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A New Protecting Group for the Synthesis of Complex Sulfonates

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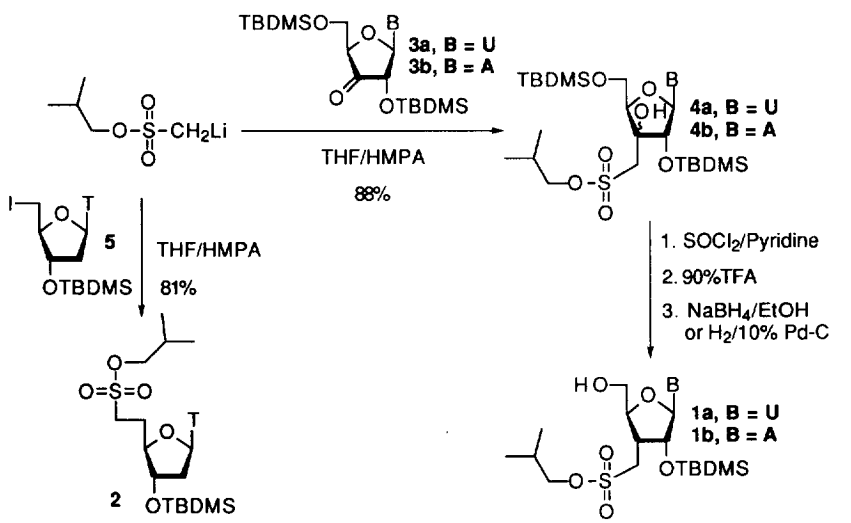
Abstract: The isobutyl ester proved to be a useful protecting group for the construction of sulfonate-containing analogs of nucleosides. The syntheses of useful uridine or adenosine 3'-C-methanesulfonate analogs **1a** or **1b** that fail when using ethyl or isopropyl sulfonate esters, are readily accomplished with the isobutyl ester as a protecting group. In addition, alkylation reactions to give homologated sulfonates such as **2** are also much more facile when using the isobutyl protecting group.

The quest for bioactive isosteres of carboxylates, phosphates and sulfates has promoted substantial interest in the development of new methodology for the synthesis of complex sulfonates and sulfonamides. Recently, a variety of new or relatively unused methods for the synthesis of these molecules have been applied to the construction of sulfonyl-containing oligonucleotide, phospholipid and peptide analogs.[1, 2a, 2b, 3] Many of these syntheses exploit the reactivity of nucleophilic α-lithio mesylates or related compounds (such as sulfonate-stabilized Horner Emmons reagents) with electrophiles such as primary iodides, aldehydes and ketones (Scheme 1). In this communication we report the development of a simple, though previously unused protecting group for the sulfonate moiety, the isobutyl ester. The use of this protecting group leads to enhanced yields during the reaction between α-lithio mesylates and various electrophiles.

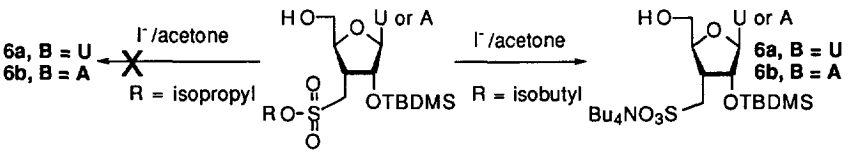
Scheme 1



A few years ago, we reported the synthesis of a variety of complex sulfonates derived from nucleoside and carbohydrate precursors. In these syntheses, we used the isopropyl ester as a blocking

group for the sulfonate, since it is relatively stable toward a variety of reaction conditions, yet is cleaved upon treatment with tetra-N-butylammonium iodide or ammonia.[4,5] Using this protecting group we were able to synthesize and homologate 5'-C-sulfonate-linked oligonucleotides.[2] More recently, we completed the stereocontrolled four steps synthesis of a 3'-C-isopropoxysulfonylmethyl derivative of uridine, initiated via the nucleophilic addition of an isopropyl mesylate anion to 3'-ketonucleoside **3a**.[6] However, we found that treatment of this 3'-C-isopropyl sulfonate with iodide ion did not result in deblocking of the protecting group (Scheme 2). Compounding this problem, we found that this ester and related 3'-C-sulfonate isopropyl ester derivatives often suffered cleavage/degradation and other undesirable reactions. For example, these esters were not completely stable to hydrogenation conditions, flash chromatography or prolonged storage. Moreover, these sulfonate esters appeared to be susceptible to degradation under the acidic conditions employed during nucleoside glycosidation or protecting group manipulations. Such difficulties with isopropyl sulfonates had also been reported by other groups.[7,8]

Scheme 2



Given the sometimes problematic nature of the isopropyl sulfonate protecting group, we sought an alternate protecting group that would be more robust toward acidic or solvolytic conditions, yet would be easily removed by soft nucleophiles such as iodide ion. We started with the initial assumption that the instability of the isopropyl sulfonates was due to relatively facile heterolysis to give a secondary carbonium ion. We therefore chose to examine the reactivity of primary sulfonate esters such as ethyl, isobutyl and neopentyl. It quickly became apparent that the ethyl sulfonate was too readily cleaved by nucleophiles, therefore limiting its utility in multistep synthetic processes. Conversely, the neopentyl ester was even harder to deblock than the isopropyl ester. We thus chose to concentrate our efforts on transformations of isobutyl mesylates.

