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# A novel synthetic route to 2-alkylpropane-1,3-sultones and its application to the synthesis of 2-alkyl derivatives of tramiprosate

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**Abstract**—A practical synthetic route to various 2-alkylpropane-1,3-sultones, the key intermediates for the preparation of 2-substituted homotaurines as analogs of tramiprosate, was developed.


Tramiprosate (3-amino-1-propanesulfonic acid or 3APS, homotaurine, ALZHEMED™) is a candidate drug that has recently completed a phase III clinical trial for treating Alzheimer's disease (AD) in North America (United States, Canada). This small ionic compound binds preferably to soluble amyloid β-peptide (Aβ) and decreases $A\beta_{42}$-induced cell death in neuronal cell culture. Treatment of TgCRND8 mice with tramiprosate resulted in significant reduction in the brain amyloid plaque load and a significant decrease in the cerebral levels of soluble and insoluble $A\beta_{40}$ and $A\beta_{42}$.[1] This compound is one of the first drug candidates that are potentially disease-modifying agents in treating AD. To understand further the impact of different substitution groups on the activity of tramiprosate, a series of analogs were necessary for biological evaluation. Compounds bearing different substituting groups at C-2 position of 3-amino-1-propanesulfonic acid skeleton are one of the sub-classes of homotaurine analogs targeted in the current project (Fig. 1).

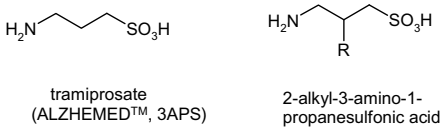


**Figure 1.**

A quick access to the C-2 substituted analogs of 3-amino-1-propanesulfonic acid is the ring-opening reaction of the corresponding 2-substituted propane-1,3-sultones with different nucleophiles; this further requires easy preparation of the corresponding 2-alkylpropane-1,3-sultones. A number of synthetic methods for preparing propane-1,3-sultones were reported in the literature.[2] Cyclization of 3-hydroxyl-1-propanesulfonic acid and its derivatives[3] and sulfonation of alkenes with sulfur trioxide[4] were the first methods for making simple sultones. For the syntheses of more complex sultones, reactions such as alkylation of sultones,[5] cyclization of alkanedisulfonate,[6] and cyclization of allylated sulfonate[7] have been reported. The synthesis specifically related to the 2-alkylpropane-1,3-sultone is the one involving sulfur dioxide or thionyl chloride insertion into functional vinylic Grignard reagents, which afforded, after oxidation, α,β-unsaturated sultones.[8–10] Another synthetic route was the cyclization of 2,3-epoxyalkanesulfonylchlorides to the unsaturated sultones.[11] Although those two last methods could be applied to some of the target compounds, a more direct, versatile, and simpler method of preparation was indeed necessary for making different analogs for the project. Here a practical synthetic route to 2-alkylpropane-1,3-sultones starting from α-bromomethyl ketones either commercially available or easily prepared from the corresponding ketones is presented (Scheme 1).

The reaction was initiated by generating the lithium salt of ethyl methanesulfonate with LiHMDS in THF at

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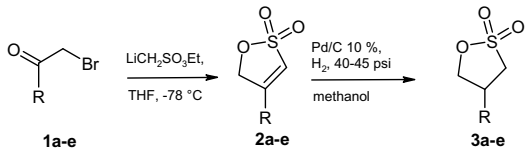



