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Synthetic studies of the formation of pyrazoloisoquinolines

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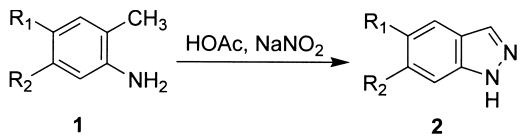
Abstract—Diazotization of 7-amino-5,8-dimethyl-6-(phenylthio)isoquinoline unexpectedly led to the formation of a new ring system, 3*H*-pyrazolo[3,4-*h*]isoquinoline as its 5-methyl-6-phenylthio derivative. In this work, the parent ring system was synthesized and characterized, along with its 5-methyl, 6-bromo-5-methyl, and 5-methyl-6-phenylthio derivatives. The mechanism for the transformation is explored.

1. Introduction

It was discovered long ago that 2-methylaniline **1** (R_1=R_2=H) formed indazole **2** (R_1=R_2=H) in very low yield when diazotized in AcOH (Scheme 1). Yields were improved when the amine **1** bore an electron-withdrawing substituent for R_1 or R_2, when the pH was increased, or when the reaction was carried out in chloroform in the presence of tetramethylammonium acetate.[1]

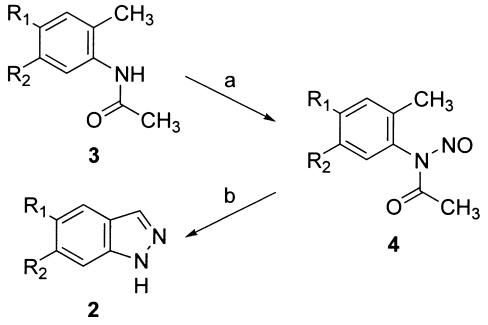
An improved method of cyclization converted amide **3** into nitroso derivative **4**, which then cyclized to indazole **2** upon heating in anhydrous benzene (Scheme 2).[2] Good yields were generally obtained with a variety of substituents, and consequently this indazole synthesis has been popular. Successful substrates similar to those in this article include aminomethylpyridines,[3] 1-methyl-2-naphthylamine[4] and 3-amino-4-methylquinoline.[5] Unfortunately, the method is less convenient, more hazardous, and more costly than simple diazotization of the amine in AcOH.

As part of testing a route to isoellipticine **9**, adaptable to the synthesis of 9-substituted ellipticines **7**, the aminoisoquinoline **5c** was diazotized in cold AcOH and then treated with NaN_3 (Scheme 3). Instead of the expected azide **8**, a mixture was obtained, containing as its major component the pyrazoloisoquinoline **6c**, which contains a new ring system.[6]



1 2

Scheme 1.



3 4 2

Scheme 2. (a) NOCl, Ac_2O, HOAc, NaOAc. (b) Anhydrous benzene, heat.

Although the biological properties of **6c** are unexplored, isomeric pyrazoloisoquinolines have shown promise as antibiotics,[7] anti-inflammatory agents,[8] and benzodiazepine antagonists.[9] The unexpected conversion of isoquinoline **5c** into pyrazoloisoquinoline **6c** without the presence of an electron-withdrawing group suggests that the improved method through the nitroso derivative may not be necessary for isoquinolines, or even polycyclic systems in general. The present paper explores which substituents on isoquinoline are necessary to allow pyrazoloisoquinolines to form, and therefore begins with the synthesis of a series of isoquinolines with varying substituents at the 5 and 6 positions.

