

## Lithiation of 1-Benzenesulfonylimidazole. Characterization of Authentic 2-Iodoimidazole

Richard J. Sundberg

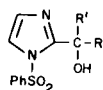
Department of Chemistry, University of Virginia, Charlottesville, VA 22901

Received January 10, 1977

Lithiation of 1-benzenesulfonylimidazole takes place readily at  $-20^{\circ}$  or  $0^{\circ}$  in THF. The lithium reagent gives products of addition to typical carbonyl compounds but only in low yield. Iodination occurs at the 2-position, in low yield, and authentic 2-iodoimidazole is obtained by cleavage of the benzenesulfonyl group.

*J. Heterocyclic Chem.*, **14**, 517 (1977).

The need for an efficient synthesis of certain 2-substituted imidazoles and successful experience with the lithiation of 1-benzenesulfonylimidazole (1) prompted an exploration of the use of 1-benzenesulfonyl-2-lithioimidazole as a synthetic intermediate. 1-Benzenesulfonylimidazole (1) was readily prepared from benzenesulfonyl chloride and the sodium salt of imidazole in DMSO. Lithiation was demonstrated to occur at  $0^{\circ}$  or  $-20^{\circ}$  by hydrolysis with deuterium oxide followed by mass spectrometric analysis. Despite these promising initial results, reactions with typical carbonyl compounds gave disappointing results. The yield of adducts **2a-c** were less than 20%. The possibility that N $\rightarrow$ O transfer of the



- 2a** R, R' = H  
**2b** R = Ph, R' = H  
**2c** R, R' =  $-(CH_2)_5-$

*N*-sulfonyl substituent is the cause of the problem was considered but no products recognizable as being derived from the resulting sulfonate ester could be identified. Yields were not improved by conditions designed to hydrolyze the benzenesulfonyl group immediately after completion of the reaction.

Iodination of 1-benzenesulfonyl-2-lithioimidazole gave only a 6.5% yield of 1-benzenesulfonyl-2-iodoimidazole (**3**). This compound was converted to the previously unknown 2-iodoimidazole by stirring with ethanolic ammonia. The 2-iodoimidazole prepared in this manner was different from the monoiodoimidazole prepared by Pauly (2). The material prepared by Pauly is actually 4-iodoimidazole as has been proved by Naidu and Bensusan (3). 2-Iodoimidazole exhibits a single line in the aromatic region ( $\delta$  7.01) in agreement with the structural assignment.

### EXPERIMENTAL

#### 1-Benzenesulfonylimidazole (1).

Imidazole (6.8 g., 0.10 mole) was dissolved in DMSO (50 ml.) and an equivalent (assuming 80% assay) of powdered potassium hydroxide was added. When the potassium hydroxide had dissolved the solution was cooled to  $0^{\circ}$  and an equivalent of benzenesulfonyl chloride was added over 30 minutes. The solution was stirred at room temperature for 30 minutes and then poured into 100 ml. of water and extracted with chloroform (3 x 50 ml.). The chloroform was washed with water dried and evaporated, leaving a yellow oil which normally crystallized on evacuation (12.4 g., 60%). Recrystallized material (8.2 g., 40%), m.p.  $78^{\circ}$  (lit (5) m.p.  $83-84^{\circ}$ ) was obtained using chloroform-hexane.

#### Lithiation.

A solution of 1.04 g. of **1** in THF was cooled to  $0^{\circ}$  and treated with an equivalent of *n*-butyllithium or *t*-butyllithium in pentane. Aliquots removed at 10, 30 and 60 minutes were quenched with deuterium oxide and analyzed by mass spectrometry, nmr and tlc. Recovery of completely deuterated material was indicated by mass spectrometry and nmr with some evidence (tlc) of decomposition in the 30 and 60 minute samples. Lithiation was also complete in 10 minutes at  $-20^{\circ}$  (carbon tetrachloride-carbon dioxide bath) but no lithiation occurred after 30 minutes at  $-78^{\circ}$ .

#### 1-Benzenesulfonyl-2-hydroxymethylimidazole (2a).

A solution of 2.08 g. of **1** in THF (30 ml.) was lithiated using *t*-butyllithium at  $-20^{\circ}$  for 0.5 hours. Over 1 hour, 5.0 g. of paraformaldehyde was thermally depolymerized and carried by a stream of nitrogen into the reaction flask. The cooling bath was removed and after 0.5 hour the solution was hydrolyzed with aqueous ammonium chloride and extracted thoroughly with chloroform. After chromatography 0.23 g. (10%) of crystalline **2a**, m.p.  $105^{\circ}$  was obtained. The analytical sample was prepared by recrystallization from ethanol-ether.

*Anal.* Calcd. for  $C_{10}H_{10}N_2SO_3$ : C, 50.42; H, 4.23; N, 11.76. Round: C, 50.20; H, 4.33; N, 11.87.

