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Neopentyl Ester Protecting Groups for Arylsulfonic Acids

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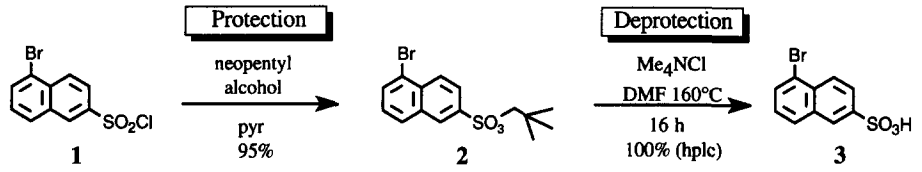
Abstract : We report that neopentylsulfonate esters are stable to a variety of standard organic reaction conditions and are easily cleaved to sulfonic acids. We also discuss the use of N-Boc-4-amino-2,2-dimethylbutyl-1-sulfonate esters which may be cleaved under conditions that are suitable for solid phase synthesis. Copyright © 1996 Elsevier Science Ltd

We wished to perform multi-step syntheses of targets which contained two or more sulfonic acid moieties. Solubility limitations of compounds that contain this polar functionality, however, made non-aqueous methods troublesome if not impossible. We therefore sought a general protecting group for sulfonic acids.

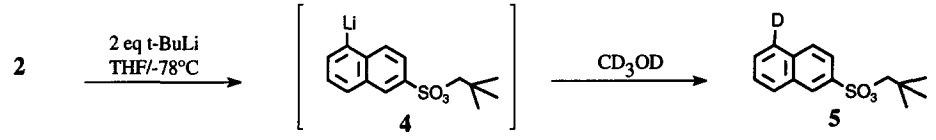
Among the few examples of sulfonic acid protection/deprotection in the literature, there were no established methods which fully met our needs. Sulfonamides of secondary amines have been used, but the deprotection step involves high temperature treatment with acid[2] or base,[3] conditions which were too harsh for our purposes. In contrast, sulfonamides of imidazoles[4] and sulfonate esters of phenols[5] proved to be too labile, especially to base. We were intrigued by the use of isopropylsulfonate esters which, when treated with NaI in acetone at reflux or ammonia in methanol at reflux, were reported to provide sulfonic acid products.[6] Stability to mild nucleophilic conditions, however, was an absolute requirement for our protecting group.

The use of neopentylsulfonate esters, more stable than the isopropyl counterparts, proved to be a successful strategy for protection. As exemplified in Scheme 1, these derivatives are easily prepared and deprotected. Sulfonylchloride **1**[7] was treated with neopentyl alcohol in pyridine to provide neopentylsulfonate ester **2** in 95% yield. Conversion to the sulfonic acid was accomplished by heating a solution of the sulfonate ester in DMF (0.01-0.05M) with excess tetramethylammonium chloride (4-5 eq./ester) for 16 h. Purified sulfonates were obtained by reverse phase HPLC (C18 column; water/acetonitrile gradient with 1% TFA) in isolated yields ranging from 60-90%. Halogen metal exchange, a critical step in many of our syntheses, was smoothly effected in the presence of the neopentyl protecting group. Bromide **2**, when treated with two equivalents of t-BuLi in THF at -78°C followed immediately by CD_3OD, was converted to deuterated compound **5** (>95% D-incorporation), evidence for the efficient generation of naphthyllithium reagent **4** (Scheme 2). Quenching the halogen exchange reaction immediately at -78 °C with substituted acetate esters effected a nucleophilic double-addition reaction providing geminal diaryl alkyl products, as shown in Scheme 3.[8,9]

