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Supplementary Material Available: ^1H NMR, DEPT, ^{13}C-^1H COSY, ^1H-^1H COSY, HMBC, and NOESY spectra of 1 and ^1H NMR, ^{13}C NMR, ^1H-^1H COSY, and HMBC spectra of 3 (10 pages). Ordering information is given on any current masthead page.

A Convenient Method for the Preparation of (Alkylsulfonyl)benzoic Acids

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(Alkylsulfonyl)benzoic acids are useful intermediates for a variety of synthetic compounds possessing pharmaceutical[1] and herbicidal[2] activity. Literature methods for the preparation of such compounds can be divided into two general categories. The first procedure involves the alkylation of a substituted thiophenol followed by oxidation of the resulting sulfide to the sulfone.[1b,3,4] Use of a strong oxidant such as potassium permanganate or sodium dichromate may allow for the simultaneous conversion of an aryl methyl group to the desired carboxylic acid moiety.[1a,5-7] The second method of preparation requires the reduction of the corresponding sulfonyl chloride followed by treatment of the intermediate sulfinate with an alkyl halide to give the (alkylsulfonyl)benzoic acid.[1c-e,3] The initial product of this process is often the corresponding ester, which must be hydrolyzed to the desired acid.[1f-g,8] All these procedures suffer from various deficiencies including low yields, the requirements for large excesses of alkylating reagent, or the need for further chemical manipulation (e.g., ester hydrolysis). We report a simple, one-pot method for the synthesis of these materials via reduction of a (chlorosulfonyl)benzoic acid to the corresponding sulfinate, selective alkylation with a 2-halo carboxylic acid, and side-chain decarboxylation. This approach affords a convenient, high-yielding preparation of a variety of (alkylsulfonyl)benzoic acids from readily available precursors that is suitable for large-scale application.

(Alkylsulfonyl)benzoic acids were prepared in the following manner (Scheme I). (Chlorosulfonyl)benzoic acid 1 was reduced with aqueous basic sodium sulfite, and the resulting aqueous solution of sulfinate 2 was treated with a slight excess of a 2-halo carboxylic acid 3. The reaction mixture was then heated until decarboxylation of the initial alkylation product, sulfonylacetic acid 4, was complete. (Alkylsulfonyl)benzoic acids 5 were obtained in overall yields of 66-95% (Table I). Although sulfinate 2 and sulfonylacetic acid 4 may be isolated, the procedure was most conveniently performed without isolation of intermediates. The starting materials for this process, (chlorosulfonyl)benzoic acid 1 and 2-halo carboxylic acid 3, are both readily available or easily prepared. A bis(acid chloride) (the chloride of both the carboxylic and sulfonic acid groups) may be substituted as the starting material with no loss in yield; additional base must be added in the reduction step to consume the acid generated by the hydrolysis of the carboxylic acid chloride. A cosolvent may be used to dissolve the bisacid chloride; however, if the solvent is not removed before the additon of the 2-halo carboxylic acid 3, the subsequent alkylation and decarboxylation reactions will be inhibited.

The reaction times required for complete conversion of (chlorosulfonyl)benzoic acids 1 to (alkylsulfonyl)benzoic acid 5 varied from 7 to 213 h. Although the reduction of (chlorosulfonyl)benzoic acid 1 required only 0.25-3.0 h, reaction times for the alkylation/decarboxylation step were much longer and were found to be dependent upon a number of factors. When chloroacetic acid was used as the alkylating reagent, total reaction times for the alkylation/decarboxylation were typically 7-21 h. Longer reaction times were necessary for the preparation of an (alkylsulfonyl)benzoic acid 5 bearing an ortho substituent (e.g., 4-chloro-3-(methylsulfonyl)benzoic acid, **5f**), presumably due to steric hindrance in the alkylation step. In this case, the use of 2-bromoacetic acid reduced the required reaction time from 42 to 24 h. The reaction times given in Table I are for reactions at reflux (ca. 105 °C). At other temperatures, the rate of decarboxylation was dramatically different. Below 80 °C, essentially no reaction occurred. At slightly elevated pressures, the higher reaction temperatures afforded a significant increase in the reaction rate; at 115 °C, the reaction time for the preparation of 2-chloro-4-(methylsulfonyl)benzoic acid (**5b**) was reduced from 21 to 3 h.

