

Michael Additions to α,β -Unsaturated Sulphoximides in Two-phase Systems. Kinetic Resolution by Means of Chiral Phase-transfer Catalysts

By Rita Annunziata, Mauro Cinquini, and Stefano Colonna, Centro CNR e Istituto di Chimica Industriale dell'Università, Via Golgi 19, 20133 Milano, Italy

Addition of nucleophiles to α,β -unsaturated sulphoximides is a facile reaction in two-phase systems. The chiral phase-transfer catalyst *N*-benzylquininium chloride is capable of asymmetric selection in the reaction of the α,β -unsaturated sulphoximides with thiols, enantiomeric excesses being in the range 1–13%.

THE Michael-type reaction of α,β -unsaturated sulphur derivatives has been reported in the case of sulphones,¹ sulphoxides,² and sulphimides.³ We have investigated the hitherto unknown addition to vinylic sulphoximides both in two-phase systems and homogeneous medium.

RESULTS AND DISCUSSION

α,β -Unsaturated sulphoximides have unique properties: the ethylenic system is strongly activated, as in the case of the sulphonyl group, towards nucleophilic addition; moreover, the presence of a chiral sulphur atom could lead in principle to the occurrence of asymmetric induction and/or kinetic resolution.

S-*p*-Tolyl-*S*-vinyl-*N*-phthalimidosulphoximide (1) was treated in CH_2Cl_2 at room temperature with various Michael donors, namely nitroethane (2), methyl 3-oxoindan-2-carboxylate (3), ethyl 2-oxocyclohexane-1-carboxylate (4), and thiophenol (5).

As basic catalysts we used (i) a free chiral amine [quinine (14)]⁴ in homogeneous medium; (ii) ammonium or phosphonium fluorides, prepared *in situ* from a large excess of potassium fluoride and the corresponding 'onium bromide or chloride [hexadecyltributylphosphonium bromide (15), *N*-benzylquininium chloride (QUIBEC) (16),^{4,5} and *N*-dodecyl-*N*-methylephedrinium bromide (17)^{4,5}]; and (iii) tetrabutylammonium fluoride bound to silica gel (18).⁶ For the sake of comparison we also examined the reaction of *p*-tolyl vinyl sulphone (10) and of the corresponding sulphoxide (11) with (5).

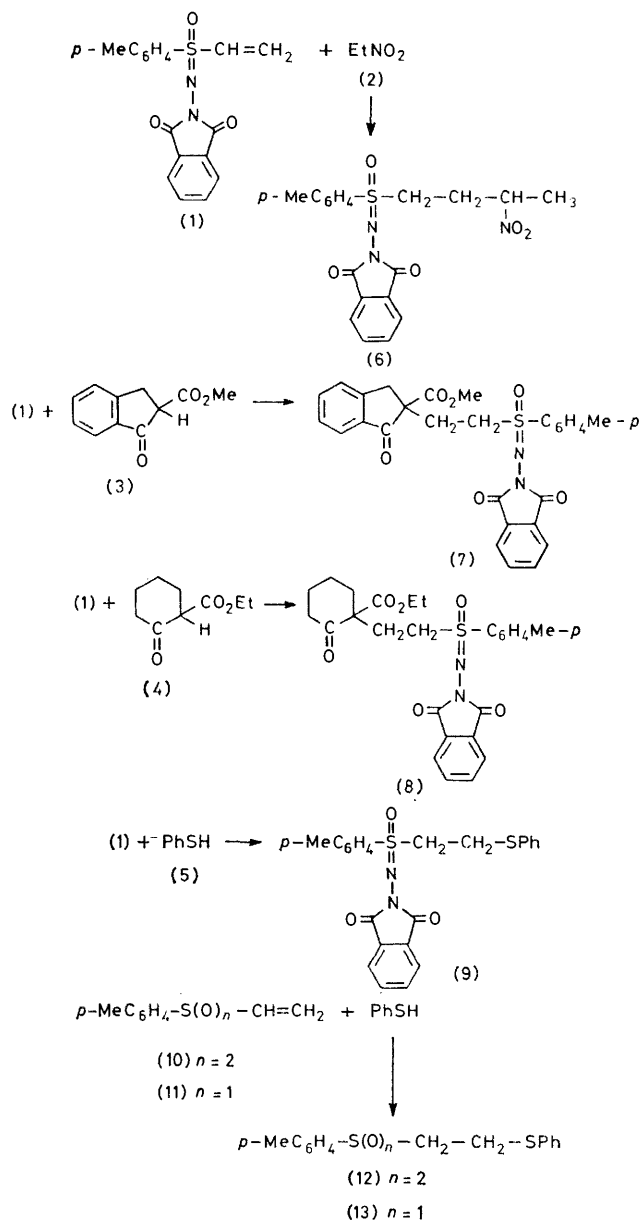
From the results (see Table 1), it appears that the