2. Results and discussion

A practical route to aminoisoquinoline **5c** was developed,

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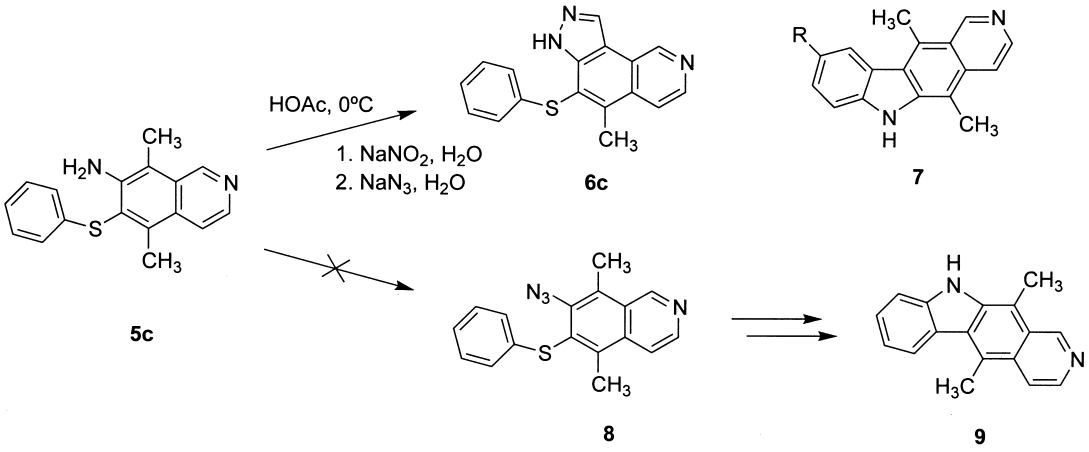
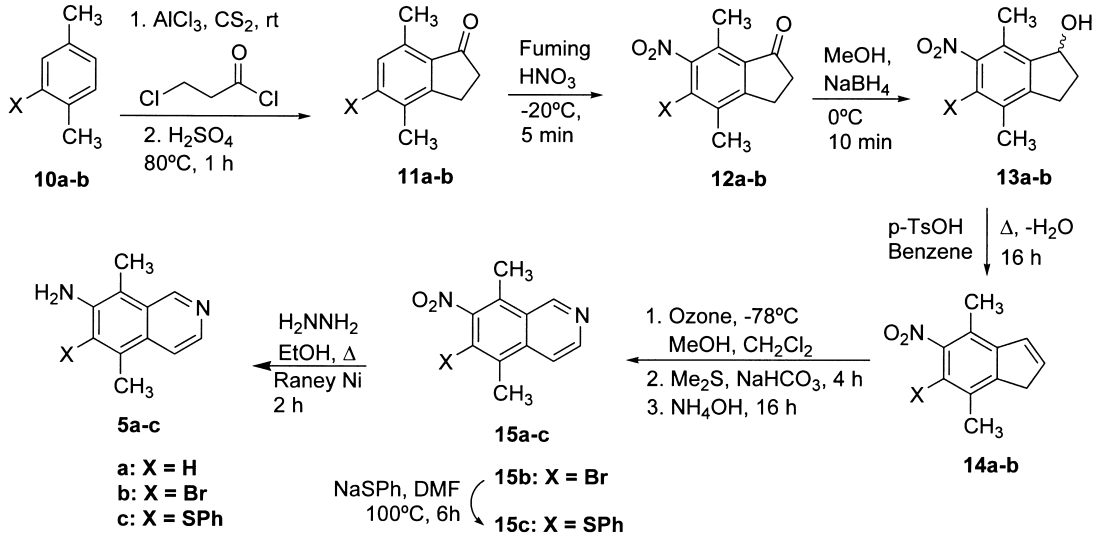


Scheme 3.

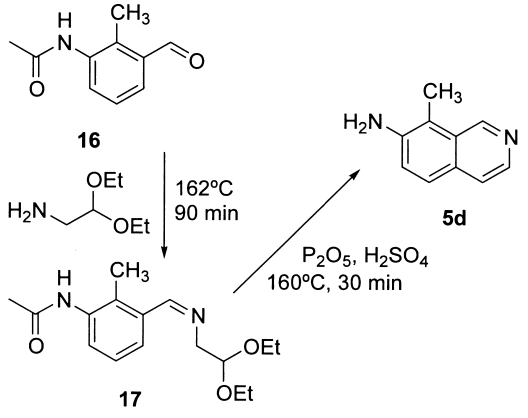


Scheme 4.

