Dihydro-5,6-benzo[c]cinnoline. This derivative is prepared by electrolysis of benzo[c]cinnoline at −1.1 V in aqueous medium (ethanol–water, 1/2, NaCl 0.2 M). After a two-electron reduction, the solution is cooled, and the dihydro derivative is separated by filtration under argon and characterized by its melting point (122 °C) and its ^{1}H NMR data. This derivative has been previously prepared by catalytic hydrogenation of benzo[c]cinnoline.[4]

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Homogeneous Nucleophile Exchange. 2. Silver-Free, Direct Synthesis of Primary Alkyl Sulfonates from Alkyl Halides

Roger C. Hahn*

Department of Chemistry, Syracuse University, Syracuse, New York 13244-1200

Jan Tompkins

Department of Liberal Arts and Sciences, College of Health Related Professions, State University of New York, Health Science Center, Syracuse, New York 13210

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Recently, on finding that homogeneous quaternary ammonium halide catalyzed alkyl halide exchange[1] never had been systematically explored, we used this process to develop a rapid, simple, solvent-free method for bromide–chloride, chloride–iodide, and bromide–iodide exchange and applied it to high-yield syntheses of certain α,ω-hetero dihalides.[2] The ability to achieve, in particular, reversible chloride–iodide exchange encouraged us to attempt the unprecedented homogeneous conversion of alkyl halides to alkyl sulfonates; some initial successes are reported herein.

Although, historically, the major role of sulfonate ions has been as leaving groups in S_N1 or S_N2 type processes, Zefirov noted recently[3] that nucleophilicity scales such as the Swain–Scott scale "completely ignore the nucleophilic properties of ... such a typical nucleofuge as the *p*-toluenesulfonate ion". Indeed, Kevill[4] has demonstrated the ability of arenesulfonate ions (as tetrabutylammonium salts) to react in S_N2 fashion with trimethyl- and triethyloxonium ion, methyl triflate, and methyl perchlorate, and MacDonald has reported oxidatively assisted displacement of iodide by tosylate.[5] However, unassisted S_N2 type displacement of halide ions by sulfonate ions has not been previously demonstrated. Synthetically, alkyl sulfonates usually are made from the corresponding alcohols or from halides through the agency of silver sulfonates.[6]

In our approach to halide–sulfonate exchange, two observations from Cl–I exchange were used: High temperatures were needed to achieve practical rates (>160 °C for Cl–I), and R′X in eq 1 had to be selectively distilled out

$$RX + R'OTs \xrightarrow[\text{heat}]{\text{catalyst}} ROTs + R'X \qquad (1)$$

$$X = Cl, Br, I$$

to drive the reaction forward. Cheaply available methyl tosylate allowed both of these conditions to be met. In the first experiment (eq 2), we were pleased to find that the reaction could be pushed essentially to completion (disappearance of CH_3OTs) in 2 h. Also, high chemoselectivity was indicated by the near absence of bromoethyl tosylate and dimethylene ditosylate; 97% pure 2-chloroethyl tosylate was isolated in 68% yield (not optimized). Rough thermal comparison with Cl–I exchange conditions suggests that displacement of bromide by tosylate is relatively facile.

$$\underset{\text{bp 106 °C}}{ClCH_2CH_2Br} + \underset{\text{144 °C (5 mm)}}{CH_3OTs} \xrightarrow[135\ °C]{Bu_4N^+Br^-} \underset{\text{bp 153 °C (0.3 mm)}}{ClCH_2CH_2OTs} + \underset{\text{bp 4 °C}}{CH_3Br} \qquad (2)$$

The above success led us to attempt benzenesulfonate–chloride exchange (eq 3); ^{1}H NMR analysis indicated ca. 30% conversion under the conditions shown, but reaction mixture darkening and deceleration of gas evolution made it appear likely that catalyst decomposition was occurring.

$$Cl(CH_2)_6Cl + CH_3O_3SPh \xrightarrow[170\ °C]{Bu_4N^+Br^-} Cl(CH_2)_6O_3SPh + CH_3Cl \qquad (3)$$

Workup gave a 23% isolated yield of 6-(chlorohexyl)-1-benzenesulfonate. A simple primary alkyl chloride thus can be replaced, but more severe conditions (and possibly more catalyst) are required, as expected.

