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ω-Aminooxyalkanesulfonic acids. Novel nucleophilic sulfoalkylation reagents

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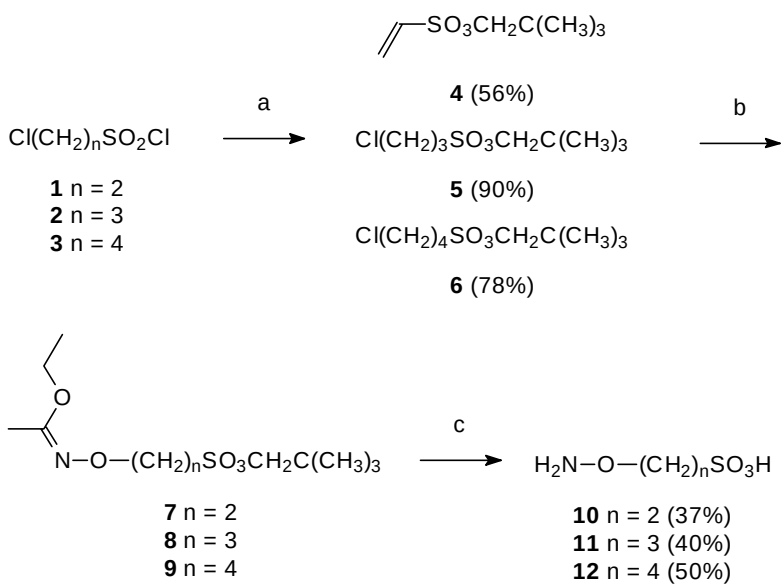
Abstract—Electrophilic sulfoalkylation reagents, such as 1,3-propanesultone, are widely used to enhance the hydrophilicity of polymers, proteins, etc. In this report, a series of nucleophilic sulfoalkylation reagents [$NH_2O(CH_2)_nSO_3H$, $n=2$, 3, 4] were prepared from the corresponding chloroalkylsulfonyl chlorides.

Organosulfonic acids (RSO_3H) have such low pK_a values (<0),[1] that they are essentially always deprotonated in aqueous solution. The ionic group has the effect of increasing the hydrophilicity of the material relative to the hydrocarbon analogue (RH). It is often desirable to modify polymers,[2] proteins,[3,4] dyes,[5] and nucleosides[6] in this manner to increase surface wetability, or aqueous solubility, or decrease non-specific binding to hydrophobic surfaces. The sulfonic acid functionality can be introduced directly onto aromatic hydrocarbons via classical electrophilic substitution. A recent twist involves the use of concentrated sulfuric acid[7] or chlorosulfonic acid[8] with dielectric heating. Alternatively, nucleophilic substitution of alkylhalides by bisulfite can lead to alkanesulfonic acids.[9] More often existing amine, alcohol, thiol, amide, or carboxylic acid groups have been reacted with 1,3-propanesultone[10] to give the 3-sulfopropyl-modified substrates. Nucleophilic sulfoalkylation reagents have received little attention by comparison. The amino acid, taurine



Scheme 1. (a) Neopentyl alcohol, pyridine, dichloromethane, 0°C to ambient; (b) ethyl *N*-hydroxyacetimidate, sodium ethoxide, ethanol; (c) 3N aq. HCl, reflux.