Isobutyl mesylate was prepared in virtually quantitative yield from mesyl chloride and isobutyl alcohol.[9] The addition of α-lithio isobutyl mesylate to 3'-ketonucleosides proceeded in excellent yields (Scheme 1).[10] The isobutyl sulfonate ester stood up well to a variety of subsequent reactions and showed no tendency to undergo degradation during chromatography or storage. Elimination to the unsaturated sulfonate, followed by reduction with sodium borohydride or hydrogenation gave the saturated uridine and adenosine analogs in excellent yield. It is especially worth noting that under similar conditions, the corresponding isopropyl sulfonates gave very poor yields, because they were unstable to hydrogenation

and chromatography. In addition, we were unable to cleanly deblock these isopropyl derivatives, even by treatment with excess iodide ion under vigorous conditions. However, the isobutyl sulfonates **1a** and **1b** were readily deblocked by treatment with Bu_4NI to give the desired nucleoside sulfonates (Scheme 2).[11]

Having completed the synthesis of two desired nucleoside sulfonates, we were interested in checking the utility of the isobutyl ester for the synthesis of the previously reported 5'-C-sulfonates (Scheme 1). The alkylation of α-lithio isobutyl mesylate with the 5'-deoxy-5'-iodo-thymidine derivative **5** gave the desired product **2** in substantially higher yield than for the analogous reaction with the isopropyl mesylate. Moreover, deblocking of isobutyl sulfonate **2** with iodide was much more facile than for the isopropyl analog. Complete deblocking of the isopropyl analog of **2** required extended reaction time and the use of 12 equivalents of Bu_4NI, whereas just 2 equivalents of Bu_4NI converted the ester **2** into its corresponding sulfonate salt in quantitative yield, with relatively short reaction times.

We have demonstrated the virtually quantitative addition of isobutyl mesylate anion to 3'-ketonucleosides, its facile alkylation with 5'-iodothymidine derivatives and the subsequent efficient deblocking processes. These reactions demonstrate the advantage of utilizing an isobutyl ester as a protecting group during the synthesis of complex sulfonates. This ester is stable to prolonged storage and a variety of reaction conditions that degrade isopropyl or ethyl sulfonates. Yet, the isobutyl ester is more easily removed than the isopropyl ester.

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9. Truce, W. E.; Vrencur, D. J. *J. Org. Chem.* **1970**, *35*, 1226. Isobutyl mesylate: ^1H NMR ($CDCl_3$) 3.91 (d, 2 H, J = 7.5 Hz), 2.92 (s, 3H), 1.97 (m, 1H), 0.92 (2d, 6H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 75.9, 37.0, 28.1, 18.5 (2C).
10. A general procedure for the addition of isobutyl mesylate anion to 3'-keto nucleosides: A dry flask containing isobutyl mesylate (21 mg, 0.15 mmol) in THF/HMPA (15:1) (1 mL) was cooled to -78 °C under N_2. To this was added n-BuLi solution in hexane (2.5 M, 65 uL, 0.16 mmol) via syringe. The solution was stirred at -78 °C for 20 min before a solution of 3'-keto nucleoside (0.1 mmol) in 0.1 mL of THF was added dropwise. The reaction was maintained at -78 °C for an additional 60 min. At this point, TLC showed a complete loss of starting material and conversion to a product of greater polarity.

The reaction was then quenched with 0.2 mL of sodium phosphate buffer (pH 7.0) and the cooling bath was removed. The suspension was filtered and evaporated. The residue was then coevaporated with water to remove residual isobutyl mesylate. The crude product was further purified by silica gel flash chromatography (starting with EtOAc : hexane = 3:7, and gradually increasing the amount of EtOAc).

