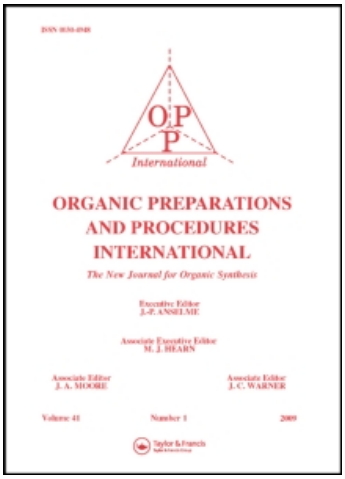

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A LITHIATION APPROACH TO 5-SUBSTITUTED-1-BENZENESULFONYLPYRAZOLES

Kenneth Turnbull[a]; Andre P. Brower[a]
[a] Department of Chemistry, Wright Slate University, Dayton, Olzio, USA

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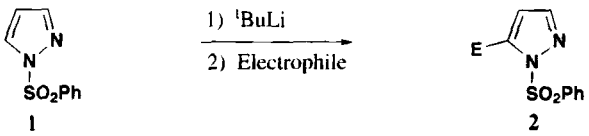
A LITHIATION APPROACH TO 5-SUBSTITUTED-1-BENZENESULFONYLPYRAZOLES

Submitted by Kenneth Turnbull* and Andre P. Brower
(09/28/00)

Department of Chemistry
Wright State University, Dayton, Ohio 45435, USA

For a projected route to acyclic analogs of pyrazofurin, a naturally occurring antiviral compound,[1] we required an entry into 5-substituted-1-benzenesulfonylpyrazoles **2**. The most attractive approach to such species was *via* directed lithiation of 1-benzenesulfonylpyrazole (**1**) and subsequent reaction with a suitable electrophile. A limited study of the efficacy of phenyllithium for lithiation of 4-bromo-1-benzenesulfonylpyrazole had been reported[2] and 5-substitution of 1-tosylpyrazole had been effected similarly.[3] Surprisingly, to the best of our knowledge, no study of the lithiation of **1** has been forthcoming. We now report that 1-benzenesulfonylpyrazole (**1**) can indeed be lithiated with *t*-butyllithium and that subsequent reaction with a variety of electrophiles yields the corresponding 5-substituted pyrazoles **2** in moderate to excellent yield (Table).

In line with Holzer's findings with the 4-bromo analog,[2] no metallation of the benzenesulfonyl group occurred. In general, the reactions (to form **2**) were complete in 1-12 hours and the identity of the products was ascertained from their satisfactory spectral and microanalytical data. In view of the potential removal of the benzenesulfonyl moiety,[4] this protocol could constitute an attractive route to unprotected 5-substituted pyrazoles.



a) E = I b) E = CMe_2OH c) E = Bn d) E = H_2C=$CHCH_2$
e) E = Me_3Si f) E = Bu_3Sn g) E = CO_2H h) E = Me

EXPERIMENTAL SECTION

All melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra (potassium bromide or thin film) were measured on a Perkin Elmer 1600 Fourier transform (FT) instrument and nuclear magnetic resonance spectra (^{1}H and ^{13}C) on an IBM NR/200 FTNMR at 200 MHz or 50 MHz, respectively, with tetramethylsilane as the internal standard, chemical shifts reported in ppm (δ). Combustion analyses were performed by Midwest Microlab, Indianapolis.

Lithiation of 1-Benzenesulfonylpyrazole (1) and Subsequent Reaction with Electrophiles: Representative Procedure.- To a stirred solution of the pyrazole **1** (1.0g, 4.8mmol) in anhydrous THF (10mL) at –78° under an atmosphere of nitrogen was added *t*-butyllithium (3.1mL, 5.27mmol,

