DESIGN AND REACTIVITY OF ORGANIC FUNCTIONAL GROUPS — 2-PYRIDYLSULFONATES AS NUCLEOFUGAL ESTERS: REMARKABLY MILD TRANSFORMATIONS INTO HALIDES AND OLEFINS*

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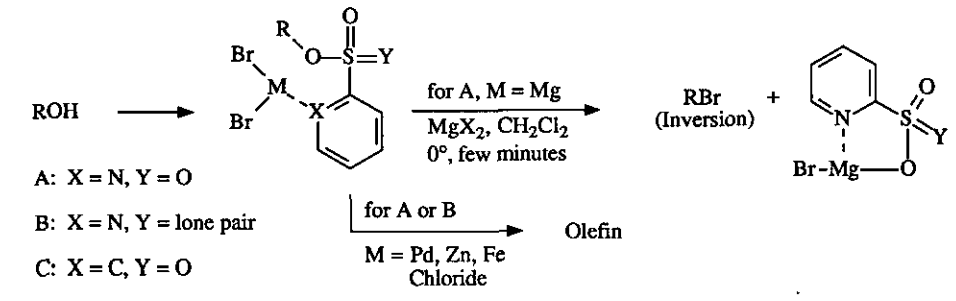
Abstract - The novel 2-pyridylsulfonate esters are excellent leaving groups for the preparation of bromides and olefins under very mild reaction conditions. Displacements occur with inversion of configuration.

The formation of carbon-halogen bonds from alcohols is a well documented, and fundamentally important reaction in organic chemistry.[1] Indeed, the chemical literature is abound with detailed mechanistic studies,[2] as well as preparatively useful examples.[3] In general, there are two protocols for the formation of halides from primary and secondary alcohols. In the classical approach, an appropriate leaving group (nucleofuge) such as a sulfonate ester is involved. In the second method, a direct conversion from the alcohol can be achieved via the intermediacy of an alkoxyphosphonium halide.[4] In spite of numerous examples of such halogenations, there is still a need to improve aspects of efficiency, mildness of reaction conditions and overall compatibility. Continueing our studies on the design, reactivity and nucleofugal character of organic functional groups,[5] we report herein on the preparation and synthetic utility of 2-pyridylsulfonate (A) and 2-pyridylsulfinate (B) esters (Scheme 1).

The conceptual basis in designing these novel esters was predicated upon the relative disposition of the nitrogen atom in the pyridyl moiety and its anticipated affinity toward electrophilic reagents, particularly metal cations. In the case of a 2-pyridylsulfonate ester,

Scheme 1



* Dedicated to Professor Sir Derek Barton on the occasion of his 70th birthday wishing him the very best in chemistry and in life.

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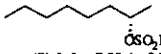
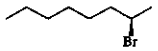
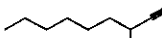
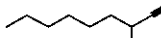
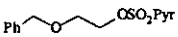
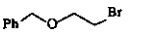
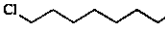
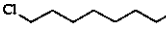
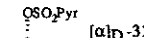
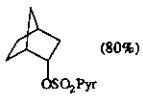
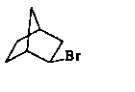
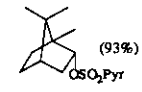
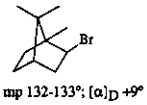
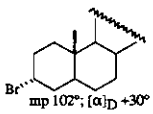
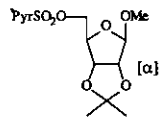
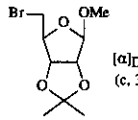
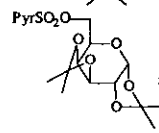
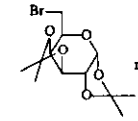
coordination with a magnesium halide for example, could bring the nucleophile in close proximity to the carbon bearing the leaving group. Displacement by halide ion either inter- or intramolecularly would be greatly facilitated compared to a classical bimolecular displacement reaction of a benzenesulfonate (C) or related ester (Scheme 1). Alternatively, by varying the nature of the metal, elimination to give an olefin could become the dominant reaction. These predictions were experimentally demonstrated in the remarkably fast formation of primary and secondary alkyl halides from 2-pyridylsulfonate and 2-pyridylsulfinate esters. The reaction conditions are, to the best of our knowledge, the mildest yet reported for such a process. Bromides can be obtained from 2-pyridylsulfonates and magnesium bromide in dichloromethane at 0°C within minutes, except when polyoxygenated substrates are involved (Table 1). Presumably in these cases, competing coordination with the reagent occurs, thus slowing down the reaction rates. Chlorides can be obtained directly from alcohols in the presence of 2-mercaptopyridine and N-chlorosuccinimide at 0°C possibly through the intermediacy of alkoxy chlorosulfonium intermediates (Table 2).

