Stereochemical Behavior of Intermediary Compounds in the Amine-Catalyzed Knoevenagel Reaction

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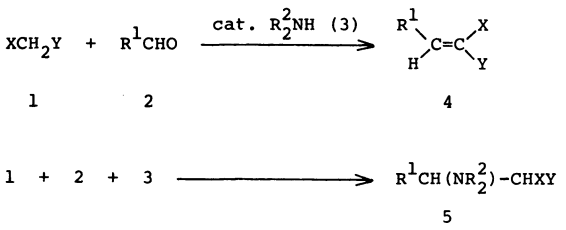
Treatment of the active methylene compounds and aldehydes with a catalytic amount of a secondary amine produces thermodynamically stable alkenes, and the intermediary amino compounds are isolated. The reaction involves many reversible steps, and the stereochemistry of products is determined in the elimination step from the intermediary compounds via stable planar carbanions, in which the small difference in the steric requirements of two electron-withdrawing groups is effective. Steric and electronic effects in the intermediates sometimes bring about the carbon–carbon bond fission with recovery of active methylene compounds, and these effects prevent the Knoevenagel reaction from occurring.

Among a number of synthetic methods for carbon–carbon bond formation the amine-catalyzed Knoevenagel reaction is frequently employed because of its high reactivity under mildly basic conditions.[1–5] The main preparative application of the reaction has been condensation of aldehydes and ketones with easily enolizable compounds usually containing two electron-withdrawing groups. The reaction, though easy to operate, seems to involve a complicated mechanism. Previously we observed that simple treatment of methyl arylsulfinylacetate **1a** (X=CO_2Me, Y=S(O)Ar) and aldehydes **2** with a catalytic amount of a secondary amine **3** produced thermodynamically stable (*E*)-alkenes (*E*)-**4**, and assumed that the stereochemistry of the reaction was determined in the elimination step from intermediary amino compounds **5** via planar carbanions **6**[5] stabilized by both a sulfur atom and a carbonyl group (Scheme 1).



Scheme 1.

However, it remains obscure whether the presence of a sulfur atom is essential for stabilization of **6**. Here we wish further to clarify what factors influence the behaviors of the intermediate **5** in the amine-catalyzed Knoevenagel reaction starting from the active methylene compound **1** containing two electron-withdrawing groups (X and Y) in general.

Results and Discussion

The following amine-catalyzed reactions were carried out with the intention of examining the stereochemistry of products. Simple treatment of **1** (10 mmol) and **2** (12 mmol) with piperidine (0.5 mmol) in acetonitrile (50 ml) produced alkenes **4** as shown in Table 1.

Thermodynamically stable **4** were always obtained regardless of the absence of a sulfinyl group, and their formation was much influenced by the small difference in the steric requirements of X and Y groups, especially near a reaction center. Although such a selectivity was not observed in the presence of small X and Y groups (e.g., X=CO_2Me, Y=COMe), the *E*:Z ratio was slightly improved by using, instead of piperidine, larger 2,6-dimethylpiperidine or dicyclohexylamine (34:66, 36:64, respectively).

These findings can be rationalized by the explanation that the steric effects of X and Y groups are more

Table 1. Preparation of Alkenes **4**

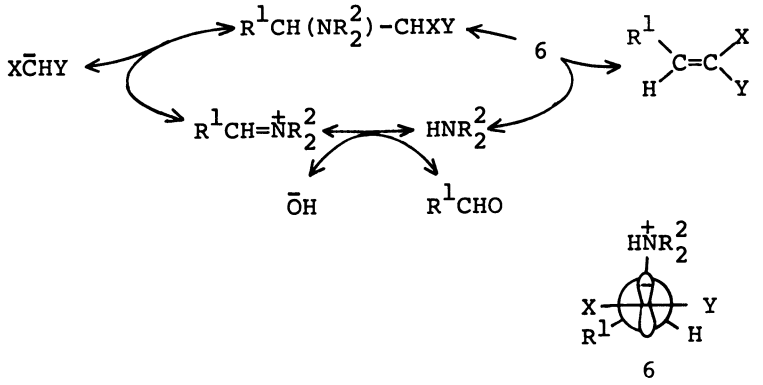
X	Y	R^1	Temp	Time	Yield[a]	*E*:*Z*[b]
			°C	h	%	
COPh	S(O)Ph	Ph	60	6	71	99:1
CO_2Bu-*t*	S(O)C_6H_4Cl-*p*	*n*-Pr	0	24	68[c]	99:1
COPr-*i*	COPh	Ph	60	6	84	99:1
COPr-*i*	COPh	*n*-Pr	20	12	63	63:37
COMe	COPh	Ph	20	12	79	99:1
COMe	COPh	*i*-Pr	20	12	74	99:1
COMe	COPh	*n*-Pr	20	12	70	98:2
CO_2Me	COPh	Ph	60	6	85	1:99
CO_2Me	COMe	Ph	20	12	77	31:69
CO_2Me	COMe	*n*-Pr	20	12	74	45:55

a) Isolated yield. b) Determined by GLPC or HPLC. c) (R_S)-**4** was obtained in 100% e.e. from (R_S)-**1**.