#### 1-Benzenesulfonyl-2-(1-hydroxyphenyl)methylimidazole.

After lithiation of 1-benzenesulfonylimidazole (1.04 g.) at 0° for 10 minutes with *t*-butyllithium, two equivalents of benzaldehyde was added. After 30 minutes the reaction was quenched with ammonium chloride solution and extracted thoroughly with chloroform. Chromatography on silica using 20% ether in benzene for elution yielded the adduct **1b** as an oil which crystallized with difficulty (0.58 g., 18%). This material was hydrolyzed in aqueous ethanolic potassium hydroxide during 1 hour to give 2-(1-hydroxyphenylmethyl)imidazole, m.p. 198-200°, (lit (6) m.p. 193-195°; 199-201°).

#### 1-Benzenesulfonyl-2-(1-hydroxycyclohexyl)imidazole (**2c**).

A solution of **1** (1.04 g.) in THF was lithiated with *n*-butyllithium at 0° for 5 minutes, then cyclohexanone (0.55 g.) was added. After 0.5 hour at room temperature the solution was hydrolyzed and extracted with chloroform. Chromatography of the crude product gave **2c** (0.42 g., 15%) m.p. 122°. The analytical sample was obtained by recrystallization from chloroform-hexane.

*Anal.* Calcd. for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>SO<sub>3</sub>: C, 58.80; H, 5.91; N, 9.14. Found: C, 58.78; H, 5.94; N, 9.18.

#### 1-Benzenesulfonyl-2-iodoimidazole (**3**).

A solution of 2.08 g. of **1** in 40 ml. of THF was lithiated with 1 equivalent of *n*-butyllithium at -10°. After 15 minutes a solution of iodine (2.55 g.) in 25 ml. THF was added. After an additional 20 minutes, the reaction mixture was treated with an aqueous solution of ammonium chloride and sodium sulfite. Color due to some unreacted iodine was rapidly discharged. The THF layer was separated and the aqueous layer was extracted with chloroform. The aqueous layer was subsequently subjected to continuous extraction but no additional material was extracted.

The combined THF-chloroform layers were dried over sodium sulfate and concentrated. The residue was redissolved in 10 ml. of ether containing ~10% ethanol. 1-Benzenesulfonyl-2-iodoimidazole (0.220 g., 6.6%) deposited and was recrystallized from ethanol-ether, m.p. 154-156°.

*Anal.* Calcd. for C<sub>9</sub>H<sub>9</sub>IN<sub>2</sub>SO<sub>2</sub>: C, 32.35; H, 2.11; N, 8.39. Found: C, 32.39; H, 2.13; N, 8.36.

The mother liquors from the original precipitation gave recovered 1-benzenesulfonylimidazole (0.510 g., 26%) and traces of benzenesulfonamide and 2-iodoimidazole after chromatography

on alumina using 20% ether in benzene for elution.

#### 2-Iodoimidazole (**4**).

Compound **3** (210 mg.) was dissolved in 15 ml. of ethanol which had been saturated with ammonia. The progress of the reaction was followed by tlc and was complete in 12-16 hours. The solution was evaporated and the residue was dissolved in a small amount of ethanol-ether. A crystalline precipitate (28 mg.) was obtained. Additional pure **4** was obtained by chromatography of the mother liquors on alumina using 20% ether in benzene for elution giving a total yield of 0.087 g., 71%. The analytical sample was prepared by recrystallization from ethanol-ether-hexane, m.p. 192-194°.

*Anal.* Calcd. for C<sub>3</sub>H<sub>3</sub>IN<sub>2</sub>: C, 18.57; H, 1.56; N, 14.44. Found: C, 18.66; H, 1.58; N, 14.39.

#### Acknowledgments.

This research was supported by NIH Grant 21572.

#### REFERENCES AND NOTES

- (1) R. J. Sundberg and H. F. Russell, *J. Org. Chem.*, **38**, 3324 (1973).
- (2) H. Pauly and K. Gunderman, *Chem. Ber.*, **41**, 3999 (1908); H. Pauly, *ibid.*, **43**, 2243 (1910); H. Pauly and E. Arauner, *J. Prakt. Chem.*, **118**, 33 (1928).
- (3) M. S. R. Naidu and H. B. Bensusan, *J. Org. Chem.*, **33**, 1307 (1968); H. B. Bensusan and M. S. R. Naidu, *Biochemistry*, **6**, 12 (1967) have shown the material frequently referred to in the literature as 2-iodoimidazole, (**4**) initially reported by Pauly (2), is 4-iodoimidazole. Unfortunately, Chemical Abstracts do not index the Naidu-Bensusan papers under either 2- or 4-iodoimidazole and the structural clarification is not readily located.
- (4) For example, I. A. Boenig, W. R. Conway and K. Niedenzu, *Synth. React. Inorg. Met.-Org. Chem.*, **5**, 1 (1975).
- (5) H. A. Staab and K. Wendel, *Chem. Ber.*, **93**, 2902 (1960).
- (6) A. F. Wagner, P. E. Wittreich, A. Lusi and K. Folkers, *J. Org. Chem.*, **23**, 785 (1969); A. Sonn and P. Greif, *Chem. Ber.*, **66**, 1900 (1933).