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3-[(Benzylsulfonyl)methyl]aniline hydrochloride

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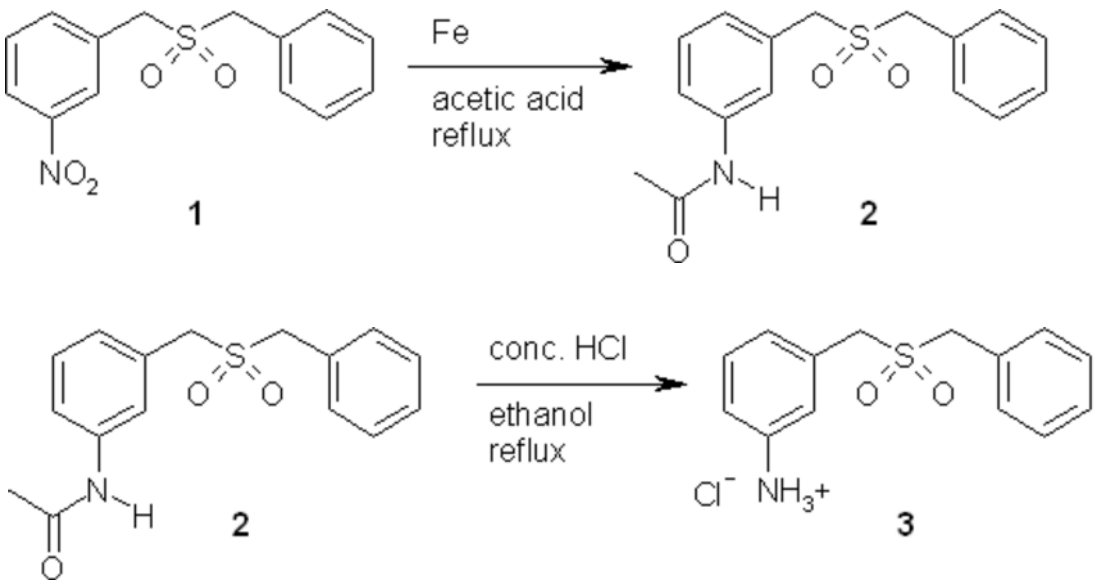
In the course of our work to prepare inhibitors of the enzyme dihydrofolate reductase, we desired to prepare sulfone analogues of some similar sulfides [1, 2]. The previously reported nitrosulfone [3] was not able to be reduced to the amine by using catalytic hydrogenation with a palladium on carbon catalyst, with tin and hydrochloric acid [4], or with iron and acetic acid in ethanol [5]. Therefore, the nitrosulfone, 1, was converted into the acetamide, 2, using iron in acetic acid [5]. The acetamide, 2, was hydrolyzed to the desired aniline, 3, using concentrated hydrochloric acid and ethanol. Unfortunately for us, the aniline was not able to be converted into the desired triazine by the reported procedure [2].



In round bottom flask 1-nitro-3-[(benzylsulfonyl)methyl]benzene, 1 (1.504 g, 5.162 mmoles), iron filings (2.017 g, 36.12 mmoles), and 75 mL of concentrated acetic acid were combined and refluxed for 4 hours. After allowing the reaction to cool, 150 mL of water was added. However, the product of the reaction became insoluble. Therefore, 90 mL dichloromethane was added. The reaction mixture was then filtered to remove unreacted iron. The organic and aqueous layers were separated. The aqueous layer was extracted two more times with dichloromethane. The organic extracts were combined and dried with anhydrous magnesium sulfate. The dichloromethane was removed with the rotavap to yield 1.439 g (4.74 mmoles) of 3-[(benzylsulfonyl)methyl]acetanilide, 2. The percent yield for the reaction was 92%.

Melting Point: 180-182°C

IR (cm^{-1}): 3248, 1655, 1541, 1443, 1296, 1284, 1116, 785, 719, 693.

^{1}H-NMR (300 MHz, DMSO-d_6): δ= 10.0 (1H, singlet), 7.6 (2H, multiplet), 7.4 (5H, multiplet), 7.3 (1H, triplet, J = 7.7 Hz), 7.0 (1H, doublet, J = 7.7 Hz), 4.5 (2H, singlet), 4.4 (2H, singlet), 2.0 (3H, singlet).

^{13}C-NMR (75 MHz, DMSO-d_6): δ= 168.9, 139.9, 131.7, 129.3, 129.0, 128.90, 128.87, 128.6, 126.3, 122.0, 119.4, 58.0, 57.9, 24.5.

GC-MS [E.I., m/z (relative intensity)]: 148 (100), 106 (92), 91 (70), 239 (58), 197 (52), 77 (28), 79 (21), 196 (16), 303 (M^+, 8).

In a round bottom flask 3-[(benzylsulfonyl)methyl)acetanilide, 2 (1.372 g, 4.52 mmoles), 8 mL of 95% ethanol, and 2 mL of concentrated hydrochloric acid were combined and refluxed for 4.5 hours. The amide dissolved in the hot ethanol forming a yellow solution. After about 1 hour, a precipitate began to form. The reaction mixture was allowed to cool, and the precipitate was collected by vacuum filtration. The precipitate was washed with three portions of cold 95% ethanol to yield 1.113 g (3.92 mmoles) of 3-[(benzylsulfonyl)methyl]aniline hydrochloride, 3, was collected. The percent yield of the reaction was 87%.

Melting Point: 225 ^{o}C (decomposed)

IR (cm^{-1}): 2881 (br), 1536, 1519, 1311, 1291, 1276, 1135, 1120, 761, 724, 709, 690, 683.

^{1}H-NMR (300 MHz, DMSO-d_6): δ= 7.5 – 7.2 (9H, multiplet), 4.55 (2H, singlet), 4.50 (2H, singlet), 3.7 (3H, broad singlet).

^{13}C-NMR (75 MHz, DMSO-d_6): δ= 132.7, 131.2, 130.3, 129.8, 129.7, 128.5, 128.4, 127.9, 125.2, 122.9, 57.7, 56.9.

GC-MS [E.I., m/z (relative intensity), free base]: 106 (100), 261 (M^+, 56), 197 (48), 91 (16), 79 (12), 77(12).

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