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ALKYLATION OF SULPHINIC ACIDS BY O-ALKYLISOUREAS: O-VERSUS S-REACTIVITY AND ASYMMETRIC SYNTHESIS OF ALKYL SULPHINATES#

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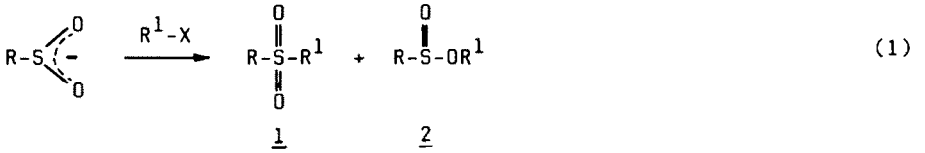
Abstract - The reaction of O-alkylisoureas with sulphinic acids was found to produce the corresponding sulphones and sulphinates, the latter being predominantly formed. The sulphinate to sulphone ratio is strongly influenced by the kind of alkyl groups in the O-alkylisourea and appeared to be also dependent on the solvent used. A few optically active sulphinates (e.e. up to 8.1%) were prepared in the reaction between benzenesulphinic acid and a series of O-alkylisoureas bearing optically active substituents at the nitrogen atom. A possible reaction mechanism is discussed.

INTRODUCTION

Anions of sulphinic acids are ambident and may undergo alkylation either on the sulphur or on the oxygen atom to produce sulphones 1 or sulphinates 2, respectively:



(1)

For many years it has been thought that the alkylation proceeds only on the sulphur atom, the only exception being the reaction of silver sulphinates with alkyl halides[2,3]. The results of later studies revealed, however, that regardless of the nature of the countercation, sulphinate anions may undergo alkylation on both nucleophilic centers. Thus, Michalski et.al.[4] investigated the reaction of alkyl alkanethiosulphonates with trialkyl phosphites and postulated a transient formation of a sulphinate anion which was alkylated by an alkoxyphosphonium salt producing both alkyl sulphinate and sulphone. Kobayashi[5] proved univocally that alkylation by means of highly reactive alkylating agents, such as oxonium salts, results in the formation of sulphinates as major products. Later on, Meek and Fowler[6] found that the use of "hard" alkylating agents, in the HSAB sense, and highly polar solvents leads almost exclusively to the products of O-alkylation. Recently, Kobayashi and Toriyabe[7] have reported that the contribution of O-alkylation may be increased by addition of crown ethers or cryptands, but only in the case when "hard" alkylating agents are used.

In a search of more versatile reagents for the alkylation of sulphinic acids we turned our attention to O-alkylisoureas 3. These compounds are known to be

#Dedicated to Professor Günther Snatzke on the occasion of his 60th birthday

effective alkylating agents and enable one to introduce a broad variety of alkyl groups since they are easily available from carbodiimides 4 and the corresponding alcohols[8]:

$$R^1N{=}C{=}NR^1 \xrightarrow{ROH/CuCl} R^1NH\text{-}\underset{\displaystyle OR}{\underset{|}{C}}{=}NR^1 \qquad (2)$$

4 3

Recently, we have reported that the alkylation of thiocarboxylic and phosphorothioic acids by O-alkylisoureas 3 resulted in the predominant formation of thioloesters[9]

In this paper we report the results of our studies on alkylation of sulphinic acids by O-alkylisoureas which results in the predominant formation of sulphinates. Moreover, we describe also a new type of asymmetric synthesis of optically active sulphinates based on this reaction.

RESULTS AND DISCUSSION

Alkylation of Benzenesulphinic Acid with O-Alkylisoureas. In the first stage of this work, benzenesulphinic acid 5, as a typical representative of sulphinic acids, was reacted with several O-alkyl-N,N'-dicyclohexylisoureas 3a-e in various solvents. The sulphinate (2) to sulphone (1) ratio was established on the basis of ^{1}H-NMR spectra of the crude reaction mixture. The overall yield of the alkylation reaction was in the range between 60 and 90%. In the case of secondary alkyl groups the reaction required more drastic conditions which caused decomposition of benzenesulphinic acid and lowered the yields of alkylation products. The pure sulphinates 2, isolated by means of preparative t.l.c., were obtained in 30-70% yield. The results are collected in Table 1.