The chain length of the 2-halo carboxylic acid 3 also affected the rate of the decarboxylation. Reaction times increased as the size of the alkyl group of the 2-halo carboxylic acid 3 increased, peaking with 2-bromobutanoic acid and then decreasing at longer chain lengths. Two independent factors can account for this phenomenon. Substitution of a hydrogen on the intermediate sulfonylacetic acid 4 with an electron-donating alkyl group destabilizes the incipient carbanion 6, inhibiting the loss of carbon dioxide (Scheme II).[9] The effect observed for R = ethyl is greater than for R = methyl due to the greater inductive effect of the larger group ($\sigma_{Me} = -0.046$ vs $\sigma_{Et} = -0.057$).[10] As the size of the alkyl chain continues to

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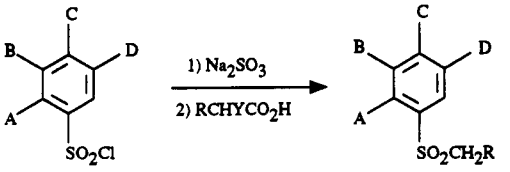
Table I. Preparation of (Alkylsulfonyl)benzoic Acids

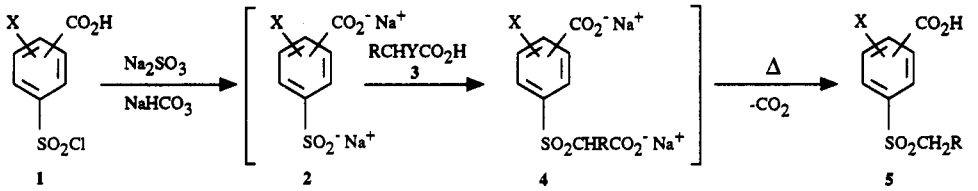


1 5

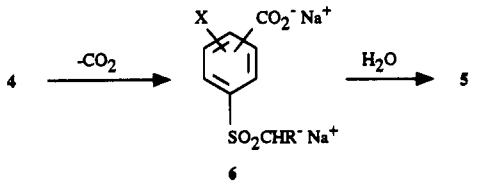
product	A	B	C	D	Y	R	reaction time (h)	technical[a,b] yield (%)	mp, °C (lit., °C)
5a	H	H	CO_2H	H	Cl	H	20	95	270–2 (274–6)[c]
5b	H	H	CO_2H	Cl	Cl	H	21	81	194–6 (198–9)[d]
5b	H	H	CO_2H	Cl	Br	H	18	75	–
5c	H	H	CO_2H	Cl	Cl	CH_3	115	87	173–5
5d	H	H	CH_3	H	Cl	H	19	86[e]	87–9 (83–7.5)[f]
5e	H	H	OCH_3	CO_2H	Cl	H	47	77	191–2 (191)[g]
5f	Cl	H	H	CO_2H	Cl	H	42	87[h]	224–8 (227.5)[i]
5f	Cl	H	H	CO_2H	Br	H	24	90[j]	–
5g	H	CO_2H	H	CO_2H	Cl	H	21	69[k]	288–91
5h	H	H	CO_2H	H	Br	*n*-Bu	54	66[l]	176–7 (173–5)[m]
5i	H	H	CO_2H	H	Br	CH_2CO_2H	19	89[n]	276–7 (258)[o]
5j	H	H	CO_2H	H	Br	Et	213	76[p]	194–5 (191–3)[q]
5k	H	H	CO_2H	H	Cl	Cl	24	89	234–6 (237–9)[r]
5l	H	H	CO_2H	H	Cl	CH_3	140	65	215–6 (220)[q]
5m	H	H	CO_2H	H	Br	*n*-Pr	160	80	174 (170–2)[s]
5n	H	H	CO_2H	NO_2	Cl	H	7	87[t]	212–5 (212–5)[u]