On the other hand, sulfonate–iodide exchange was anticipated to occur readily, and we were particularly interested in selective conversion of the now economically available chloroiodomethane[2] to chloromethyl tosylate; this simple compound has not been reported previously. The reaction indicated in eq 4 therefore was attempted.

$$\underset{10\%\ \text{excess}}{ClCH_2I} + CH_3OTs \xrightarrow[\text{heat}]{Bu_4N^+Br^-} ClCH_2OTs + CH_3I \qquad (4)$$

However, it was found that, under the conditions used, $ClCH_2OTs$ was transformed into $CH_2(OTs)_2$ faster than it was being formed (eq 5). Because $ClCH_2OTs$ is the first known example of an α-tosyloxy halide, this behavior was not entirely predictable, but it is consistent with reports that α-alkoxy and α-acyloxy substituents greatly increase halide nucleofugality.[7] It is known also that α-halides

$$ClCH_2OTs + CH_3OTs \xrightarrow[\text{heat}]{Bu_4N^+OTs^-} TsOCH_2OTs + CH_3Cl \qquad (5)$$

greatly *decrease* leaving-group nucleofugality;[8] the iodide in $ClCH_2I$ therefore is less reactive than is an ordinary primary alkyl iodide.

The known, stable $CH_2(OTs)_2$[6a] readily crystallizes out of the reaction mixture; originally made by reaction of CH_2I_2 and AgOTs, and rarely studied since,[9] it now can

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be prepared easily and cheaply on any scale. Chloromethyl tosylate is easily separated from $CH_2(OTs)_2$ by vacuum distillation; at 1 atm and 25 °C it is an essentially nonvolatile liquid, stable to air, light, and moisture. It can be prepared also from $CH_2(OTs)_2$ by reaction with lithium chloride; the above-noted α-halide effect allows the reaction to be stopped after complete conversion of $CH_2(OTs)_2$, with no detectable formation of dichloromethane (eq 6).

$$TsOCH_2OTs + MX \xrightarrow[heat]{acetone} XCH_2OTs + MOTs \quad (6)$$

$$M = Li, Na; X = Cl, Br, I$$

In similar fashion, $CH_2(OTs)_2$ is converted rapidly and nearly quantitiatively to $BrCH_2OTs$ or ICH_2OTs by reaction with lithium bromide or sodium iodide, respectively (eq 6). In all of these reactions of $CH_2(OTs)_2$, we estimate displacement of the first tosylate group to occur at least 10^3 times faster than the second one. $BrCH_2OTs$ and ICH_2OTs also are nonvolatile liquids; ICH_2OTs is somewhat light-sensitive. *All of these halomethyl tosylates have been handled with great care to avoid exposure or contact, in view of their expected functional similarities to known carcinogens.*

The halide–sulfonate exchange methodology described herein is a novel, silver-free, acid-free route to primary sulfonates, including ω-haloalkyl sulfonates. Some of these are derivatives of alcohols that either are not readily available or simply do not exist as stable entities (e.g. the halomethanols). It is also a very convenient route to large-scale synthesis of quaternary ammonium (and presumably phosphonium) sulfonates, which already see use as supporting electrolytes and which now are under study as stoichiometric nucleophilic reagents.

The previously unknown halomethyl sulfonates, as heterodifunctional methanes and novel formaldehye equivalents, can be electrophiles, nucleophile sources, radical sources, carbenoid sources, and precursors to other novel difunctional methanes. Their properties and synthetic applications are under study.[10] The methodology by which they have been obtained, homogeneous nucleophile exchange, has not reached its full scope; this also is under active investigation.

Experimental Section

Starting materials (97% or higher purity) usually were used without further purification; preparative procedures have not been optimized. **Warning**: *Many of these compounds are known or suspected to be toxic and/or carcinogenic; geminal difunctional compounds are expected to be quite reactive.* Previously known compounds were identified by comparison of boiling points/melting points and ^1H NMR spectra with literature data. New compounds were assigned structures on the basis of chemical origin, physical properties, NMR spectra, and elemental analyses. NMR spectra were recorded for $CDCl_3$ solutions on a GE QE-300 spectrometer.

2-Chloroethyl Tosylate. The following conditions were used after an initial experiment with Amberlyst A-26 (chloride form) as the catalyst produced less than 10% conversion to the desired product before apparent catalyst breakdown occurred. 1-Bromo-2-chloroethane (28.6 g, 0.20 mol), methyl tosylate (28.0 g, 0.15 mol), and Bu_4NBr (2.2 g, ca. 2%) were heated together in a round-bottom flask fitted with a vigreux column. Vigorous bubbling occurred above 120 °C; after 2 h, the pot temperature was 135 °C, and bubbling had nearly ceased. Analysis (^1H NMR) showed a trace of CH_3OTs (δ 3.75, s), strong triplets at δ 4.25 and 3.67 (perfect fit for $ClCH_2CH_2OTs$), residual peaks for $Br(CH_2)_2Cl$, and small triplets (ca. 5%) at δ 4.29 and 3.49, assigned to $BrCH_2CH_2OTs$. The mixture was taken up in Et_2O (100 mL), washed with water (3 × 100 mL) and saturated brine, dried ($MgSO_4$), and stripped of solvent. The residue still contained Bu_4NBr, which was removed by column chromatography on SiO_2 (Et_2O). Solvent removal and careful distillation of the residue gave 24 g (68%) of $ClCH_2CH_2OTs$ (containing ca. 3% of $BrCH_2CH_2OTs$), bp 130–135 °C (0.2 mmHg) [lit.[11] bp 153 °C (0.3 mm)].

