Versatile Synthesis of Sulphamate Esters by Phase-transfer Methods

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The syntheses of sulphamate esters of the general types $R^1R^2NSO_3R^3$, $RNHSO_3R^3$, and $H_2NSO_3R^3$, where R^3 may be aliphatic or aromatic, have been achieved in good yield by reaction of the appropriate sulphamoyl chlorides with alcohols and phenols under mild phase-transfer conditions. The present methods have led to generally higher yields, and to shorter reaction times and lower reaction temperatures than were hitherto found necessary. The prior preparation of the alkoxide has also been obviated. Some esters have been rearranged to the isomeric betaines.

THE synthesis of sulphamate esters has frequently been achieved by reaction (1) with or without the appropriate

$$R^1R^2NSO_2Cl + R^3OH \longrightarrow R^1R^2NSO_3R^3 \quad (1)$$

alkoxide, R^3O^-.[1-8] However, in some instances, yields are low,[1] or are not reported [3,4,6,8] (perhaps because, at least in one case, the work was mechanistically orientated [8]), or the rearranged or betaine form of the ester, $R^1R^2R^3NSO_3$, has been isolated.[5] Furthermore, alkoxides where used are troublesome to prepare and handle and sometimes the formation of the ester involves the use of reflux temperatures or long reaction periods. Other methods, while frequently giving good yields, appear to be somewhat limited as to the type and range of esters that can be prepared [9-12] and involve the preparation of special reagents, *e.g.* azides,[9] chlorosulphonyl isocyanates,[10] sulphamides,[11] or may involve long reaction periods and high temperatures.[12]

In the present paper we set out to find a phase-transfer method(s) which would give a practical and convenient synthetic route to sulphamate esters of the general types: $R^1R^2NSO_3R^3$, $RNHSO_3R^3$, and $H_2NSO_3R^3$, where R^3 can be aliphatic or aromatic.

EXPERIMENTAL

Materials.—*N,N*-Dimethylsulphamoyl chloride (Ralph Emmanuel) was used as obtained. Its i.r. spectrum was identical with that reported by Merian.[13] *N,N*-Diethylsulphamoyl chloride was obtained in 69% yield using the method of Binkley and Degering.[1] Its i.r. spectrum was similar to that of *N,N*-dimethylsulphamoyl chloride and satisfactory C, H, and N analyses were obtained. *N*-Cyclohexylsulphamoyl chloride was prepared by reaction of cyclohexylsulphamic acid with phosphorus pentachloride, yield 60%, b.p. 136—140 °C/0.2 mmHg (lit.,[7] 120 °C/1 mmHg). *N*-t-Butylsulphamoyl chloride, b.p. 97 °C/2 mmHg (lit.,[14] 76—78 °C/0.6 mmHg), was obtained in 39% yield using the method of Kloek and Leschinsky.[14] Sulphamoyl chloride was synthesised from chlorosulphonyl isocyanate in 96% yield, m.p. 38—40 °C (lit.,[15] 40 °C). The quaternary salts used as phase-transfer catalysts were obtained from the usual commercial sources. The alcohols, phenols, and ethyl acetate were laboratory reagent grade and were used as obtained except in the case of method B (see below) when they were first dried. Benzene and dichloromethane were technical grade and were used as obtained but were dried for use in Method B.

G.l.c. Analysis.—In all the ester syntheses the reactions could be monitored by gas chromatography by on-column injection of 1 μl samples from the benzene, dichloromethane, or ethyl acetate layers into a 5% SE-30 Chromosorb AW (100—120 mesh) (temperature 120 °C; N_2 flow rate 60 ml/min) column (5 ft). For example, in experiment 2 (in Table 1) the retention times of $(CH_3)_2NSO_2Cl$ and $(CH_3)_2NSO_3C_2H_5$ were 1.4 and 1.85 min respectively, the sulphamoyl chloride peak decreasing as the ester peak increased. Neither the sulphamoyl chlorides nor the esters in Table 2 could be identified on this column but these reactions could be monitored conveniently on the column (at 80 °C) from the alcohol or phenol peaks.

