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ALKYLATION OF SULFONATE ANIONS VIA SUBSTRATE-REAGENT ION-PAIR (SRIP) REACTIONS OF [2]BETYLATES. PREPARATION OF ALKYL ESTERS OF HYDROXYALKANESULFONIC ACIDS

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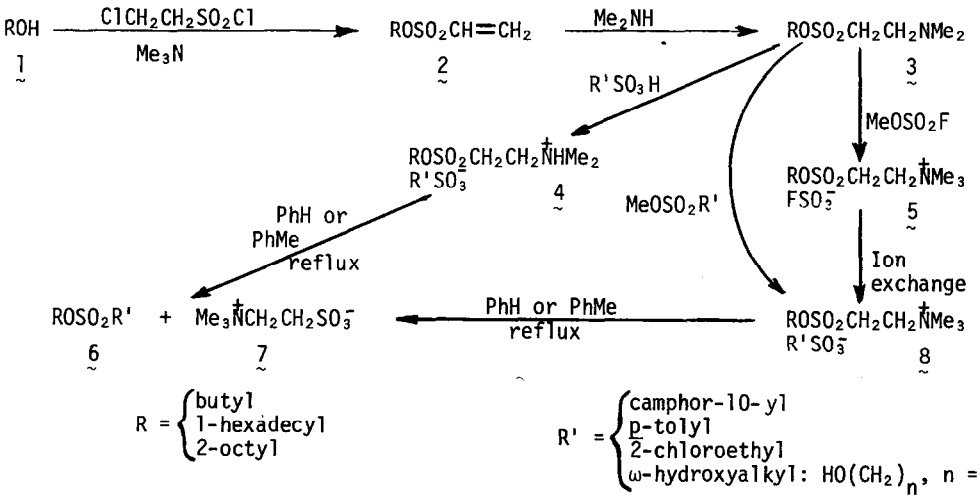
[2]Betylate sulfonates (4 or 8) give alkyl sulfonate esters (6) in refluxing toluene or benzene, chiral esters being formed with inversion. Preparation of alkyl hydroxyalkanesulfonates in this way (a) is a simple route to a little-known class of compounds, and (b) shows sulfonate anions to be more nucleophilic than hydroxyl groups in this system.

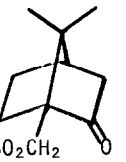
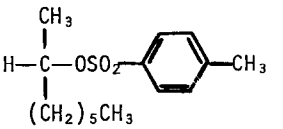
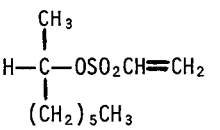
Possibly because sulfonate anions have a reputation as feeble nucleophiles, synthesis of sulfonic esters by alkylation of sulfonate anions is but little practised, being limited essentially to reactions with dimethyl or diethyl sulfate, or to silver salt-alkyl halide procedures.[1] We wish to point out that under the conditions of substrate-reagent ion-pair (SRIP) reactions of [2]betylates[2], sulfonate anions are more reactive than hydroxyl groups and give clean nucleophilic displacements. This method provides a route to sulfonic esters in general, and in particular to alkyl hydroxyalkanesulfonates, a class of compounds hitherto practically inaccessible. Scheme 1 shows the reactions.

SCHEME 1



The route by way of the 'norbetylate' (4) dispenses with the methylation step and is particularly convenient. Table 1 summarizes our results.