Table. Yields, m.p., Elemental Analyses and NMR Data for Pyrazoles **2**

Cmpd	Yield (%)	mp. (°C)	Elemental Analysis (Found) C H N	^{1}H NMR (δ)	^{13}C NMR (δ)
2a	93	106-108	32.32 2.09 8.37 (32.17)(1.99)(8.28)	8.02 (m, 2H), 7.92 (d, 1H, J = 13.4Hz, C-3), 7.60 (m, 3H), 6.54 (d, 1H, J = 13.4Hz, C-4)	136.6 (aromatic C), 132.6, 129.5, 128.2 (aromatic CH), 134.9 (C-3), 118.0 (C-4), 103.0 (C-5)
2b	89	76-78	54.12 5.29 10.52 (53.98)(5.24)(10.46)	8.02 (d, 2H), 7.58 (m, 4H), 6.23 (d, 1H, C-4), 1.75 (s, 6H)	137.7 (aromatic C), 134.4, 128.2, 128.1 (aromatic CH), 143.2 (C-3), 108.0 (C-4), 155.7 (C-5), 68.3 (C-OH), 30.6 (CH_3)
2c	88	72-74	64.44 4.69 9.39 (64.35)(4.71)(9.29)	7.99 (m, 3H), 7.55 (m, 3H), 7.19 (m, 5H), 6.11 (d, 1H, C-4), 3.96 (s, 2H)	138.1, 137.5 (aromatic C), 132.4, 129.3, 128.7, 128.5, 127.9, 126.5 (aromatic CH), 134.3 (C-3), 109.1 (C-4), 158.6 (C-5), 34.6 (CH_2)
2d	83	60-62	58.30 4.45 11.32 (58.28)(4.69)(11.24)	7.99 (m, 3H), 7.58 (m, 3H), 6.24 (d, 1H, C-4), 5.87 (m, 1H), 5.06 (m, 2H), 3.39 (d, 2H)	157.8 (C-5), 137.5 (aromatic C), 134.3 (C-3, possibly + vinyl CH), 132.2, 129.3, 127.9 (aromatic CH), 117.1 (vinyl CH_2), 108.9 (C-4), 32.8 (CH_2)
2e	76	oil	51.42 5.71 10.00 (51.34)(5.75)(10.03)	7.55 (m, 2H), 7.19 (d, 1H, J = 14Hz, C-3), 7.09 (m, 3H), 6.08 (d, 1H, J = 14 Hz, C-4), 0.10 (s, 9H)	148.0 (C-5), 144.2 (C-3), 137.9 (aromatic C), 134.1, 129.1, 128.0 (aromatic CH), 118.7 (C-4), 103.0 (CH_3)
2f	69	oil	50.74 6.84 5.63 (50.82)(6.93)(5.73)	7.63 (m, 2H), 7.38 (d, 1H, C-3), 7.23 (m, 3H), 6.11 (d, 1H, C-4), 1.86-0.58 (m, 27H)	147.3 (C-5), 145.1 (C-3), 137.9 (aromatic C), 134.0, 129.0, 127.8 (aromatic CH), 118.0 (C-4), 28.6, 27.2, 13.6, 11.6 (CH_2, CH_3)
2g	66	114-116	47.63 3.17 11.10 (47.57)(3.20)(10.99)	11.7 (brd s, 1H), 8.14 (m, 2H), 7.75 (m, 4H), 6.93 (d, 1H, C-4)	206.2 (C=O), 160.4 (C-5), 143.7 (C-3), 138.7 (aromatic C), 135.8, 130.2, 129.4 (aromatic CH), 113.7 (C-4)
2h	55	58-60	54.05 4.50 12.61 (53.94)(4.57)(12.48)	7.97 (m, 2H), 7.56 (m, 4H), 6.09 (d, 1H, C-4), 2.57 (s, 3H)	143.7 (C-3), 143.4 (C-5), 138.1 (aromatic C), 134.2, 129.3, 127.7 (aromatic CH), 109.8 (C-4)

1.7M) dropwise by syringe over 15min. The resulting bright yellow solution was stirred for a further 0.5h whereupon the electrophile was added. After a further 2h, the reaction either was quenched or held at –23° for 1h followed by warming to room temperature. When reaction was complete (TLC

evidence), saturated brine (25mL) was added and the mixture was extracted with dichloromethane (3 x 25mL). The combined organic layers were dried ($MgSO_4$) and reduced *in vacuo* to yield crude product, which was purified by column chromatography followed by recrystallization.

1-Benzenesulfonyl-5-iodopyrazole (2a): Using iodine [1.83g, 7.2mmoles] in the representative procedure gave, after 17h, **2a** as a dark brown solid which was purified by column chromatography (silica gel, dichloromethane / hexane 1:1). Subsequent recrystallization from methanol gave the title compound as colorless crystals; 1.503g (93% yield).