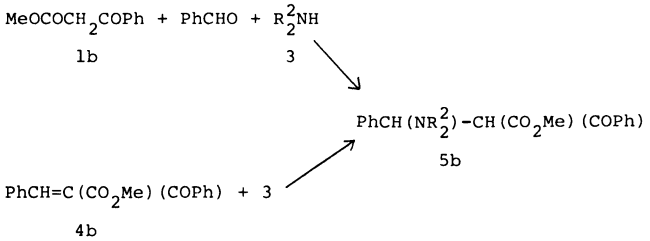
Table 2. Formation of **4b** from **5b** in Acetonitrile or Acetic Acid

5b		MeCN[a]		AcOH[b]	
R^2	threo: erythro	Yield/%	$E:Z$[d]	Yield/%	$E:Z$[d]
$-(CH_2)_4-$	39:61	71	0:100	82	40:60
$-(CH_2)_5-$	29:71	90	0:100	90	45:55
$-(CH_2)_2CHMe(CH_2)_2-$	39:61	71	0:100	94	49:51
$-(CH_2)_6-$	32:68	82	0:100	90	38:62

a) 60 °C, 6 h. b) 20 °C, 10 min. c) Isolated yield. d) Determined by GLPC.



Scheme 2. Reaction mechanism (X<Y).

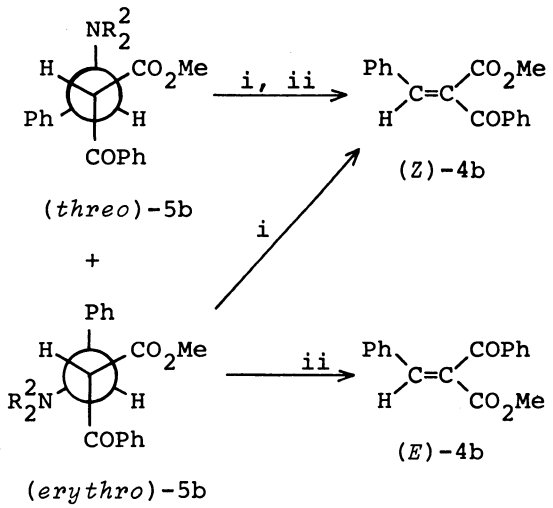


Scheme 3.

effective in planar carbanions **6**, in which two groups R^1 and X, or R^1 and Y are brought close together (Scheme 2).[5,6] Interestingly, the formation of **6** did not accompany loss of enantiomercal purity of a sulfinyl group (Y=(*R*)-S(O)C_6H_4Cl-*p*).

When a solution of methyl benzoylacetate (**1b**)(10 mmol), benzaldehyde (12 mmol), and secondary amine **3** (12 mmol) in a small quantity of acetonitrile was allowed to stand at 0 °C, the diastereoisomeric amino compounds *threo*- and *erythro*-**5b** crystallized directly with time in 70—92% yields. The amino compounds **5b** were also obtained with the same threo:erythro ratio from alkenes **4b** (10 mmol) and **3** (12 mmol) (Scheme 3).

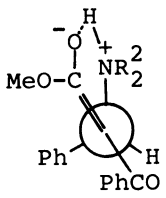
Previously we reported that thermodynamically stable (*E*)-alkenes (*E*)-**4**, that is, the Knoevenagel reaction products were obtained simply by dissolving **5a** derived from **1a** in acetonitrile at 20—60 °C, whereas on treatment with acetic acid anti-elimination occurred to afford mixtures of (*E*)- and (*Z*)-**4a**.[5] Similar treatment of mixtures of *threo*- and *erythro*-**5b** lead to the results as listed in Table 2.



Scheme 4. Reaction conditions: i, MeCN; ii, AcOH

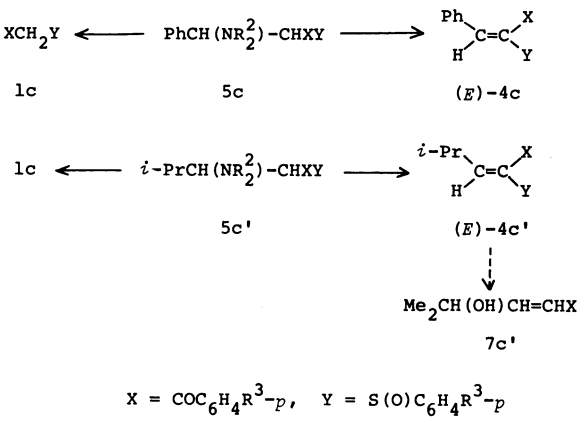
High selectivity in the Knoevenagel reaction was realized in an elimination step from **5b** rather than in its formation probably because steric repulsion between COPh and Ph groups is considerable in a planar carbanion **6** if R^1=Ph and Y=COPh in Scheme 2. Since the carbanion **6** is enolizable, the elimination may occur via an intermediate such as **6b′**. The stereochemistry in the elimination step can be interpreted essentially in the same way.