TABLE 1
Michael addition to (1), (15), and (16) in methylene chloride at room temperature

Substrate	Reagent	Catalyst *	Time/h	Product	Yield (%)
(1)	(2)	(16)	4	(6)	100
(1)	(2)	(17)	4	(6)	100
(1)	(2)	(14)	504	(6)	70
(1)	(3)	(15)	2	(7)	100
(1)	(3)	(16)	2	(7)	100
(1)	(3)	(14)	336	(7)	62
(1)	(4)	(16)	134	(8)	34
(1)	(4)	(14)	336		
(1)	(4)	(18)	144	(8)	30
(1)	(5)	(16)	0.5	(9)	100
(1)	(5)	(14)	0.5	(9)	100
(10)	(5)	(16)	0.5	(12)	75
(10)	(5)	(16)	2	(12)	100
(10)	(5)	(14)	3.5	(12)	66
(11)	(5)	(16)	192	(13)	10
(11)	(5)	(14)	192	(13)	80

* Concentration 0.025 mol equiv.

reactivity of the sulphoximide (1) is much higher than that of sulphoxide (11) and is similar to that of the



sulphone (10), in agreement with the electronic effect of the activating sulphur moiety.

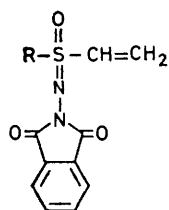
In the case of *S*-*p*-tolyl-*S*-vinyl-*N*-phthalimidosulph-

oximide and of *p*-tolyl vinyl sulphone the reaction in homogeneous medium is much slower than in the two-phase systems, especially with carbanions as donors. It is puzzling that the sulphoxide (11) reacts faster with thiophenol (5) when quinine (14) is used as a catalyst instead of QUIBEC-KF.

Potassium fluoride bound to silica, and 'onium fluorides derived from (15)—(17) give practically the same conversions into the Michael adducts. Moreover, the reaction rate of sulphoximide (1) is about the same when phosphonium (15) or ammonium salts [(16) and (17)] are used. No asymmetric induction was found when Michael additions to sulphoximide (1) were carried out in the presence of the chiral phase-transfer catalysts (16) and (17). Only in the reaction of (1) with nitroethane in the presence of quinine was an optically active nitro-derivative (6) obtained as a diastereoisomeric mixture, $[\alpha]_D^{25} +5.4^\circ$ (CHCl₃); the recovered starting sulphoximide (1) was also optically active, $[\alpha]_D^{25} +2.04$ (CHCl₃), the enantiomeric excess (e.e.) being 7%,^{7,8} clearly showing that asymmetric selection has occurred. The results as a whole indicate that addition of nucleophiles to α,β -unsaturated sulphoximides is a facile reaction in a two-phase system, and thus constitutes a powerful tool for the formation, *inter alia*, of C-C and C-S bonds.