1-Benzenesulfonyl-5-(1-hydroxy-1-methylethyl)pyrazole (2b): Using dry, distilled acetone [0.71mL, 9.6mmoles] in the representative procedure gave, after 2h, a clear oil which solidified on standing. Recrystallization from ethanol afforded the title compound as colorless crystals; 1.14g (89% yield).

1-Benzenesulfonyl-5-benzylpyrazole (2c): Using redistilled benzyl bromide [0.86mL, 7.2mmoles] in the representative procedure gave, after 2h at –78° and 1h at –23°, a clear oil which solidified on standing at 5°. Recrystallization from ethanol afforded the title compound as colorless crystals; 1.26g (88% yield).

1-Benzenesulfonyl-5-allylpyrazole (2d): Using allyl bromide [0.68mL, 7.8mmoles] in the representative procedure gave, after 2h at –78°, 1h at –23°, and 5h at room temperature, a light yellow oil which was chromatographed (silica gel, dichloromethane / petroleum ether 1:1 as eluant) to yield an off-white solid. Recrystallization from ethanol afforded the title compound as colorless needles; 0.98g (83% yield).

1-Benzenesulfonyl-5-(trimethylsilyl)pyrazole (2e): Using chlorotrimethylsilane [0.914mL, 7.2mmoles] in the representative procedure gave, after 2h at –78° and 10h at room temperature, a yellow oil which was purified by column chromatography (silica gel, dichloromethane / petroleum ether 70:30 as eluant) to afford the title compound as a clear oil; 1.02g (76% yield).

1-Benzenesulfonyl-5-(tri-*n*-butylstannyl)pyrazole (2f): Using tri-*n*-butyltin chloride [1.95mL, 7.2mmoles] in the representative procedure gave, after 1h, an off-white solid which was purified by column chromatography (silica gel, dichloromethane / petroleum ether 60:40 as eluant) to give the title compound as a clear oil; 1.66g (69% yield).

1-Benzenesulfonyl-5-carboxypyrazole (2g): Using dry carbon dioxide [bubbled in for 45min] in the representative procedure gave, after 2h, the title compound as colorless crystals; 0.794g (65.5% yield).

1-Benzenesulfonyl-5-methylpyrazole (2h): Using iodomethane [0.56mL, 9.6mmoles] in the representative procedure gave, after 4h, a light yellow oil which was purified by column chromatography (silica gel, dichloromethane / hexane 70:30 as eluant) to yield the title compound as colorless crystals; 0.59g (55% yield).

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SILICA GEL PROMOTED SOLVENT-FREE SYNTHESIS OF ARYLCARBINOLS AND FERROCENYLCARBINOLS

Submitted by (09/25/00)

Wan-yi Liu, Qi-hai Xu and Yong-xiang Ma*

National Laboratory of Applied Organic Chemistry
Lanzhou University, Lanzhou 730000, P. R. China

In general, $NaBH_4$ is a popular reagent of choice for its ease of manipulation and its insensitivity to moisture compared to other metal hydride reducing reagents.[1-3] However the activity of the $NaBH_4$ is relatively poor and the reduction process requires higher temperature or longer reaction time compared with those using $LiAlH_4$ and $LiBH_4$. Therefore an improvement of the reducing potency of $NaBH_4$ would provide an added tool for synthetic chemists. Ranu and co-workers described silica gel-supported zinc borohydride as an efficient and highly selective reagent for the reduction of conjugated ketones and aldehydes to the corresponding allylic alcohols, but this method requires keeping the reaction mixture at –5 to –10° for 7-8 h.[4] Recently, it has also been demonstrated that silica gel has a remarkable ability to promote the various reactions.[5, 6] Hirano and co-workers reported the reduction of ketones and aldehydes with $NaBH_4$ in hexane in the presence of silica gel.[6] This method requires dry hexane as solvent and is carried out under a dry argon atmosphere at 40° for several hours. This tedious, inconvenient, and lengthy procedure may therefore, reduce its value.

It is well known that solvent-free syntheses have many advantages over conventional solution procedures. Typically, solvent-free synthesis features short reaction time, cleaner reaction and