Table 1: SRIP Reactions of Alkyl [2]Betylate Sulfonates

Starting Material: Formula, R, R' (mmol)	Solvent, Reaction Time (h)	Product: Structure	% Yield[a]
4, 1-Hexadecyl, camphor-10-yl(2.6)	Toluene, 6	 $CH_3(CH_2)_{15}OSO_2CH_2$	66
8, 1-Hexadecyl, camphor-10-yl(2.6)	Benzene, 1.5	"	80
4, Butyl, 2-chlorethyl(2.0)	Toluene, 1	$CH_3(CH_2)_3OSO_2CH_2CH_2Cl$	80
4, R-(-)-2-Octyl, p-tolyl(6.6)	Toluene, 1		68[b]
8, R-(-)-2-Octyl, ethenyl(15.5)	Toluene, 1		72[c]
8, 1-Hexadecyl, hydroxymethyl(2.0)	Toluene, 2.5	$CH_3(CH_2)_{15}OH$	98
4, Butyl, 2-hydroxyethyl(7.0)	Toluene, 1	$CH_3(CH_2)_3OSO_2(CH_2)_2OH$	55(60)[d]
4, 1-Hexadecyl, 2-hydroxyethyl(2.3)	Toluene, 3	$CH_3(CH_2)_{15}OSO_2(CH_2)_2OH$	62(68)[d]
8, 1-Hexadecyl, 2-hydroxyethyl(2.5)	Benzene, 2.5	$CH_3(CH_2)_{15}OSO_2(CH_2)_2OH$	46(51)[d]
8, 1-Hexadecyl, 3-hydroxypropyl(1.4)	Benzene, 3	$CH_3(CH_2)_{15}OSO_2(CH_2)_3OH$	40(67)[d]
8, 1-Hexadecyl, 4-hydroxybutyl(0.9)	Benzene, 3	$CH_3(CH_2)_{15}OSO_2(CH_2)_4OH$	53(71)[d]
4, 1-Hexadecyl, 5-hydroxypentyl(3.4)	Toluene, 3	$CH_3(CH_2)_{15}OSO_2(CH_2)_5OH$	70(77)[d]

[a] A solution of the substrate (4 or 8) in the specified solvent was refluxed for the given time and the mixture (except as noted below for the hydroxyalkanesulfonates) worked up by partitioning between CH_2Cl_2 and water; the yields refer to the material remaining after drying the organic layer and evaporation of the solvent, and judged >98% pure by n.m.r. spectra.

[b] Estimated 95% inversion from $[\alpha]_D^{21}$+6.3°; the i.r. and ^1H n.m.r. spectra were identical to those of an authentic specimen of its enantiomer.

[c] Estimated >89% inversion by conversion[2b] to R-(-)-2-bromooctane $[\alpha]_D^{21}$-34.5°, and comparison with S-(+)-2-bromooctane, $[\alpha]_D^{21}$+38.6°, prepared from the same R-(-)-2-octanol by the direct betylate procedure[2b].

[d] The number within parentheses refers to the total product, that without to the yield of 9 estimated by n.m.r.; direct comparison with an authentic mixture of 9 and 10 (n = 4) confirmed the validity of this procedure with the mixture from 4-hydroxybutanesulfonate. The product was obtained by evaporation of the solvent, trituration of the residue with dry ether, and evaporation of the ether.

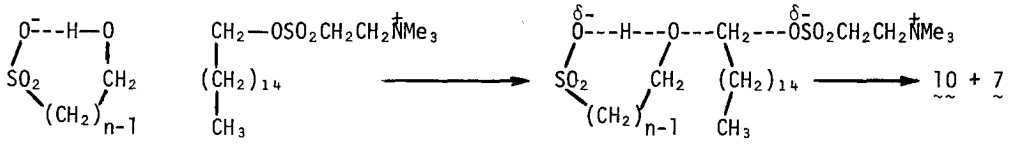
The conversion of R-(-)-2-octanol into S-(+)-2-octyl tosylate (6, R = 2-octyl, R' = p-tolyl) with 95±5% inversion, indicates a clean S_N2 process. R-(-)-2-octyl ethenesulfonate (2) is transformed into its enantiomer by the sequence 2 → 3 → 8 → 6. This observation, when taken with our previous description[2b] of the stereoselective conversion of 2-octyl ethenesulfonate via the [2]betylate to an array of nitrogen, sulfur and halogen derivatives, provides a route to either enantiomer of any of these compounds from one enantiomer of 2-octanol.