2-Pyridylsulfonates are easily prepared by treatment of primary and secondary alcohols with the crystalline 2-pyridylsulfonyl chloride[6] in the presence of an amine, much the same way as for the preparation of the commonly used sulfonates. 2-Pyridylsulfinates can be prepared by treatment of the alcohol with 2,2'-dipyridyl disulfide[7] in the presence of N-bromosuccinimide. Oxidation of the 2-pyridylsulfinate ester with m-CPBA gave the corresponding sulfonate. These novel esters can be subjected to chromatographic purification in the usual manner, and they are often crystalline with excellent stability on storage.

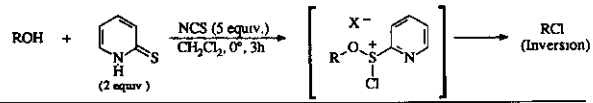
Of particular preparative significance is the mild reaction conditions, and the remarkably fast reactions especially in the case of unactivated secondary esters (Table 1, entries 2,7,8,9).Since the displacement involves inversion of configuration, it is possible that a metal-coordinated ion-pair in a solvent cage is actually involved. We should note that qualitative comparisons of reaction rates of various norbornylsulfonates (1.3 equiv. $MgBr_2 \cdot Et_2O$, CH_2Cl_2 5 ml/mmol) show the exceptional nucleofugal character of the axial 2-pyridylsulfonate (30 sec, 70% of isolated bromide), compared with the 8-quinolylsulfonate (120 min); tosylate (70 min), and p-nitrobenzenesulfonate (40 min). It should be pointed out that a variety of primary and secondary tosylates have been previously converted into bromides and iodides with inversion of configuration by treatment with the corresponding magnesium halide (25°C or reflux in ether/CH_2Cl_2).[8] Reaction of 2-pyridylsulfonates with magnesium bromide occurs at low temperature and is faster than arylsulfonates. Displacement with other sources of bromide (LiBr, Bu_4NBr in DMF or CH_2Cl_2) required heating and longer reaction times (30-50 min). Addition of an external source of bromide ion had no accelerating effect on the reaction with magnesium bromide. In the light of these

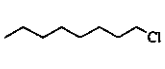
TABLE 1

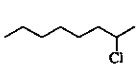
	2-Pyridylsulfonate (%)	Bromide (a) $MgBr_2$, Et_2O/CH_2Cl_2 (1.3 equiv)	Temp /Time	Yield (isolated)
1.	 (94%)		0°, 5 min	88%
2.	 (85%) (S)-$[\alpha]_D$ -7 3° (c, 3 77)	 $[\alpha]_D$ +33 4° (c, 4.23)	0°, 30 sec	74%
3	 (97%)		0°, 30 sec.	71%
4	 (99%)		0°, 30 min	94%
5	 (79%)		0°, 30 min	76%
6	 $[\alpha]_D$ -31.4° (c, 1.5) (93%)	 $[\alpha]_D$ +32.4° (c, 3 93)	0°, 10 min	81%
7.	 (80%)		0°, 30 sec	70%
8	 (93%) mp 99-100°, $[\alpha]_D$ -9.5° (c, 1.0)	 mp 132-133°; $[\alpha]_D$ +9° (c, 0.16)	0°, 30 min	95%
9	3-Cholestanyl 2-Pyridylsulfonate (90%) mp 127-128°; $[\alpha]_D$ -10.2° (c, 0 9)	 mp 102°; $[\alpha]_D$ +30° (c, 1 0)	0°, 5 min	82%
10	 $[\alpha]_D$ -40.2° (99%) (c, 1.0)	 $[\alpha]_D$ -78.1° (c, 3.7)	25°, 8h	84%
11	 (97%) mp 89-90°, $[\alpha]_D$ -59.8° (c, 1.0)	 mp 55°, $[\alpha]_D$ -51° (c, 1.0)	reflux, 18h	98%

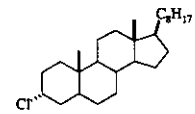
a. Rotations measured in chloroform at 25°C.

