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DESIGN AND REACTIVITY OF ORGANIC FUNCTIONAL GROUPS: IMIDAZOLYLSULFONATE (IMIDAZYLATE) - AN EFFICIENT AND VERSATILE LEAVING GROUP

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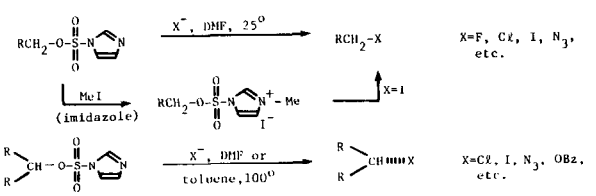
The preparation and reactivity of the novel imidazolylsulfonate group is described.

Nucleophilic displacement reactions, eliminations and related processes have a played a pivotal role in the development of synthetic and mechanistic organic chemistry.[1] The formation of bonds to carbon by solvolysis or S_N2 - type reactions of sulfonate esters for example, are operational necessities in the daily practice of functional group manipulations. We wish to report on the formation and reactivity of a novel sulfonate group namely the imidazolylsulfonate (imidazylate or Ims) group, which offers some unique advantages over existing systems. The conceptual basis for developing such a group and its anticipated favorable reactivity was predicated upon the following kinetic and thermodynamic criteria: a. increased nucleofugal character, b. possibility of remote activation involving a nitrogen atom, and c. the prospects of generating a leaving group that could self-destruct, hence add an added dimension to inherent reactivity.

We have chosen a number of representative alcohols particularly from the carbohydrate area, because of the recorded reluctance of their sulfonate esters[2] to undergo nucleophilic substitution due, in major part, to steric and stereoelectronic factors.[3,4]

Formation of Imidazolylsulfonates - We suggest three methods for the preparation of imidazylates from alcohols. In the first two, (methods A and B), the alkoxide is generated directly (NaH, DMF), or from the corresponding TMSi ether (n-Bu_4NF, THF, DMF) and allowed to react with excess N,N'-sulfuryldiimidazole.[5] The sulfuryl chloride method (method C) proceeds through initial formation of a chlorosulfate ester (-40°, DMF, then imidazole) and offers the option of regioselectivity as in the formation of chloro derivatives from glycosides.[6] Imidazylates are crystalline solids or syrups which have excellent shelf life.

Reactivity of Primary Imidazolylsulfonates - Primary imidazylates react with nucleophiles such as azide, fluoride, chloride, and iodide *at room temperature* to provide the corresponding displacement products in high yields (Scheme 1; Table 1, entry 1). Based on the functional design of the imidazylate group, it was found that *treatment with methyl iodide* gave the *corresponding iodide* in high yield (entry 1). Nucleophilic displacements of sulfonates at C-6



in the D-galactopyranose system are relatively sluggish and require heating, presumably due to a polar field effect exerted by the lone pairs of electrons on the axial O-4 and the ring oxygen atom.[3,4] The extremely facile reactions of imidazylates in this series are therefore of preparative interest. The syrupy imidazylate derived from neopentyl alcohol via method A (NaH, THF, N,N'-sulfurylidimidazole) gave the corresponding iodide when treated with Bu_4NI in HMPA at *room temperature*.[7]

