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STEREOCHEMISTRY OF TWO-PHASE AND SUBSTRATE-REAGENT ION-PAIR REACTIONS OF BETYLATES: COMPLETE INVERSION IN THE SYNTHESIS OF HALOGEN, SULFUR, AND NITROGEN DERIVATIVES FROM R-(-)-2-OCTANOL

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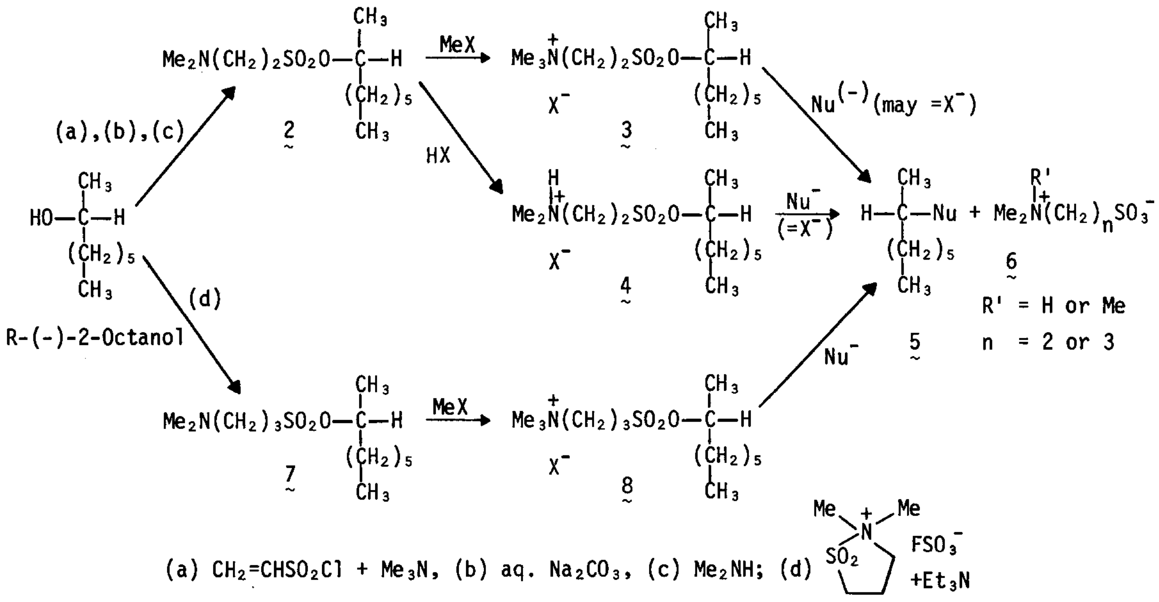
Conversion of a chiral secondary alcohol into a chiral halogen, sulfur or nitrogen derivative may be conveniently carried out by way of a "betylate" ester. The overall reaction gives reasonable (40-80%) yields with high stereoselectivity (100% inversion in seven of eight examples).

We have previously[1] noted the utility of "betylates" (ammonioalkanesulfonate esters) as intermediates in the conversion of primary and secondary alcohols into a wide array of derivatives by way of bimolecular nucleophilic substitution reactions. We pointed particularly to the value of betylates in effecting reaction with hydrophilic nucleophiles, either in aqueous medium (often with an immiscible organic solvent) or in non-polar media via substrate-reagent ion-pair (SRIP) reactions. Since any individual bimolecular nucleophilic substitution is believed to occur with complete inversion of configuration[2], the general S_N2 route with various substrates is much used in stereospecific synthesis. In practice, however, problems often arise either from the incursion of unwanted reactions (such as elimination, solvolysis, rearrangement, and racemization) or simply from low reactivity. To determine if the use of betylates could overcome some of these difficulties, we have investigated the reactions of R-(-)-2-octyl betylates with nucleophiles, using especially the two-phase and SRIP methods.