$$H_{11}C_6N{=}\underset{\displaystyle OR}{\underset{|}{C}}\text{-}NHC_6H_{11} + PhS\text{-}\underset{\displaystyle O}{\underset{\|}{S}}\text{-}OH \longrightarrow PhS\text{-}\underset{\displaystyle O}{\underset{\|}{S}}\text{-}OR + Ph\underset{\displaystyle O}{\overset{\displaystyle O}{\overset{\|}{S}}}R + H_{11}C_6NH\underset{\displaystyle O}{\underset{\|}{C}}NHC_6H_{11} \qquad (3)$$

3a-e 5 2 1

An inspection of Table 1 reveals that sulphinates 2, i.e. the products of O-alkylation, predominate in all cases. At first sight, it is difficult to correlate the influence of the solvent used on the product ratio. Thus, on the one hand, O-alkylation is only slightly more preferred in polar THF as compared with benzene and tetrachloromethane (compare entry 2 with entries 1 and 4 and entry 9 with entry 10). On the other hand, on passing to highly polar nitromethane contribution of O-alkylation decreases considerably (entry 3). A similar decrease is observed for dioxane (entry 5) which is known to be a strongly complexing solvent. It should be stressed, however, that there is a clear relationship between the O/S selectivity and the nature of the alkyl group R in 3. Thus, in the case of primary alkyl groups, contribution of O-alkylation varies from 61 to 91% (in THF), being lowest for the benzyl group (entry 9) and highest for the ethyl group (entry 8). Sulphinates become practically the only products in the case of secondary alkyl groups, independent of the solvent used (entries 11-15).

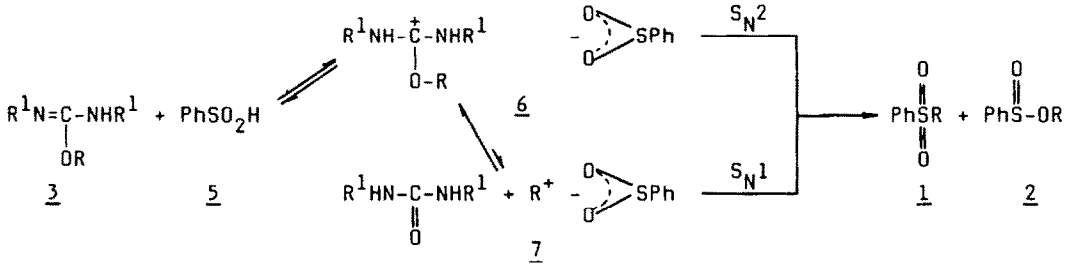
Mechanistic Considerations. The results presented above may be rationalized in terms of the mechanism which is shown in Scheme I. The reaction is believed to proceed in two steps. The initial fast and reversible step involves protonation of O-alkylisourea 3 by sulphinic acid 5, leading to a salt 6. The intermediacy of 6 can account for two facts observed. The first is the predominant formation of sulphinates 2 because the cation in 6 may be considered as a hard electrophilic reagent as compared with alkyl halides. The second one is the unexpected decrease of the percentage of O-alkylation in strongly polar or complexing solvents. This may be explained by assuming complexation and hence "softening" of the protonated O-alkyl isourea. The latter observation is consistent with the results of Kobayashi

TABLE 1. Product ratio in the alkylation of benzenesulphinic acid 5 with O-alkylisoureas 3

Entry	O-alkylisourea	R	Solvent	Product ratio sulphinate 2	sulphone 1
1.	3a	Me	benzene	70	30
2.	3a	Me	THF	75	25
3.	3a	Me	$MeNO_2$	57	43
4.	3a	Me	CCl_4	70	30
5.	3a	Me	dioxane	66	34
6.	3b	Et	CCl_4	75	25
7.	3b	Et	benzene	73	27
8.	3b	Et	THF	90	10
9.	3c	CH_2Ph	THF	61	39
10.	3c	CH_2Ph	CCl_4	56	44
11.	3d	i-Pr	CCl_4	~100	trace(t.l.c)
12.	3d	i-Pr	THF	~100	trace(t.l.c)
13.	3e	sec-Bu	CCl_4	100	0
14.	3e	sec-Bu	THF	100	0
15.	3f	2-Hexyl	THF	100	0

and Toriyabe. They have found that when alkyl oxosulphonium salts were applied as alkylating agents, the use of polar aprotic solvents, such as DMF, resulted in a decrease of the contribution of O-alkylation[7].