[a] Reaction conditions (except where noted): 100 mol % Na_2SO_3, 300 mol % $NaHCO_3$, H_2O, 75 °C, 1 h, then 150 mol % alkylating agent, 150 mol % NaOH, H_2O, reflux. [b] Satisfactory spectra (^1H and ^{13}C NMR) were obtained for all compounds; satisfactory elemental analysis were obtained for all new compounds. [c] Reference 1a. [d] Reference 5. [e] 200 mol % $NaHCO_3$. [f] Field, L.; Clark, R. D. Methyl *p*-Tolyl Sulfone. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 674. [g] Reference 5. [h] 250 mol % $ClCH_2CO_2H$ and 400 mol % NaOH. [i] Reference 1f. [j] 200 mol % each $BrCH_2CO_2H$ and NaOH. [k] 400 mol % $NaHCO_3$. [l] 250 mol % 2-bromohexanoic acid and 350 mol % NaOH. [m] Reference 1b. [n] 250 mol % each 2-bromosuccinic acid and NaOH. [o] Trave, R. *Farmco (Pavia) Ed. Sci.* **1960**, *15*, 474; *Chem. Abstr.* **1961**, *55*, 2547d. [p] 350 mol % each 2-bromobutanoic acid and NaOH. [q] Reference 3. [r] Bordwell, F. G.; Cooper, G. D. *J. Am. Chem. Soc.* **1957**, *79*, 916. [s] Fusco, R.; Trave, R. *Ann. Chim. (Rome)* **1951**, *41*, 139; *Chem. Abstr.* **1951**, *45*, 9221c. [t] Reduction temperature 10–15 °C. [u] Reference 2a.

Scheme I



Scheme II



increase, a second factor becomes significant. The hydrophobic nature of the longer alkyl groups tends to reduce the solvation of 4 by water molecules. As the presumed reaction mechanism involves desolvation of 4,[9] longer alkyl groups would lower the activation energy and thereby facilitate the decarboxylation.

Experimental Section

General. Proton magnetic resonance (^1H NMR) and carbon magnetic resonance (^{13}C NMR) spectra were recorded on 60- and 300-MHz spectrometers, respectively. Melting points are uncorrected. Combustion analyses were performed by the Environmental Chemistry Section of the Western Research Center, ICI Americas.

4-(Methylsulfonyl)benzoic Acid (5a) (General Procedure). To a slurry of 2.86 g (22.6 mmol) of Na_2SO_3, 5.72 g (68.1 mmol) of $NaHCO_3$, and 20 mL of water at 75 °C was added portionwise over 10 min 4-(chlorosulfonyl)benzoic acid (**1a**) (5.15 g, 22.6 mmol). After heating at 75 °C for 1 h, 3.22 g (34.0 mmol) of chloroacetic acid and 1.8 mL (34.0 mmol) of 50% (w/w) aqueous NaOH were charged sequentially, and the resulting solution was heated at reflux (105 °C) for 20 h. The reaction mixture was cooled to ambient temperature and acidified to pH 1 with 3 M HCl. The precipitate was collected by filtration and dried at 115 °C to give 4.30 g (95%) of 4-(methylsulfonyl)benzoic acid (**5a**) as a white solid: mp 270–2 °C (H_2O/EtOH, lit.[1a] mp 274–6 °C).

