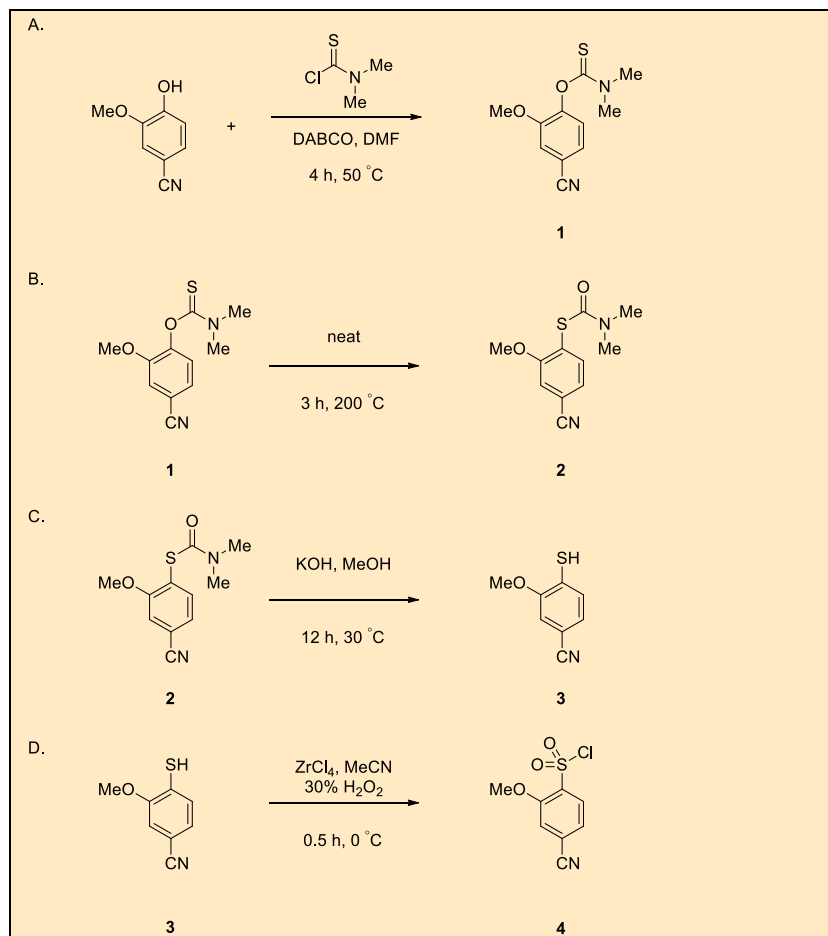


## 4-Cyano-2-methoxybenzenesulfonyl Chloride

Elliott D. Bayle, Niall Igoe, and Paul V. Fish\*<sup>1</sup>

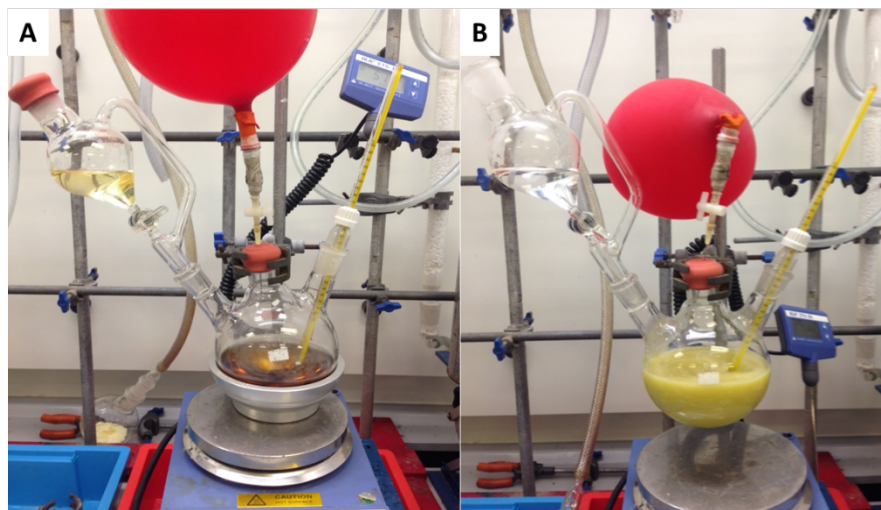
UCL School of Pharmacy, University College London, 29-39 Brunswick Square, London, WC1N 1AX, UK