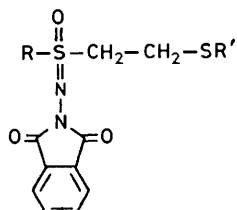
A further objective in this investigation was to examine the possibility of kinetic resolution of sulphoximides in a two-phase system in the presence of chiral catalysts. Although much effort has recently been devoted to the study of asymmetric induction under phase-transfer conditions,^{9,10} only two examples of kinetic resolution induced by optically active 'onium salts have been reported, namely the ring closure of racemic halogenohydrins¹⁰ and the formation of 2-phthalimido-esters.¹¹

Reactions of *S-p*-tolyl- (1), *S*-benzyl- (19), and *S*- β -naphthyl- (20) *S*-vinyl-*N*-phthalimidosulphoximides



(19) R = PhCH₂

(20) R = β -naphthyl



(21) R = *p*-MeC₆H₄, R' = PhCH₂

(22) R = *p*-MeC₆H₄, R' = β -naphthyl

(23) R = PhCH₂, R' = Ph

(24) R = PhCH₂, R' = PhCH₂

(25) R = PhCH₂, R' = β -naphthyl

(26) R = β -naphthyl, R' = Ph

(27) R = β -naphthyl, R' = PhCH₂

(28) R = β -naphthyl, R' = β -naphthyl

with a deficiency of thiophenol (5), phenylmethanethiol (29), or β -naphthylthiol (30) in toluene in the presence of QUIBEC and KF resulted in the recovery of optically active starting sulphoximide (see Table 2).

Enantiomeric excesses, in the range 1—13%, were

TABLE 2

Kinetic resolution of sulphoximides (1), (19), and (20) *via* addition of thiols in the presence of the chiral catalyst (16) (0.025 mol equiv.)

Sulphoximide	Thiol ^a	<i>T</i> (°C)	Adduct	$[\alpha]_D^{25}$ ^b (°)	$[\alpha]_D^{25}$ ^b (°)	Recovered sulphoximide Enantiomeric excess
(1)	(5)	0	(9)	+13.1	+2.6	9
(1)	(29)	0	(21)	+1.1	+1.0	3
(1)	(30)	0	(22)	+17.2	+3.8	13
(19)	(5)	-78	(23)	+0.5	-3.2	10
(19)	(5)	0	(23)	+0.5	-3.2	10
(19)	(29)	0	(24)	+0.5	-2.3	7
(19)	(30)	0	(25)	+0.3	-1.2	4
(20)	(5)	-78	(26)	+15.5	+1.2	5
(20)	(5)	0	(26)	+15.5	+1.2	5
(20)	(5)	25	(26)	+8.2	+0.5	2
(20)	(29)	25	(27)	+3.6	+0.3	1
(20)	(30)	25	(28)	+12.5	+1.5	5
(20)	(30)	0	(28)	+15.2	+2.1	8

^a All the reactions were carried on for 1 h with 0.5 mol equiv. of thiol. ^b In CHCl₃.

practically the same when the reaction were carried at 0 or -78 °C, and decreased at higher temperatures. They depend upon the nature of the substrate and of the thiol used. Although the optical purities of the resolved sulphoximides are rather low, they are of the same order of magnitude as that (6%) reported by Wynberg¹⁰ in epoxide formation. It must be pointed out that they are achieved by using only catalytic amounts (0.025 mol equiv.) of an easily accessible chiral 'onium salt.

EXPERIMENTAL

General.—¹H N.m.r. spectra were recorded with a Varian A-60 and/or a Varian HA 100 instrument; i.r. spectra were recorded on a Perkin-Elmer 377 spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in chloroform as solvent. Quinine, $[\alpha]_{546}^{20} -154^\circ$ (*c* 1.5 in CHCl₃) and hexadecyltributylphosphonium bromide were commercial products. (—)-(1*R*,2*S*)-*N*-Dodecyl-*N*-methyl-ephedrinium bromide,¹² (—)-benzylquininium chloride,¹² *N*-phthalimido-*S-p*-tolyl-*S*-vinylsulphoximide,⁷ *S*-benzyl-*N*-phthalimido-*S*-vinylsulphoximide,⁷ *S*- β -naphthyl-*N*-phthalimido-*S*-vinylsulphoximide,^{7,*} and *p*-tolyl vinyl sulphoxide⁷ were prepared as previously reported. *p*-Tolyl vinyl sulphone,¹³ tetrabutylammonium fluoride supported on silica,⁶ and methyl 3-oxoindan-2-carboxylate¹⁴ were obtained by literature methods.