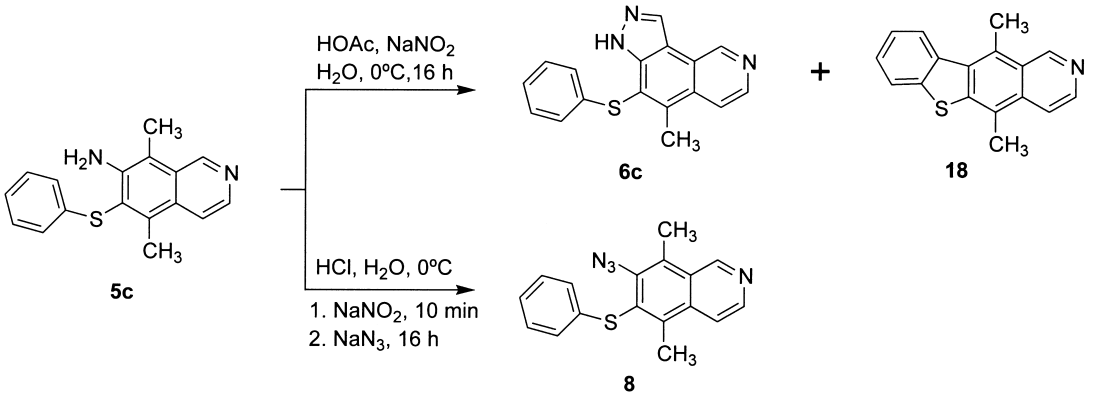
beginning with cyclization of substituted xylene **10b** to 5-bromo-4,7-dimethylindanone (**11b**, Scheme 4). Subsequent nitration with fuming nitric acid gave nitroindanone **12b**, which was then reduced to indanol **13b**. Dehydration with catalytic *p*-TsOH in refluxing benzene led to indene **14b**. Ozonolysis in the presence of MeOH, followed by reduction with Me_2S and treatment with conc. NH_4OH furnished 6-bromo-5,8-dimethyl-7-nitroisoquinoline **15b** in 89% yield. Treatment of isoquinoline **15b** with NaSPh in hot DMF led to 5,8-dimethyl-7-nitro-6-(phenylthio)isoquinoline **15c**. Limiting the reaction time prevented displacement of the nitro group by thiophenoxide. Reduction of the nitro group using hydrazine and catalytic Raney nickel in refluxing EtOH gave amine **5c** in 33% overall yield. Similar processes were used to prepare 7-amino-5,8-dimethylisoquinoline **5a** (54%) and 7-amino-6-bromo-5,8-dimethylisoquinoline **5b** (35%) from **10a** and **10b**, respectively.

The fortunate availability of 3-acetamido-2-methylbenzaldehyde[10] **16** allowed convenient synthesis of 7-amino-8-methylisoquinoline **5d** through condensation with aminoacetaldehyde diethyl acetal and subsequent cyclization[11] of imine **17** using hot H_2SO_4/P_2O_5 (Scheme 5). The cyclization step gave very poor yield (8.5, 6.6% overall) and purity of product.

In attempting to prepare azide **8** as a precursor to isoellipticide **9** (Scheme 3), diazotization of 7-amino-5,8-dimethyl-



Scheme 5.



Scheme 6.

Table 1. Diazotization of **5c** (X=SPh) under various conditions

Structure	HOAc, no azide[a] (%)	HOAc+azide[b] (%)	HCl, no azide[a] (%)	HCl+azide[b] (%)
5c	20	7	5	21
6c	58	32	68	2
18	21	36	27	1
8	0	25	0	75

Yields were determined by ^{1}H NMR of the crude reaction mixture. Structures **5c**, **6c**, **18** and **8** accounted for almost all the peaks, so the total of their integrations was defined as 100% yield.

[a] Aqueous ammonia was added the day following diazotization.

[b] Azide was added 10 min after diazotization.

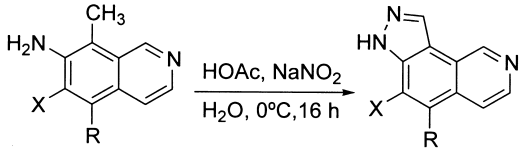
6-(phenylthio)-isoquinoline **5c** in cold AcOH led instead to a mixture of 5-methyl-6-phenylthio-3*H*-pyrazolo[3,4-*h*]isoquinoline **6c** and thiaellipticine[12] **18** (Scheme 6). Attempts to add NaN_3 solution quickly after diazotization usually led to the same mixture and little or no azide derivative **8**. Although the azide derivative **8** did form in one instance, this result could not be reproduced. In dilute HCl, however, clean conversion to azide **8** was obtained.

The effects of acid type and of added NaN_3 are demonstrated in Table 1. The purpose of adding azide was to show the extent of cyclization after 10 min of reaction. Cyclization was mostly complete in acetic acid after 10 min, but in HCl the reaction took overnight. The yields of cyclization products (**6c** and **18**) were higher in HCl, and this may be the acid of choice for some substrates, but poor solubility of amine **5c** in HCl was the original motivation to try AcOH as a solvent. The ratio of **6c** and **18** in HOAc (58–21%) was different when the reaction was run on a larger scale (41–34% following chromatography), possibly because the concentration of water in the reaction was lower. The ratio was also affected by the presence of NaN_3, perhaps due to increased pH.

The other aminoisoquinolines (**5a**, **5b**, **5d**) were diazotized in AcOH in the same manner as **5c** (Table 2). Since electron-withdrawing groups facilitate cyclization of aniline derivatives,[1] it was surprising that the bromo group (**5b**) led to a lower yield than the corresponding unbrominated substrate **5a**. On the other hand, 7-amino-8-methylisoquinoline **5d** produced the prototype ring system **6d** in excellent yield (96%), showing that a substituent at the 6-positon is unnecessary for cyclization.