6-Chlorohexyl 1-Benzenesulfonate. After an initial experiment showed that complete sulfonate decomposition occurred at 190 °C, the following procedure was used: 1,6-Dichlorohexane (15.5 g, 0.10 mol), CH_3O_3SPh (17.2 g, 0.10 mol), and Bu_4NBr (2.0 g, ca. 3%) were heated together to 170 °C over 1.5 h; heating was stopped when the pot began to darken (very slow gas evolution). Analysis (^1H NMR) showed triplets for $ClCH_2$ (3.55) and $PhSO_3CH_2$ (4.06) in a ca. 4:1 ratio, corresponding to a dichloride–chlorohexyl sulfonate ratio of ca. 3:2. The crude product mixture was taken up in Et_2O, washed with water (4 × 75 mL), and dried over K_2CO_3. Solvent removal at 1 atm, $Cl(CH_2)_6Cl$ removal at 7 mm (bp 60 °C), CH_3O_3SPh removal at 0.7 mm (bp 85 °C), and Kugelrohr distillation of the residue afforded 6.5 g (23%) of the chlorohexyl sulfonate as a nearly colorless oil, bp 150–160 °C (0.2 mm): ^1H NMR δ 1.35 (m, 4 H), 1.68 (m, J = 7.3 Hz, 4 H), 3.48 (t, J = 6.6 Hz, 2 H, CH_2Cl), 4.05 (t, J = 6.65 Hz, 2 H, CH_2O_3SPh), 7.56 (t, J = 7.8 Hz, 2 H), 7.67 (t, J = 7.3 Hz, 1 H), 7.91 (d, J = 7.8 Hz, 2 H); ^{13}C NMR δ 24.49, 25.96, 28.47, 32.07, 44.67, 70.52, 127.61, 129.12, 133.61, 135.89. Anal. Calcd for $C_{12}H_{17}ClO_3S$: C, 52.07; H, 6.19. Found: C, 53.60; H, 6.20.

Reaction of Chloroiodomethane and Methyl Tosylate; Methylene Ditosylate and Chloromethyl Tosylate. CH_3OTs (41.0 g, 0.22 mol) and Bu_4NBr (4.0 g, ca. 0.012 mol) were heated together to 85 °C and then cooled to 40 °C. $ClCH_2I$ (35.2 g, 0.20 mol) was added, and the yellow-orange mixture was heated to 137 °C over 2 h; 1.4 mL of distillate (bp 36 °C; CH_3I) was collected. A ^1H NMR spectrum of the mixture showed peaks for CH_3I (δ 2.17), CH_3OTs (strongest), $ClCH_2I$ (4.97; next strongest), $ClCH_2OTs$, and $CH_2(OTs)_2$, the last two in ca. 2:1 ratio. *Absent* were peaks for CH_3Br, CH_2I_2, CH_2Cl_2, and ICH_2OTs; all of these had appeared in a previous mixture heated to higher temperatures. Heating of the current mixture 1 h more, to 141 °C, yielded 1.4 mL more of the distillate; the mixture turned dark cherry red. NMR analysis: CH_3OTs was gone; appreciable $ClCH_2I$ remained, and the $ClCH_2OTs$:$CH_2(OTs)_2$ ratio had changed to <1:2; traces of CH_2I_2, CH_2Cl_2, and ICH_2OTs were present. The pot material solidified. Crystallization from Et_2O gave a tan solid, which contained traces of quaternary salt; solution in hot benzene and flash chromatography gave a violet-pink solution, which was decolorized with aqueous $NaHSO_3$. Cooling deposited colorless crystals, which retained benzene tenaciously; overnight pumping at 0.1 mm removed 20 g of solvent to leave 15 g of $CH_2(OTs)_2$, mp 116–117 °C (lit.[6a] mp 117 °C). Concentration of the benzene mother liquor yielded a second crop (4 g). Samples of $CH_2(OTs)_2$ stored at room temperature in air for months show no detectable decomposition: ^1H NMR δ 2.46 (s, 6 H), 5.82 (s, 2 H), 7.27 (d, 4 H), 7.61 (d, 4 H); ^{13}C NMR δ 21.63, 87.89 (CH_2), 127.86, 129.71, 133.21, 145.35. $Bu_4N^+OTs^-$, the only quaternary salt seen in the product mixture, showed ^1H NMR absorptions at δ 1.12 (t, CH_3CH_2), 1.49 (clean sext, γ-CH_2), 1.69 (broad quint, β-CH_2), 2.32 (s, CH_3Ar; ca. 0.15 δ upfield from covalent tosylates), 3.32 (broad t, α-CH_2), 7.14 (d, Ar (H's ortho to CH_3), and 7.79 (d, H's meta to CH_3). The filtrate from the Et_2O crystallization contained ca. 3:1 $ClCH_2OTs/CH_2(OTs)_2$; on standing, more $CH_2(OTs)_2$ deposited. This was filtered off and washed with Et_2O, and the washings were combined with the filtrate. The precipitate afforded another 4 g of $CH_2(OTs)_2$ (total 23 g, 65%). The filtrate, on flash chromatography (SiO_2, Et_2O), $NaHSO_3$ decolorization, solvent removal, and distillation, gave 7.95 g (18%) of $ClCH_2OTs$ as a nearly colorless oil, bp 99–101 °C (0.4 mmHg): ^1H NMR δ 2.46 (s, 3 H), 5.77 (s, 2 H), 7.36 (d, 2 H), 7.83 (d, 2 H); ^{13}C NMR δ 21.62, 73.85 (CH_2), 128.12, 129.89, 133.33, 145.69. Anal. Calcd for $C_8H_9ClO_3S$: C, 43.54; H, 4.11. Found: C, 43.63; H, 3.95.