Scheme I

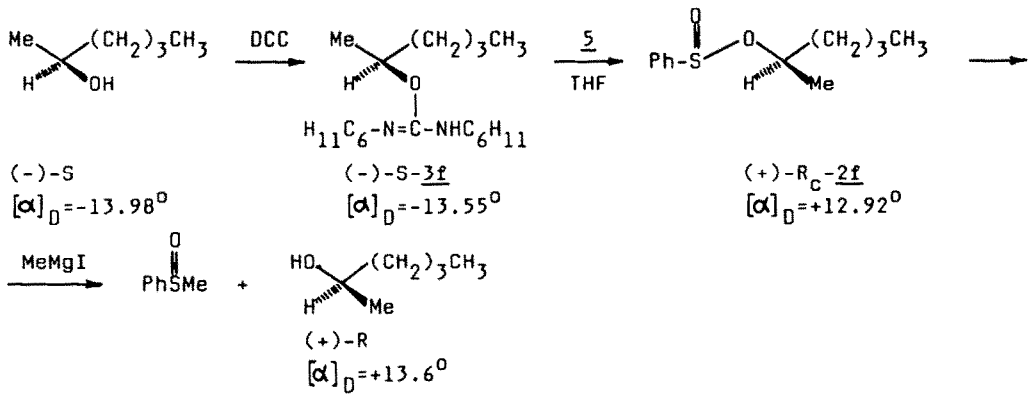


The second step of the proposed mechanism consists in a nucleophilic attack of the sulphinate anion on the carbon atom of the O-alkyl group in the protonated O-alkylisourea 6. This attack should, in principle, take place according to the S_N2 mechanism, the urea being a good leaving group. However, when the S_N2 attack is difficult due to steric hindrance, an alternative mechanism should also be considered which would involve the formation of a carbenium ion 7. It is of interest to point out that some evidence for the formation of carbenium ions in the alkylation of phosphoric acids by O-allyl and O-benzylisoureas was obtained by Khorana[10]. The carbenium ion involvement in the alkylation by O-tert-butylisoureas was also suggested and discussed by Mathias in his review[8]. The higher contribution of O--alkylation of sulphinate anion in the case of secondary alkyl groups might speak in favour of this assumption. However, the reaction of (-)-O-2-hexyl-N,N'-dicyclohexylisourea (3f), obtained from (-)-S-2-hexanol and DCC, with benzenesulphinic acid (5) resulted in the formation of (+)-R_C-2-hexyl benzenesulphinate which,after the reaction with methylmagnesium iodide, gave (+)-R-2-hexanol with optical purity of about 98% (SchemeII).

This indicates that the reaction between 3f and 5 proceeds at least with 99% inversion at C-2 in the alkyl group. Such a result strongly speaks against the

formation of the carbenium ion 7 as the reactive intermediate in the reaction discussed.

Scheme II



Another factor which should be taken into account is the steric effect exerted by the large electrophile. Due to this fact the alkyl groups in the cation of 6 may be more susceptible to nucleophilic attack by the oxygen atoms than by the sulphur atom in the ambident sulphinate anion.

Asymmetric Synthesis of Sulphinates. Optically active sulphinates are important precursors of chiral sulphinyl compounds especially sulphoxides which are common substrates in modern organic synthesis[11]. In a recent report from our laboratory we described the asymmetric synthesis of optically active sulphinates with e.e. up to 10% by condensation of sulphinic acids with alcohols by means of optically active carbodiimides 4[12]. On the basis of these results it was expected that the use of optically active O-alkylisoureas for alkylation of sulphinic acids might also result in the formation of optically active sulphinates. Therefore, a series of reactions between benzenesulphinic acid 5 and a number of O-alkylisoureas (3g-m) bearing optically active substituents at the nitrogen atoms was carried out. As a result of the above reactions, we have obtained the desired optically active sulphinates 2, which were isolated and purified by preparative t.l.c. The results are collected in Table 2.