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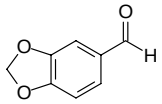
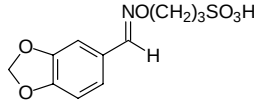
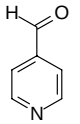
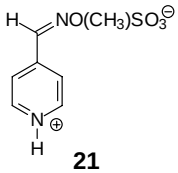
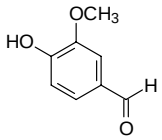
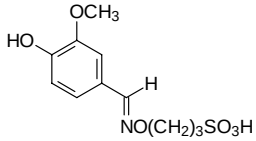
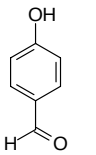
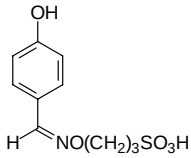
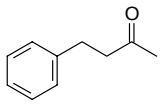
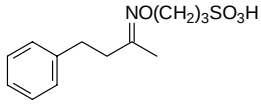
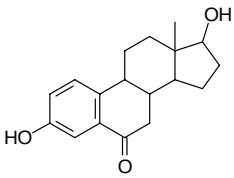
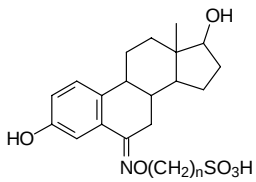
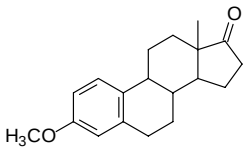
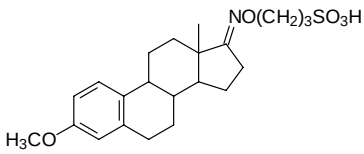
Table 1. Sulfoalkylation of aldehydes and ketones

Sulfoalkylation Reagent	Carbonyl Substrate	Oxime
11	 **13**	 **20**
11	 **14**	 **21**
11	 **15**	 **22**
11	 **16**	 **23**
11	 **17**	 **24**
10 **11** **12**	 **18**	 **25** n = 2 **26** n = 3 **27** n = 4
11	 **19**	 **28**

($NH_2CH_2CH_2SO_3H$) has been used to enhance the aqueous solubility of peptidic renin inhibitors,[11] improve the biocompatibility of polyurethane implants,[12] prevent protein fouling of polysulfone membranes,[13] and modify the surface of polyacrylonitrile fibers.[14] In each case taurine was coupled to free carboxylic acid groups on the substrate. The paucity of nucleophilic sulfoalkylation reagents may lie in the relatively narrow reactivity of ω-aminoalkanesulfonic acids like taurine. Coupling to carboxylic acids requires neutral to basic pH; reaction with aldehydes and ketones usually requires removal of the generated water, and the imines that are formed are subject to hydrolysis. We reasoned that ω-aminooxyalkanesulfonic acids would have broader applicability. Such *O*-substituted hydroxylamines have lower pK_a values than the corresponding amines and thus can be coupled to carboxylic acids even under acidic conditions.[15] They

also react with aldehydes and ketones to form stable oximes. To our knowledge no examples of ω-aminooxyalkysulfonic acids have been reported.

ω-Aminooxyalkanesulfonic acids (**10**–**12**) were prepared according to Scheme 1. Thus, ω-chloroalkanesulfonyl chlorides **2**, and **3**[16,17] were treated with neopentyl alcohol to afford the sulfonates **5**[18] and **6**. Under the same conditions 2-chloroethanesulfonyl chloride **1**, afforded the vinyl sulfonate **4**. Sulfonates **4**–**6** all reacted with the sodium salt of ethyl *N*-hydroxyacetimidate to give the *N*-protected *O*-substituted hydroxylamine derivatives **7**–**9**. Hydrolysis in refluxing hydrochloric acid cleaved the imidate protecting group yielding the desired ω-aminooxyalkanesulfonic acids **10**–**12**[†] in the yields shown.

The newly synthesized ω-aminooxyalkanesulfonic acids **10**–**12** were reacted with representative aldehydes and ketones (Table 1) to demonstrate their effectiveness as sulfoalkylation reagents. Thus, simple aromatic aldehydes (**13**–**16**) reacted rapidly and efficiently with 3-aminooxypropanesulfonic acid **11** to afford the corresponding 3-sulfopropyl aldoximes **20**–**23** in 90–99% yield.[‡] Ketones (**17**–**19**) required longer reaction times (up to 3 days) at ambient temperatures, but gave equally efficient yields of the oximes **24**–**28**.[§]