Similar treatment of 1-aryl-2-(arylsulfinyl)ethanone (**1c**) and an aldehyde (R^1=Ph or *i*-Pr) with a secondary amine **3** gave the amino compounds **5c**, **5c′** as crystalline solids, and interestingly **5c** or **5c′** appeared



6b′

to be well suited for studies of the intermediate in the amine-catalyzed Knoevenagel reaction because both **1c** and (*E*)-alkenes (*E*)-**4c**, (*E*)-**4c′** were obtained by dissolving **5c** or **5c′** in a suitable solvent. Since a secondary amine is known to cause (*E*)-**4c′** to undergo further reactions yielding an allylic alcohol **7c′**,[7] it is important to neutralize the amine **3** formed as a by-product. Therefore, **5c′** was dissolved in dichloromethane containing aqueous ammonium chloride in which the Knoevenagel reaction proceeded as usual. These results are given in Table 3 (Scheme 5).



Scheme 5.

Table 3. Formation of **1c** and (*E*)-**4c**, **4c′** from **5c**, **5c′**[a,b]

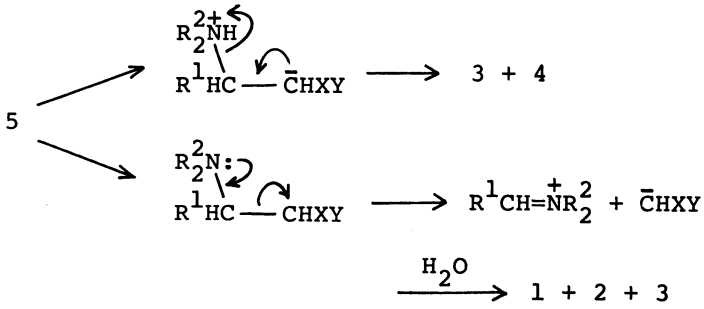
R^1	R^2_2	R^3	Yield/%[c]	
			1c	(*E*)-**4c**, **4c′**[d]
Ph	Me, Me	H	39	49
Ph	$-(CH_2)_4-$	H	25	63
Ph	$-(CH_2)_5-$	H	42	58
Ph	$-CHMe(CH_2)_4-$	H	43	51
i-Pr	Me, Me	H	80	8
i-Pr	$-(CH_2)_5-$	H	94	3
i-Pr	$-(CH_2)_2CHMe(CH_2)_2-$	H	100	0
Ph	Me, Me	Me	98	0
Ph	$-(CH_2)_4-$	Me	69	17
Ph	$-(CH_2)_5-$	Me	78	14
Ph	$-(CH_2)_2CHMe(CH_2)_2-$	Me	80	19
i-Pr	Me, Me	Me	92	1
i-Pr	$-(CH_2)_4-$	Me	84	0
i-Pr	$-(CH_2)_5-$	Me	100	0
i-Pr	$-(CH_2)_2CHMe(CH_2)_2-$	Me	100	0

a) A mixture of threo- and erythro-isomers was used. b) Reaction conditions: **5c**; MeCN, 60 °C, 6 h; **5c′**; CH_2Cl_2, 20 °C, 12 h. c) Isolated yield. d) No (*Z*)-isomer was obtained.

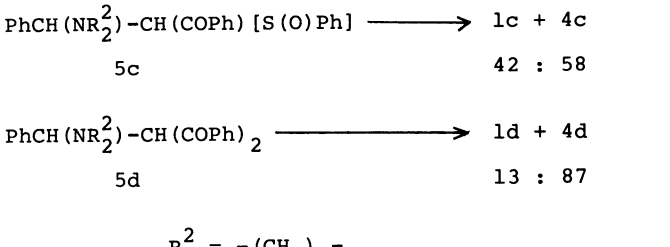
The absence of (*Z*)-**4c**, (*Z*)-**4c′** means that the elimination is affected by the difference in the steric requirements of C=O and S→O groups [bond distance, 1.23 (C=O) and 1.44 Å (S→O);[8] van der Waals radius, 1.55 (C atom) and 1.85 Å (S atom)[9]]. Construction of a molecular model suggests considerable steric restraints for the formation of **5**, and actually preparation of **5** with bulky R^1 and R^2 [e.g., R^1=*i*-Pr, and R^2=$-CHMe(CH_2)_4-$] was impossible. This steric hindrance may also have contributed to weakening the linkage of both C–N and C–C bonds though the C–C bond fission mechanism has not yet been clarified (Scheme 7).

The **1c**/(*E*)-**4c** or **1c**/(*E*)-**4c′** ratio increased with the relative bulkiness of R^2_2 in the order; $-(CH_2)_4- < Me_2 \approx -(CH_2)_5- < -(CH_2)_2CHMe(CH_2)_2-$, that is, a bulky R^2_2N group favored the C–C bond fission. Since the elimination reaction from **5** might be initiated by removal of the proton at the α-position of X and Y groups, the formation of the alkene **4** was depressed by the presence of an electron-donating group, e.g., R^1=*i*-Pr or R^3=Me, and accelarated by replacement of a sulfinyl group by a carbonyl group (Scheme 7).

The reversibility of the amine-catalyzed Knoevenagel reaction is supported by the findings that the intermediate **5** was obtained from both the starting compound **1** and the product **4** (Scheme 3), and at the same time, **5** produced **1** and **4** (Scheme 5). Solidification of **5** might make it possible to shift the equilibrium yielding **5**. In a solution, however, the equilibrium between **1c** and **5c** (or **5c′**) was sometimes found to be more in favor to **1c** (e.g., R^1=*i*-Pr in Table 3), and in fact the Knoevenagel reaction never occurred from **1c** and *i*-PrCHO. Neither usage of an equimolar



Scheme 6.



