 110 °C/1.5 mmHg; $\nu_{max.}$(neat) 1 720 cm^{-1} (C=O); δ_H($CDCl_3$) 0.98 (3 H, t, *J* 7 Hz, Me), 1.51 (2 H, sextet, *J* 7 Hz, CH_2), 2.52 (2 H, q, *J* 7 Hz, CH_2), 3.64 (3 H, s, MeO), 6.47 (1 H, t, *J* 7 Hz, 3-H), and 7.2—7.5 (5 H, m, Ph); *m*/*z* 236 (M^+, 70%).

Similar reduction of (*Z*)-methyl 2-phenylsulphinylhex-2-enoate (*Z*)-(**3a**) yielded (Z)-*methyl 2-phenylthiohex-2-enoate* (*Z*)-(**4a**) (100%), b.p. 110 °C/1.5 mmHg; $\nu_{max.}$(neat) 1 720 cm^{-1}; δ_H 0.98 (3 H, t, *J* 7 Hz), 1.51 (2 H, sextet, *J* 7 Hz), 2.53 (2 H, q, *J* 7 Hz), 3.64 (3 H, s), 7.43 (1 H, t, *J* 7 Hz), and 7.2—7.6 (5 H, m); *m*/*z* 236 (M^+, 60%).

NaI could be used in place of Me_2S.[25]

Oxidation of the Sulphide (**4**) *to the Sulphoxide* (**3**).—Oxidation of (*E*)-(**4a**) in CH_2Cl_2 was carried out with one equivalent MCPBA at 0 °C in the usual way. After ordinary work-up and removal of the solvent, pure (*E*)-(**3a**) was obtained in quantitative yield. Similarly, (*Z*)-(**4a**) was quantitatively oxidized to (Z)-*methyl 2-phenylsulphinylhex-2-enoate* (*Z*)-(**3a**), liquid; $\nu_{max.}$(neat) 1 720 (C=O) and 1 050 cm^{-1} (S→O); δ^H 0.98 (3 H, t, *J* 7 Hz, Me), 1.60 (2 H, sextet, *J* 7 Hz, CH_2), 2.72 (2 H, q, *J* 7 Hz, CH_2), 3.64 (3 H, s, MeO), 7.24 (1 H, t, *J* 7 Hz, 3-H), and 7.4—7.8 (5 H, m); *m*/*z* 252 (M^+, 100%).

Preparation of the Alcohol (**5a**).—To a stirred solution of lithium di-isopropylamide, [prepared from butyl-lithium (15% in hexane; 37.1 ml, 60 mmol) and di-isopropylamine (8.4 ml, 60 mmol) in tetrahydrofuran (THF) (40 ml)], was added dropwise a solution of methyl phenylthioacetate (10.9 g, 60 mmol) in THF (150 ml) at −78 °C under an atmosphere of argon. The solution was allowed to warm to 0 °C, when anhydrous $ZnCl_2$ (11.5 g, 76 mmol) and butanal (9.7 ml, 98 mmol) were added successively. The resulting mixture was stirred for a further 10 min, and then quenched with saturated aqueous NH_4Cl (50 ml) and extracted with Et_2O. The organic phase was washed with water, and dried (anhydrous Na_2SO_4). The residue after having removed the solvent was column chromatographed on silica gel eluting with hexane–EtOAc (3:1 v/v) to give methyl 3-hydroxy-2-phenylthiohexanoate (**12a**) (12.7 g, 92%) as a yellow liquid, δ_H($CDCl_3$) 0.8—1.2 (3 H, m, Me), 1.2—2.0 (4 H, br, CH_2), 3.2 (1 H, br s, 2-H), 3.67 (3 H, s, OMe), 3.95 (1 H, m, 3-H), 4.3 (1 H, br s, OH), and 7.2—7.6 (5 H, m, Ph); $\nu_{max.}$ 1 720 cm^{-1} (C=O); *m*/*z* 181 [100%, M^+ − PrCH(OH)].