The general methods, which have been described previously[1,3], are shown in the Scheme. The betylates were formed from the alcohol (1) in 80 - 90% yields, and as may be seen from the Table, their further reaction with nucleophile gave 50 to 90% yields. A more notable feature of the Table, however is the stereospecificity of the reactions: all but one gave complete inversion within experimental uncertainty, and even with the exception the product was largely (~95%) inverted. Note particularly the 2-octyl iodide and bromide. The usual preparation of these halides commonly also gives some racemization[9,12] arising presumably, as was suggested many years ago by Holmberg[13], from reaction of the alkyl halide with excess halide anion; products of high optical purity are usually obtained only with considerable care and sacrifice in yield[9,14].

The success of the preparation of (+)-2-octyl iodide from 3 (X = I) is ascribed at least partly to two features of SRIP reactions: (a) only the stoichiometric amount of I^- is present, and (b) the I^- is present as the paired counterion of the substrate in a non-polar medium.



(a) $CH_2=CHSO_2Cl$ + Me_3N, (b) aq. Na_2CO_3, (c) Me_2NH; (d)

SCHEME

The two-phase reaction of the [3]betylate (8, X = FSO_3) gives largely inverted product, a much greater amount, for example, than the 31% inversion reported[12] for the reaction of 2-octyl tosylate with LiI in a homogeneous medium. The separation of the sodium and octyl iodides in two different phases presumably helps to cut down the racemization of the 2-octyl iodide, but, as is shown by a reported phase transfer catalysis experiment which gave almost completely racemized 2-octyl iodide[15], a two-phase system does not in itself ensure high levels of inversion. Current evidence points to a "double phase transfer" mechanism for the two-phase reaction, i.e. phase transfer of I^- into the organic phase (as 8, X = I) followed by a SRIP reaction, with its capacity to minimize racemization. If some (or all) of the reaction were to take place in the aqueous phase, the much greater solubility in water of the 2-octyl [3]betylate cation as compared with 2-octyl iodide, would probably help to increase the difference in rate between octyl iodide formation and its subsequent racemization.

The isothiuronium fluorosulfate from the reaction of 3 (X = FSO_3) with thiourea in 1,2-dimethoxyethane (DME), was not isolated but simply treated with Cl_2 in water to give S-(+)-2-octanesulfonyl chloride, $[\alpha]_D$ +3.1 and $[\alpha]_{546}$ +3.9° (neat and in absolute ethanol, c 8.3) in 63% overall yield from R-(-)-2-octanol. Our specific rotations are slightly higher than those given by earlier workers[10,16] for this sulfonyl chloride, and the extent of inversion was adduced by comparison of previous data[10] with the rotations of (a) the S-(+)-2-octanethiol, $[\alpha]_{546}$ +35.7° (abs. EtOH, c 5.1), obtained by $LiAlH_4$ reduction of the sulfonyl chloride, and (b) the 2,4-dinitrophenyl S-(-)-2-octyl sulfide, $[\alpha]_{546}$ -51.1° ($CHCl_3$, c 5.7), made from the thiol. We have prepared other alkanesulfonyl chlorides from alcohols in this way[17], and in our view ease, good yields, and (where relevant) stereospecificity commend it as an excellent method.

Although the Table may suggest that a wide array of reaction media may be used for these