Scheme 7.

amount of an amine nor removal of water from the reaction mixture improved the yield of **4**.

In conclusion, the amine-catalyzed Knoevenagel reaction involves many reversible steps as shown in Scheme 2, the stereochemical behavior of an intermediary amino compound plays an important role, and the usage of a catalytic amount of a secondary amine forces this thermodynamically-controlled reaction to completion giving the most stable product.

Rappoport has studied the stereochemical behavior in vinylic substitution (via addition-elimination) of halosubstituted electrophilic olefins containing two electron-withdrawing groups by a nucleophile such as ArS^- and ArO^-, and interestingly proposed the planar carbanion similar to **6** in the elimination step.[10,11] Our present results may provide significant information concerning an addition-elimination reaction.

Experimental

^1H NMR spectra were determined at 100 MHz with a JEOL JNM-PS-100 or at 400 MHz with a JEOL JNM-GX-400 spectrometer, and refer to deuteriochloroform solution with tetramethylsilane as internal standard. IR spectra were recorded with a Hitachi 215 spectrometer, and MS with a JEOL JMX-DX-300 instrument. GLPC analysis was carried out with a Varian 920 instrument using a column packed with 20% silicone DS-550. Column chromatography and TLC were performed, using Wakogel 200 silica gel and Merck plastic sheets silica gel 60 F_{254} respectively. HPLC analysis was carried out with a Shimadzu LC-6A system containing a column packed with a commercially-available chiral cellulose derivative (Daicel Chemical Industry's CHIRALCEL-OC) or a ODS column.

Commercial 1-phenyl-1,3-butanedione, methyl benzoylacetate (**1b**), methyl acetoacetate, 1,3-diphenyl-1,3-propanedione (**1d**), aldehydes **2**, and amines **3** were purified before use. 4-Methyl-1-phenyl-1,3-pentanedione, 1-phenyl-2-(phenylsulfinyl)ethanone, and 1-(*p*-tolyl)-2-(*p*-tolylsulfinyl)ethanone were prepared by the reported methods.[12,13]

***t*-Butyl (*R*S)-*p*-Chlorophenylsulfinylacetate.** To a stirred solution of ethylmagnesium bromide [prepared from Mg (2.43 g, 0.1 mol) and bromoethane (10.9 g, 0.1 mol) in diethyl ether (50 ml)] under argon atmosphere was added diisopropylamine (14 ml, 0.1 mol). The resulting solution was refluxed for 30 min and cooled to −40 °C. To the solution was added successively a solution of *t*-butyl acetate (8.13 g, 0.07 mol) in tetrahydrofuran (THF) (5 ml) and a solution of menthyl (*S*S,*S*C)-*p*-chlorobenzenesulfinate[14] (9.45 g, 0.03 mol) in diethyl ether (80 ml)–THF (8 ml). The solution was stirred for further 10 h at −40 °C, and quenched with saturated aqueous ammonium chloride (50 ml). The aqueous layer was extracted with chloroform, and the combined organic phases were washed with water, and dried (anhydrous magnesium sulfate). After having removed the solvent column chromatography on silica gel eluting with hexane–ethyl acetate (3:1) and recrystallized from hexane–ethyl acetate (5:1) gave *t*-butyl (*R*S)-*p*-chlorophenylsulfinylacetate (6.26 g, 76%): mp 123.5 °C; $[\alpha]_D^{23.5}$ +169.7° (*c* 1.09, MeOH)(100% e.e. by HPLC); IR (KBr) 1720 (C=O) and 1040 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=1.40 (9H, s, Me), 3.57 (1H, d, *J*=13 Hz, CH_2), 3.81 (1H, d, *J*=13 Hz, CH_2), 7.51 (2H, d, *J*=7 Hz, Ar), and 7.67 (2H, d, *J*=7 Hz, Ar); Found: C, 52.25; H, 5.32%. Calcd for $C_{12}H_{15}ClO_3S$: C, 52.44; H, 5.50%.

Knoevenagel Reaction of Compounds 1 and Aldehydes 2. A solution of **1** (10 mmol), **2** (10 mmol), and an amine **3** (0.5 mmol) in acetonitrile (50 ml) was kept under the conditions given in Table 1. After having removed the solvent under the reduced pressure the residue was chromatographed on silica gel using hexane–ethyl acetate (4:1) to give the alkene **4** in the yield as shown in Table 1. A minimum quantity of the reaction mixture was withdrawn prior to isolation to determine the *E*:*Z* ratio of **4** by GLPC, HPLC, or ^1H NMR. The enantiomeric excess was determined by HPLC using a chiral derivative. By this route the following compounds were obtained.

(2*E*)-1,3-Diphenyl-2-phenylsulfinyl-2-propen-1-one [(*E*)-4c]: Mp 90 °C; IR (Nujol) 1640 (C=O) and 1060 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=6.9—7.8 (11H, m, Ph, CH=C); MS *m*/*z* 332 (M^+, 8%); Anal. ($C_{21}H_{16}O_2S$) C, H.

