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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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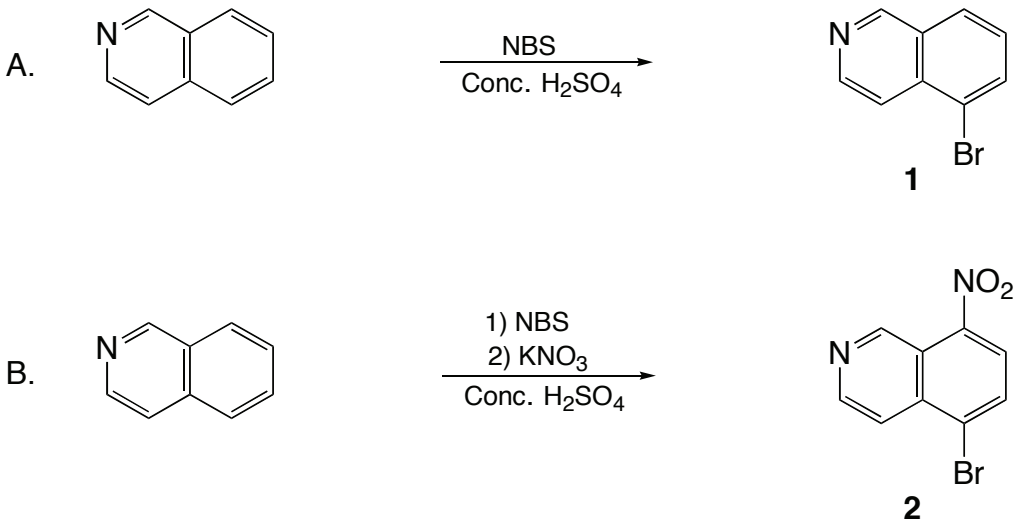
SYNTHESIS OF 5-BROMOISOQUINOLINE AND 5-BROMO-8-NITROISOQUINOLINE

(Isoquinoline, 5-bromo- and Isoquinoline, 5-bromo-8-nitro-)



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1. Procedure

A. 5-Bromoisoquinoline. A 1-L, three-necked, round-bottomed flask equipped with an internal thermometer, mechanical stirrer, and an addition funnel fitted with a nitrogen inlet is charged with concentrated sulfuric acid (96%, 340 mL, Note 1) and cooled to 0 °C. Isoquinoline (40 mL, 44.0 g, 330 mmol) is slowly added to the well-stirred acid at a rate such that the internal temperature is maintained below 30 °C. The solution is cooled to –25 °C in a dry ice-acetone bath and *N*-bromosuccinimide (64.6 g, 363 mmol; Note 2) is added to the vigorously stirred solution in portions such that the internal temperature is maintained between –22 and –26 °C (Note 3). The suspension is efficiently stirred for 2 hr at –22 ± 1 °C and then for 3 hr at –18 ± 1 °C. The resulting homogeneous reaction mixture is poured onto 1.0 kg of crushed ice in a 5-L flask placed in an ice water bath. The reaction flask is quickly washed with ice-cold water, which is added to the 5-L flask. The resulting mixture is stirred while the pH is adjusted to 9.0 using 25% aq

NH_3 with the internal temperature maintained below 25 °C. The resulting alkaline suspension is added to 800 mL of diethyl ether and the biphasic system is vigorously mixed (Note 4). The two clear phases are separated and the aqueous phase is extracted with two 200-mL portions of diethyl ether. The combined organic phases are washed with 200 mL of 1M NaOH (aq) and 200 mL of H_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated to afford 47 g of a light brown solid. Fractional distillation under reduced pressure (bp 145-149 °C at 14 mm, Note 5) furnishes 34-36 g (47-49%) of 5-bromoisoquinoline as a white solid (Notes 6 and 7).