Checked by Kevin Gayler, Aoi Kimishima, and John Wood



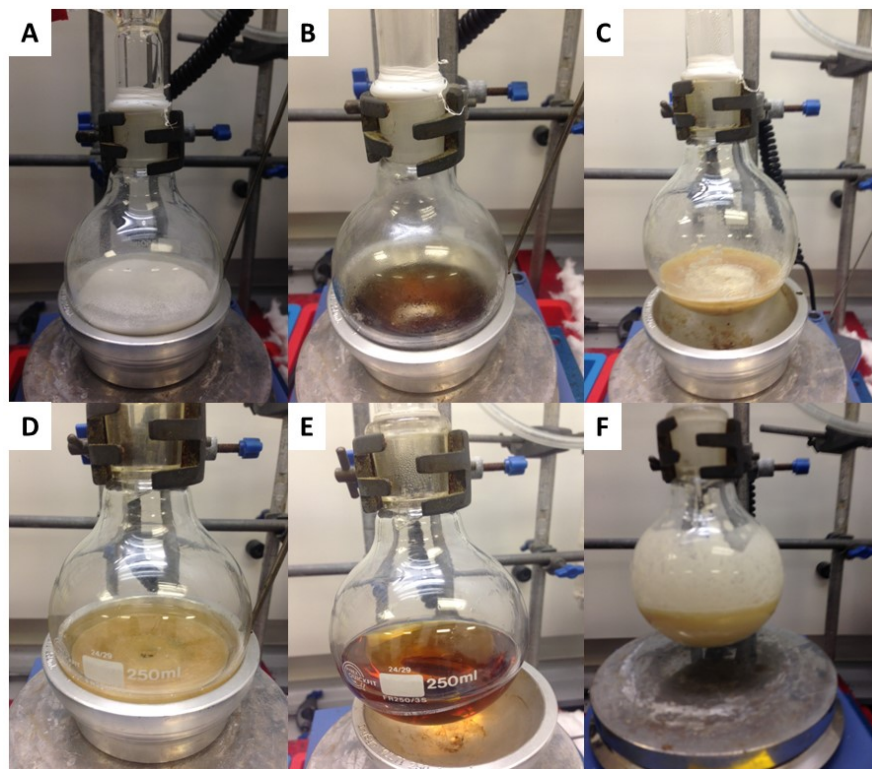
## Procedure (Note 1)

A. *O*-(4-Cyano-2-methoxyphenyl) dimethylcarbamothioate (**1**). To a flame dried 500 mL three-necked round-bottomed flask equipped with a 40 x 20 mm oval-shaped Teflon-coated magnetic stir bar, a dried 100 mL pressure-equalizing dropping funnel and a thermometer adaptor fitted with an internal thermometer is added 4-hydroxy-3-methoxybenzonitrile (25.0 g, 168 mmol, 1.0 equiv) (Note 2) followed by 1,4-diazabicyclo[2.2.2]octane (19.8 g, 176 mmol, 1.05 equiv) (Note 3). The remaining neck is sealed with a rubber septum. The system is flushed with nitrogen using a double Schlenk manifold (nitrogen and vacuum) and charged with DMF (100 mL) (Note 4) *via* syringe. The resultant slurry is warmed to an internal temperature of 50 °C in an oil bath (Note 5) during which time it became a homogenous brown solution. In the interim, dimethylthiocarbamoyl chloride (20.7 g, 168 mmol, 1.0 equiv) (Note 6) is charged to a 100 mL single-necked round-bottomed flask that had been capped with a rubber septum, flame dried, and evacuated and back-filled with nitrogen three times. Dimethylformamide (DMF, 30 mL) (Note 4) is added *via* syringe and the flask gently swirled until all of the dimethylthiocarbamoyl chloride had dissolved, at which point the solution is transferred to the pressure-equalizing dropping funnel *via* syringe. The solution of dimethylthiocarbamoyl chloride is added dropwise to the reaction mixture over a period of 10 min resulting in a 12 °C exotherm and a turbid reaction mixture (Note 7). The resulting mixture is stirred for an additional 4 h at 50 °C. The reaction mixture is then allowed to cool to room temperature and water (2 x 75 mL) (Note 8) is added *via* the dropping funnel. After approximately 20–30 mL of water had been added, the reaction mixture became homogenous (brown/greenish hue) (Note 9). After approximately 75 mL of water had been added, significant precipitation of the desired product is observed along with a 10 °C exotherm. After all of the water had been added, the resultant slurry is stirred for an additional 0.5 h before the product is collected by vacuum filtration onto a 100 mL sintered-glass funnel. The white crystals are washed with two portions of cold water (50 mL) and dried under high vacuum for 12 h (<1 mmHg) to give *O*-(4-cyano-2-methoxyphenyl) dimethylcarbamothioate (**1**) as white crystals (28.2 g, 71%) (Notes 10, 11, and 12).



**Figure 1.** Reaction Assembly for Step A. **A:** Reaction during dimethylthiocarbamoyl chloride addition; **B:** Reaction during water addition

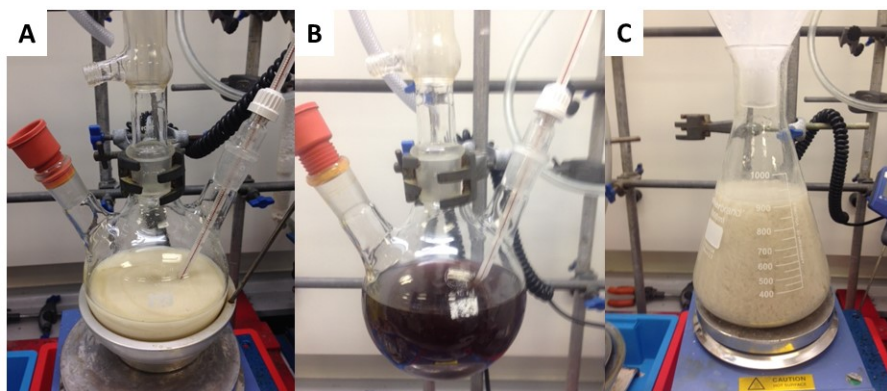
B. *S*-(4-Cyano-2-methoxyphenyl) dimethylcarbamothioate (**2**). To a 250 mL single-necked round-bottomed flask fitted with a reflux condenser and a 25 x 15 mm oval-shaped Teflon-coated magnetic stir bar is added *O*-(4-cyano-2-methoxyphenyl) dimethylcarbamothioate (**1**) (28.0 g, 118 mmol, 1.0 equiv). The flask is evacuated and back-filled with nitrogen gas three times and then heated at 200 °C on a Heidolph aluminum heating block (Notes 13 and 14). After 3 h, the reaction mixture is allowed to cool to ambient temperature (Note 15), and toluene (48 mL) (Note 16) is added *via* the reflux condenser in order to wash trace amounts of sublimed material into the flask. The reaction mixture is heated to reflux or until all of the solid had dissolved. Once all of the solid had dissolved, rapid stirring is commenced (>800 rpm) and the reaction mixture is cooled to ambient temperature, during which time the desired product precipitates as colorless crystals. The reaction mixture is then cooled in an ice-water bath to 0 °C and stirred for a further 2 h. The precipitate is then collected by vacuum-filtration (375 mmHg) onto a 250 mL sintered-glass funnel, washed with two portions of hexane (2 x 57 mL) (Note 17) and allowed to dry under vacuum to give analytically pure *S*-(4-cyano-2-methoxyphenyl)dimethylcarbamothioate (**2**) (23.8 g, 85%) (Notes 18, 19, and 20).