2-Chloro-4-(ethylsulfonyl)benzoic acid (5c): mp 173–5 °C (H_2O/EtOH); ^1H NMR (d_6-DMSO) δ 1.13 (t, J = 7.5 Hz, 3 H), 3.42 (q, J = 7.5 Hz, 2 H), 7.93–8.07 (m, 3 H); ^{13}C NMR (d_6-DMSO) δ 8.18, 50.23, 127.93, 130.72, 132.65, 133.47, 137.96, 142.98, 167.19. Anal. Calcd for $C_9H_9ClO_4S$: C, 43.5; H, 3.6. Found: C, 43.2; H, 3.6.

5-(Methylsulfonyl)-1,3-benzenedicarboxylic acid (5g): mp 288–91 °C (H_2O/EtOH); ^1H NMR (d_6-DMSO) δ 3.20 (s, 3 H), 8.73 (bs, 2 H), 8.90 (bs, 1 H), 15.07 (bs, 2 H); ^{13}C NMR (d_6-DMSO) δ 43.14, 131.21, 132.53, 134.03, 141.73, 165.03. Anal. Calcd for $C_9H_8O_6S$: C, 44.3; H, 3.3. Found: C, 43.9; H, 3.2.

2-Chloro-4-(methylsulfonyl)benzoic Acid (5b) from 2-Chloro-4-(chlorosulfonyl)benzoyl Chloride. Forty-four grams (0.137 mol) of 2-chloro-4-(chlorosulfonyl)benzoyl chloride was added dropwise over 11 min to a slurry of 18.9 g (0.15 mol) of Na_2SO_3, 63.1 g (0.75 mol) of $NaHCO_3$, and 150 mL of water at 40 °C. After heating at 40 °C for 3 h, the reaction mixture was heated to 75 °C, charged sequentially with 19.4 g (0.205 mol) of chloroacetic acid and 5.0 mL (0.095 mol) of 50% (w/w) aqueous

NaOH, and heated at reflux (105 °C) for 21 h. The cooled reaction mixture was acidified to pH 1 with 3 M HCl. The precipitated solids were collected by filtration and dried at 125 °C to give 32.1 g (100%) of 2-chloro-4-(methylsulfonyl)benzoic acid (**5b**) as a white solid: mp 194–6 °C (H_2O, lit.[5] mp 198–9 °C).

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Registry No. **1a**, 10130-89-9; **1b**, 61953-04-6; **1d**, 98-59-9; **1e**, 51904-91-7; **1f**, 2494-79-3; **1g**, 134178-04-4; **1h**, 10130-89-9; **1n**, 54090-40-3; **5a**, 4052-30-6; **5b**, 53250-83-2; **5c**, 118939-05-2; **5d**, 3185-99-7; **5e**, 50390-76-6; **5f**, 51522-07-7; **5g**, 134178-05-5; **5h**, 32910-75-1; **51**, 98948-26-6; **5j**, 99186-88-6; **5k**, 101349-84-2; **5l**, 21571-66-4; **5m**, 100059-51-6; **5n**, 110964-79-9; Na_2SO_3, 7757-83-7; $ClCH_2CO_2H$, 79-11-8; $BrCH_2CO_2H$, 79-08-3; $H_3CCHClCO_2H$, 598-78-7; $H_3C(CH_2)_3CHBrCO_2H$, 616-05-7; $HO_2CCH_2CHBrCO_2H$, 923-06-8; $H_3CCH_2CHBrCO_2H$, 80-58-0; Cl_2CHCO_2H, 79-43-6; $H_3C(CH_2)_2CHBrCO_2H$, 584-93-0; 2-chloro-4-(chlorosulfonyl)-benzoyl chloride, 130264-17-4.