B. 5-Bromo-8-nitroisoquinoline. A 1-L, three-necked, round-bottomed flask fitted with an internal thermometer, mechanical stirrer, and an addition funnel fitted with a nitrogen inlet is charged with concentrated sulfuric acid (96%, 340 mL, Note 1) and cooled to 0 °C. Isoquinoline (40 mL, 44.0 g, 330 mmol) is slowly added from the addition funnel to the well-stirred acid such that the internal temperature is maintained below 30 °C. The solution is cooled to –25 °C in a dry ice-acetone bath and N-bromosuccinimide (76.4 g, 429 mmol; Note 2) is added to the vigorously stirred solution in portions such that the internal temperature is maintained between –22 and –26 °C (Note 3). The suspension is efficiently stirred for 2 hr at –22 °C ± 1 °C and then for 3 hr at –18 °C ± 1 °C. Potassium nitrate (35.0 g, 346 mmol) is then added at a rate such as to maintain the internal temperature below –10 °C and the mixture is then stirred at ~10 °C for 1 hr. The cooling bath is removed and the solution is stirred overnight. The resulting homogeneous reaction mixture is poured onto 1.0 kg of crushed ice in a 5-L flask and the reaction flask is quickly washed with ice-cold water, which is added to the 5-L flask. The resulting mixture is stirred while the pH is adjusted to 8.0 using 25% aq NH_3 with the internal temperature maintained below 30 °C. The resulting suspension is stirred in an ice water bath for 2 hr and the precipitated solids are isolated by filtration using a glass filter funnel. The solids are thoroughly washed three times with 1-L portions of ice-cold water and then air-dried to constant weight to afford 65 g of a slightly yellow solid. This material is suspended in 1000 mL of heptane and 250 mL of toluene (Note 8) in a 2-L, round-bottomed flask and heated at reflux for 1.5 hr with stirring. The hot solution is then filtered through Celite using vacuum suction (Note 9). The volume of the filtrate is reduced by distillation to 1000 mL and the resulting orange solution is

allowed to slowly cool with stirring overnight. The solids are isolated by filtration, washed with 350 mL of ice-cold heptane, and air-dried to constant weight to afford 40-44 g (47-51%) of 5-bromo-8-nitroisoquinoline (Notes 10 and 11).

2. Notes

1. Sulfuric acid 96% (technical quality) and diethyl ether (technical quality) were purchased from Bie & Berntsen A/S, Sandbaekvej 7, DK-2610 Roedovre, Denmark and used without further purification. Isoquinoline (97%) and potassium nitrate (99%) were purchased from Aldrich Chemical Company, Inc. and used without further purification.

2. Isoquinoline must be completely dissolved prior to the addition of *N*-bromosuccinimide. *N*-Bromosuccinimide (99%) was purchased from Aldrich Chemical Company, Inc. and recrystallized[2] and air-dried prior to use. Recrystallization is essential in order to obtain high yield and pure product. The use of more NBS than stated (i.e., more than 1.1 equiv for the synthesis of 5-bromoisoquinoline and 1.3 equiv for the synthesis of 5-bromo-8-nitroisoquinoline) to obtain complete transformation of isoquinoline should be avoided as this leads to formation of 5,8-dibromoisoquinoline, which cannot easily be separated from 5-bromoisoquinoline and which will also lead to a lower yield of 5-bromo-8-nitroisoquinoline.

3. The temperature is controlled throughout the reaction by intermittently adding additional pieces of dry ice to the dry ice-acetone bath. Strict temperature control throughout the bromination reaction is important to obtain high regioselectivity and purity of the product as the side products cannot be removed with ease.

4. Vigorous shaking for at least 5 min is required.

5. A 40-cm column insulated with cotton and aluminum foil is used for the fractional distillation. The condenser is heated to a constant temperature of 80 °C by attaching an 80 °C water bath and a circulatory pump. As distillation progresses, the temperature rises smoothly, settling at 126-128 °C for some time, and then rising to 144 °C (at 14 mm), at which temperature and pressure the product starts to solidify in the condenser.

Increased heating (heating the water bath to 85-90 °C) allows for a steady flow of product through the condenser. All fractions boiling below 144 °C/14 mm are discarded. As an alternative to the preheated condenser, a heat gun may be used to melt the solidifying product.

6. The isolated product typically contains 0-3% isoquinoline. Physical data for 5-bromoisoquinoline: TLC: R_f = 0.30 (9:1 dichloromethane/diethyl ether); IR ($CHCl_3$) cm^{-1}: 3053, 1582, 1509, 1484, 1352, 1263, 1222, 1112, 1000; ^1H NMR (500 MHz, DMSO-d_6) δ: 7.62 (t, 1 H, *J* = 7.8), 7.91 (d, 1 H, *J* = 6.0), 8.15 (d, 1 H, *J* = 7.5), 8.19 (d, 1 H, *J* = 8.2), 8.66 (d, 1 H, *J* = 5.9), 9.37 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ: 118.5, 120.3, 127.9, 128.4, 129.3, 133.9, 134.3, 144.6, 152.9.