**Figure 2. Reaction Assembly for Step B.** A: Solid 1 in 250 mL round bottom flask; B: 1 melts upon heating to 200 °C; C: Solidified 2 upon cooling of the reaction mixture; D: Toluene added and 2 reheated under reflux conditions; E: Homogenous solution of 2 in toluene; F: 2 crystallizes upon cooling as colorless crystals

C. 4-Mercapto-3-methoxybenzonitrile (3). To a 500 mL three-necked round-bottomed flask fitted with a reflux condenser on the center neck and a 40 x 20 mm oval-shaped Teflon-coated magnetic stir bar, is charged S-(4-cyano-2-methoxyphenyl) dimethylcarbamothioate (2) (23.0 g, 97 mmol, 1.0 equiv) followed by methanol (184 mL) (Note 21). To the slurry is added potassium hydroxide flakes (16.4 g, 292 mmol, 3.0 equiv) (Note 22) in three portions over 30 min, an exotherm of 12 °C was observed upon addition of the first portion of potassium hydroxide. One side-arm is fitted with a septa and the other with a thermometer adaptor fitted with a thermometer. The reaction is then warmed to an internal temperature of 30 °C using a silicone

oil bath and rapidly stirred (1000 rpm) for 12 h (Note 23). During the course of the reaction the slurry became a dark-colored homogeneous solution. At the end of the aforementioned time period the contents of the flask are transferred to a 1 L Erlenmeyer flask fitted with a 55 x 10 mm cylindrical stir bar. Methanol (20 mL) is used to rinse the three-necked round-bottomed flask and is then added to the Erlenmeyer flask. The stirred solution is then acidified to pH 2 with 3.0 M aqueous hydrochloric acid (110 mL) (Note 24), during which a fluffy off-white precipitate forms (Note 25). An additional portion of water (230 mL) is then added and the slurry stirred for a further 0.5 h at ambient temperature. The heterogeneous solution is then filtered through a 500 mL sintered funnel into a 2 L Erlenmeyer flask. The precipitate that had collected in the funnel is then washed with an additional portion of water (230 mL) and dried under vacuum overnight ( $\leq 1$  mmHg) to give 4-mercapto-3-methoxybenzonitrile (**3**) (14.4 g, 90%) as a slightly pungent white solid (Notes 26, 27, 28, 29, and 30).

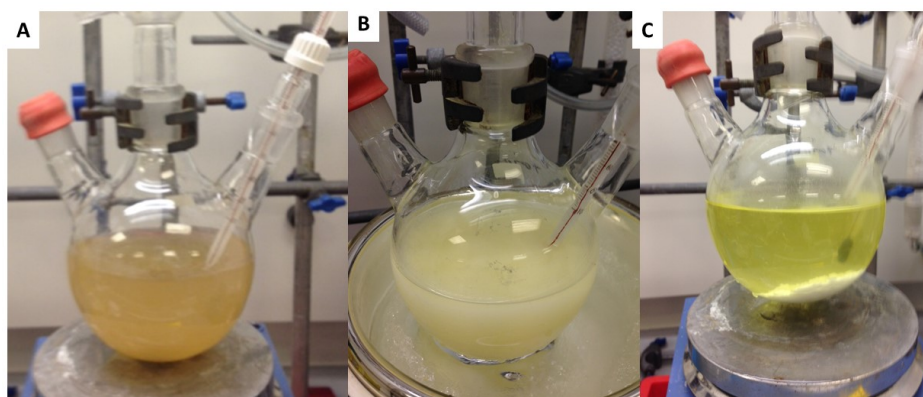


**Figure 3.** Reaction Assembly for Step C. **A:** Reaction mixture before heating; **B:** Reaction mixture after stirring for 12 hours; **C:** Precipitation of **3** upon acidification with 3.0 M aqueous HCl

