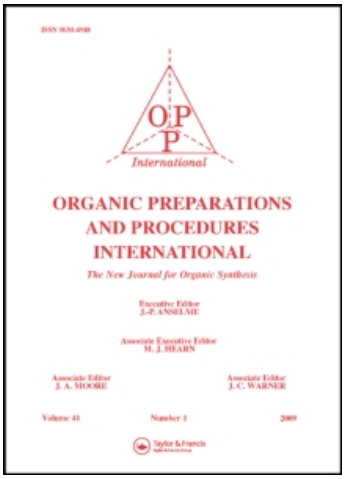

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1-(BENZENESULFONYL)PYRROLE-3-CARBOXALDEHYDE

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1-(BENZENESULFONYL)PYRROLE-3-CARBOXALDEHYDE

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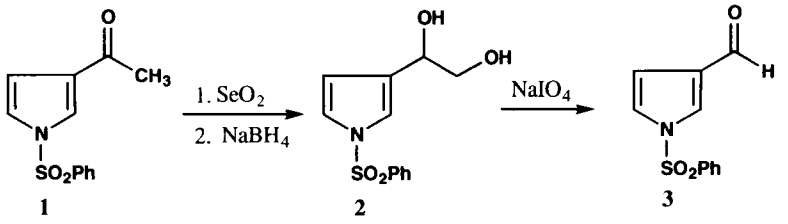
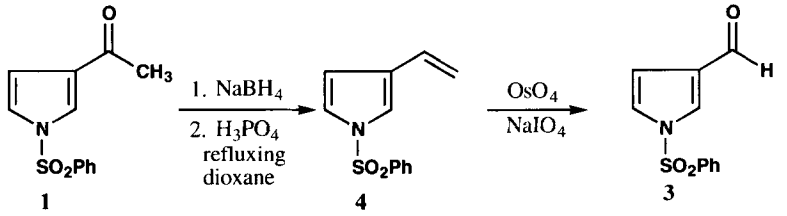
The value of 1-(benzenesulfonyl)pyrrole-3-carboxaldehyde as a synthon in heterocyclic chemistry, especially for the preparation of highly functionalized indoles,[1] has impelled the search for methods of preparation based on direct formylation.[2] However, although 1-(benzenesulfonyl)pyrrole displays an unusual proclivity toward β-substitution in aluminum chloride mediated Friedel-Crafts acylations,[3] all previous attempts to introduce one carbon units at the β-position by this process have failed. Thus, even in the presence of aluminum chloride, one carbon "acylations" using oxalyl chloride or 1,1-dichloromethyl methyl ether proceed exclusively at the α-position, as does cyanation with cyanogen bromide.[3a,c,d]

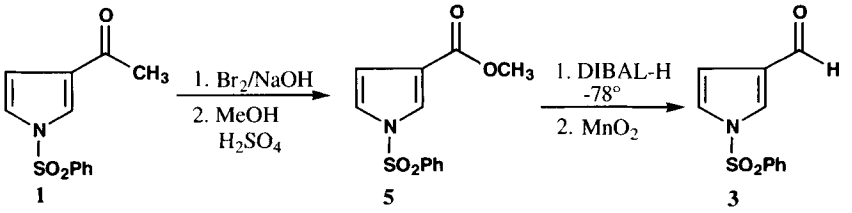
Recently, Natsume[4] devised a method for converting readily available 3-acetyl-1-(benzenesulfonyl)pyrrole[3] to the corresponding 3-formyl derivative. In this approach, 3-acetyl-1-(benzenesulfonyl)pyrrole (**1**) was oxidized by selenium dioxide to a vicinal ketoaldehyde which was reduced *in situ* with sodium borohydride to afford the vicinal diol **2**. This diol was then cleaved with sodium metaperiodate[5] to afford 1-(benzenesulfonyl)pyrrole-3-carboxaldehyde (**3**) in 85% overall yield. Despite the efficacy of this three-step procedure, the major drawback of this method is that a four fold excess of selenium dioxide is required.



To circumvent the necessity of employing selenium dioxide, we devised two alternative approaches for the preparation of 1-(benzenesulfonyl)pyrrole-3-carboxaldehyde from the corresponding 3-acetyl derivative. The first approach involves the preparation of 3-vinyl-1-(benzenesulfonyl)-pyrrole (**4**) by a sequence involving the sodium borohydride reduction of **1** to afford an intermediate alcohol which need not be purified but can be dehydrated in high yield using phosphoric acid in refluxing dioxane.[6] Subsequent Lemieux-Johnson cleavage of the vinyl species **4** is effected by catalytic osmylation followed by cleavage of the resulting diol with sodium metaperiodate to afford 1-(benzenesulfonyl)pyrrole-3-carboxaldehyde (**3**) in 82% yield.



Alternatively, **1** can be converted to methyl 1-(benzenesulfonyl)pyrrole-3-carboxylate (**5**) by hypohalite oxidation[7] with aqueous alkaline bromine solution followed by Fischer esterification of the intermediate carboxylic acid. Although attempted partial reduction of the ester **5** with DIBAL-H at -78° produced only the corresponding alcohol, reoxidation of the alcohol to 1-(benzenesulfonyl)-pyrrole-3-carboxaldehyde (**3**) could be effected chemoselectively using a large excess of MnO_2.



These methods successfully take advantage of the modified reactivity imparted upon the pyrrole nucleus by virtue of the N-benzenesulfonyl protecting group and allow for the facile and safe preparation of **3** in good yields.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries with an Electrothermal melting point apparatus

and are uncorrected. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN. Infrared spectra were recorded on a Perkin-Elmer 1600 Fourier transform (FT) instrument. ^1H and ^{13}C NMR data were obtained on an IBM NR/100 FT NMR at 200 MHz in $CDCl_3$ solution unless otherwise indicated. Chemical shifts are reported in δ (ppm) downfield from TMS as an internal standard; coupling constants (J) are in Hertz (Hz). Mass spectra (CI) were obtained using a Finnigan INCOS 50 spectrometer. Flash column and thin layer chromatography were performed on silica gel with the indicated solvent systems.