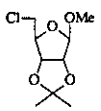
TABLE 2

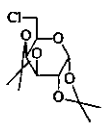


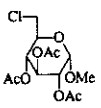
 83%

 82%

 81.5%
mp 104-105°, $[\alpha]_D$ 30° ($CHCl_3$) (c, 1.0)

 80%, $[\alpha]_D$ -89.8° (c, 1 32)

 70%, $[\alpha]_D$ -62.1° (c, 2.67)

 Selective Chlorination
48% (after acetylation), mp 97°

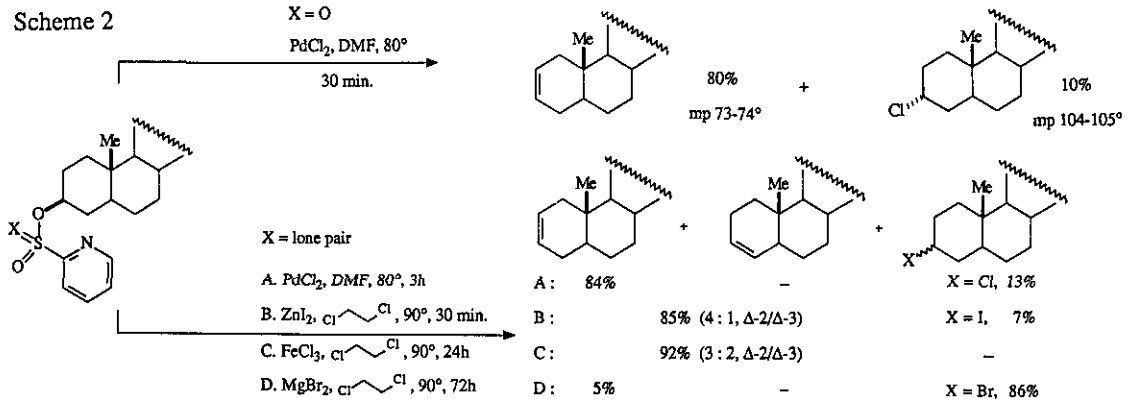
observations, it is reasonable to assume, much as we had anticipated in designing this leaving group, that coordination to the cation and internally assisted halide attack seems to be taking place. *This process may be reinforced by the stability of the magnesium halide salt of the nucleofugal* 2-pyridylsulfonate.

Ashby and coworkers[9] have recently presented experimental evidence that certain S_N2 displacement reactions of optically active 2-tosyloxyoctanes proceed via an electron transfer mechanism. Based on the results obtained to date with 2-pyridylsulfonates with magnesium bromide, an electron transfer process appears to be unlikely, but it cannot be excluded a priori (see examples involving other metal halides below).

2-Pyridylsulfonates are also subject to a number of other reactions, well known for classical sulfonates. Thus, reduction of 3-cholestanyl 2-pyridylsulfonate ($NaBH_4$, DMF, 80°C) gave the deoxygenated alcohol cholestane in 78% yield, and displacement with azide ion (LiN_3, DMF, 80°C, 4 h) gave α-3-azidocholestane (63%) accompanied by 2-cholestene[10] (15%).

Of particular interest is the ability of 2-pyridylsulfonates and 2-pyridylsulfinates to undergo metal-assisted elimination reactions. For example, treatment of 3-cholestanyl 2-pyridylsulfonate with palladium chloride in DMF at 80°C afforded 2-cholestene[10] in 80% yield together with α-3-chlorocholestane (16%).[11] This chloride is formed by a competing mechanism since it is stable under the reaction conditions (Scheme 2).