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[†] Typical procedure: 3-Aminooxypropanesulfonic acid (**11**). To a freshly prepared solution of sodium ethoxide, prepared from sodium (246 mg, 10.7 mmol) and absolute ethanol (5 mL), was added a solution of ethyl *N*-hydroxyacetimidate (1.14 g, 10.7 mmol) in absolute ethanol (2 mL) dropwise with stirring under argon. After stirring at ambient temperature for 10 min, a solution of neopentyl 3-chloropropanesulfonate **5** (2.28 g, 10 mmol) in absolute ethanol (3 mL) was added. Stirring was continued for 7 days. The reaction mixture was poured into a saturated ammonium chloride solution (50 mL) and the mixture was extracted with ethyl acetate (100 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting mixture was refluxed with 3N hydrochloric acid (40 mL) for 90 min. After cooling to ambient temperature, the reaction mixture was evaporated to dryness and the remaining material was triturated with methanol (~10 mL). The white solid was filtered off and dried in the air to give pure product (660 mg).
All compounds had satisfactory CHN analysis for the structure shown. **10**: mp 258–260°C (dec.). ^{1}H NMR (D_2O) δ 4.22 (2H, t, J=5.8), 3.09 (2H, t, J=5.8). ^{13}C NMR (D_2O) δ 71.2, 50.3; **11**, mp 190–192°C (dec.). ^{1}H NMR (300 MHz, D_2O) δ 4.06 (2H, t, J=6.2), 2.88 (2H, t, J=6.6), 1.98 (2H, m). ^{13}C NMR (D_2O) δ 74.4, 48.0, 23.9; **12**, ^{1}H NMR (D_2O) δ 3.97 (2H, m), 2.80 (2H, m), 1.70 (4H, m). ^{13}C NMR (D_2O) δ 75.7, 51.3, 26.8, 21.5.

[‡] Typical aldoxime formation: A mixture of **11** (31.0 mg, 0.2 mmol), **13** (0.2 mmol) and anhydrous sodium acetate (85 mg, 1 mmol) in dry methanol (2 mL) was stirred at ambient temperature for 3 h. Desired product was separated by reversed phase preparative HPLC (μ-Bondapak C^{18}; 30:70 acetonitrile/0.05% aqueous trifluoroacetic acid; λ=254 nm; 45 mL/min). Fractions were collected and lyophilized to give **20**. ^{1}H NMR (300 MHz, CD_3OD) δ 8.00 (1H, s), 7.16 (1H, d, J=1.7), 6.99 (1H, dd, J=1.7, 6.9), 6.81 (1H, d, J=8.1), 5.97 (2H, s), 4.21 (2H, t, J=6.3), 2.96–2.88 (2H, m), 2.22–2.10 (2H, m). ^{13}C NMR (75 MHz, CD_3OD) δ 149.8, 128.2, 124.2, 109.3, 106.4, 102.9, 73.4, 49.5, 26.2. ESI-MS m/z 288.0 $(M+H)^+$.

[§] Typical ketoxime formation: A mixture of **11** (23 mg, 0.15 mmol), **17** (14.8 mg, 0.1 mmol) and anhydrous sodium acetate (62 mg, 0.75 mmol) in dry methanol (1 mL) was stirred at ambient temperature for 72 h. Desired product was isolated by reversed phase preparative HPLC (μ-Bondapak C^{18}; 30:70 acetonitrile/0.05% aqueous trifluoroacetic acid; λ=254 nm; 45 mL/min). Fractions were collected and lyophilized to give **24**. ^{1}H NMR (300 MHz, CD_3OD) δ 7.40–7.10 (5H, m), 4.1–4.04 (2H, two sets of triplets), 2.92–2.76 (4H, m), 2.60 and 2.45 (2H, m, ratio: 1/1.5), 2.16–2.00 (2H, m), 1.84 and 1.74 (3H, s, ratio: 1.5/1). ^{13}C NMR (75 MHz, CD_3OD) δ 159.8, 159.1, 142.6, 129.6, 129.5, 129.4, 127.3, 127.2, 49.6, 49.5, 38.5, 33.8, 32.6, 32.4, 26.1, 20.2, 14.3. ESI-MS m/z 286.2 $(M+H)^+$.