**D. 4-Cyano-2-methoxybenzenesulfonyl chloride (**4**).** To a 500 mL three-necked round-bottomed flask fitted with a reflux condenser on the center neck and a 40 x 20 mm oval-shaped Teflon-coated magnetic stir bar is charged 4-mercapto-3-methoxybenzonitrile (**3**) (12.0 g, 72.6 mmol, 1.0 equiv) followed by zirconium(IV) chloride (16.9 g, 72.6 mmol, 1.0 equiv) (Note 31). One side-arm is fitted with a septa and the other with a screw-thread adaptor fitted with a thermometer. Acetonitrile (250 mL) (Note 32) is added



and the reaction mixture stirred rapidly until all solids dissolve and a yellow homogenous solution is obtained (approximately 5 min) (Note 33). The reaction mixture is next cooled to 0 °C in an ice bath and hydrogen peroxide (30% w/w aqueous, 24.7 mL, 217.9 mmol, 3.0 equiv) (Note 34) is added dropwise, maintaining the internal temperature below 10 °C (Caution! Highly exothermic) (Note 35). After the addition of the hydrogen peroxide is complete, the ice bath is removed and the yellow homogenous solution stirred for an additional 0.5 h at ambient temperature during which time a pale precipitate forms. Water (150 mL) is added and the reaction mixture stirred until all of the precipitate dissolves. This mixture is then transferred to a 1 L separatory funnel, diluted further with water (200 mL) and extracted with ethyl acetate (Note 36) (3 x 150 mL). The organic phases are combined and washed with saturated brine (250 mL), transferred to a 2 L Erlenmeyer and dried with anhydrous sodium sulfate (Note 37). The organic layer is then filtered through a 250 mL sintered-glass funnel into a 2 L Erlenmeyer flask and concentrated under reduced pressure to give 4-cyano-2-methoxybenzenesulfonyl chloride (**4**) as a yellow solid (13.0 g, 78%) (Notes 38, 39, 40, 41, 42, and 43).



**Figure 4. Reaction Assembly for Step D. A: Reaction mixture prior to addition of  $\text{H}_2\text{O}_2$ ; B: Reaction mixture during  $\text{H}_2\text{O}_2$  addition; C: Reaction mixture at ambient temperature prior to aqueous work up**

## Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical

substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at <https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical>).

See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at <https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html>. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with 4-hydroxy-3-methoxybenzonitrile, 1,4-diazabicyclo[2.2.2]octane, dimethylformamide (DMF), dimethylthiocarbamoyl chloride, toluene, hexane, potassium hydroxide, methanol, acetonitrile, hydrogen peroxide, zirconium tetrachloride, sodium sulfate, and ethyl acetate. *Step D involves the use of 30 % aqueous hydrogen peroxide. During the reaction workup, any presence of excess peroxides should be determined with potassium iodide starch test paper, and if detected, destroyed with aqueous sodium thiosulfate solution.*

2. 4-Hydroxy-3-methoxybenzonitrile was purchased from Sigma Aldrich (98%) and used as received.
3. 1,4-Diazabicyclo[2.2.2]octane was purchased from Sigma Aldrich (>99%) and used as received. Checkers used 1,4-diazabicyclo[2.2.2]octane purchased from Alfa Aesar (98%). In some test reactions, the Checkers had used 1,4-diazabicyclo[2.2.2]octane purchased from Sigma Aldrich (>99%). No difference was observed using different sources of DABCO.
4. Anhydrous dimethylformamide was purchased from Acros Organics (99.8%) and used as received.
5. The Checkers used an oil bath for this step instead of a DrySyn aluminum heating block, which was used by the Submitters.
6. Dimethylthiocarbamoyl chloride was purchased from Sigma Aldrich (97%) and used as received.
7. The Checkers observed an additional 12 °C exotherm during dimethylthiocarbamoyl addition, and both the Checkers and

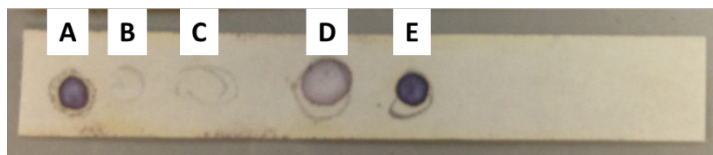
- Submitters observed a 10 °C exotherm upon the addition of water to the reaction.
8. In-house deionized water was used.
  9. After the initial addition of water, the color was observed to vary between brown/yellow to green in different batches. This variability in color change did not affect the yield or purity of the desired product.
  10. The weight percent (wt%) purity was determined to be 98.0 wt% by quantitative <sup>1</sup>H NMR (QNMR) using 1,2,4,5-tetrachloro-3-nitrobenzene purchased from Sigma Aldrich as an internal standard (99.86%).
  11. *O*-(4-Cyano-2-methoxyphenyl) dimethylcarbamothioate characterization data: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.36 (s, 3H), 3.46 (s, 3H), 3.86 (s, 3H), 7.14 (d, *J* = 8.2 Hz, 1H), 7.21 (d, *J* = 1.8 Hz, 1H), 7.31 (dd, *J* = 8.2, 1.8 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ: 39.0, 43.6, 56.4, 110.6, 115.9, 118.6, 125.3, 125.4, 146.6, 152.3, 186.6; IR (film) 2942, 2230, 1599, 1541, 1505, 1396, 1284, 1264, 1203, 1150, 1120, 1023, 923, 861, 827, 810, 741, 623, 483 cm<sup>-1</sup>; HRMS ESI-MS *m/z* calcd for C<sub>11</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub>S [M + H]<sup>+</sup>: 237.0698, found: 237.0694.
  12. The Checkers obtained a 71% yield on full scale and a 72% yield on half scale with 98.0 wt% purity. The Submitters report 76% yield with a 97.0 wt% purity.
  13. The reaction is solvent-free. Care should be taken to ensure all of the starting material is in contact with the heated part of the vessel wall during the reaction.
  14. The starting material **1** begins to melt around 130 °C. Once all the solid melted, stirring was commenced at a slow speed (<200 rpm). Traces of sublimed **1** may be observed on the reflux condenser during the reaction.
  15. Product **2** begins to form a glassy solid at approximately 150 °C. Stirring is maintained while the reaction cools to allow the stir bar to continue freely rotating, thereby enabling stirring upon addition of toluene and facilitating dissolution of the crude product prior to recrystallization.
  16. Toluene, extra pure (>99%), was purchased from Fisher Scientific and used as received. Checkers used toluene, certified ACS (99.9%), purchased from Fisher Scientific.
  17. HPLC grade hexane (>95%) was purchased from Sigma Aldrich and used as received.