TABLE 2. Asymmetric synthesis of optically active sulphinates

Entry	O-alkyl isourea	Solvent	R	Sulphinate				
				Symbol	Yield [%]	$[\alpha]_D^{20}$ [deg]	e.e. [%]	Abs. conf.
1.	**3g**	benzene	Me	**2a**	55	+ 2.2[a]	1.2[d]	R
2.	**3g**	MeCN	Me	**2a**	39	0[a]	0	-
3.	**3h**	benzene	Me	**2a**	35	+ 8.1[b]	4.3[d]	R
4.	**3i**	benzene	$PhCH_2$	**2c**	59	- 5.4[b]	3.6[e]	S
5.	**3k**	benzene	i-Pr	**2d**	62	+16.4[b]	7[d]	R
6.	**3l**	benzene	s-Bu	**2e**	65	+ 6.8[b,c]	8.1[c,e]	R
7.	**3m**	benzene	i-Bu	**2g**	52	+12.6[b]	6.2[e]	R

[a]Measured in EtOH; [b]measured in benzene; [c]mixture of diastereoisomers; e.e. refers only to chirality on sulphur; [d]based on the values reported in Ref.12; [e]e.e.values and absolute configuration of 2c, 2e and 2g were determined chemically via their conversion into the known methyl phenyl sulphoxide[13] assuming that the reaction with methylmagnesium iodide proceeds with full inversion of configuration at sulphur

$$\overset{*}{R}^1NH\text{-}\underset{\underset{OR}{|}}{C}\text{=}NH^2 + PhSO_2H \longrightarrow Ph\overset{*}{S}\text{-}OR + \overset{*}{R}^1NH\text{-}\underset{\underset{O}{\|}}{C}\text{-}NHR^2 \qquad (4)$$

3 5 2

g: $\overset{*}{R}^1$=myrtanyl; R^2=Ph; R=Me

h÷m: $\overset{*}{R}^1$=R^2=Ph$\overset{*}{C}$HMe; R - given in Table 2

As can be seen from Table 2, the optical purities of the sulphinates obtained appeared to be low and therefore the above synthesis has no preparative value.

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were measured with a Bruker MSL 300 instrument. Melting and boiling points are uncorrected.

O-Alkyl N,N'-dicyclohexylisoureas were obtained from DCC and the corresponding alcohols in the presence of catalytic amounts of CuCl, according to the standard procedure[8]. O-Alkylisoureas 3a-d have been described previously[14,15].

O-sec-Butyl-N,N'-dicyclohexylisourea (3e). Yield 74%; bp 97°C at 0.01 Torr. ^1H NMR δ($CDCl_3$): 0.88 (t,3H); 1.0÷2.0 (m,25H); 2.76 (m,1H); 3.34 (m,1H); 4.81 (sext.,1H). ^{13}C NMR δ($CDCl_3$): 9.56, 19.06, 25.09, 25.18, 25.82, 26.13, 28.90, 34.46, 34.58, 50.27, 54.71, 70.96, 150.66. Anal.Calcd for $C_{17}H_{32}N_2O$: C, 72.81; H, 11.50; N, 9.99. Found.: C, 72.87; H, 11.48; N, 9.81.

O-2-Hexyl-N,N'-dicyclohexylisourea (3f). It was obtained from DCC and (-)-2-hexanol ($[\alpha]_D$=-13.98°, c 7.4, benzene). Yield 76%, bp. 109°C at 0.01 Torr. $[\alpha]_D$=-13.55° (c 7.6, hexane). ^1H NMR δ($CDCl_3$): 0.88 (t, 3H); 1.0÷2.0 (m,29H); 2.77 (m,1H); 3.35 (m,1H); 4.88 (sext.,1H). ^{13}C NMR δ($CDCl_3$): 14.08, 19.70, 22.78, 25.18, 25.84, 26.15, 27.56, 34.46, 34.60, 35.86, 50.21, 54.71, 69.91, 150.63 ppm. Anal.Calcd for $C_{19}H_{36}N_2O$: C, 73.97; H, 11.76; N, 9.08. Found: C, 73.68; H, 11.70; N, 8.74.