Method A.—The esters in Table 1 were prepared by this method. The general procedure involved the following: the sulphamoyl chloride (500 mmol) in benzene (2.5 ml) was added to the alcohol/phenol (10 mmol), benzyltriethylammonium chloride (0.2 mmol) (or other quaternary salt, see footnotes to Table 1) in benzene (2.5 ml), and 30% (w/w) NaOH (2.5 ml). Vigorous stirring was maintained using a submersible magnetic stirrer in a 50 °C thermostatically controlled bath. After completion of the reaction (g.l.c.) the organic layer was separated, washed with water until neutral, and dried with anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave the crude ester. Esters were purified by distillation or recrystallization from chloroform.

Method B.—(a) *For esters of type* $RNHSO_3R^3$. The sulphamoyl chloride (5 mmol) in dry CH_2Cl_2 (2.5 ml) was added to the dry alcohol/phenol (10 mmol), tetraoctylammonium bromide (1 mmol) in dry CH_2Cl_2 (5 ml), and anhydrous sodium carbonate (3 g).

(*b*) *For esters of type* $H_2NSO_3R^3$. Sulphamoyl chloride (10 mmol) in dry ethyl acetate (2.5 ml) was added to the dry alcohol/phenol (10 mmol), benzyltriethylammonium chloride (1 mmol) in dry ethyl acetate (5 ml), and anhydrous sodium carbonate (3 g). For both reactions (*a*) and (*b*) vigorous stirring was maintained. At the end of the reaction the solids were filtered off and washed with CH_2Cl_2 or ethyl acetate and the washings added to the filtrate which was then dried. Evaporation of the solvent gave crude ester as product. Esters of the type $H_2NSO_3R^3$ were purified by washing with ethyl acetate and recrystallization from light petroleum (b.p. 40—60 °C); other esters in Table 2 by distillation or recrystallization from diethyl ether.

Rearrangement Runs.—The neat ester (*ca.* 0.5 g) was placed in a small Pyrex reaction tube which was then sealed and placed in a 130 °C thermostatically controlled oil-bath. The progress of the reaction could be roughly monitored by removing the tube from the bath from time to time and

chilling it in ice, then forming the solid betaine which was deposited at the bottom of the tube. Reaction was continued in each case until the contents of the tube solidified completely on chilling and no sign of the liquid ester remained.

I.r. Spectra.—All the compounds in Table 1 gave characteristic i.r. frequencies as follows: N–S 900—960 (for dimethyl esters), 690—730 (for diethyl esters); SO_2, 1 350—1 390, 1 150—1 200 (for dimethyl esters), and 1 205—1 250 cm^{-1} (for diethyl esters). All the esters of type $RNHSO_3R^3$ had characteristic bands as follows: N–H 3 250—3 380; SO_3 1 320—1 380, 1 100—1 190; and N–S 880—980 cm^{-1}. Esters of type $H_2NSO_3R^3$ had the following bands: N–H 3 250—3 370; SO_3 1 350—1 380, 1 100—1 190; and N–S 920—970 cm^{-1}. The four betaines prepared had the following bands: SO_3 1 240—1 300 and 1 060—1 100; and N–S 900—980 and 800 cm^{-1}.

RESULTS AND DISCUSSION

There is one report in the literature of sulphamoylation, under phase-transfer conditions, of the phenolic hydroxy-group of estrogens,[16] and several recent reports of phase-transfer sulphonylation.[17] Method A is a modification of the procedures used in these references. Initially in method A we used a 1 : 1 molar ratio of alcohol and sulphamoyl chloride but, both at 25 and 50 °C, the reaction always gave a mixture of ester and starting halide irrespective of the reaction time. By employing a 2 : 1 ratio instead we were able to achieve generally high yields (see Table 1). Where comparison was possible with yields given in the literature it is seen that the present phase-transfer method gives significantly improved yields. Not surprisingly the tetra-n-butylammonium ion is a better catalyst than the benzyltriethylammonium ion and a good yield of the hindered ester, $Me_2NSO_3Bu^t$, can be obtained with the former catalyst (compare runs 4 and 5, Table 1).[18,19] A significant lowering of the yield occurs, however, if the counteranion is bromide rather than iodide (compare experiments 5 and 6, Table 1).[18] No effort was made in this study to find the 'best' catalysts since the yields are seen to be reasonable and superior to those previously reported.

