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EXPERIMENTAL PAPER

Improved Synthesis of 5-Ethylsulfonyl-2-methoxyaniline

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5-Ethylsulfonyl-2-methoxyaniline is an extremely versatile molecule used in the preparation of a number of different compounds with biological activities targeting kinases, including several VEGFR2 inhibitors[1–3] and a CLK inhibitor.[1] Closely related sulfone analogues of 5-ethylsulfonyl-2-methoxyaniline have also been used in the preparation of antimalarials,[4] muscarinic M1 agonists,[5] topoisomerase inhibitors[6] and utrophin upregulators.[7] A compound synthesized from 5-ethylsulfonyl-2-methoxyaniline is featured in the Protein Database (PDB ID: 1y6a).[3] Our lab became interested in the preparation of this compound when we were designing inhibitors of serine/threonine-protein kinase 16 (STK16). Since the compound is not commercially available, we first tried to reproduce a recently reported procedure[8] detailed in Scheme 1.

The reported yields at each step were 90% or more, except for the nitration step which had a reported yield of 73%. While we were able to successfully synthesize the sodium 4-methoxybenzenesulfinate in comparable yields, we observed significantly lower yields in subsequent steps, with the ethyl iodide alkylation giving particularly poor yields—oftentimes less than 20%. These lower yields were observed by multiple independent researchers all following the reported procedure at the same scale. Our group tried to optimize the procedure with modifications designed to improve our yields such as the use of different solvents and larger excesses of reactants, but none of these modifications provided yields comparable to those reported. This was a serious issue as we were trying to synthesize 5-(ethylsufonyl)-2-methoxyaniline on a multi-gram scale with the intention of using it as a key building block for a kinase inhibitor library. Because of this, we needed to develop a new procedure on a multi-gram scale that reliably provided product in good yields.

We developed a new synthetic route (Scheme 2) starting with the reaction of commercially available 4-methoxybenzenethiol (**1**) with ethyl iodide and potassium carbonate in acetonitrile at 60 °C to make 1-ethylsulfanyl-4-methoxybenzene (**2**). This sulfide was then reacted with *meta*-chloroperoxybenzoic acid (mCPBA) in dichloromethane to produce 1-ethylsulfonyl-4-methoxybenzene (**3**). This sulfone was subsequently treated with nitric

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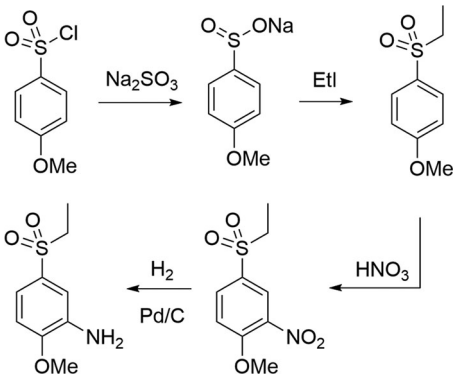
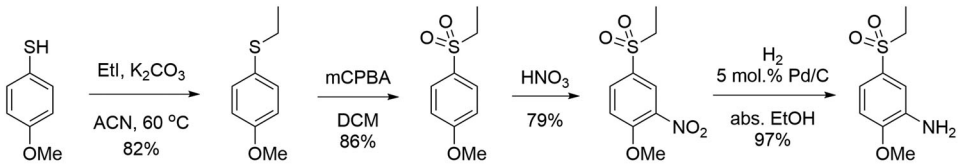


Scheme 1. Previously reported synthesis of 5-(ethylsufonyl)-2-methoxyaniline.



Scheme 2. Synthetic pathway starting from the commercially available 4-methoxybenzenethiol leading to the desired 5-(ethylsufonyl)-2-methoxyaniline final product. Yields are the averages of 3 independent runs performed by 3 different researchers.

acid to provide 4-(ethylsulfonyl)-1-methoxy-2-nitrobenzene (**4**) which was finally subjected to catalytic hydrogenation to afford the desired 5-ethylsufonyl-2-methoxyaniline (**5**).