3-Vinyl-1-(benzenesulfonyl)pyrrole (4).- To a solution of **1**[3d] (0.5 g, 2.0 mmol) in ethanol (15 mL) at 0° was added sodium borohydride (0.15 g, 4.0 mmol) and the resulting mixture was stirred at room temperature for 2 hrs. After this time, the mixture was quenched with water (10 mL), the whole was separated and the aqueous layer extracted with methylene chloride (3 x 20 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate, water and brine, dried over sodium sulfate, filtered and evaporated to give 1-[1-(benzenesulfonyl)pyrrol-3-yl]ethanol as a colorless oil (0.50 g, 99%).

To the crude alcohol (0.5 g, 2.0 mmol) in 1,4-dioxane (15 mL) was added 85% phosphoric acid (0.5 g, 5.1 mmol) in 1,4-dioxane (15 mL). The resulting mixture was refluxed at 120° for 12 hrs, allowed to cool, diluted with water, and extracted with methylene chloride. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, water and brine, dried over sodium sulfate, and evaporated to afford a brown oil. The residue was then subjected to flash chromatography (hexanes-methylene chloride, 3:1) to afford a colorless oil which solidified on standing (0.35 g, 75%). Recrystallization from methanol afforded analytically pure **4**, mp. 41-42°; IR (neat): 3137, 1639, 1371, 1175, 1100, 1062, 728 cm^{-1}; ^1H NMR: δ 5.14 (1H, dd, J = 1.1, 10.9 Hz), 5.41 (1H, dd, J = 1.1, 17.6 Hz), 6.47 (2H, m), 7.12 (2H, m), 7.45-7.63 (3H, m), 7.87 (2H, m); ^{13}C NMR: δ 111, 113.5, 118.4, 121.7, 126.8, 128.0, 128.2, 129.4, 133.6, 138.9; MS: *m/e* 234 $(M+1)^+$.

Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.69; H, 4.63; N, 5.99

1-(Benzenesulfonyl)pyrrole-3-carboxaldehyde (3).- To a solution **4** (0.70 g, 3.16 mmol) in 1,4-dioxane (15 mL) and water (5 mL) was added osmium tetraoxide (7.5 mg) and sodium periodate (1.37 g, 6.4 mmol) at room temperature. After 8 hrs, the reaction mixture was diluted with water and extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and evaporated to afford a yellow oil which was submitted to flash chromatography (methylene chloride) to yield an amorphous solid (0.58, 82%). IR (neat): 1683 cm^{-1}; ^1H NMR: δ 9.82 (1H, s), 7.53-7.96 6H, m), 7.20 (1H, m), 6.71 (1H, m); ^{13}C NMR: δ 184.9, 138.1, 134.7, 129.8, 127.8, 127.2, 122.4, 111.0. The ^1H NMR of this sample was in accord with previously reported data.[3]

Methyl 1-(Benzenesulfonyl)pyrrole-3-carboxylate (5).- To a solution of **1** (20.0 g, 80.3 mmol) in 1,4-dioxane (1 L) and H_2O (250 mL) at 0° was added a steady stream of a cold solution of sodium hypobromite [freshly prepared from 12% aqueous sodium hydroxide (500 mL) and bromine (60 g, 375.5 mmol) in 1,4-dioxane (100 mL)] while stirring. After 2 hrs, acetone (200 mL) was added and the resulting solution was acidified with concentrated hydrochloric acid to pH 1, and the mixture was extracted with methylene chloride. The combined organic extracts were washed with saturated

aqueous sodium bicarbonate, water and brine, dried over sodium sulfate, filtered and evaporated to give a clear oil which was dissolved in methanol (200 mL). To this solution was added sulfuric acid (10 mL) and the whole was heated under reflux overnight . Water (200 mL) was then added to the solution and the resulting mixture was extracted with methylene chloride. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, water and brine, dried over sodium sulfate, filtered and evaporated to afford a brown residue which was recrystallized from methanol to yield **5** as colorless crystals (15.8 g, 75%): mp. 95-96.5°; IR (KBr): 3124, 1727, 1560, 1375, 1178, 729, 590 cm^{-1}; ^1H NMR: δ 7.91 (2H, m), 7.77 (1H, t, J = 2.5 Hz), 7.49-7.67 (3H, m), 7.14 (1H, dd, J = 2.5, 3.3 Hz), 6.67 (1H, dd, J = 1.5 , 3.3 Hz), 3.81 (3H, s); ^{13}C NMR: δ 163.7, 138.3, 134.5, 129.7, 127.1, 125.1, 121.2, 120.8, 113.5, 51.6; MS: *m/e* 266 $(M+1)^+$.

Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28. Found: C, 54.29; H, 4.10; N, 5.23

1-(Benzenesulfonyl)pyrrole-3-carboxaldehyde (3).- To a solution of **5** (1.05 g, 3.8 mmol) in chloroform (50 mL) was added DIBAL-H solution (4.8 mL, 8.36 mmol, 25% in toluene) at room temperature. After 3 hrs, manganese dioxide (10.5 g) was added to the solution and the mixture was refluxed for 4 hrs. The mixture was then filtered and the filtrate was concentrated under vacuum to afford a yellow oil which was subjected to flash chromatography (methylene chloride) to afford **3** as an amorphous solid (0.85 g, 91%) identical to the sample prepared the alternate method.

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