**R**: **a,** 1-adamantyl; **b,** *t*-butyl; **c,** α,α-dimethylbenzyl; **d,** phenyl; **e,** ethyl.

**Scheme 1.** A two-step transformation of α-bromomethyl ketones to 2-substituted propane-1,3-sultones.

−78 °C,[12] and the resulting anion was reacted with α-bromomethyl ketones (**1a**–**e**) to afford, after warming to −50 °C, the corresponding 1,2-unsaturated sultones (**2a**–**e**). Hydrogenation of the 1-propene-1,3-sultones led to the corresponding 2-alkylpropane-1,3-sultones (**3a**–**e**) in good yields (Table 1). This two-step transformation proceeded smoothly with a variety of α-bromomethyl ketones, including sterically hindered ones. For example, this two-step transformation starting from 1-adamantyl bromomethyl ketone (**1a**) gave 2-(1-adamantyl)-propane-1,3-sultone (**3a**) in almost quantitative yield. Good yields (40–67%) were also achieved with other sterically hindered α-bromomethyl ketones such as bromomethyl *t*-butyl ketone (**1b**) and bromomethyl α,α-dimethylbenzyl ketone (**1c**). Aryl bromomethyl ketone **1d** and bromomethyl ethyl ketone **1e** also provided the corresponding 1,2-unsaturated sultones in good yields. In the case of phenyl derivative **2d**, the hydrogenation step resulted in sultone ring-opening, providing 2-phenyl-1-propanesulfonic acid as the final product.

Figure 2 describes a plausible mechanism explaining how the unsaturated sultone is formed. The initial step is presumably the nucleophilic attack of the methanesulfonate anion to the carbonyl in **I**, followed by an intramolecular $S_N2$ displacement of the bromine by the in situ formed oxygen anion at the adjacent carbon to give epoxide **II**. Base-catalyzed ring-opening of the epoxide led to allylic alcoholate **III**, which is transformed to 1,2-unsaturated sultone **IV** upon cyclization. Similar base-catalyzed reactions in which epoxy esters provided cyclic α,β-unsaturated lactones have been reported in the literature.[13,14] An example closely related to the current work, in which 2,3-epoxyalkanesulfonylchlorides were cyclized to unsaturated sultones upon the treatment with base, has been published.[11]

**Table 1.** Reaction of α-bromomethyl ketones with lithioethylmethanesulfonate and the preparation of propane-1,3-sultones

| **1a**–**e** | R | **2a**–**e** (%) | **3a**–**e** (%) |
|---|---|---|---|
| **a** | 1-Adamantyl | 97 | 98 |
| **b** | *t*-Butyl | 75 | 89 |
| **c** | α,α-Dimethylbenzyl | ND | 40[a] |
| **d** | Phenyl | 70 | 96[b] |
| **e** | Ethyl | 55 | 59 |

[a] Yield for two steps.
[b] 2-Phenylpropane-1-sulfonic acid isolated.

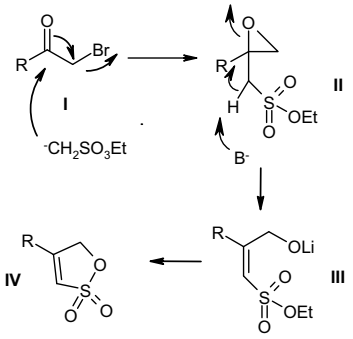
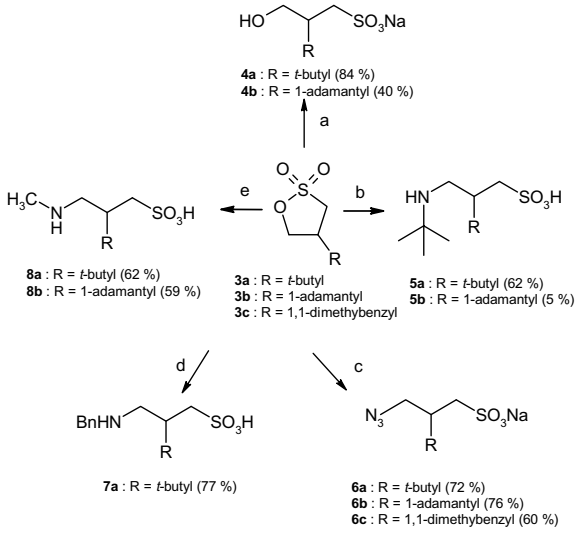