Method A fails for esters of type $RNHSO_3R^3$. Thus, for example, $C_6H_{11}NHSO_2Cl$ gives an immediate white precipitate of sodium cyclohexylsulphamate under the conditions of Method A. Method B is based on a phase-transfer method previously used for the synthesis of carboxylic acid esters.[20] In Table 2, experiments 1—8, method B(*a*) was employed. Dichloromethane is a superior solvent to benzene when benzyltriethylammonium chloride is used as the catalyst (compare experiments 2, 3, 4, and 5). Interestingly in the syntheses of these types of esters benzyltriethylammonium chloride is as good as tetra-n-butylammonium bromide (compare experiments 2 and 4). The order of catalytic ability is tetra-n-octylammonium bromide > tetra-n-butylammonium bromide > benzyltriethylammonium chloride (compare experiments 1, 5, and 3). In the latter part of Table 2 (experiments 9—13) method B(*b*) was employed. The yields of the esters $H_2NSO_3R_3$ obtained are generally comparable with those obtained by standard methods.

The esters in Tables 1 and 2 were characterized using at least two (and generally more) of the following methods (i) comparison of their i.r. spectra with the spectra reported in the literature for both esters and betaines; [3a,12] (ii) comparison of b.p.s and m.p.s with those given in the literature (see Tables); (iii) independent synthesis of esters, for example, by the method of ref. 2; (iv) rearrangement to betaines (Table 3); and (v) ^{13}C spectra. All the esters and betaines synthesised gave satisfactory microanalysis (C, H and N).

There are many reports in the literature [21] of the ester ⟶ betaine rearrangement which was first observed by Behrend in 1884.[22] The intermolecularity of the rearrangement is well established.[3,23] At one stage it was thought that only small alkyl (methyl and ethyl) groups could be rearranged [3a] but groups such as Ph(Me)CH– and Ph_2CH– have been rearranged onto a dimethylamino-moiety.[5] The last two entries in Table 3 are two further examples of the rearrangement of bulkier groups.

In summary, the present phase-transfer methods for

TABLE 1

Synthesis of sulphamate esters $R^1R^2NSO_3R^3$ by Method A at 50 °C

Expt.	Ester R^1	R^2	R^3	Reaction time (h)	Yield [a]	M.p./b.p. [b]
1	Me	Me	Me	2	90	75 °C/3 mmHg* (72 °C/2 mmHg) [3a]
2	Me	Me	Et	4	90	72 °C/3 mmHg* (70 °C/1.5 mmHg) [3a]
3	Me	Me	Ph	2	91	145 °C/6 mmHg*
4	Me	Me	Bu^t	9	30	65—68 °C
5	Me	Me	Bu^t	8	60 [c]	65—68 °C
6	Me	Me	Bu^t	18	22 [d]	65—68 °C
7	Me	Me	1-$C_{10}H_7$	6	94	74 °C (77 °C) [4]
8	Me	Me	4-$NO_2C_6H_4$	9	63	121—122 °C (124 °C) [4]
9	Et	Et	Me	4	58(*ca.* 20) [1]	81 °C/2 mmHg* (74—75 °C/1.5 mmHg) [3a]
10	Et	Et	Et	12	60 [e] (*ca.* 33) [1]	78 °C/4 mmHg* (62—64 °C/1 mmHg) [1,3a]
11	Et	Et	Pr^n	20	57(*ca.* 31) [1]	85 °C/4 mmHg* (80.5 °C/3 mmHg) [1]
12	Et	Et	Bu^n	24	35(*ca.* 29) [1]	70—72 °C/2 mmHg* (73.5 °C/2.5 mmHg) [1]
13	Et	Et	Ph	3	67(21) [12]	118 °C/4 mmHg*
14	Et	Et	*p*-PhC_6H_4	24	34(15)	64 °C (62 °C) [12]

[a] Best literature yields in parentheses. [b] Literature m.p. or b.p. in parentheses. [a, b] The superscript numbers are references. [c] Using Bu^n_4NI. [d] Using Bu_4^nNBr. [e] Without the catalyst, after 12 h a 6% yield was obtained.