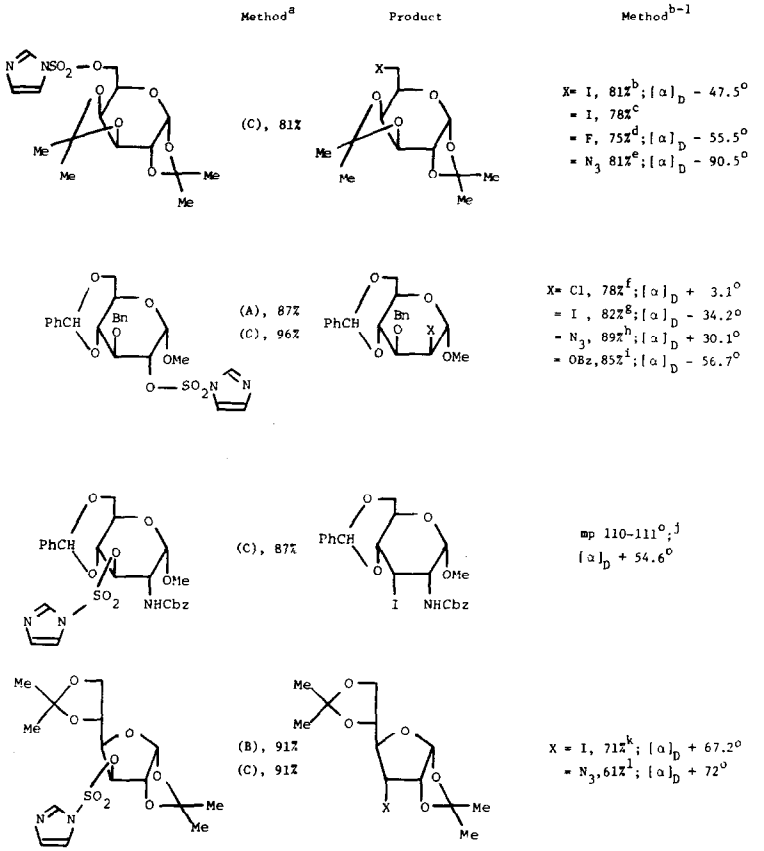
Reactivity of Secondary Imidazolysulfonates - The examples selected (entries 2-4) have been known to be notoriously resistant to nucleophilic displacement, affording rearranged products, low yields, elimination, or failing altogether.[3,4] Thus, displacement of 2-sulfonates and other derivatives in alkyl α-D-glucopyranosides are, with very few exceptions,[8] yet to be achieved. The 2-imidazylate (Table 1, entry 2) is subject to displacement by several nucleophiles, as their tetrabutylammonium salts and in excellent yields. The 2-halo derivatives so formed could afford easy access to derivatives of 2-deoxy-D-*arabino*-hexopyranose (2-deoxy-D-glucose). Indeed, reduction (Bu_3SnH, AIBN, reflux, toluene)[9] gave the corresponding known 2-deoxy derivative (73%) identical with an authentic sample. The azido derivative is a convenient precursor to derivatives of 2-amino-2-deoxy-D-mannose, otherwise obtained by more laborious methods.[10] Displacement with an oxygen nucleophile such as benzoate is particularly interesting and unprecedented to the best of our knowledge.

Displacement reactions at C-3 in alkyl α-D-glucopyranosides can be impaired because of 1,3 non-bonded interactions between the anomeric substituent and the incoming nucleophile. In the presence of a benzyloxycarbonylamino group at C-2, neighboring group participation may occur with the formation of an oxazolidone derivative [11] rather than the anticipated substitution. Displacement of the crystalline imidazylate (entry 3) with iodide ion affords the crystalline iodide in excellent yield, a reaction which may have important application in the chemical modification of aminocyclitol antibiotics, since 3'-deoxy analogs are potent broad spectrum antibiotics. Indeed, reduction of the iodide (Bu_3SnH, AIBN, 80° toluene) gave the corresponding 3-deoxy derivative (90%) mp 175°;$[\alpha]_D$ + 50.9°. [12]

The tosylate ester of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose is particularly resistant to nucleophilic displacement reactions presumably due to the *exo*-orientation of the sulfonate group in the trioxabicyclo [3,3,0] octane system. This ester has succumbed only to the action of electrically neutral nucleophiles such ammonia,[13] hydrazine,[14] and to a limited extent, azide ion.[15] A common side-reaction is elimination[16] of the sulfonyloxy group with the favorably disposed C-4 hydrogen. Displacement with iodide ion has been recently possible with the advent of triflate esters[17,18] as well as via the intermediacy of alkoxyphosphonium derivatives.[19] Treatment of the crystalline 3-imidazylate ester of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose with azide and iodide ions respectively gave the corresponding displacement products under mild conditions and in good yields (entry 4) (compare for the corresponding tosylate: sodium azide, DMF 115°, 2 weeks, 53%).[15]