2', 5'-Di(*t*-butyldimethylsilyl) -3'-(Isobutoxysulfonylmethyl)Uridine (**4a**): 55 mg, 88%. Major isomer: ^{1}H NMR ($CDCl_3$) δ 8.78 (br s, 1 H), 7.86 (d, 1 H, $J_{6,5}$ = 8.4 Hz), 5.71 (s, 1 H), 5.61 (d, 1 H, $J_{5,6}$ = 8.4 Hz), 4.79 (s, 1H), 4.34 (s, 1H), 4.23 (s, 2H), 4.05 (m, 1H), 4.01 (d, 2H, J = 6.4 Hz), 3.59 (dd, 2H, J = 14.4 Hz), 2.01 (m, 1H)), 0.96 (2d, 6H, J = 6.4 Hz), 0.93, 0.91 (2s, 18 H), 0.24, 0.20, 0.17, 0.15 (4s, 12 H); ^{13}C NMR ($CDCl_3$) δ 162.8, 150.2, 140.7, 101.1, 90.8, 82.2, 82.1, 79.4, 76.0, 61.5, 52.1, 28.2 (2C), 25.9 (3C), 25.7 (3C), 18.6 (2C), -4.4, -5.4, -5.6, -5.7; HRMS for $C_{26}H_{51}N_2O_9SSi_2$ [M + H$^+$], calcd. 623.2855; found, 623.2875.

2', 5'-Di(*t*-butyldimethylsilyl)-3'-(Isobutoxysulfonylmethyl)Adenosine (**4b**): 56 mg, 87%. ^{1}H NMR ($CDCl_3$) δ 8.34 (s, 1 H), 7.99 (s, 1 H), 5.80 (s, 1 H), 5.66 (br s, 2 H), 4.78 (s, 1 H), 4.17 (m, 1H), 4.05 (m, 2H), 3.95 (m, 2H), 3.76 (d, 2 H, J = 7.2 Hz), 2.04 (m, 1H), 0.98 (2d, 6H, J = 7.2 Hz), 0.95, 0.91 (2s, 18 H), 0.15, 0.09, 0.06 (4s, 12 H); ^{13}C NMR ($CDCl_3$) δ 155.5, 152.5, 148.5, 140.0, 119.8, 91.8, 82.9, 82.3, 79.3, 75.8, 60.6, 51.7, 28.3, 25.9 (6C), 18.7 (2C), 18.2, 17.9, -3.9, -5.1, -5.5, -5.6; HRMS for $C_{27}H_{52}N_5O_7SSi_2$ [M + H$^+$], calcd. 646.3113; found, 646.3147.

11. A general procedure for deblocking of isobutyl sulfonates: The isobutyl sulfonate **1a** or **1b** (0.02 mmol) and Bu_4NI (15 mg, 0.04 mmol) were stirred in acetone (0.5 mL) at 55 °C overnight. Acetone was then removed under reduced pressure. Silica gel chromatography with EtOAc/EtOH containing 2% (v/v) Et_3N (starting with EtOAc : EtOH = 7:1, and gradually increasing the amount of EtOH) gave a yellowish foam.

2'-*t*-Butyldimethylsilyl-3'-Deoxy-3'-(Tetrabutyl Ammonium Salt Sulfonylmethyl)Uridine (**6a**): 13 mg, 97%; ^{1}H NMR ($CDCl_3$) δ 8.34 (d, 1H, $J_{6,5}$ = 8.4 Hz), 5.63 (d, 1H, $J_{5,6}$ = 8.4 Hz), 5.59 (s, 1H), 4.62 (m, 1H), 4.33 (m, 1H), 4.22 (m, 1H), 4.01 (m, 1H), 3.72 (m, 1H), 3.27 (m, 8H), 3.13 (dd, 1H), 3.06 (m, 1H), 2.86 (m, 1H), 2.60 (m, 1H), 1.66 (m, 8H), 1.43 (m, 8H), 1.00 (t, 12H), 0.89 (s, 9H), 0.24, 0.13 (2s, 6H); ^{13}C-NMR ($CDCl_3$) δ 163.0, 150.0, 140.8, 100.8, 91.0, 86.9, 80.3, 60.8, 59.1, 48.4, 37.9, 25.8, 24.1, 19.7, 13.5, -4.4, -5.2.

2'-*t*-Butyldimethylsilyl -3'-(Tetrabutyl Ammonium Salt Sulfonylmethyl)-3'-Deoxy Adenosine (**6b**): 13 mg, 95%; ^{1}H NMR ($CDCl_3$) δ 8.41 (s, 1 H), 8.18 (s, 1 H), 5.94 (s, 1 H), 4.43 (m, 1 H), 4.12 (d, 1H, J = 8.8 Hz), 3.98 (d, 1H, J = 16.0 Hz), 3.69 (d, 1H, J = 16.0 Hz), 3.14 (m, 8H), 2.75 (m, 1H), 2.52 (m, 1H), 2.33 (m, 1H), 1.58 (m, 8H), 1.37 (m, 8H), 0.95 (t, 12H, J = 9.5 Hz), 0.90 (s, 9H), 0.23, 0.15 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.5, 152.3, 148.5, 139.8, 119.8, 92.2, 86.1, 77.6, 61.7, 58.8, 38.7, 34.3, 25.5, 23.9, 19.6, 13.4, -4.7, -5.1.

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