Addition of Michael Donors to *N*-Phthalimidosulphoximide (1), Sulphoxide (11), and Sulphone (10). **General Procedure.**—(a) *In homogeneous medium.* The Michael donor (1 mmol) was added at room temperature to a stirred solution of the unsaturated sulphur compound (1 mmol) and (—)-quinine (0.025 mmol) in anhydrous methylene chloride (10 ml). The mixture was stirred for the appropriate time (see Table 1), and poured into water. The organic layer was separated off, washed with dilute hydrochloric acid, dried over anhydrous sodium sulphate, and evaporated. The crude mixture was separated by column chromatography (SiO₂, diethyl ether, then methylene chloride). Physical properties and analytical data for the Michael adducts are reported in Table 3.

* This product was erroneously reported⁷ as *S*- α -naphthyl-*N*-phthalimido-*S*-vinylsulphoximide.

TABLE 3

Physical properties and analytical data of the Michael adducts

Adduct	M.p. (°C)	Formula	Analysis (%)					
			Found			Required		
			C	H	N	C	H	N
(6) ^a	52—54	C ₁₉ H ₁₉ N ₃ O ₃ S	56.6	4.9	10.5	56.8	4.8	10.5
(7) ^a	172—175	C ₂₈ H ₂₄ N ₂ O ₆ S	65.0	4.6	5.3	65.1	4.7	5.4
(8) ^a	42—45	C ₂₆ H ₂₈ N ₂ O ₆ S	62.8	5.7	5.5	62.9	5.7	5.6
(9) ^a	167	C ₂₅ H ₂₆ N ₂ O ₃ S ₂	63.3	4.6	6.4	63.3	4.6	6.4
(12)	139—140 ^b	C ₁₅ H ₁₆ O ₃ S ₂						
(13)	66—68	C ₁₅ H ₁₆ O ₃ S ₂	65.1	5.7		65.2	5.8	
(21)	99—101	C ₂₄ H ₂₂ N ₂ O ₃ S ₂	64.0	4.9	6.0	64.0	4.9	6.2
(22)	125—127	C ₂₇ H ₂₂ N ₂ O ₃ S ₂	66.4	4.6	5.7	66.6	4.6	5.8
(23)	38—40	C ₂₃ H ₂₀ N ₂ O ₃ S ₂	63.2	4.4	6.5	63.3	4.6	6.4
(24)	117	C ₂₄ H ₂₂ N ₂ O ₃ S ₂	63.9	5.0	6.2	64.0	4.9	6.2
(25)	54—56	C ₂₇ H ₂₂ N ₂ O ₃ S ₂	66.6	4.6	5.8	66.6	4.6	5.8
(26)	50	C ₂₆ H ₂₀ N ₂ O ₃ S ₂	65.9	4.4	5.9	66.1	4.3	5.9
(27)	125—127	C ₂₇ H ₂₂ N ₂ O ₃ S ₂	66.6	4.6	5.8	66.6	4.6	5.8
(28)	58—60	C ₃₀ H ₂₂ N ₂ O ₃ S ₂	68.8	4.3	5.4	68.95	4.25	5.4

^a Mixture of diastereoisomers. ^b Lit.,¹⁵ m.p. 139—140 °C.

(b) *In a two-phase system.* The Michael donor (1 mmol) was added at room temperature to a stirred mixture of the unsaturated sulphur compound (1 mmol) and catalyst [either anhydrous potassium fluoride (1.5 mmol) and 'onium salt (15)—(17) (0.025 mmol) or tetrabutylammonium fluoride (0.025 mmol) supported on silica] in anhydrous methylene chloride (10 ml). The mixture was worked up as described in (a).

Kinetic Resolution of Sulphoximides (1), (19), and (20).—Kinetic resolutions of sulphoximides were carried out with 0.5 mol equiv. of thiols (5), (29), and (30) in the presence of QUIBEC (0.025 mol equiv.) under the conditions described above. Reaction temperature, optical rotations of the

adducts and of the recovered sulphoximides, and enantiomeric excesses of the latter are reported in Table 2. Particular care must be taken in the separation of the adducts from the recovered sulphoximides: in blank experiments it was shown that enantiomeric enrichment occurs during separation by column chromatography on silica. Physical properties and analytical data of the adducts are reported in Table 3.

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