(-)-N-Myrtanyl-N'-phenylcarbodiimide. Optically active myrtanylamine, $[\alpha]_D$=-30.5°, neat (Aldrich) (5.95 g, 0.05 mol) and phenyl isocyanate (7.65 g, 0.05 mol) were mixed in ethanol solution (25 ml) and kept at room temperature overnight. After evaporation of ethanol, the crude N-myrtanyl-N'-phenylurea formed was dissolved in methylene chloride (40 ml) containing CCl_4 (7.8 g, 0.05 mol) and triethylamine (5.05 g, 0.05 mol). To this solution triphenylphosphine (13.1 g, 0.05 mol) was added and the mixture stirred and refluxed for 5 h. After evaporation of CH_2Cl_2, the solid residue was extracted with pentane (4 x 30 ml). The extract was evaporated and the residue was distilled to give the optically active carbodiimide. Yield 6.4 g (50%), bp 126÷130° at 0.3 Torr. $[\alpha]_D$=-8.7° (c,3.9,$CHCl_3$). ^1H NMR δ($CDCl_3$): 0.925 (s,3H); 1.125 (s,3H); 1.375÷2.50 (m,9H); 3.325 (d,2H,J=8 Hz); 6.875÷7.375 (m,5H). Anal.Calcd for $C_{17}H_{22}N_2$: C, 80.31; H, 8.66; N, 11.02. Found: C, 80.22; H, 8.45; N, 11.10.

O-Methyl-N-myrtanyl-N'-phenylisourea (3g). It was obtained from equimolar amounts of N-myrtanyl-N'-phenylcarbodiimide and methanol according to the standard procedure[8]. Yield 89%, bp 135° at 0.6 Torr. $[\alpha]_D$=+17.18° (c, 1.92, $CHCl_3$). ^1H NMR δ($CDCl_3$) 0.9 (s,3H); 1.1 (s,3H); 1.375÷2.50 (m,9H); 2.75÷3.225 (m,2H); 3.79 (s,3H); 6.65÷÷7.40 (m,5H). Anal.Calcd for $C_{18}H_{26}N_2O$: C, 75.52; H, 9.09; N, 9.79. Found: C,75.35; H, 8.95; N, 9.82.

O-Alkyl-N,N'-di-α-phenylethylisoureas 3h-m were synthesized from optically active N,N'-di-α-phenylethylcarbodiimide, $[\alpha]_D$=+26.6° (c,2.2 hexane), obtained from (+)-(R)-α-phenylethylamine, $[\alpha]_D$=+30° (c,10 EtOH) according to the procedure given in Ref.[12], and appropriate alcohols and purified by distillation in vacuo.

O-Methyl-N,N'-di-α-phenylethylisourea (3h). Yield 58%. $[\alpha]_D$=-134.4° (c, 2.5, hexane) ^1H NMR δ($CDCl_3$): 1.37 (d,3H); 1.46 (d,3H); 3.64 (s,3H); 4.23 (m,1H); 4.65 (m,1H); 6.7÷7.5 (m, 10H). ^{13}C NMR δ($CDCl_3$): 23.86, 26.61, 51.05, 52.02, 55.32, 125.32, 126.42, 126.53, 128.26, 128.50, 145.13, 147.48, 152.65. Anal.Calcd. for $C_{18}H_{22}N_2O$: C, 76.56; H 7.85; N, 9.92. Found: C, 76.33; H, 7.90; N, 10.16.

O-Benzyl-N,N'-di-α-phenylethylisourea (3i). Yield 66%. $[\alpha]_D$=-140.3° (c, 1.8,hexane) ^1H NMR δ($CDCl_3$): 1.29 (d,3H); 1.47 (d,3H); 4.25 (q,1H); 4.68 (q,1H); 5.08 and 5.14 (AB,2H); 6.7÷6.72 (m,2H); 7.0÷7.4 (m,13H). ^{13}C NMR δ($CDCl_3$): 24.58, 27.46, 51.93, 56.07, 67.70, 126.05, 127.17, 127.86, 128.23, 128.98, 138.46, 146.01, 148.01, 152.41. Anal.Calcd. dor $C_{24}H_{26}H_2O$: C, 80.41; H, 7.31; N, 7.81 Found: C, 80.27; H, 7.33; N, 7.76.