We observed good yields for each reaction step and from a diverse group of individuals in our laboratory, including experienced chemists and undergraduate research students. This reproducibility highlights the ease and practicality of our synthetic method. Moreover, the starting material 4-methoxybenzenethiol (**1**) and the reagents in our scheme are inexpensive and readily available. Our procedure does not require any chromatography and instead uses only liquid-liquid extraction and filtration to isolate the intermediates and final product. NMR and HPLC data indicate excellent purity at all steps and no recrystallization was needed (see Supplementary Materials). We believe that this new reaction scheme provides a robust and reliable alternative to previously reported methods.

Experimental section

^{1}H Nuclear Magnetic Resonance (NMR) spectra were obtained on a 300 MHz Bruker instrument using $CDCl_3$ as the solvent. Chemical shifts were reported as δ values in parts per million (ppm) relative to the solvent. All reactions were performed open to the atmosphere unless indicated otherwise. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 250 μm layer silica plates visualized with either 254 or 365 nm wavelengths. All solvents were used without purification and no attempts were made to exclude atmospheric moisture unless indicated otherwise in the following

procedures. Glassware was dried for at least 1h in a 90 °C oven prior to use. HPLC was performed on an Agilent 1260 Infinity system equipped with an Agilent Eclipse Plus C18 column, 100 mm x 4.6 mm, 3.5 μm. Known intermediate compounds in Scheme 2 were identified by matching their ^{1}H NMR spectra with the literature data in the references cited in the individual compound descriptions below. Copies of the NMR spectra and the HPLC chromatogram were submitted for review.

1-Ethylsulfanyl-4-methoxybenzene (2)

The following procedure is representative and was performed on a 25 mmol scale. In a round-bottom flask with a stir bar, 100 mL of ACN and 6.91 g of K_2CO_3 (50 mmol, 2 eq.) were added and placed over an oil bath at 60 °C. Once the oil bath was at a stable temperature (60 ± 2 °C), the reaction flask was lowered into the oil bath. Next, 3.1 mL of 4-methoxybenzenethiol (25 mmol, 1 eq.) was added to the stirring mixture in the reaction flask followed by 4 mL (50 mmol, 2 eq.) of ethyl iodide. The reaction mixture was gently capped with a septum and allowed to run overnight (16 h) with completion confirmed by TLC using a 7:1 hexanes/ethyl acetate mixture. The reaction flask was then removed from the oil bath and cooled to room temperature before the solvent was removed under rotary evaporation to isolate the crude product. Next, 25 mL of D.I. water, 25 mL of saturated NaCl solution, and 25 mL of ethyl acetate were added to the reaction flask containing the crude material. This mixture was mixed well then transferred to a separatory funnel where the layers were allowed to separate. The organic layer was removed and set aside. The aqueous layer was extracted twice more using roughly 50 mL of ethyl acetate each time for a final combined volume of approximately 150 mL of ethyl acetate. The combined ethyl acetate layers were then dried over magnesium sulfate and filtered through a vacuum filter. The filtered ethyl acetate layers were evaporated under reduced pressure to obtain 3.401 g of (**2**) as a slightly yellow oil (81% yield). ^{1}H NMR (300 MHz, CDCl3) δ = 7.36 (m, 2H), 6.86 (m, 2H), 3.80 (s, 3H), 2.85 (q, J = 7.3 Hz, 2H), 1.26 (t, J = 7.3 Hz, 3H).[9]

1-Ethylsulfonyl-4-methoxybenzene (3)