***t*-Butyl (*R*S, 2*E*)-2-(*p*-Chlorophenylsulfinyl)-2-hexenoate:** Liquid; $[\alpha]_D^{22}$=166.9° (*c* 1.10, MeOH)(100% e.e.); IR (neat) 1720 (C=O) and 1050 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=0.98 (3H, t, *J*=7 Hz, Me), 1.35 (9H, s, Me_3C), 1.6—2.7 (4H, m, CH_2), 7.11 (1H, t, *J*=8 Hz, CH=C), 7.48 (2H, d, *J*=8 Hz, Ar) and 7.69 (2H, d, *J*=8 Hz, Ar); MS *m*/*z* 328 (M^+, 10%); Anal. ($C_{16}H_{21}ClO_3S$) C, H.

(4*E*)-4-Benzoyl-2-methyl-5-phenyl-4-penten-3-one: Liquid; IR (neat) 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.13 (6H, d, *J*=6 Hz, Me), 3.13 (1H, hept, CH), 7.76 (1H, s, CH=C), and 7.1—8.1 (10H, m, Ph); MS *m*/*z* 278 (M^+, 6%); Anal. ($C_{19}H_{18}O_2$) C,H.

4-Benzoyl-2-methyl-4-octen-3-one: Liquid; IR (neat) 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=0.5—2.7 (7H, m, Me, CH_2), 1.08 (6H, d, *J*=7 Hz, Me_2C), 3.11 (1H, m, CH), 6.46 (1H, t, *J*=7 Hz, *Z* CH=C), 6.96 (1H, t, *J*=7 Hz, *E* CH=C), and 7.2—8.1 (5H, m, Ph); MS *m*/*z* 244 (M^+, 1%); Anal. ($C_{12}H_{20}O_2$) C, H.

(3*E*)-3-Benzoyl-4-phenyl-3-buten-2-one: Mp 98 °C (lit,[15] mp 98—99 °C).

(3*E*)-3-Benzoyl-5-methyl-3-hexen-2-one: Liquid; IR (neat) 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.00 (6H, d, *J*=6 Hz, Me_2C), 2.32 (3H, s, MeCO), 3.10 (1H, hept, *J*=6 Hz, CH), 6.71 (1H, d, *J*=10 Hz, CH=C), and 7.2—8.1 (5H, m, Ph); MS *m*/*z* 216 (M^+, 12%); Anal. ($C_{14}H_{16}O_2$) C, H.

(3*E*)-3-Benzoyl-3-hepten-2-one: Liquid; IR (neat) 1720 cm^{-1}; (C=O); ^1H NMR ($CDCl_3$) δ=0.6—2.2 (7H, m, Me, CH_2), 2.31 (3H, s, MeCO), 6.96 (1H, t, *J*=7 Hz, CH=C), and 7.2—8.1 (5H, m, Ph); MS *m*/*z* 216 (M^+, 18%); Anal. ($C_{14}H_{16}O_2$) C, H.

Methyl (2*Z*)-2-Benzoyl-3-phenyl-2-propenoate [(*Z*)-4b]: Liquid; IR (neat) 1740(O–C=O) and 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=3.68 (3H, s, MeO), 7.92 (1H, s, CH=C), and 6.9—8.1 (10H, m, Ph); MS *m*/*z* 266 (M^+, 7%); Anal. ($C_{17}H_{14}O_3$) C, H.

Methyl 2-Acetyl-3-phenyl-2-propenoate: Liquid; IR (neat) 1730 (O–C–O) and 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) (*E*)-isomer δ=2.30 (3H, s, MeCO), 3.81 (3H, s, MeO), 7.0—7.5 (5H, m, Ph), and 7.66 (1H, s, CH=C), (*Z*)-isomer δ=2.40 (3H, s, MeCO), 3.87 (3H, s, MeO), 7.2—7.6 (5H, m, Ph), and 7.57 (1H, s, CH=C).

Methyl 2-Acetyl-2-hexenoate: Liquid; IR (neat) 1730 (O-C=O) and 1690 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) (*E*)-isomer δ=0.9—2.8 (7H, m, Me, CH_2), 1.16 (3H, s, MeCO), 3.80 (3H, s, MeO), and 6.68 (1H, d, J=11 Hz, CH=C), (*Z*)-isomer δ=0.9—2.8 (7H, m, Me, CH_2), 1.30 (3H, s, MeCO), 3.85 (3H, s, MeO), and 6.60 (1H, d, J=11 Hz, CH=C).

The elemental analyses found were in good agreement with the calculated values throughout.

Formation of the Amino Compounds 5. A solution of **1** (10 mmol), **2** (15 mmol), and **3** (15 mmol) in acetonitrile (20 ml) was kept at 0 °C for 24 h. The product precipitated was filtered off, washed several times with cold acetonitrile, and dried in vacuo. Almost pure diastereoisomeric **5** was obtained as a colorless solid. Further purification by recrystallization or column chromatography proved to be impossible owing to ready elimination reactions. The configuration of *threo*- and *erythro*-**5** were assigned on the basis of the results obtained by anti-elimination using acetic acid,[5] and their ratio was determined by ^1H NMR. Mass spectra of **5** indicated the absence of M^+ peaks.

By this route the following compounds were obtained.