18. The weight percent (wt%) purity was determined to be 99.0 wt% by quantitative  $^1\text{H}$  NMR (QNMR) using 1,2,4,5-tetrachloro-3-nitrobenzene purchased from Sigma Aldrich as an internal standard (99.86 wt%).
19. *S*-(4-Cyano-2-methoxyphenyl) dimethylcarbamothioate characterization data: mp 150–151 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 2.87–3.11 (m, 6H), 3.85 (s, 3H), 7.43 (dd,  $J = 7.9, 1.6$  Hz, 1H), 7.58 (d,  $J = 1.4$  Hz, 1H), 7.60 (d,  $J = 7.9$  Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$ : 36.6, 56.6, 113.2, 114.9, 118.4, 123.5, 124.3, 124.5, 137.9, 159.6, 163.2; IR (film): 2951, 2228, 1791, 1721, 1657, 1558, 1559, 1481, 1445, 1401, 1358, 1281, 1260, 1168, 1097, 1055, 1028, 908, 874, 828, 685, 665, 628, 532  $\text{cm}^{-1}$ ; HRMS ESI-MS  $m/z$  calcd for  $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}_2\text{S}$   $[\text{M} + \text{Na}]^+$ : 259.0517, found: 259.0517.
20. The Checkers were able to obtain 85% yield of **2** on full scale and 78% yield on the half scale procedure with 99.0 wt% purity. The Submitters report a 94% yield with 99.5 wt% purity.
21. HPLC grade methanol was purchased from Sigma Aldrich (>99.9%) and used as received.
22. Reagent grade potassium hydroxide flakes were purchased from Sigma Aldrich (90%) and used as received.
23. The Checkers used an oil bath for this step instead of a DrySyn aluminum heating block which was used by the Submitters.
24. The Submitters prepared the 3.0 M aqueous hydrochloric acid solution adding 123 mL of reagent grade 37% w/w aqueous hydrochloric acid solution (Sigma Aldrich) to 125 mL deionized water and adjusting the volume to 500 mL with deionized water. The Checkers prepared the hydrochloric acid solution adding 250 mL of 12.0 M HCl (Fisher Scientific) to 750 mL of deionized water.
25. After approximately 80 mL of the 3.0 M aqueous HCl had been added the solution turned a greenish hue and a precipitate began to form. A mild exotherm was observed upon addition of the HCl solution.
26. Drying of the product could be achieved more readily by suspending in 100 mL of reagent grade toluene and azeotropically removing trace water under reduced pressure (rotary evaporator, <80 mmHg).
27. The weight percent (wt%) purity was determined to be 98.0 wt% by quantitative  $^1\text{H}$  NMR (QNMR) using 1,2,4,5-tetrachloro-3-nitrobenzene purchased from Sigma Aldrich as an internal standard (99.86 wt%).
28. The Checkers obtained 90% yield on full scale and 85% yield on half scale with 98.0 wt%. The Submitters reported 95% yield with purity of 91.0 wt%.

29. The Submitters provided additional recrystallization procedures to improve purity. The following was suggested: "A 1.0 g sample of the material was recrystallized by dissolving in hot hexane/toluene (8 mL, 5:3) and filtering through a plug of cotton wool. This gave 860 mg of the desired product with a wt% purity of 97.1%." The Checkers did not perform an additional recrystallization since the purity of the initially derived product was sufficient.
30. 4-Mercapto-3-methoxybenzonitrile characterization data: mp 66–67 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.94 (s, 3H), 4.13 (s, 1H), 7.04 (d,  $J = 1.6$  Hz, 1H), 7.16 (dd,  $J = 7.9, 1.6$  Hz, 1H), 7.31 (d,  $J = 7.9$  Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 56.4, 109.2, 113.1, 119.0, 125.1, 129.1, 129.3, 154.4. IR (film) 3069, 3007, 2946, 2572, 2228, 1592, 1560, 1481, 1466, 1406, 1285, 1266, 1173, 1074, 1031, 868, 818, 619  $\text{cm}^{-1}$ ; HRMS ESI-MS  $m/z$  calcd for  $\text{C}_8\text{H}_8\text{NOS}$   $[\text{M} + \text{Na}]^+$ : 188.0146, found: 188.0141.
31. Zirconium(IV) chloride was purchased from Sigma Aldrich (>99.5%) and used as received.
32. HPLC grade acetonitrile was purchased from Sigma Aldrich (>99.9%) and used as received.
33. The intensity of the yellow color of the solution was observed to be dependent on the freshness of the zirconium(IV) chloride. However, the intensity of color did not appear to affect the outcome of the reaction.
34. Aqueous hydrogen peroxide (30% w/w) was purchased from Sigma Aldrich and used as received.
35. The exotherm is greatest during the addition of the first equivalent of hydrogen peroxide (8 mL). It is important to carefully monitor the internal temperature during the addition. During this addition period a precipitate was observed to temporarily form and then redissolve.
36. HPLC grade ethyl acetate was purchased from Sigma-Aldrich (>99.7%) and used as received.
37. Anhydrous sodium sulfate was purchased from Sigma Aldrich (>99.0%) and used as received. Checkers used anhydrous sodium sulfate purchased from Fisher Scientific (>99.0%).
38. Before the organic phase was concentrated, it was tested for the presence of peroxides using potassium iodide starch test paper (Precision Laboratories). As shown in Figure 5C the organic phase did not contain observable levels of peroxides. Prior to disposal the aqueous phase containing hydrogen peroxide (Figure 5A) was treated with 2.0 M aqueous sodium thiosulfate solution (200 mL) and stirred