The product 5-ethylsulfonyl-2-methoxyaniline (**2**) isolated in the previous step (3.401 g, 20.2 mmol, 1 eq.) was added to a round-bottom flask along with 202 mL DCM and a stir bar. Next, 10.46 g mCPBA (70% pure, 42.4 mmol, 2.1 eq.) was slowly added to the reaction flask with stirring. The reaction was loosely capped with a septum and allowed to run overnight (16 h) with completion confirmed by TLC using a 1:1 hexanes/ethyl acetate mixture. After the reaction was confirmed complete, the solution was quenched by adding 5 mL conc. $Na_2S_2O_3$ to the stirring solution. The solution was then transferred to a large separatory funnel and approximately 100 mL of D.I. water and 50 mL of chloroform were added and mixed. After the layers separated, the bottom organic layer was drained and the remaining aqueous layer was extracted twice more with fresh chloroform, combining the organic layers after each extraction. The combined organic layers were then placed back into an empty separation funnel and extracted three times with 35 mL of a conc. sodium carbonate solution. The organic layers were dried over

magnesium sulfate, vacuum filtered to remove the solids, then evaporated under reduced pressure to obtain 3.506 g of (**3**) as an off-white solid (87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.84 (m, 2H), 7.04 (m, 2H), 3.90 (s, 3H), 3.10 (q, J = 7.4 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H).[10]

4-(Ethylsulfonyl)-1-methoxy-2-nitrobenzene (4)

The sulfone (**3**) made in the previous step (3.506 g, 17.5 mmol, 1 eq.) was added along with 43.75 mL conc. nitric acid to a round-bottom flask with a stir bar. A condenser was connected to the reaction flask and the reaction mixture was gently refluxed for 2 hours. Once the reaction was complete by TLC using a 1:1 hexanes/ethyl acetate mixture, it was removed from the heat and allowed to cool to room temperature. An ice-water mixture was prepared in a large beaker with a total volume equal to 10x the initial volume of conc. nitric acid (in this case, equal to approximately 435 mL). The room temperature nitric acid solution was then slowly poured into the ice-water mixture while stirring with a glass stir rod. As the nitric acid solution was poured, a white precipitate formed. Once all the nitric acid solution was added, the mixture was stirred until all the ice had melted. The cold water was then filtered through a vacuum filter and the captured solid was washed twice with D.I. water. The solid was dried to obtain 3.406 g of an off-white solid (79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 2.3 Hz, 1H), 8.08 (dd, J = 8.8, 2.3 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 4.08 (s, 3H), 3.16 (q, J = 7.5 Hz, 2H), 1.32 (t, J = 7.5 Hz, 3H).[8]

5-Ethylsufonyl-2-methoxyaniline (5)

The nitration product (**4**) from the previous step (3.406 g, 13.9 mmol, 1 eq.) was added to a round-bottom flask with 141 mL of absolute EtOH and 0.753 g of Pd/C (5 mol. % Pd of a 10% by weight powder) with a stir bar. The flask was then sealed with a septum. A balloon was filled with hydrogen gas and attached to a syringe bottom with a needle threading. A needle was added to the end of a vacuum line in the hood. Using the vacuum line with the needle, the atmosphere was removed from the flask while gentle stirring occurred. Once the air was removed, the flask was filled with hydrogen by briefly inserting the needle attached to the hydrogen balloon through the septum and allowing some of the hydrogen to leave the balloon. This process was repeated two more times, and the balloon with the hydrogen was left in the septum after the last time. The reaction was allowed to run overnight (16 h). Reaction completion was confirmed by running a ^{1}H NMR of an aliquot removed from the reaction via a needle and syringe. Once the reaction was confirmed complete, it was filtered through a celite pad to remove the Pd/C. The filtered solution was then evaporated under reduced pressure to obtain 2.868 g of the final product as an off-white solid (96% yield, HPLC purity at 254 nm 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (dd, J = 2.2, 8.4 Hz, 1H), 7.18 (d, J = 2.2 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 4.06 (br s, 2H), 3.93 (s, 3H), 3.07 (q, J = 7.4 Hz, 2H), 1.26 (t, J = 7.4 Hz, 3H).[8]

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