7. Alternatively, the product can be isolated in >99% purity by column chromatography on 63-200 μm silica gel eluting with 9:1 → 5:1 dichloromethane/ethyl acetate and then 9:1 → 4:1 dichloromethane/diethyl ether. The product obtained in this manner has mp 81-82 °C (lit. 82-84 °C,[3] 79.5-80.5 °C,[4] 82-83 °C[5]). Anal. Calcd for C_9H_6BrN: C, 51.96; H, 2.91; Br, 38.40; N, 6.73. Found: C, 52.06; H, 2.74; Br, 38.21; N, 6.65.

8. Heptane was purchased from Fisher Chemicals and toluene (technical quality) was purchased from SvedaKemi A/S, Rosenoerns Allé 9, DK-1970 Frederiksberg, Denmark.

9. The glass filter funnel containing Celite was preheated using a heat gun to avoid precipitation of product in the funnel. After filtration, an additional preheated mixture of 120 mL of heptane and 30 mL of toluene was passed through the Celite using suction. A precipitate forms in the filtrate, which is redissolved by heating to reflux.

10. The isolated product typically contains 0-1% 8-bromo-5-nitroisoquinoline, 0-1% 5,8-dibromoisoquinoline, and 0-1% 5-nitroisoquinoline. Physical data for 5-bromo-8-nitroisoquinoline: mp 137-139 °C (lit. 139-141 °C,[3] 138-140 °C,[4] 139-141 °C[5]); TLC R_f = 0.57 (9:1 dichloromethane/ethyl acetate); IR ($CHCl_3$) cm^{-1}: 3053, 1619, 1580, 1485, 1374, 1265, 1201; ^1H NMR (500 MHz, DMSO-d_6) δ: 8.12 (dd, 1 H, J_A = 0.8, J_B = 6.0), 8.33† (d, 1 H, *J* = 8.3), 8.35 (AB, 1 H, *J* = 8.2), 8.84 (d, 1 H, *J* = 5.9), 9.78 (s, 1 H); ^{13}C NMRδ: 118.9, 120.0, 125.8, 127.8, 133.4, 134.5, 145.3, 145.7, 148.1.

11. Alternatively, the product can be isolated in >99% purity by column chromatography on 63-200 μm silica gel, elution with 9:1 → 6:1

dichloromethane/diethyl ether followed by recrystallization to yield 5-bromo-8-nitroisoquinoline with mp 139 -141 °C. Anal. Calcd for C_9H_6BrN: C, 42.72; H, 1.99; Br, 31.58; N, 11.07. Found: C, 43.03; H, 1.82; Br, 31.19; N, 10.94.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Previously published methods for electrophilic bromination of isoquinoline[3-5] lead to mixtures of isomers only separable with difficulty, use expensive additives or large excesses of reactants, or involve multistep procedures.

The present procedure describes conditions, which allow for the formation of 5-bromoisoquinoline in good yield and high purity using easily available and inexpensive starting materials. In order to obtain the desired product, it is important to ensure careful temperature control to suppress the formation of 8-bromoisoquinoline, which is difficult to remove. By choosing sulfuric acid as solvent for the bromination, a convenient one-pot procedure to prepare 5-bromo-8-nitroisoquinoline, without prior isolation of 5-bromoisoquinoline, has been developed. Finally, the method can easily be scaled up from grams to kilograms of the title compounds.

Many pharmacologically active compounds have been synthesized using 5-bromoisoquinoline or 5-bromo-8-nitroisoquinoline as building blocks.[6-11] The haloaromatics participate in transition-metal couplings [8,10,12] and Grignard reactions. The readily reduced nitro group of 5-bromo-8-nitroisoquinoline provides access to an aromatic amine, one of the most versatile functional groups. In addition to *N*-alkylation, *N*-acylation and diazotiation, the amine may be utilized to direct electrophiles into the *ortho*-position.

The heterocyclic ring may be reduced under very mild conditions after *N*-alkylation, giving access to bicyclic amines[7-10,13] or enamines[5] Use of 5-bromoisoquinoline in a metalation reaction yielded 6-aminoisoquinoline, a compound otherwise accessed with difficulty.[14]