TABLE 2

Synthesis of sulphamate esters, $RNHSO_3R^3$ and $H_2NSO_3R^3$, by Method B at 20 °C

Expt.	Ester R	Ester R^3	% Yield [a]	M.p./b.p. [b]
1 [c]	c-Hex	Et	70	78 °C/3 mmHg*
2 [c]	c-Hex	Et	30 [e]	
3 [c]	c-Hex	Et	52 [f]	
4 [c]	c-Hex	Et	30 [g]	
5 [c]	c-Hex	Et	60 [h]	
6 [c]	c-Hex	Pr^n	80	110 °C
7 [c]	c-Hex	*o*-HOC_6H_4	89(99)	70 °C (71—73 [j])
8 [c]	c-Hex	Bu^t	81	160 °C
9 [d]		Me	81(81.5)	22—24 °C (25—27 °C) [2]
10 [d]		Et	87(91)	39—40 °C (40—41 °C) [2]
11 [d]		Pr^n	82(93)	22—23 °C (24.5—25.5 °C) [2]
12 [d]		Bu^n	78(53)	23 °C (24—26 °C) [2]
13 [d]		Ph	78(86) [9b]	86—90 °C (86 °C) [9b,10b,k]
14 [i]	Bu^t	Me	0	

[a] Best literature yields in parentheses. [b] Literature m.p. or b.p.* in parentheses. [a,b] The superscript numbers are references. [c] Reaction time, 10 min. [d] Reaction time 1 h. [e] Using $BzEt_3NCl$ and C_6H_6. [f] Using $BzEt_3NCl$. [g] Using Bu_4^nNBr and C_6H_6. [h] Using Bu_4^nNBr. [i] Reaction time, 5 h. Starting chloride recovered quantitatively. [j] G.E. DuBois and R. A. Stephenson, *J. Org. Chem.*, 1980, **45**, 5371. [k] Hoechst Faberwerke A.-G. French Patent 1/554/976 (1969).

TABLE 3

Rearrangement of $(Me)_2NSO_3R$ at 130 °C

R	Betaine	Reaction time (h)	% Yield	M.p.
Me [a]	Me_3NSO_3	1	97	237 °C (239 °C) [3a]
Et	Me_2EtNSO_3	8	95	131—132 °C (133—135 °C) [3a]
Et	Me_2EtNSO_3	*b*	50	
Pr^n	$Me_2Pr^nNSO_3$	24	96	117 °C
Bu^t	$Me_2Bu^tNSO_3$	24	98	105—110 °C

[a] The following ^{13}C data (in p.p.m.) were obtained (all relative to and downfield from TMS): Me_3NSO_3, 39.5; $\overset{b}{Me}_2NSO_3\overset{c}{C}H_2\overset{a}{C}H_3$ a 14.94, b 38.46, c 66.9; $\overset{b}{Me}_2(\overset{a}{C}H_3\overset{c}{C}H_2)NSO_3$ a 9.22, b 39.5, c 51.72. [b] This ester partially rearranged at 0 °C over a six month period.

the syntheses of sulphamate esters, by the reaction given in equation (1), are: (i) versatile in that esters of several types can be synthesised, (ii) capable of giving higher or comparable yields, frequently at lower temperatures and/or shorter reaction times, and (iii) convenient in that the prior preparation of the alkoxide has been avoided and the starting sulphamoyl chlorides can be readily synthesised or are commercially available.

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