Short Synthesis of (±)-5-(3-Furyl)octahydro-8-methylindolizines, Alkaloids Related to a Component of Castoreum. Use of Radical Cyclization

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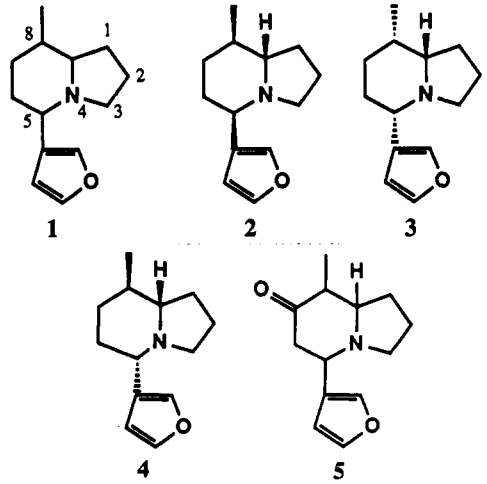
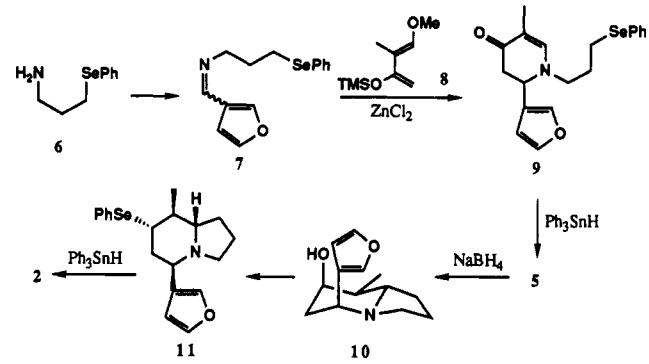
Castoreum, an extract from the scent glands of the Canadian beaver (*Castor fiber* L.), is a commercial product used in perfumery.[1] The material contains a minute amount of a substance believed to be 5-(3-furyl)octahydro-8-methylindolizine (**1**),[2] which is a simple member of the Nuphar alkaloid[3] class. The structural assignment is based on mass spectral considerations, as there was insufficient material for further characterization.[2]



1 **2** **3** **4** **5**

Of the possible isomers corresponding to the proposed structure, three have been synthesized in racemic form,

Scheme I



and these have the relative stereochemistries shown in **2**,[4] **3**,[4] and **4**.[5] The latter was made from the bicyclic ketone **5** (obtained as a mixture of stereoisomers) by base-catalyzed equilibration and removal of the carbonyl (C=O → CH_2). We report here an alternative and very short route to a ketone of gross structure **5** and its conversion into **2**. Our bicyclic ketone **5** was identical (^1H NMR) with the major isomer obtained previously,[5a] and so the present work also represents a formal synthesis of **4**. The approach we have used is based on Diels–Alder cycloaddition followed by radical closure[6] (Scheme I).

The required imine **7** was assembled by mixing the readily available amine **6**[7] with commercial 3-furaldehyde. The crude imine was then treated with an excess of diene **8**[8] in the presence of 2 equivalents of anhydrous zinc chloride.[9] It was then possible to isolate the adduct **9** in 72% yield. This material underwent efficient ring closure (83%) upon treatment with triphenyltin hydride to give a single ketone **5**. Reduction ($NaBH_4$) afforded alcohol **10**, and the structure of this compound was determined by X-ray analysis. Treatment of **10** with phenyl selenocyanate in the presence of tributylphosphine[10] produced the corresponding selenide **11**, and stannane reduction[11] then gave **2**. The stereochemistry assigned to **2** follows from that established for the alcohol **10**.

Experimental Section

General. The same experimental techniques were used as reported previously.[12]

***N*-(3-Furylmethylene)-3-(phenylseleno)propylamine (7).** A mixture of amine **6**[7] (58 mg, 0.271 mmol), 3-furaldehyde (26 mg, 0.271 mmol), and $MgSO_4$ (ca. 100 mg) in ether (2 mL) was stirred at room temperature for 1 h. Filtration, followed by evaporation of the solvent, gave the crude imine in near quantitative yield (^1H NMR, 200 MHz), and the material was used directly without purification: ^1H NMR ($CDCl_3$, 200 MHz) δ

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