TABLE: Reaction of R-(-)-2-Octyl Betylates with Nucleophiles

			Product			
Betylate, Opt. Purity[a]	Nucleophile	Reaction Conditions	Structure (yield)	$[\alpha]_D$	Estimated[c] max. $[\alpha]_D$(ref.)	Estimated[d] % Inversion
4 (X = Cl), 94.6%	(Cl^-)	Benzene 80°, 0.5h	RCl (85%)	+34.4°	36.15° (4) 37.4° (8) 37.1° (9)	101 97 98
4 (X = Br), 93.5%	(Br^-)	Benzene 80°, 1h	RBr (90%)	+38.6°	40.64° (4) 40.3° (8) 41.3° (9)	102 102 100
3 (X = I), 93.5	(I^-)	Benzene 80°, 1.5h	RI (71%)	+45.8°	47.87° (4) 48.6° (8) 49.7° (9)	102 101 99
3 (X = FSO_3), 94.4%	$(NH_2)_2CS$[e]	DME 75°, 2h	$[RSC(NH_2)_2]^+$ FSO_3^- (>70%)	—	—	~100 (see text)
3 (X = FSO_3), 94.6%	SCN^- (NaSCN)[f]	$H_2O:CH_2Cl_2$ 25°, 1h	RSCN (60%)	+61.6° +81.0°[g]	64.7° (5) 85.1°[g](10)	101 101
8 (X = FSO_3), 94.6%	SCN^- (NaSCN)[f]	$H_2O:CH_2Cl_2$ 25°, 15h	RSCN (75%)	+62.4° +83.6°[g]	64.7° (5) 85.1°[g](10)	102 104
8 (X = FSO_3), 94.6%	N_3^- (NaN_3)[f]	$H_2O:CH_2Cl_2$ 25°, 15h	RN (72%)	+44.2°	45.4° (11) 48.1° (12)	103 97
8 (X = FSO_3), 94.6%	I^- (NaI)[f]	$H_2O:CH_2Cl_2$ 25°, 15h	RI (53%)	+43.7°	47.87° (4) 48.6° (8) 48.9°	96 95 94

[a] Different samples of R-(-)-2-octanol (from Aldrich Chemical Co.) showed slightly different rotations[b]; optical purities were estimated using $[\alpha]_D^{20}$ 9.93° for optically pure 2-octanol[4].

[b] Except as otherwise noted all $[\alpha]_D$ values refer to neat samples and were determined at 21-22°C. The following densities were used to convert α to $[\alpha]$: ROH, 0.8205[4]; RCl, 0.8655[4]; RBr, 1.1055[4]; RI, 1.3219[4]; RSCN, 0.919[5]; RN_3, 0.8555[6].

[c] Values taken from Brauns[4] were obtained from 2-octanol having $[\alpha]_D^{20}$ 9.93° and are quoted directly. Others are highest reported specific rotations after correcting for the optical purity of the starting material using $[\alpha]_D$ 9.93°[4] (or $[\alpha]_{546}$ 11.8°[7]), and the above densities.

[d] Estimated % inversion = $$\frac{10^4([\alpha] \text{ of product})}{(\text{\% Optical purity of alcohol})(\text{Estimated maximum } [\alpha] \text{ of product})}$$

[e] In five-fold excess.

[f] The two-phase reactions were carried out as previously described[1]. Saturated aqueous NaSCN solution was used in the reaction with **3** (X = FSO_3); a roughly 20-fold excess of nucleophile was used in the reactions with the [3]betylate (**8**, X = FSO_3).

[g] $[\alpha]_{546}$, c 5 in absolute ethanol.

reactions, the high reactivity of [2]betylates prescribes two limitations. (1) Basic reaction conditions should be avoided owing to the ease with which 3 may give ethenesulfonate esters[1]. (2) Aqueous media are often precluded owing to rapid hydrolysis of secondary alkyl [2]betylates. With a sufficiently concentrated solution of a powerful nucleophile, hydrolysis may be largely suppressed: the crude product of the reaction 3 (X = FSO_3) with saturated (~8 M) thiocyanate consisted of mainly the 2-octyl thiocyanate plus apparently some (<10%) octene (and a similar amount of the isothiocyanate). With a weaker (1.3 M) solution of NaSCN, considerable (~35%) 2-octanol was formed, and with thiourea only hydrolysis products were observed in the two-phase system. The [3]Betylates (8), though slower to react, are not subject to these restrictions.

We point to two conclusions:

(1) Betylates provide a serviceable route for converting a chiral secondary alcohol into assorted chiral derivatives.

(2) The high level of stereoselectivity found in these reactions shows that both the SRIP and two-phase methods may significantly improve reaction selectivity, and we would expect this feature to find general synthetic use beyond the stereoselective S_N2 processes described here.

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