(10) The CH_2 ^1H chemical shifts of this family of compounds comprise an anomalous series. The order is $ClCH_2OTs < CH_2(OTs)_2 < BrCH_2OTs < ICH_2OTs$ (δ 5.77, 5.82, 5.84, and 5.90, respectively), reversing the order seen for the mono- and dihalomethanes. The CH_2 ^{13}C shifts are more normal (δ 73.85, 87.89, 61.27, and 32.51 for the same order).

(11) *Catalog Handbook of Fine Chemicals*; Aldrich: Milwaukee, WI, 1988–1989; p 342.

Reaction of Methylene Ditosylate and Lithium Chloride. To a solution of $CH_2(OTs)_2$ (1.07 g, 3.00 mmol) in acetone (4 mL) was added a solution of LiCl (191 mg, 4.50 mmol) in methanol. After the resulting solution had been refluxed 10 h, it was poured into Et_2O–water (25 mL each); the organic layer was washed with water (25 mL) and saturated aqueous NaCl (25 mL), dried ($MgSO_4$), and filtered. The filtrate was stripped of solvent to leave 544 mg (98%) of essentially pure $ClCH_2OTs$.

Bromomethyl Tosylate. To a solution of $CH_2(OTs)_2$ (1.068 g, 3.00 mmol) in acetone (2.5 mL) was added a solution of LiBr (391 mg, 4.50 mmol) in acetone (1.5 mL). On heating to reflux (2 min), the solution suddenly filled with colorless crystals (LiOTs). Analysis (^1H NMR) indicated ca. 90% conversion to $BrCH_2OTs$. On standing overnight (25 °C), conversion was 100%; no $CH_2(OTs)_2$ or CH_2Br_2 was detectable. Addition of CH_2Cl_2 to precipitate Li salts, filtration, and removal of solvent left 780 mg (>98%) of pale yellow oil. An analytical sample, mp <20 °C, was obtained by recrystallization from MeOH (0–5 °C) or by distillation (bp 112–114 °C, 0.4 mmHg): ^1H NMR δ 2.46 (s, 3 H), 5.84 (s, 2 H), 7.37 (d, 2 H), and 7.83 (d, 2 H); ^{13}C NMR δ 21.61, 61.27, 128.21, 129.88, 132.75, 145.81. Anal. Calcd for $C_8H_9BrO_3S$: C, 36.24; H, 3.42. Found: C, 37.62; H, 3.38.