To a stirred solution of the sulphide (**12a**) (2.54 g, 10 mmol) in CH_2Cl_2 (50 ml) was added dropwise, with stirring a solution of MCPBA (80%; 2.16 g, 10 mmol) in CH_2Cl_2 (180 ml) at −20 °C during 30 min. After 15 min, the organic phase was washed with aqueous $NaHCO_3$ and water, and dried (anhydrous Na_2SO_4). Removal of the solvent under reduced pressure afforded *methyl 3-hydroxy-2-phenylsulphinylhexanoate* (**5a**) (2.70 g, 100%) as a colourless liquid. The *threo*:*erythro* ratio was *ca.* 50:50; δ_H($CDCl_3$) 0.8—1.1 (3 H, m, Me), 1.2—1.8 (4 H, br, CH_2), 3.56 (1 H, d, *J* 12 Hz, *erythro* 2-H), 3.58 (1 H, d, *J* 12 Hz, *threo* 2-H), 3.56 (3 H, s, OMe), 4.4 (1 H, br s, OH), and 7.4—7.8 (5 H, m, Ph); $\nu_{max.}$ 1 720 (C=O) and 1 040 cm^{-1} (S→O); *m*/*z* 197 [100%, M^+ − PrCH(OH)]. Elemental analysis was satisfactory.

The alcohol (**5a**) was stable to piperidine or AcOH.

Formation of the Amino Compounds (**8**).—A solution of the sulphoxide (**1b**) (2.32 g, 10 mmol), benzaldehyde (1.59 g, 15 mmol), and piperidine (1.28 g, 15 mmol) in MeCN (20 ml) was kept at 0 °C for 24 h. The product precipitated was filtered off, washed several times with cold MeCN, and dried *in vacuo*. Almost pure diastereoisomeric *methyl* 2-(p-*chlorophenylsulphinyl*)-3-*phenyl*-3-*piperidinopropanoate* (**8c**) (3.33 g, 82%) was

* See Instructions for Authors (1987), *J. Chem. Soc., Perkin Trans. 1*, 1987, Issue 1.

obtained as a colourless solid. Further purification by recrystallization or column chromatography proved to be impossible owing to ready elimination reactions. The *threo*:*erythro* ratio was determined by ^{1}H n.m.r. spectroscopy.

Simple mixing of benzaldehyde (2.12 g, 20 mmol) with piperidine (4.25 g, 50 mmol) generated phenyldipiperidinomethane (**7**) (4.64 g, 90%) as a colourless solid, m.p. 80 °C from EtOH–hexane (1:1 v/v). From a solution of compound (**1b**) (2.32 g, 10 mmol) and (**7**) (3.10 g, 12 mmol) in dry MeCN (20 ml), compound (**8c**) (3.17 g, 78%) crystallized with time at 0 °C. When a solution of (*E*)-(**3g**) (3.20 g, 10 mmol) and piperidine (0.85 g, 10 mmol) in MeCN (20 ml) was kept at 0 °C for 2 days, compound (**8c**) was also obtained. The *threo*:*erythro* ratio was 15:85 in every case.

Similar treatment of compound (**1b**) (10 mmol) and the aldehyde (**2**) (15 mmol) with secondary amines (15 mmol) resulted in the formation of the following.

Methyl 2-(p-*chlorophenylsulphinyl*)-3-(N,N-*dimethylamino*)-3-*phenylpropanoate* (**8a**): m.p. 124 °C; $\nu_{max.}$(Nujol) 1 720 (C=O) and 1 060 cm^{-1} (S→O); δ_H($CDCl_3$) 2.28 (6 H, s, Me_2N), 7.0—7.8 (9 H, m, Ph and ArH), and others given in Table 3; *m*/*z* 161 (M^+ − ArSO − R^2_2NH, 100%) and 159 (ArSO, 36).

Methyl 2-(p-*chlorophenylsulphinyl*)-3-*phenyl*-3-*pyrrolidinopropanoate* (**8b**): 128 °C; $\nu_{max.}$(Nujol) 1 725 and 1 060 cm^{-1}; δ_H (*inter alia*) 1.4—2.8 (8 H, m) and 7.0—7.9 (9 H, m); *m*/*z* 161 (100%) and 159 (35).

Methyl 2-(p-*chlorophenylsulphinyl*)-3-*phenyl*-3-*piperidinopropanoate* (**8c**), m.p. 149 °C; $\nu_{max.}$(Nujol) 1 720 and 1 060 cm^{-1}; δ_H (*inter alia*) 1.0—2.9 (10 H, m), and 7.0—7.8 (9 H, m); *m*/*z* 161 (100%) and 159 (34).

Methyl 2-(p-*chlorophenylsulphinyl*)-3-(2-*methylpiperidino*)-3-*phenylpropanoate* (**8d**): m.p. 145 °C; $\nu_{max.}$(Nujol) 1 720 and 1 060 cm^{-1}; δ_H (*inter alia*) 0.7—2.5 (12 H, m) and 7.0—7.8 (9 H, m); *m*/*z* 161 (100%) and 159 (44).