Nucleophilic displacement reactions at C-4 in alkyl hexopyranosides [3,20] and at C-5', in nucleosides[21] are normally reasonably facile. Nevertheless, introduction of chlorine at these positions was greatly facilitated via the sulfuryl chloride-imidazole method, which was found to be superior to the original sulfuryl chloride - pyridine procedure[6] particularly in the case of polyfunctional derivatives.[22]

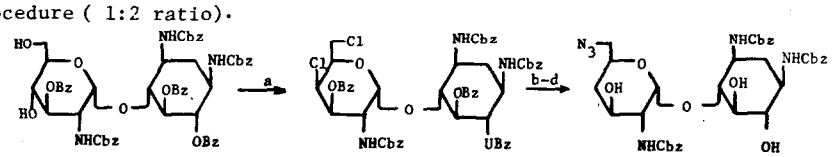
Scheme 1



a. Method A: NaH (1.2 equiv.), DMF, 0°; 30 min; N,N'-sulfurylimidazole (2 equiv.), -40°; 25°, 1h; Method B: OTMSi derivative, Bu_4NF, THF (1M); N,N'-sulfuryldiimidazole (1.5 equiv.), reflux, 4h; Method C: SO_2Cl_2 (2 equiv.), DMF, -40°→25°; add imidazole (10 equiv.), 25°;1-24hr
b. NaI (2.5 equiv.), DMF, 25°, 6h; c. MeI, imidazole (0.5 equiv.) DMF, 25°, 8h ; d. Bu_4NF, THF (1M) toluene, 25°, 3h; e. NaN_3 (2 equiv.), DMF, 25°, 6h; f. Bu_4NCl (3 equiv.), toluene, reflux, 6h; g. Bu_4NI (3 equiv.), toluene, reflux, 8h; h. Bu_4NCl (3 equiv.); NaN_3 (3 equiv.), toluene, reflux 6h; i. Bu_4NOBz, (4 equiv.), toluene, reflux, 4h; j. Bu_4NI (3 equiv.), benzene, reflux, 24h; k. Bu_4NI (3 equiv.), benzene, reflux, 72h; l. Bu_4NCl (3 equiv.), NaN_3 (3 equiv.); toluene, 80°, 5h.

Chlorination via imidazylate intermediates was found to be particularly suitable in the area of aminocyclitol antibiotics as exemplified by the synthesis of an immediate precursor to Seldomycin factor 2[23](4'-deoxyneamine) from the readily available paromamine derivative[24], by the sequence shown in Scheme 2. The yields in the chlorination step in this synthesis as well as in the recent syntheses [25] of 4'-deoxyparomamine and the biologically active 4'-deoxyneomycin can be dramatically improved by adopting the SO_2Cl_2-imidazole procedure (1:2 ratio).

Scheme 2



a. SO_2Cl_2, imidazole, DMF, -40°, 30 min; 25°, 2d.(85%), $[\alpha]_D$+ 90.3°($CHCl_3$);
b. Bu_3SuH, AiBN, toluene, 80°, 1.5h(86%); c. NaN_3, DMF, 100°, 2d(74%);
d. NaOMe, MeOH;

The utility of imidazylate esters in elimination reactions is illustrated in the case of dihydrocholesterol. Thus treatment of dihydrocholesterol (0.77 mmole) in THF (6 mL) with NaH (1.2 equiv.), N,N'-sulfuryldiimidazole (1.5 equiv.) and n-Bu_4NI (2 equi.) gave after 72 h at 25° or 3 h at reflux, an 84% yield of Δ2- and Δ3-cholestenes (~1:1 ratio). Monitoring the reaction by t.l.c. showed the formation of the iodide as an intermediate.

The latter could be isolated after 5 h at 25°, in 48%, mp 106-107°.

It is thus clear that imidazylates are versatile functional groups that can be complimentary to triflates in displacement reactions[18] but with an added measure of hydrolytic stability. They should find wide application in organic transformations as leaving groups mediated by remote activation on nitrogen or in the presence of appropriate nucleophiles.[26]

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