A particularly useful application of the present reaction is the preparation of sulfonic esters that are not readily made by the usual methods from the alcohol and sulfonyl chloride. Alkyl 2-chloroethanesulfonates, for example, are not formed directly from 2-chloroethanesulfonyl chloride (see 1 → 2 in Scheme 1), but may be made[3] readily via the [2]betylate (see below). More noteworthy is the preparation of alkyl ω-hydroxyalkanesulfonates (9, n = 2 to 5). Except for 2-hydroxyethanesulfonyl chloride, which has recently been synthesized[4] and found to give alkyl esters in modest (~30%) yield,[4,5] hydroxyalkanesulfonyl chlorides are unknown and most other ways of making sulfonic esters[1,3] do not seem well-suited to 9. We find that the SRIP reaction of a [2]betylate hydroxyalkanesulfonate gives the ω-hydroxyalkanesulfonate ester (9, n = 2 to 5) as the major product along with a variable amount of the isomeric alkoxyalkanesulfonic acid (10).

$$\underset{9}{ROSO_2(CH_2)_nOH} \qquad\qquad \underset{10}{RO(CH_2)_nSO_2OH}$$

The one ester (9) not isolated by this procedure is that in which n = 1, i.e. $ROSO_2CH_2OH$, the alcohol (ROH) being obtained quantitatively instead. One likely possibility is that 9 (n = 1) was in fact formed but decomposed rapidly to formaldehyde, sulfur dioxide, and the alcohol.[8]

In those reactions which give 9 and 10, the relative yields presumably reflect the relative nucleophilic reactivities of the hydroxyl and sulfonate anion functions in this system, since control experiments show both 9 and 10 to be stable under the reaction conditions. It is evident from Table 1 that the relative nucleophilicities vary with n, the number of methylene groups separating the reacting functions. We suggest that the attack of the hydroxyl group is facilitated by intramolecular general base catalysis by the sulfonate anion, as indicated in 11.



8 11

Such assistance would be expected to be most favoured when n = 3 or 4, but could well occur to some extent with the other hydroxyalkanesulfonate anions in Table 1 as well. If this picture is correct, it follows from the yields in Table 1 that in the absence of this assistance the nucleophilic reactivity of the hydroxyl group is one tenth or less that of the sulfonate anion in the displacement of a sulfonic ester from a saturated carbon atom in a non-polar solvent.

To illustrate the experimental procedure we describe the preparation of butyl 2-chloroethanesulfonate. Dimethylamine (~1.5 ml) was added to butyl ethenesulfonate (2, R = butyl) (0.9 g, 5.5 mmol, prepared by the general method[2a,2c]) in CH_2Cl_2 (50 ml), and the ice-cooled solution stirred for 10 min; evaporation of the solvent gave the amino-ester 3 (R = butyl). 2-chlorethanesulfonic

acid (0.95 g, 6.1 mmol), which had been prepared via ion-exchange (Rexyn 101 H^+ form) from sodium 2-chloroethanesulfonate (Aldrich), was added to a solution of the amino-ester (3) in CH_2Cl_2 and after 10 min the solvent was evaporated. The product crystallized upon addition of anhydrous ether and filtration gave the norbetylate 4 (R = butyl, R' = 2-chloroethyl) as a white solid (1.85 g, 95% yield). A solution of the norbetylate (4) (1.8 g, 5 mmol) in dry toluene (50 ml) was refluxed for 1 h. Upon evaporation of the toluene the product was taken up in CH_2Cl_2-water and the organic layer washed with NaCl solution and dried. Evaporation of the CH_2Cl_2 gave butyl 2-chloroethanesulfonate as a colourless oil (0.8 g, 80% yield from 4). The ^1H n.m.r. spectrum (except for weak solvent peaks) was identical to that of the analytical sample obtained by short-path cold finger distillation (at 0.001 Torr); the analytical specimen showed appropriate ^1H and ^{13}C n.m.r. and i.r. spectra, and C,H,S, and Cl analyses.

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