Methyl 2-(p-*chlorophenylsulphinyl*)-3-(3-*methylpiperidino*)-3-*phenylpropanoate* (**8e**): m.p. 146 °C; $\nu_{max.}$(Nujol) 1 720 and 1 060 cm^{-1}; δ_H (*inter alia*) 0.5—3.1 (12 H, m) and 7.0—7.8 (9 H, m); *m*/*z* 161 (100%) and 159 (40).

Methyl 2-(p-*chlorophenylsulphinyl*)-3-*hexamethyleneimino*-3-*phenylpropanoate* (**8f**): m.p. 151 °C; $\nu_{max.}$(Nujol) 1 720 and 1 060 cm^{-1}; δ_H (*inter alia*) 1.2—3.0 (12 H, m) and 7.0—7.8 (9 H, m); *m*/*z* 161 (100%) and 159 (37).

Methyl 2-(p-*chlorophenylsulphinyl*)-3-(4-*methoxyphenyl*)-3-*piperidinopropanoate* (**8g**): m.p. 155 °C; $\nu_{max.}$(Nujol) 1 725 and 1 060 cm^{-1}; δ_H (*inter alia*) 1.1—2.8 (10 H), 3.77 (3 H, s, MeO), and 6.7—7.8 (8 H, m); *m*/*z* 191 (M^+ − ArSO − R^2_2NH, 100%) and 159 (36).

Methyl 2-(p-*chlorophenylsulphinyl*)-4-*methyl*-3-*piperidinopentanoate* (**8h**): m.p. 97 °C; $\nu_{max.}$(Nujol) 1 725 and 1 070 cm^{-1}; δ_H (*inter alia*) 0.88 (3 H, d, *J* 8 Hz, Me), 0.98 (3 H, d, *J* 8 Hz, Me), 1.9—2.3 (1 H, m, 4-H), 1.1—3.2 (10 H, m, R^2-H), and 7.48 (4 H, s, ArH); *m*/*z* 127 (M^+ − ArSO − R^2_2NH, 100%) and 159 (40).

Methyl 2-(p-*chlorophenylsulphinyl*)-4-*methyl*-3-(2-*methylpiperidino*)*pentanoate* (**8i**): m.p. 97 °C; $\nu_{max.}$(Nujol) 1 720 and 1 060 cm^{-1}; δ_H (*inter alia*) 0.87 (3 H, d, *J* 8 Hz), 0.97 (3 H, d, *J* 8 Hz), 1.0—2.3 (1 H, m), 1.2—3.1 (12 H, m), and 7.51 (4 H, s); *m*/*z* 127 (100%) and 159 (44).

Methyl 2-(p-*chlorophenylsulphinyl*)-4-*methyl*-3-(4-*methylpiperidino*)*pentanoate* (**8j**): m.p. 108 °C; $\nu_{max.}$(Nujol) 1 720 and 1 060 cm^{-1}; δ_H 0.86 (3 H, d, *J* 8 Hz), 0.96 (3 H, d, *J* 8 Hz), 1.8—2.3 (1 H, m), 1.1—3.2 (12 H, m), and 7.52 (4 H, s); *m*/*z* 127 (100%) and 159 (30).

Some of the ^{1}H n.m.r. data for compound (**8**) are given in Table 3. The results of elemental analyses were moderately satisfactory.

Reaction of Compound (**8**) *in* AcOH.—A solution of compound (**8**) (5 mmol) in AcOH (10 ml) was stirred at 20 °C for 10 min. Water (50 ml) was added and the mixture was extracted twice with Et_2O (50 ml). The organic phase was washed with three portions of saturated aqueous $NaHCO_3$ and aqueous NaCl, and dried (anhydrous Na_2SO_4). After the solvent had been removed, the residue obtained was purified by column chromatography on silica gel eluting with hexane–EtOAc (4:1 v/v). Although the *E*- and the *Z*-isomers were isolable, the *E*:*Z* ratio was determined using a diastereomeric mixture of (**3**) by the method described previously. These results are shown in Table 4.

This *anti*-elimination provided the following compounds.