Methyl 2-Benzoyl-3-pyrrolidino-3-phenylpropionate: Yield 70%; mp 128 °C; IR (Nujol) 1730 (O-C=O) and 1685 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.3—1.9 (4H, m, CH_2), 2.1—3.0 (4H, m, CH_2-N), 3.30/3.76 (3H, s, threo/erythro MeO), 4.71—4.81 (1H, d, J=12 Hz, CH-N), 5.15/5.27 (1H, d, J=12 Hz, threo/erythro CH-CO), and 7.0—8.2 (10H, m, Ph); Anal. ($C_{21}H_{23}O_3N$) C, H, N.

Methyl 2-Benzoyl-3-phenyl-3-piperidinopropionate: Yield 92%; mp 145—146 °C; IR (Nujol) 1730 (O-C=O) and 1685 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=0.9—1.8 (6H, m, CH_2), 1.8—2.9 (4H, m, CH_2-N), 3.51/3.79 (3H, s, threo/erythro MeO), 4.66/4.71 (1H, d, J=11 Hz, threo/erythro CH-N), 5.28/5.25 (1H, d, J=11 Hz, threo/erythro CH-CO), and 7.0—8.2 (10H, m, Ph); Anal. ($C_{22}H_{25}O_3N$) C, H, N.

Methyl 2-Benzoyl-3-(4-methylpiperidino)-3-phenylpropionate: Yield 78%; mp 130—132 °C; IR (Nujol) 1725 (O-C-O) and 1690 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=0.6—1.9 (8H, m, Me, CH, CH_2), 2.0—3.1 (4H, m, CH_2-N), 3.46/3.76 (3H, s, threo/erythro MeO), 4.47/4.73 (1H, d, J=11 Hz threo/erythro CH-N), 5.24/5.33 (1H, d, J=11 Hz, threo/erythro CH-CO), and 7.0—8.1 (10H, m, Ph); Anal. ($C_{23}H_{27}O_3N$) C, H, N.

Methyl 2-Benzoyl-3-(perhydro-1-azepinyl)-3-phenylpropionate: Yield 82%; mp 128—129 °C; IR (Nujol) 1730 (O-C-O) and 1685 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=0.9—1.8 (8H, m, CH_2), 2.1—3.1 (4H, m, CH_2-N), 3.46/3.77 (3H, s, threo/erythro MeO), 4.74/4.83 (1H, d, J=11 Hz, threo/erythro CH-N), 5.22/5.28 (1H, d, J=11 Hz, threo/erythro CH-CO), and 7.1—8.2 (10H, m, Ph); Anal. ($C_{23}H_{27}O_3N$) C, H, N.

3-Dimethylamino-1,3-diphenyl-2-phenylsulfinyl-1-propanone: Yield 84%; mp 139 °C; IR (Nujol) 1650 (C=O) and 1060 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=2.04 (3H, s, Me), 2.52 (3H, s, Me), 4.6—5.2 (2H, br, CH), and 6.8—7.7 (15H, m, Ph); very slightly soluble in $CDCl_3$; Anal. ($C_{23}H_{23}O_2NS$) C, H, N.

1,3-Diphenyl-2-phenylsulfinyl-3-(1-pyrrolidinyl)-1-propanone: Yield 94%; mp 139—140 °C; IR (Nujol) 1660 (C=O) and 1060 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=1.6—1.9 (4H, m, CH_2), 2.5—2.9 (4H, m, CH-N), 5.0—6.3 (2H, br, CH), and 6.9—7.8 (15H, m, Ph); very slightly soluble in $CDCl_3$; Anal. ($C_{25}H_{25}O_2NS$) C, H, N.

1,3-Diphenyl-2-phenylsulfinyl-3-piperidino-1-propanone: Yield 70%; mp 154—155 °C; IR (Nujol) 1660 (C=O) and 1055 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=1.0—2.0 (6H, m, CH_2), 2.0—3.0 (4H, m, CH_2-N), 4.21 (1H, d, J=11 Hz, CH-N), 5.90 (1H, d, J=11 Hz CH-SO), and 6.9—7.9 (15H, m, Ph); slightly soluble in $CDCl_3$; Anal. ($C_{26}H_{27}O_2NS$) C, H, N.

1,3-Diphenyl-3-(4-methylpiperidino)-2-phenylsulfinyl-1-propanone: Yield 91%; mp 147—149 °C; IR (Nujol) 1660 (C=O) and 1055 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=0.6—3.2 (12H, m, Me, CH, CH_2), 4.6—5.5 (2H, br, CH), and 6.8—7.9 (15H, m, Ph); very slightly soluble in $CDCl_3$; Anal. ($C_{27}H_{29}O_2NS$) C, H, N.

3-Dimethylamino-4-methyl-1-phenyl-2-phenylsulfinyl-1-pentanone: Yield 80%; mp 87—79 ° C; IR (Nujol) 1660 (C=O) and 1055 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=0.72—1.28 (6H, m, Me), 2.0 (1H, m, CH), 2.50/2.59 (6H, s, threo/erythro Me_2N), 3.22/3.61 (1H, d, J=11 Hz, threo/erythro CH-N), 4.82/5.26 (1H, d, J=11 Hz, threo/erythro CH-SO), and 6.8—7.9 (10H, m, Ph); Anal. ($C_{20}H_{25}O_2NS$) C, H, N.