Scheme 2



The corresponding 2-pyridylsulfinate undergoes the same transformations but the reactions are slower. Other metal salts are also effective in promoting an elimination reaction, but they are not as site-specific as palladium chloride. Control reactions with 3-cholestanyl benzenesulfonate and palladium chloride led to traces of olefin after prolonged reaction times.

Enhancement of nucleofugal ability has not been extensively explored in preparative organic chemistry.[12] Our work in this area has focused on the design of organic functional groups having a judicious combination of potentially activatable atoms or sites.[5] Such reagent-induced

(metal or other electrophile) activation enhances reactivity and promotes transformations under much milder conditions relative to their more traditional counterparts.

From the results shown in this work, it is clear that the well-known notion of metal-assisted catalysis of 2-pyridyl derivatives [13,14] can be extended to preparatively useful displacement and elimination reactions. In this regard, the 2-pyridylsulfonates offer excellent opportunities for further exploration and exploitation.

Preparation of 2-pyridylsulfonyl chloride[6] - Chlorine gas was passed through a solution of 40 ml of conc. HCl containing 5 g of 2-mercaptopyridine at 0°C during 1.5 h with stirring. The reaction mixture was poured into 100 ml of ice-water and the solid was filtered, washed with water and dried over phosphorus pentoxide in vacuo for 3h at 0°C. The title compound was thus obtained as a colorless solid in 54% yield (4.3 g). It could be kept at 0°C for several weeks.

General procedure for 2-pyridylsulfonylation - A mixture of the alcohol (3 mmol) and triethylamine (3.6 mmol) was added dropwise to a solution of 2-pyridylsulfonyl chloride (3.6 mmol) in 10 ml of dichloromethane at 0°C with stirring. After being stirred for 1-4 h, the reaction mixture was diluted with ether, and the solution was washed successively with 2N HCl, satd.NaCl, then water. Usual processing gave the 2-pyridylsulfonate which could be crystallized or purified by flash column chromatography (see Table 1). Alternatively, the reaction could be done in pyridine at 0°C (1-18 h) and processed the same way.

General procedure for the formation of bromides from 2-pyridylsulfonates - A solution of magnesium bromide etherate in ether (prepared[8] from 1,2-dibromoethane and magnesium in ether, 1.3 mmol equiv.) was added to a solution of the 2-pyridylsulfonate in dichloromethane at 0°C with stirring. The reaction mixture was stirred at the prescribed temperature (see Table 1), then it was poured into ether and the solution was processed in the usual way. The products were purified by distillation (Kugelrohr) or by column chromatography. Bromides could also be prepared in a one-pot sequence, without isolating the 2-pyridylsulfonates, by addition of magnesium bromide to the 2-pyridylsulfonylation reaction mixture in dichloromethane.

General procedure for the chlorination of alcohols - A solution of 3-cholestanol (0.5 mmol in 5 ml of dichloromethane) was added to a freshly prepared solution containing 2-mercaptopyridine (1 mmol) and N-chlorosuccinimide (2.5 mmol) in dichloromethane (15 ml) at 0°C. After stirring at 0°C for 3h, the reaction mixture was poured into aq. bicarbonate, and the organic phase was extracted and processed as usual to give 82% of 3-α-chlorocholestane, mp 104-105°C; $[\alpha]_D$ + 30° (c 1, $CHCl_3$); reported[11] mp 107-108°C; $[\alpha]_D$ + 29.1° (c 1, $CHCl_3$).

General procedure for the preparation of 2-pyridylsulfinates - A solution of 3-cholestanol (0.5 mmol) and 2,2'-dipyridyl disulfide(1 mmol) in 10 ml of dichloromethane was cooled to -15°C and

treated with 1 mmol of N-bromosuccinimide in one portion. After stirring for 1.5 h at -15°C, the reaction mixture was poured into aq. bicarbonate and the organic phase was processed in the usual manner. Chromatographic purification gave 3-cholestanyl 2-pyridylsulfinate (66%), mp 104-108°C; $[\alpha]_D$ + 7.4° (c 1, $CHCl_3$), together with α-3-bromocholestane (15%) and Δ^2-cholestene (4%)

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