(Z)-*Methyl* 2-(p-*chlorophenylsulphinyl*)-4-*methylpent*-2-*enoate* (*Z*)-(**3e**): liquid; $\nu_{max.}$(neat) 1 710 (C=O) and 1 055 cm^{-1} (S→O); δ_H ($CDCl_3$) 1.12 (6 H, t, *J* 6 Hz, 2 Me), 3.3—3.8 (1 H, m, CH), 3.70 (3 H, s, MeO), 7.25 (1 H, d, *J* 11 Hz, 3-H), 7.48 (2 H, d, *J* 7 Hz, ArH), and 7.62 (2 H, d, *J* 7 Hz, ArH); *m*/*z* 286 (M^+, 85%).

(Z)-*Methyl* 2-(p-*chlorophenylsulphinyl*)-3-*phenylprop*-2-*enoate* (*Z*)-(**3g**): m.p. 111 °C; $\nu_{max.}$(Nujol) 1 700 and 1 050 cm^{-1}; δ_H 3.68 (3 H, s, MeO), 7.6—8.0 (9 H, m, Ph + ArH), and 8.40 (1 H, s, 3-H); *m*/*z* 320 (M^+, 15%).

(E)-*Methyl* 2-(p-*chlorophenylsulphinyl*)-3-(4-*methoxyphenyl*)-*prop*-2-*enoate* (*E*)-(**3h**), m.p. 118 °C; $\nu_{max.}$(Nujol) 1 725 and 1 060 cm^{-1}; δ_H 3.71 (3 H, s, MeO), 3.90 (3 H, s, MeO), and 6.8—7.9 (9 H, m, ArH + 3-H); *m*/*z* 350 (M^+, 10%).

(Z)-*Methyl* 2-(p-*chlorophenylsulphinyl*)-3-(4-*methoxyphenyl*)-*prop*-2-*enoate* (*Z*)-(**3h**), m.p. 115 °C: $\nu_{max.}$(Nujol) 1 725 and 1 060 cm^{-1}; δ_H 3.66 (3 H, s), 3.90 (3 H, s), 6.8—7.9 (8 H, m, ArH), and 8.20 (1 H, s, 3-H); *m*/*z* 350 (25%).

Decomposition of Compound (**8**) *in* MeCN.—A solution of compound (**8**) (5 mmol) in MeCN (25 ml) was kept under the reaction conditions given in Table 1. Ether (50 ml) was added and the organic phase was washed with 10% hydrochloric acid (50 ml) and aqueous NaCl (50 ml). The aqueous layer was extracted with two portions of Et_2O (50 ml), and the combined organic phases were again washed with aqueous NaCl before being dried, and dried (anhydrous Na_2SO_4). Removal of the solvent gave a residue which was chromatographed on a silica-gel column eluting with hexane–EtOAc (4:1 v/v) to afford (*E*)-(**3**) and (**1b**). The *E*:*Z* ratio was determined as described previously. These results are shown in Table 4.

An n.m.r. tube containing a 2—5% solution of diastereoisomeric (**8h**) in CD_3CN or $CDCl_3$ was placed in an n.m.r. instrument. As both signals of *threo*-(**8h**) at δ 3.58 and of *erythro*-(**8h**) at δ 3.26 disappeared at similar rates, a new resonance due to (*E*)-(**3e**) at δ 6.98 appeared, but no signal of (*Z*)-(**3e**) at δ 7.25 was detected during the course of reaction.

Formation of the Sulphide (**4a**) *from the Sulphoxide* (**10a**).—To a stirred suspension of NaH (50%; 3.70 g, 77 mmol) in THF (40 ml) and hexamethylphosphoric triamide (20 ml) under an argon atmosphere, was added successively a solution of (**1a**) (13.8 g, 70 mmol) in THF (30 ml), and a solution of 1-bromobutane (10.7 g, 77 mmol) in THF (30 ml) at 0 °C. The resulting mixture was stirred for 10 h at room temperature and quenched with 5% hydrochloric acid (30 ml). The aqueous layer was extracted with Et_2O (100 ml), and the combined organic phase and washed three times with water and dried (anhydrous Na_2SO_4). Evaporation of the volatile components under reduced pressure gave crude methyl 2-phenylsulphinylhexanoate (**10a**) (*ca.* 16 g, 90%). The crude compound (**10a**) was used without purification in the subsequent reaction, because (**10a**) was susceptible to elimination of benzenesulphinic acid to form methylhex-2-enoate.