O-Isopropyl-N,N'-α-phenylethylisourea (3k). Yield 78%. $[\alpha]_D$=-143.8° (c 2.9, hexane). ^1H NMR δ($CDCl_3$): 0.85 (d,3H); 1.18 (d,3H); 1.2÷1.5 (m,6H); 4.22 (m,1H); 4.60 (m,1H); 5.1 (sept., 1H); 6.72 (br.s,2H); 7.05÷7.45 (m,8H). ^{13}C NMR δ($CDCl_3$): 21.56, 21.94, 23.58, 26.79, 51.24, 55.33, 67.33, 125.49, 126.38, 128.09, 128.39, 145.60, 147.80, 151.41. Anal.Calcd. dor $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.02. Found.: C, 77.30; H, 8.60; N, 9.30.

O-sec-Butyl-N,N'-di-α-phenylethylisourea (3l). Yield 54% (mixture of diastereoisomers). $[\alpha]_D$=-150.9° (c,1.8, hexane). ^{1}H NMR δ(CDCl$_3$): 0.53 and 0.89 (dt,3H); 0.082 and 1.19 (dd,3H); 1.2÷1.6 (m,8H); 4.26 (m,1H); 4.60 (m,1H); 4.87 (m,1H); 6.65÷6.80 (m,2H); 7.0÷7.45 (m,8H). ^{13}C NMR δ(CDCl$_3$): 9.09, 9.56, 18.77, 19.27, 23.79, 26.90, 28.66, 28.77, 51.26, 55.29, 71.87, 125.49, 126.39, 128.33, 145.23, 147.68, 152.42. Anal.Calcd. for $C_{21}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.63. Found: C, 77.50; H, 8.69; N, 8.63.

O-Isobutyl-N,N'-di-α-phenylethylisourea (3m). Yield 66%. $[\alpha]_D$=-150.2° (c, 2.5, hexane). ^{1}H NMR δ(CDCl$_3$): 0.75 (d,3H); 0.89 (d,3H); 1.2÷1.6 (m,6H); 1.77 (nonet, 1H); 3.81 (d,2H); 4.23 (m,1H); 4.65 (m,1H); 6.65÷6.85 (m,2H); 7.0÷7.45 (m,8H) ^{13}C NMR δ(CDCl$_3$): 19.27, 19.32, 24.16, 26.97, 28.07. 51.47, 55.49, 71.84, 126.6 (broad), 128.47, 125.10, 147.50, 152.57. Anal.Calcd for $C_{21}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.63. Found: C, 77.55; H, 8.84; N, 8.68.

Reaction of O-alkylisoureas (3) with Benzenesulphinic Acid (5).General Procedure. A solution of equimolar amounts of an O-alkylisourea 3 and benzenesulphinic acid 5 in a proper solvent was stirred at room temperature for 24 h (for 3g-m) or refluxed for 0.5-4 h (for other O-alkylisoureas). The urea which separated was filtered off and the filtrate evaporated. Ether was added and the second crop of urea was filtered off. Ether was removed and ^{1}H NMR spectra of the residue were measured to establish the product ratio. Sulphinates 2 and sulphones 1 were separated and purified by preparative t.l.c. using hexane: ether (1:1) as an eluent. The results are collected in Tables 1 and 2.

Sulphinates 2a-d and 2g were described previously (2a,2c and 2g - Ref.12; 2b and 2d - Ref.16). Structure of sulphinates 2e and 2f was supported by ^{1}H NMR spectra and elemental analysis (%,C,H,S ± 0.3%).

Sec-Butyl Benzenesulphinate (2e): ^{1}H NMR δ(CDCl$_3$): 0.74 (t,3H,J=7.4 Hz); 1.19 (d, 3H,J=6.3 Hz); 1.4-1.7 (m,2H), 4.52 (sx,1H,J=6.3 Hz); 7.4-8.0 (m,5H).

2-Hexyl Benzenesulphinate (2f): ^{1}H NMR δ(CDCl$_3$): 0.7÷1.19 (m,12H); 4.64 (sx,1H); 7.4-8.1 (m,5H).

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