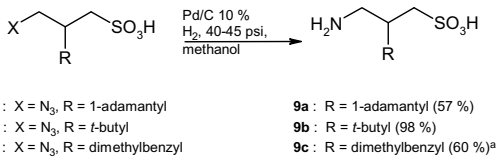

**Figure 2.** Proposed mechanism for the formation of 1-propene-1,3-sultones **IV**.

With 2-substituted propane-1,3-sultones in hand, we turned our attention to the sultone ring-opening with various nucleophiles (Scheme 2). Opening of different sultones ($R$ = *t*-butyl, 1-adamantyl, α,α-dimethylbenzyl) was performed using various nucleophiles such as sodium azide, water, as well as hindered and unhindered amines. The solvent of choice for performing these reactions has been found to be DMF with prolonged reaction times (between 24 and 72 h) and at elevated temperature (up to 130 °C). Under these conditions, good yields (59–77%) of 3-amino-1-propropanesulfonic acid derivatives (**5a**, **6a**–**c**, **7a**, and **8a**,**b**) were obtained with the exception of **5b** (5% yield), which seems to have encountered severe double steric effect from both the sultone (1-adamantyl) and the nucleophile (*t*-butyl). Sodium hydroxide opening of the sultones also gave in modest to good yields the sulfonates (**4a**,**b**). Sultones (**3a**–**c**) ring-opening by sodium azide[15] gave the corresponding azido compounds (**6a**–**c**) in good yields (60–72%).

Finally, the three azido derivatives **6a**–**c** were converted, upon hydrogenolysis, to the corresponding 2-substituted




**Scheme 2.** Ring opening of sultones with various nucleophiles. Reagents and conditions: (a) NaOH, DMF/water, reflux, 24 h; (b) *t*-butylamine, DMF, 130 °C, 48 h; (c) $NaN_3$, DMF, 130 °C, 36 h; (d) $BnNH_2$, DMF, 130 °C; (e) $MeNH_2$, THF, 130 °C, sealed tube, 72 h.




**6a** : X = $N_3$, R = 1-adamantyl
**6b** : X = $N_3$, R = *t*-butyl
**6c** : X = $N_3$, R = dimethylbenzyl

**9a** : R = 1-adamantyl (57 %)
**9b** : R = *t*-butyl (98 %)
**9c** : R = dimethylbenzyl (60 %)[a]

**Scheme 3.** Formation of 2-alkyl-3-amino-1-propanesulfonic acids **9a**–**c**. [a] Yield from sultone **3c**.

derivatives of 3-amino-1-propanesulfonic acid (**9a**–**c**) in good yields (Scheme 3).

In conclusion, a novel methodology has been developed that allows rapid construction of several 2-alkyl-propane-1,3-sultones in good to excellent yields. The two-step transformation is easy, practical, and utilizes only simple reagents such as ethyl methanesulfonate and α-bromomethyl ketones, the latter often commercially available or conveniently synthesized. The sultone products, as the key intermediates for the preparation of 2-alkyl-3-amino-1-propanesulfonic acids, were successfully converted to the desired tramiprosate derivatives in good yields.

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12. To a stirred solution of lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 42 mL, 42 mmol, 1.5 equiv) at −78 °C was added dropwise a solution of ethyl methanesulfonate (4.3 mL, 10 mmol, 1.5 equiv) in dry THF (5 mL). The mixture was stirred at −78 °C for 30 min followed by the addition of a solution of 1-bromopinacolone (5.0 g, 28 mmol) in dry THF (10 mL). The mixture was then stirred at −78 °C for 2 h and later stirred at −50 °C for an additional 2 h. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (100 mL), extracted with EtOAc (3 × 100 mL). The combined organic layers were washed subsequently with water (2 × 50 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography using hexane/EtOAc (90:10) to provide 3.8 g of **2b** (75% yield): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.21 (s, 9H), 5.12 (d, $J = 2.0$ Hz, 2H), 6.45 (t, $J = 2.0$ Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 28.7, 33.8, 71.7, 116.4, 161.7. HRMS for $C_7H_{13}O_3S$; *m/z* 177.0585 (expected), 177.0593 (found).
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