4-Methyl-1-phenyl-2-phenylsulfinyl-3-piperidino-1-pentanone: Yield 94%; mp 99—101 °C; IR (Nujol) 1660 (C=O) and 1050 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=0.6—1.9 (6H m, CH_2), 2.1 (1H, m, CH), 2.4—3.1 (4H, m, CH_2-N), 3.23/3.57 (1H, dd, J=11, 6 Hz, threo/erythro CH-N), 4.71/5.21 (1H, d, J=11 Hz, threo/erythro CH-SO), and 6.9—7.9 (10H, m, Ph); Anal. ($C_{23}H_{29}O_2NS$) C, H, N.

4-Methyl-3-(4-methylpiperidino)-1-phenyl-2-phenylsulfinyl-1-pentanone: Yield 93%; mp 96—98 °C; IR (Nujol) 1660 (C=O) and 1055 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=0.5—1.8 (14H, m, Me, CH, CH_2), 2.0 (1H, m, CH), 2.2—3.3 (4H, m, CH_2-N), 3.30/3.62 (1H, dd, J=12, 7 Hz, threo/erythro CH-N), 4.72/5.21 (1H, d, J=12 Hz, threo/erythro CH-SO), and 6.9—7.9 (10H, m, Ph); Anal. ($C_{24}H_{31}O_2NS$) C, H, N.

3-Dimethylamino-3-phenyl-1-(*p*-tolyl)-2-(*p*-tolylsulfinyl)-1-propanone: Yield 77%; mp 148—149 °C; IR (Nujol) 1660 (C=O) and 1055 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=2.06/2.17 (3H, s, Me), 2.31 (1H, s, Me), 2.2—2.5 (6H, Me_2N), 4.1—5.1 (2H, CH), and 6.8—8.0 (13H, m, Ph, Ar); slightly soluble in $CDCl_3$; Anal. ($C_{25}H_{27}O_2NS$) C, H, N.

3-Phenyl-3-pyrrolidino-1-(*p*-tolyl)-2-(*p*-tolylsulfinyl)-1-propanone: Yield 99%; mp 145—147 °C; IR (Nujol) 1665 (C=O) and 1055 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=1.5—1.8 (4H, m, CH_2), 2.16/2.22 (3H, s, Me), 2.36 (3H, s, Me), 2.5—3.0 (4H, m, CH_2-N), 4.1—5.1 (2H, CH), and 6.8—7.9 (13H, m, Ph, Ar); slightly soluble in $CDCl_3$; Anal. ($C_{27}H_{29}O_2NS$) C, H, N.

3-Phenyl-3-piperidino-1-(*p*-tolyl)-2-(*p*-tolylsulfinyl)-1-propanone: Yield 66%; mp 165—166 °C; IR (Nujol) 1660 (C=O) and 1060 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=1.0—1.9 (6H, m, CH_2), 2.16/2.21 (3H, s, Me), 2.36 (3H, s, Me), 2.0—2.2 (4H, m, CH_2-N), 4.2—5.9 (2H, br, CH), and 6.7—8.0 (13H, m, Ph, Ar); very slightly soluble in $CDCl_3$; Anal. ($C_{28}H_{31}O_2NS$) C, H, N.

3-(4-Methylpiperidino)-3-phenyl-1-(*p*-tolyl)-2-(*p*-tolylsulfinyl)-1-propanone: Yield 68%; mp 167—168 °C; IR (Nujol) 1660 (C=O) and 1060 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=0.5—3.2 (18H, m, Me, CH, CH_2), 4.6—5.4 (2H, m, CH), and 6.7—8.0 (13H, m, Ph, Ar); very slightly soluble in $CDCl_3$; Anal. ($C_{29}H_{33}O_2NS$) C, H, N.

4-Methyl-3-dimethylamino-1-(*p*-tolyl)-2-(*p*-tolylsulfinyl)-

1-pentanone: Yield 68%; mp 104—105 °C; IR (Nujol) 1660 (C=O) and 1060 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=0.6—1.3 (6H, m, Me), 1.8—2.8 (13H, m, Me, CH), 3.17/3.61 (1H, dd, J=10, 5 Hz, CH-N), 4.69/5.22 (1H, d, J=10 Hz, CH-SO), and 6.8—7.9 (8H, m, Ar); slightly soluble in $CDCl_3$; Anal. ($C_{22}H_{29}O_2NS$) C, H, N.

4-Methyl-3-(1-pyrrolidinyl)-1-(*p*-tolyl)-2-(*p*-tolylsulfinyl)-1-pentanone: Yield 74%; mp 89—90 °C; IR (Nujol) 1660 (C=O) and 1060 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=0.7—3.2 (21H, m, Me, CH, CH_2), 4.0—4.8 (2H, m, CH), and 6.8—7.9 (8H, m, Ar); slightly soluble in $CDCl_3$; Anal. ($C_{24}H_{31}O_2NS$) C, H, N.

4-Methyl-3-piperidino-1-(*p*-tolyl)-2-(*p*-tolylsulfinyl)-1-pentanone: Yield 85%; mp 108—109 °C; IR (Nujol) 1660 (C=O) and 1060 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=0.7—3.1 (23H, m, Me, CH, CH_2), 3.20/3.58 (1H, dd, J=10, 4 Hz, CH-N), 4.65/5.26 (1H, d, J=10 Hz, CH-SO), and 6.8—7.4 (8H, m, Ar); slightly soluble in $CDCl_3$; Anal. ($C_{25}H_{33}O_2NS$) C, H, N.