Iodomethyl Tosylate. To a solution of $CH_2(OTs)_2$ (712 mg, 2.0 mmol) in acetone (4.5 mL) was added a solution of NaI (450 mg, 3.0 mmol) in acetone (1.5 mL). On warming to 50 °C (5 min), the pale yellow solution was filled with colorless, heavy crystals. After being allowed to stand for 0.5 h, the mixture was poured into a mixture of Et_2O and water (30 mL ea), decolorized with a pinch of $NaHSO_3$, washed with water and saturated brine (30 mL ea), and dried in the dark over $MgSO_4$. Filtration and solvent removal left 635 mg (>100%) of pale yellow oil. Analysis (^1H NMR) showed ca. 10% of unreacted $CH_2(OTs)_2$ remaining; Kugelrohr distillation (115–120 °C, 0.2 mmHg) yielded 455 mg (73%) of ICH_2OTs as a nearly colorless oil: ^1H NMR δ 2.46 (s, 3 H), 5.90 (s, 2 H), 7.38 (d, 2 H), and 7.81 (d, 2 H); ^{13}H NMR δ 21.67, 32.51, 128.37, 129.93, 132.13, 145.86. A refrigerated sample appeared unchanged (NMR) after several months. Anal. Calcd for $C_8H_9IO_3S$: C, 30.78; H, 2.91. Found: C, 31.18; H, 2.84.

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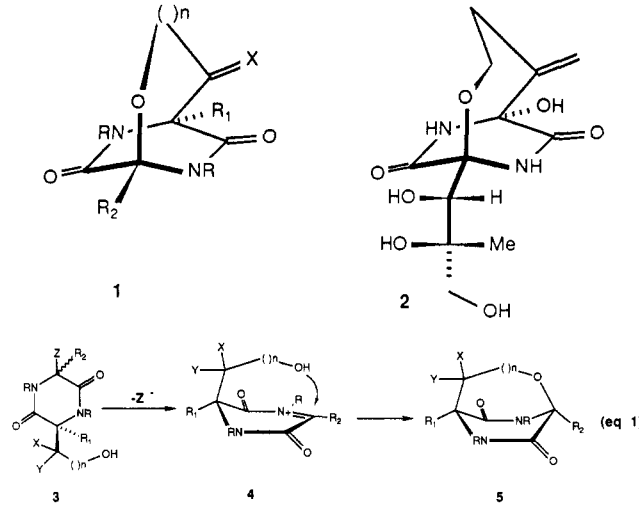
Communications

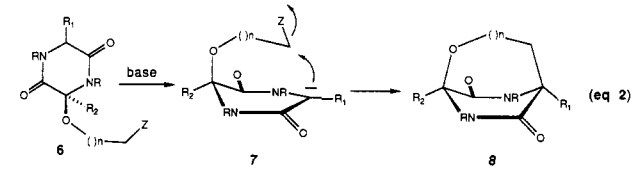
Versatile New Approach to the Synthesis of Monosubstituted and Bicyclic Piperazine-2,5-diones: Unusual in Situ Generation and Enolate Addition to a Cumulene

Summary: Dichloroacetyl chloride condenses with glycinamide **9** to furnish the versatile precursor **10**, which cyclizes to the mono (ether) substituted piperazinediones **11** upon treatment with alkoxides. A new intramolecular enolate C–C bond-forming cyclization from these derivatives furnishes three new bicyclo[*n*.2.2]piperazinediones **14**, **17**, and **18**.

Sir: Bicyclo[*n*.2.2]piperazinediones **1** have proven to be valuable, versatile templates from which the total synthesis of bicyclomycin[1] (**2**) and a variety of interesting analogues[2] have been prepared. A primary synthetic difficulty that has been encountered in constructing such systems is the incorporation of the branched β,γ-unsaturated amino acid residue. While this problem has been solved in various ways,[3] the multistep pathways that have been developed to install this functionality preclude convenient access to reasonable quantities of these compounds for further elaboration and study. Additionally, the most successful strategies[1] have employed an intramolecular O–C bond construction to form the bicyclic ring system (eq 1).



Reported herein is an entirely new approach to this class of compounds that features intramolecular C–C bond-forming cyclization reactions (eq 2). Dichloroacetyl



chloride efficiently acylates glycinamide **9** to afford the dichloride **10**[4] (mp 105–106 °C, 88% yield). Condensation of **10** with a variety of alcohols (Table I) in the presence of base furnishes the piperazinediones **11**.[4] This technique gives access to the deceptively simple yet difficult to prepare monoethers of piperazinediones **11**. For example, selective monobromination of various glycine anhydride

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(3) For a review, see: Williams, R. M.; Durham, C. *Chem. Rev.* **1988**, *88*, 511.

(4) All new compounds exhibited satisfactory spectroscopic and analytical data consistent with the assigned structures.

0022-3263/88/1953-5785$01.50/0