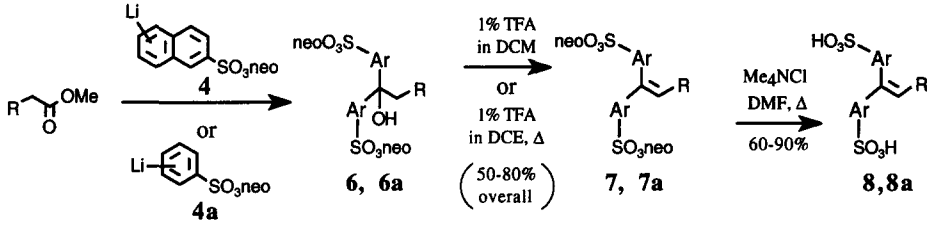
Scheme 1: Neopentyl Sulfonates



Scheme 2: Halogen-Metal Exchange



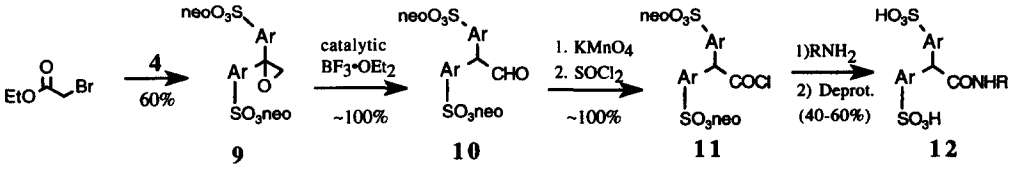
Scheme 3: Double Addition Reactions



R = 3-cholestanyl

This methodology has been used quite generally in our laboratory to prepare a series of potential inhibitors of HIV infectivity.[10] A further illustration of the synthetic utility and chemical compatibility of this protecting group is outlined in Scheme 4,[9] wherein an α-bromoacetate was used as the quenching agent; the resulting epoxide underwent smooth rearrangement and transformation to the synthetically versatile acid chloride **11**.

Scheme 4



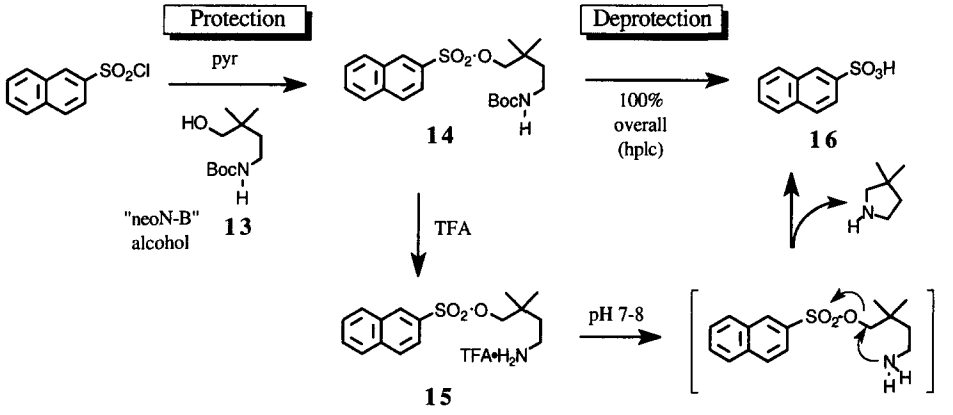
RNH_2 = aliphatic amines

Ar = 6-(neopentyloxysulfonyl)naphth-1-yl

In addition to those transformations outlined, we have found neopentyl sulfonates to be compatible with reagents such as vinyl-MgBr, CrO_3, NBS/benzoyl peroxide, H_2/RaNi, DIBAL, NaI, aqueous HBr or NaOH, $HONH_2$ and NaH.

We turned our attention to neopentyl-based protecting groups which might be cleaved at room temperature. After examination of a small variety of systems with internal nucleophilic moieties, we identified the N-Boc-4-amino-2,2-dimethylbutyl group (termed "neoN-B" reflecting its derivation from the neopentyl group) as one which fulfilled our requirements (Scheme 5). Naphthalene-2-sulfonyl chloride was readily converted to neoN-B sulfonate ester **14** by treatment with neoN-B alcohol **13**[11] in pyridine. Cleavage of the Boc group in derivative **14** with 10 eq of TFA, rapidly leads to TFA salt **15**. When this solid is dissolved in water and adjusted to pH 7-8, sulfonic acid **16** is instantaneously generated in 100% yield (hplc) via internal nucleophilic attack. The two steps may be performed sequentially in a single reaction vessel. This group is fully compatible with standard peptide synthesis (Fmoc-chemistry) and has been successfully used on solid phase supports.