To a stirred solution of crude (**10a**) in CH_2Cl_2 (100 ml) was added dropwise a solution of $(CF_3CO)_2O$ (17.6 g, 84 mmol) and CF_3CO_2H (1.14 g, 10 mmol) in CH_2Cl_2 (100 ml) at

0 °C, and stirring was continued for 4 h at room temperature. The solution was quenched carefully with saturated aqueous $NaHCO_3$ (30 ml), washed several times with water, and dried (anhydrous Na_2SO_4). After the solvent had been removed methyl 2-phenylthiohex-2-enoate (**4a**) (10.7 g, 65% overall yield) was obtained as a yellow liquid by distillation, b.p. 110 °C at 1.5 mmHg, *E*:*Z* 20:80 by g.l.c. Isolation of the two isomers proved to be rather difficult.

Compound (**4a**) (4.72 g, 20 mmol) was oxidized to (**3a**) with MCPBA as described previously; (*E*)-(**3a**) (0.98 g, 19%) and (*Z*)-(**3a**) (4.00 g, 79%) were isolated by column chromatography on silica gel using hexane–EtOAc (4:1 v/v). The sulphoxides (*E*)-(**3a**) and (*Z*)-(**3a**) were then reduced to the corresponding sulphides (*E*)-(**4a**) and (*Z*)-(**4a**) by the method described previously.

Acknowledgements

We thank the Ministry of Education of Japan for a Grant-in-Aid for Special Project Research.

References

1 R. L. Reeves, 'The Chemistry of the Carbonyl Group,' ed. S. Patai, Interscience, London, 1966, p. 593.
2 G. Jones, *Org. React.* (*N.Y.*), 1967, **15**, 204.
3 H. O. House, 'Modern Synthetic Reactions,' W. A. Benjamin, Inc., Menlo Park, 1972, 2nd edn., p. 646.
4 J. Mathieu and J. Weill-Raynal, 'Formation of C–C Bonds,' G. Thieme Publishers, Stuttgart, 1975, vol. 2, p. 515.
5 J. Zabicky, *J. Chem. Soc.*, 1961, 683.
6 M. Schwarz, *J. Chem. Soc., Chem. Commun.*, 1969, 212.
7 D. A. R. Happer and B. E. Steenson, *Synthesis*, 1980, 806.
8 N. Kunieda, J. Nokami, and M. Kinoshita, *Tetrahedron Lett.*, 1974, 3997.
9 T. R. Hoye and M. J. Kurth, *J. Org. Chem.*, 1980, **45**, 3549.
10 Q. B. Cass, A. A. Jaxa-Chamiex, and P. G. Sammes, *J. Chem. Soc., Chem. Commun.*, 1981, 1248.
11 R. Tanikaga, T. Tamura, Y. Nozaki, and A. Kaji, *J. Chem. Soc., Chem. Commun.*, 1984, 87.
12 R. Tanikaga, K. Nakayama, K. Tanaka, and A. Kaji, *Chem. Lett.*, 1977, 395.
13 R. Tanikaga, Y. Nozaki, T. Tamura, and A. Kaji, *Synthesis*, 1983, 134.
14 Ref. 2, p. 206.
15 S. J. Cristol and P. Pappas, *J. Org. Chem.*, 1963, **28**, 2066.
16 F. G. Bordwell, D. D. Phillips, and J. M. Williams, Jr., *J. Am. Chem. Soc.*, 1968, **90**, 426.
17 R. P. Redman, P. J. Thomas, and C. J. M. Stirling, *J. Chem. Soc., Chem. Commun.*, 1978, 43.
18 R. P. Redman, P. J. Thomas, and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1978, 1135.
19 C. J. M. Stirling, *Acc. Chem. Res.*, 1979, **12**, 198.
20 Z. Rappoport, *Acc. Chem. Res.*, 1981, **14**, 7, and references cited therein.
21 Z. Rappoport and A. Gazit, *J. Org. Chem.*, 1985, **50**, 3184.
22 T. Durst, 'Comprehensive Organic Chemistry,' ed. D. N. Jones, Pergamon Press, Oxford, 1979, vol. 3, p. 139.
23 R. Tanikaga, Y. Hiraki, N. Ono, and A. Kaji, *J. Chem. Soc., Chem. Commun.*, 1980, 41.
24 R. Tanikaga, Y. Nozaki, M. Nishida, and A. Kaji, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 729.
25 J. Drabowicz and S. Oae, *Synthesis*, 1977, 404.

Received 1*st April* 1986; *Paper* 6/628