for 0.5 hours. After such time large amounts of precipitate was observed to have formed, and the supernatant then tested negative for peroxides (Figure 5B).



**Figure 5.** Potassium iodide starch test paper for the presence of peroxides. A blue color change indicates peroxide species are present. A: Aqueous phase after work-up. B: Aqueous phase after treatment with sodium thiosulfate. C: Organic phase after reaction work-up. D: 3.0 M aqueous HCl. E: Aqueous hydrogen peroxide (30% w/w) reagent

39. The weight percent (wt%) purity of the crude material was determined to be 95 wt% and the recrystallised material to be 99 wt% by quantitative  $^1\text{H}$  NMR (QNMR) using 1,2,4,5-tetrachloro-3-nitrobenzene purchased from Sigma Aldrich as an internal standard (99.86 wt%).
40. The Checkers observed a 78% yield on full scale and 75% yield on half scale with 95 wt% purity, prior to recrystallization. The Submitters report 92% yield and 84 wt% purity on a full scale, prior to recrystallization.
41. 4-Cyano-2-methoxybenzenesulfonyl chloride characterization data: mp 114–116 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.13 (s, 3H), 7.38–7.44 (m, 2H), 8.09 (d,  $J$  = 8.2 Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 57.4, 116.8, 120.4, 123.9, 130.7, 135.3, 157.4. IR (film) 3108, 2238, 1594, 1566, 1478, 1466, 1406, 1378, 1283, 1173, 1052, 1018, 929, 881, 837, 723, 637, 602, 567, 544, 502, 479, 434  $\text{cm}^{-1}$ ; HRMS ESI-MS  $m/z$  calcd for  $\text{C}_8\text{H}_7\text{NO}_3\text{SCl}$   $[\text{M} + \text{Na}]^+$ : 253.9655, found: 253.9658.
42. The Submitters provided an additional recrystallization procedure to improve purity of **4**. The following was suggested: “10.0 g of 4-cyano-2-methoxybenzenesulfonyl chloride (**4**) was added to a 250 mL single-necked round-bottomed flask fitted with a 40 x 20 mm oval-shaped Teflon-coated magnetic stir bar. Under an atmosphere of air, toluene-hexane (40 mL, 2:1) was added and the slurry warmed to 50 °C and stirred for a minimum of 15 min. This warm yellow solution was then filtered through a 100 mL glass sintered funnel under house vacuum

into a 100 mL round-bottomed flask and cooled to room temperature, followed by further cooling in an ice-water bath for 1 h. The crystalline product was collected on a 100 mL glass sintered disk, washed with *n*-hexane (2 x 50 mL) and dried under high vacuum for a minimum of 2 h to provide **4** (7.8 g, 99 wt%)."

43. The Checkers were unable to reproduce the recrystallization procedure of the Submitters. The Checkers started with 13.0 g of **4** (95 wt% purity) to receive 5.2 g yield of 99 wt% purity on full scale. On half scale the Checkers started with 6.3 g of 94 wt% purity **4** to provide a 1.8 g of 99 wt% purity material.

## Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record\\_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

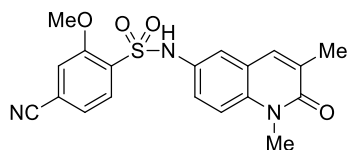
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any

injuries or damages claimed to have resulted from or related in any way to the procedures herein.

## Discussion

The sulfonamide functional group ( $R^1SO_2NR^2R^3$ ) is frequently found in small molecule drug candidates and its efficient synthesis has become an essential part of the medicinal chemist's toolbox of reactions.<sup>2</sup> The synthesis of sulfonamides is most commonly achieved by the reaction of a sulfonyl chloride ( $R^1SO_2Cl$ ) with an amine ( $HNR^2R^3$ ) under basic conditions.<sup>3</sup> However, the application of substituted sulfonyl chlorides that incorporate polar groups, to offer additional specific binding interactions and to attenuate the overall lipophilicity of the drug candidate, can be hampered due to limited availability.