Scheme 5: neoN-B Sulfonates



In summary, we have identified the neopentyl ester functionality as a useful protecting group for arylsulfonic acids, which is compatible with a wide range of standard organic synthetic methodologies. For the specific use in solid phase synthesis, the neoN-B group was developed. These sulfonate derivatives allow for synthetic transformations in organic solvents, and are prepared and cleaved in high yield.[12]

References and Notes

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8. Naphthyl reagents **4** (5,2- and 8,2-substituted) and phenyl reagents **4a** (meta- and para-substituted) have been used in these studies. Whereas sterically congested dinaphthyl alcohols **6** underwent facile dehydration (1% TFA in methylene chloride, room temperature, 0.5h), diphenyl alcohols **6a** required more forcing conditions (1% TFA in dichloroethane, reflux, 2h) to effect this conversion.

9. *General procedure for double addition*: To a cooled (-78° C) solution of the bromoarylsulfonate ester in anhydrous ether (0.1M) was added 2 eq. of tert-butyllithium (1.7M in pentane) followed immediately by 0.5 eq. of the acetate ester (neat). The mixture was allowed to warm to room temperature and after 2h, was quenched and extracted with water, dried ($MgSO_4$), concentrated and purified by silica gel chromatography. Dehydrations were preferably carried out directly on crude alcohols **6** and **6a** as described above (ref 8) prior to chromatographic purification.

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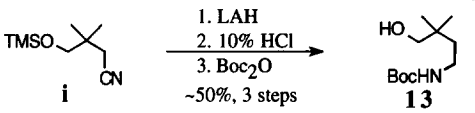
11. *Preparation of NeoN-B alcohol 13*: An ice-cooled solution of nitrile **i** (ref. 13, 75 g, 0.5 mol) in diethyl ether (250 mL) was transferred via cannula over a period of 1 h, to an ice-cooled 2L flask containing 1M LAH in diethyl ether (1 L; 1 mol). Upon completion of addition, the reaction mixture was allowed to slowly rise to room temperature (without removal of the ice bath), and stirring was



continued for a total of 16 h. The excess reagent was quenched at 0°C with 40 mL water, then 80 mL 5% NaOH, and then 40 mL water. The aluminum salts were filtered through a sintered glass funnel, and the ethereal solution was concentrated to pale yellow oil (69 g; 93% mass balance) which was dissolved in dioxane (200 mL) and 6 M aqueous hydrochloric acid (60 mL). After 30 min, the reaction mixture was brought to pH 8 by slow addition of saturated aqueous sodium bicarbonate solution and the total volume of the reaction mixture was brought to ~500 mL by addition of water. Di-tert-butyl dicarbonate (89 g; 410 mmol) was added portionwise and stirring was allowed to proceed for 16 h. The mixture was concentrated to ~300 ml and extracted (3x) with ethyl acetate. The combined organics were washed with saturated aqueous ammonium chloride, water, and brine, dried over magnesium sulfate, and concentrated to afford 114 g of a pale yellow oil. This crude material was dissolved in hot hexane and slowly crystallized upon cooling to -4°C. The colorless crystals were filtered to provide 44 g (50%, 3 steps) of neoN-B alcohol (**13**). ^1H NMR ($CDCl_3$) δ 4.67 (bs, 1 H), 3.37 (s, 2H), 3.13 (m, 2H) 1.50 (m, 2H), 1.43 (s, 9H), 0.90 (s, 6H).

12. The structures of all numbered compounds were consistent with the IR, ^1H-NMR, ^{13}C-NMR, and mass spectra obtained with the exception of intermediates **4** and **4a**, which were not isolated.

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