4-Methyl-3-(4-methylpiperidino)-1-(*p*-tolyl)-2-(*p*-tolylsulfinyl)-1-pentanone: Yield 88%; mp 109—110 °C; IR (Nujol) 1655 (C=O) and 1060 cm^{-1} (S→O); ^1H NMR δ ($CDCl_3$) δ= 0.6—3.3 (25H, m, Me, CH, CH_2), 4.0—4.8 (2H, CH), and 6.8—7.9 (4H, m, Ar); slightly soluble in $CDCl_3$; Anal. ($C_{26}H_{35}O_2NS$) C, H, N.

2-Benzoyl-1,3-diphenyl-3-piperidino-1-propanone: Yield 90%; mp 150 °C; IR (Nujol) 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.0—1.7 (6H, m, CH_2), 2.0—2.6 (4H, m, CH-N), 4.70 (1H, d, J=13 Hz, CH-N), 5.38 (1H, d, J=13 Hz, CH-CO), and 7.0—8.1 (15H, m, Ph); Anal. ($C_{27}H_{27}O_2N$) C, H, N.

The elemental analyses found were in good agreement with the calculated values throughout. Assignment between threo and erythro isomers sometimes was difficult because the compound **5** was slightly soluble in $CDCl_3$.

Reaction of Compounds 5b in Acetic Acid. A solution of **5b** (5 mmol) in acetic acid (10 ml) was stirred at 20 ° C for 10 min. Water (50 ml) was added and the mixture was extracted twice with diethyl ether (50 ml). The organic phase was washed with three portions of saturated aqueous $NaHCO_3$ and NaCl, and dried (anhydrous $MgSO_4$). After the solvent had been removed, the residue obtained was purified by column chromatography on silica gel eluting with hexane–ethyl acetate (4:1). The *E*:*Z* ratio was determined by GLPC using a diastereoisomeric mixture of **4b**.

Methyl (2*E*)-2-Benzoyl-3-phenyl-2-propenoate [(*E*)-4b]: Liquid; IR (neat) 1740 (O-C=O) and 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=3.68 (3H, s, MeO), and 6.9—8.1 (11H, m, Ph, CH); MS m/z 266 (M^+, 5%); Anal. ($C_{17}H_{14}O_2$) C, H.

Reaction of Compounds 5b, 5c, 5c′ in Acetonitrile. A solution of **5b** or **5c** (5 mmol) in acetonitrile (100 ml) or **5c′** (5 mmol) in dichloromethane–saturated aqueous NH_4Cl (4:1, 50 ml) was kept under the reaction conditions given in Tables 2 and 3. Dichloromethane (100 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 dichloromethane (50 ml), and the combined organic phases were again washed with aqueous NaCl before being dried (anhydrous $MgSO_4$). Removal of the solvent gave the residue which was chromatographed on a silica-gel column eluting hexane–ethyl acetate (4:1) to afford **1** and (*Z*)-**5b**, (*E*)-**5c**, or (*E*)-**5c′**. These results are given in Tables 2 and 3.

(2*E*)-3-Phenyl-2-(*p*-toluenesulfinyl)-1-(*p*-tolyl)-2-propen-1-one: Mp 83 °C; IR (Nujol) 1670 (C=O) and 1050 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ=2.25 (6H, s, MeO) and 6.8—7.8 (14H, m, Ph, Ar, CH); MS m/z 360 (M^+, 2%); Anal. ($C_{23}H_{20}O_2S$) C, H.

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References

1) R. L. Reeves, "The Chemistry of the Carbonyl Group," ed by S. Patai, Interscience, London (1966), p. 593.
2) G. Jones, *Org. React.*, **15**, 204 (1967).
3) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Inc., Menlo Park (1972), p. 646.
4) J. Mathieu and J. Weill-Raynal, "Formation of C-C Bonds," G. Thieme Publishers, Stuttgart (1975), Vol. 2, p. 515.
5) R. Tanikaga, N. Konya, T. Tamura, and A. Kaji, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 825, and references cited therein.
6) R. P. Redman, P. J. Thomas, and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, **1978**, 1135, and references cited therein.
7) R. Tanikaga, Y. Nozaki, T. Tamura, and A. Kaji, *Synthesis*, **1983**, 134.
8) G. Cilento, *Chem. Rev.*, **60**, 147 (1960).
9) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell Univ. Press, (1960), p. 260.
10) Z. Rappoport, *Acc. Chem. Res.*, **14**, 7 (1981).
11) Z. Rappoport and A. Gazit, *J. Org. Chem.*, **51**, 4112 (1986).
12) N. Kunieda, A. Suzuki, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, **54**, 1143 (1981).
13) H. D. Murdoch and D. C. Nonhebel, *J. Chem. Soc.*, **1962**, 2153.
14) J. Nokami, T. Mandai, A. Nishimura, T. Takeda, and S. Wakabayashi, *Tetrahedron Lett.*, **27**, 5109 (1986).
15) M. Sekiya and K. Suzuki, *Chem. Pharm. Bull.*, **18**, 1530 (1970).