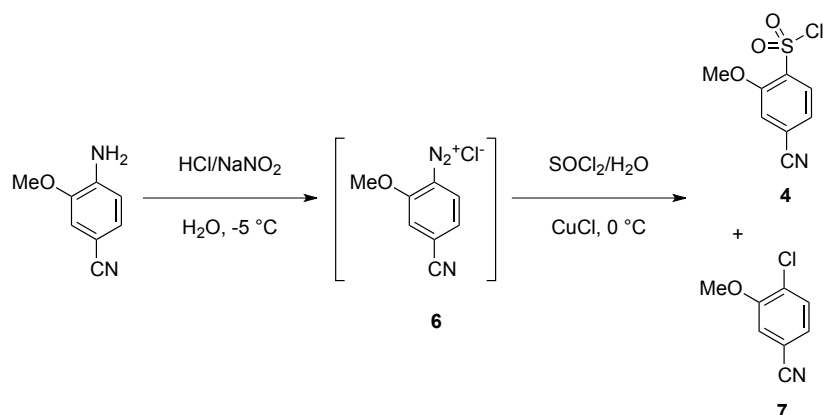
Our own work, in collaboration with the Structural Genomics Consortium (SGC, Oxford UK), identified sulfonamide **NI-57** (**5**) as a chemical probe for the bromodomain of the BRPF family of proteins.<sup>4</sup> In order to produce **NI-57** on a scale to make it available to the scientific community, we required an efficient, large scale synthesis of sulfonyl chloride **4** to couple with 6-amino-1,3-dimethylquinolin-2(1*H*)-one.<sup>5</sup> This synthetic route would need to be short, operationally simple, enacted from readily available, cheap starting materials, and with minimal air sensitive operations and chromatographic purifications. In this *Organic Syntheses* procedure we describe a high-yielding and chromatography-free synthesis of sulfonyl chloride **4** from commercially available 4-hydroxy-3-methoxybenzonitrile utilizing a thermal Newark-Kwart Rearrangement (NKR) to thiol **3** followed by zirconium(IV) chloride-promoted oxidative chlorination reaction as the key steps.



**NI-57** (**5**)

**Figure 6. Chemical Structure of NI-57 (5); a Chemical Probe for the bromodomain of the BRPF family of proteins**

To date, there have been no published preparations for **4** and our original approaches to the synthesis of **4** were flawed. Only the diazotization of 4-amino-3-methoxybenzonitrile then treatment with  $\text{SO}_2\text{-HCl}$  gave modest yields of **4**. 4-Amino-3-methoxybenzonitrile was converted to diazonium chloride salt **6** with sodium nitrite and hydrochloride acid under standard conditions. The *in situ* conversion of **6** to sulfonyl chloride **4** was achieved with a Sandmeyer procedure developed by the AstraZeneca Process Group whereby sulfur dioxide is generated *in situ* through the careful hydrolysis of thionyl chloride in water.<sup>6</sup> This procedure gave the desired sulfonyl chloride **4**, but equimolar amounts of aryl chloride **7** were also formed and the overall yield was poor and variable. Our attempts to systematically optimize this procedure were unsuccessful as the reaction with this substrate proved to be somewhat capricious in our hands. Sulfonyl chloride **4** was found to be unstable to purification by silica gel chromatography and, as such, the mixture of **4** and **7** was used crude in sulfonamide coupling reactions, necessitating the use of chromatography to remove **7** from the sulfonamide products. Clearly, a better procedure was required.



Scheme 1. Sandmeyer approach to **4**

Towards this goal, we identified 4-hydroxy-3-methoxybenzonitrile as a cheap starting material, available on a multi-gram scale, which we envisaged converting into the corresponding thiol **3** via an NKR reaction.<sup>7,8</sup> *O*-Aryl dimethylcarbamothioate **1** was prepared using conditions described by Burns.<sup>9</sup> This reaction was simple to perform and the crystalline product



could be isolated in high yield and purity simply by precipitating directly from the reaction mixture by the addition of water.

We then investigated the thermal NKR reaction by heating one gram of **1** to 200 °C under solvent-free conditions under an inert atmosphere. *O*-Aryl dimethylcarbamothioate **1** was found to melt at around 130 °C to become an oil that was easily stirred at this temperature. Sampling the reaction mixture every 30 minutes showed that the rearrangement had gone to completion within 2 hours giving the desired product *S*-aryl dimethylcarbamothioate **2** in quantitative yield, albeit with the product in a plastic state that was difficult to remove from the reaction flask. No issues were encountered when scaling this reaction to decagram quantities, however 3 h heating was preferred to guarantee all of the starting material had been converted to **2**. Recrystallization of **2** in the reaction flask with toluene allowed the product to be isolated as a convenient free-flowing crystalline powder. Alternative conditions have been reported for enacting the NKR reaction under milder conditions; these include microwave irradiation,<sup>10-12</sup> palladium catalysis<sup>13</sup> and most recently visible-light photocatalysis.<sup>14</sup> Such processes may have allowed the NKR reaction to be conducted under less forcing conditions, however given the effectiveness of the thermal reaction for this particular substrate, such approaches were not explored.

*S*-Aryl dimethylcarbamothioate **2** was readily hydrolyzed to aryl thiol **3** under basic conditions. On a small scale, neutralization of the excess potassium hydroxide with aqueous hydrochloric acid followed by extraction with ethyl acetate, concentration of the reaction mixture and then filtration through a small plug of silica eluting with 20% diethyl ether/hexane proved satisfactory. When the reaction was scaled to 25 grams, the desired product **3** precipitated from solution during the neutralization process in excellent yield and with reasonable purity.

Having developed a reliable route to thiol **3**, our attention was then directed to the oxidative chlorination of thiol **3** into sulfonyl chloride **4**. Numerous methods have been developed for this transformation using a variety of inorganic oxidants,<sup>15-18</sup> and both organic<sup>15, 18, 19</sup> and inorganic chloride sources.<sup>16, 17</sup> After exploring various methods with limited success, we discovered that a zirconium(IV) chloride promoted oxidative chlorination of **3** was a convenient procedure to prepare sulfonyl chloride **4** on multi-gram scale.