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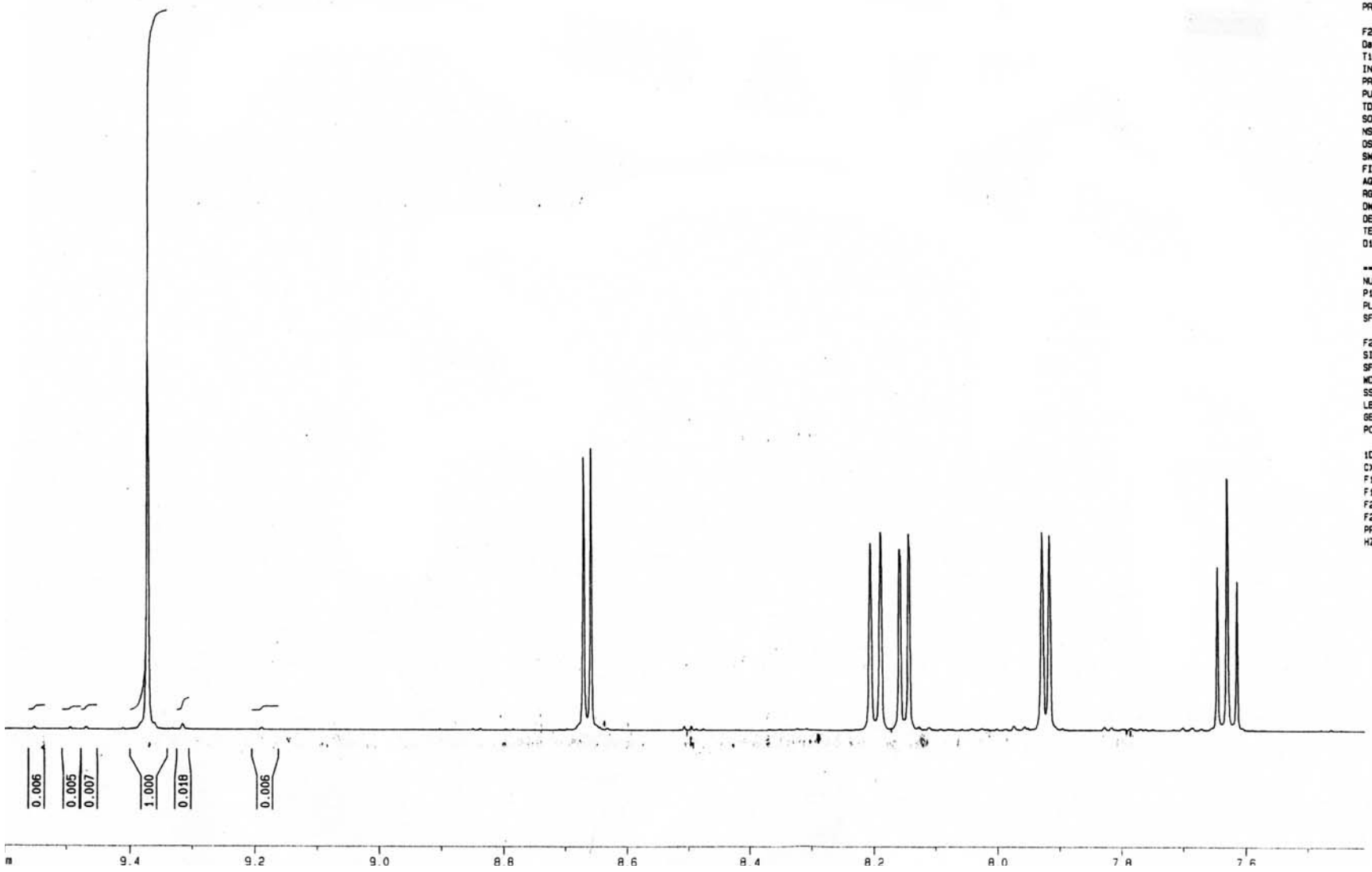
Appendix

Chemical Abstracts Nomenclature (Registry Number)

Isoquinoline; (119-65-3)
N-Bromosuccinimide: 2,5-Pyrrolidinedione, 1-bromo-; (128-08-5)
5-Bromoisoquinoline: Isoquinoline, 5-bromo-; (34784-04-8)
5-Bromo-8-nitroisoquinoline: Isoquinoline, 5-bromo-8-nitro-; (63927-23-1)
Potassium nitrate; (7757-79-1)

5-Bromoisoquinoline (distilled product)

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PROCNO                   1

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PULPROG                 zg
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DS                       4
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FIDRES            0.213709 Hz
AQ                2.3396852 sec
RG                     181
DW                  71.400 usec
DE                   6.00 usec
TE                  300.0 K
D1               10.00000000 sec

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PL1                 -6.00 dB
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F2 - Processing parameters
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SSB                     0
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GB                      0
PC                   1.40

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F2P                 7.408 ppm
F2                3705.21 Hz
PPMCM             0.06316 ppm/cm
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