Bahrami reported that the oxidative chlorination of aryl and alkyl thiols and disulfides with hydrogen peroxide and zirconium(IV) chloride

proceeded rapidly to give sulfonyl chlorides in high yields and fast reaction times.<sup>20</sup> We were delighted to find that conversion of **3** to **4** occurred rapidly at room temperature (under 5 min) with quantitative conversion. However, it should be noted that a large exotherm in the region of +30 °C (Caution!) was observed when the reaction was performed on a 1.0 gram scale following the original procedure. We recommend the temperature of the reaction mixture is closely monitored and maintained below 10 °C during the addition of the hydrogen peroxide. The crude product **4** showed no obvious organic impurities, however QNMR gave a purity ca. 84 wt% suggesting an inorganic zirconium salt impurity. If required, the purity of **4** could be improved to ca. 99 wt% by recrystallization from a mixed solvent system of toluene-hexane. Alternatively, the crude material **4**, directly obtained from the reaction work-up, was found to be sufficiently pure to undergo sulfonamide coupling reactions with amines in good yield with no apparent deleterious effects from the inorganic contaminant as illustrated in the procedure for the preparation of **NI-57** (**5**).<sup>4</sup>

In conclusion, we have reported a high yielding, chromatography-free and operational simple synthesis of 4-cyano-2-methoxybenzenesulfonyl chloride (**4**) on multigram scale. We believe that **4** will become a valuable building block in organic synthesis as polar sulfonyl chlorides are under-represented in monomer collections when compare to more lipophilic examples. This will help to expand the chemical space of sulfonamides when applied to diversity in drug candidate synthesis. In addition, as substituted phenols are readily available, this 4-step procedure may prove to have general utility in the preparation of other difficult to obtain aryl sulfonyl chlorides as *Organic Syntheses* procedures are frequently applied to related substrates.

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1. Current address: Alzheimer's Research UK UCL Drug Discovery Institute, University College London, The Cruciform Building, Gower Street, London, WC1E 6BT, UK. Email: [p.fish@ucl.ac.uk](mailto:p.fish@ucl.ac.uk). We are grateful to both UCL's MRC Confidence in Concept Scheme (E.D.B) and the UCL School of Pharmacy (N.I.) for financial support. HRMS were recorded at the EPSRC UK National Mass Spectrometry Facility (NMSF) at Swansea University, UK.

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## Appendix

### Chemical Abstracts Nomenclature (Registry Number)

- 4-Hydroxy-3-methoxybenzonitrile: Benzonitrile, 4-hydroxy-3-methoxy-;  
(4421-08-3)
- 1,4-Diazabicyclo[2.2.2]octane: 1,4-Diazabicyclo[2.2.2]octane; (280-57-9)
- Dimethylformamide: Formamide, *N,N*-dimethyl-; (68-12-2)
- Dimethylthiocarbamoyl chloride: Carbamothioic chloride, *N,N*-  
dimethyl-; (16420-13-6)
- Potassium hydroxide: Potassium hydroxide; (1310-58-3)
- Zirconium(IV) chloride: Zirconium chloride; (10026-11-6)
- Aqueous hydrogen peroxide: Hydrogen peroxide; (7722-84-1)
- Sodium sulfate: Sulfuric acid disodium salt; (7757-82-6)
- Pyridine: Pyridine; (110-86-1)



Elliott Bayle completed his MSci at Imperial College London in 2008 before moving to the University of Cambridge to do his Ph.D. with Professor Matthew Gaunt. In 2013 he moved to University College London to undertake post-doctoral research involving the development of chemical probes for epigenetic targets with Professor Paul Fish. Since 2015 he has been working as a Medicinal Chemist in Early Discovery at Charles River.



Niall Igoe received his MChem from the University of Oxford in 2012 completing his Masters project under the supervision of Professor Stuart Conway. He then joined Professor Paul Fish's research group at University College London to undertake a Ph.D. focusing on the design and synthesis of small molecule inhibitors of class IV bromodomain proteins.



Paul Fish undertook his Ph.D. studies in synthetic organic chemistry at the University of Nottingham with Professor Gerry Pattenden and subsequently moved to the USA where he performed postdoctoral research at Harvard University with Professor E. J. Corey and then at Stanford University with Professor William Johnson. He started his career in drug discovery in 1994 as a medicinal chemist in the pharmaceutical industry with Pfizer (Sandwich, UK). In 2012 he was appointed as Professor and Chair of Medicinal Chemistry at the UCL School of Pharmacy. In 2016, Paul moved to his current position as Head of Chemistry for the Alzheimer's Research UK UCL Drug Discovery Institute.



Kevin Gayler completed his B.Sc. in chemistry and philosophy at the University of Tennessee Knoxville in 2014. He is currently pursuing a Ph.D. degree in the Department of Chemistry at Baylor University under the direction of John L. Wood.



Aoi Kimishima completed his B.Sc. in chemistry at Kitasato University in 2011. He then undertook his Ph.D. in synthetic studies of natural products with Professor Toshiaki Sunazuka at Kitasato University in 2016. He is currently performing postdoctoral research in the Department of Chemistry at Baylor University under the direction of John L. Wood.