Based on studies of the formation of indazole,[2] the expected mechanism involves diazotization followed by deprotonation of the *ortho* methyl group which is facilitated by the strongly electron-withdrawing diazo group and any other groups in a position to withdraw electrons through

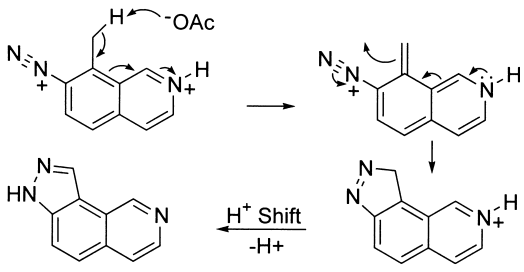
Table 2. Cyclization of diazotized aminoisoquinolines **5a–d**



5a-d **6a-d**

Product	X	R	% Yield
6a	H	CH_3	83
6b	Br	CH_3	66
6c	SPh	CH_3	41[a]
6d	H	H	96

[a] Plus 34% thiaellipticine **18**.



Scheme 7.

resonance. In the case of isoquinolines, deprotonation may be facilitated by the electron-accepting ability of the ring nitrogen when protonated (Scheme 7). The need for a base to initiate the cyclization explains the sluggishness of cyclization in strong acid.

The present work establishes that 7-amino-8-methylisoquinolines, which may bear various substituents, cyclize to pyrazoloisoquinolines in good yield upon diazotization, unlike most 2-methylanilines **1**.

3. Experimental

3.1. General

Reactions were generally run unprotected from the air. IR spectra were taken on NaCl, and NMR spectra were taken in $CDCl_3$, unless noted otherwise. Silica gel used for chromatography was 230–400 mesh.

3.1.1. 5-Bromo-2,3-dihydro-4,7-dimethyl-1*H*-indene-1-one (11b, X=Br). A solution of 1-bromo-2,5-dimethylbenzene (**10b**, X=Br) (37.0 g, 200 mmol) and 3-chloropropionyl chloride (24.46 g, 210 mmol) in 50 mL of CS_2 was added slowly over 1 h to a powerfully stirred slurry of $AlCl_3$ (30.0 g, 240 mmol) in 150 mL of CS_2 under a dry atmosphere. After 16 h, the solvent was removed under reduced pressure and 250 mL of conc. H_2SO_4 was added slowly. Constant vigorous stirring was required to contain the foaming. The mixture was stirred at 80°C for 1 h, after which the evolution of gas subsided. The cooled mixture was quenched with 250 g of crushed ice and extracted with CH_2Cl_2. The combined extracts were washed with saturated $NaHCO_3$, dried (Na_2SO_4) and evaporated to a dark residue. Chromatography through 300 g of Florisil™ (3:7 CH_2Cl_2/pentane) gave 40.3 g (85% yield) of light yellow solid. Recrystallization (MeOH) gave light yellow needles of **11b** (X=Br): mp 105–106°C; ^{1}H NMR δ 2.31 (s, 3H), 2.52 (s, 3H), 2.62 (br t, 2H, J=5.3 Hz), 2.94 (br t, 2H, J=5.3 Hz), and 7.26 (s, 1H); ^{13}C NMR δ 17.3, 25.0, 30.7, 36.6, 131.0, 132.6, 132.9, 133.2, 136.7, 155.7, 206.9; IR (capillary melt) 1700, 1565, 1465, 1255, 1185 cm^{-1}. Anal. calcd for $C_{11}H_{11}OBr$: C, 55.25; H, 4.63. Found: C, 55.17; H, 4.67.

3.1.2. 2,3-Dihydro-4,7-dimethyl-6-nitro-1*H*-indene-1-one (12a, X=H). Fuming 90% nitric acid (29 mL, 625 mmol) was cooled to −20°C and 2,3-dihydro-4,7-dimethyl-1*H*-indene-1-one[13] (**11a**, X=H) (2.502 g, 15.6 mmol) was added portionwise over 5 min with stirring. After 5 min the reaction mixture was poured over ice and extracted with 1:1 EtOAc/heptane. The combined extracts were washed with saturated $NaHCO_3$ until the washings remained basic, then they were washed with brine, dried (Na_2SO_4) and evaporated to a red–brown solid (3.7 g). Chromatography on silica gel ($CHCl_3$) gave 2.1058 g (66% yield) of orange solid. Recrystallization (*i*-PrOH) gave dark yellow needles of **12a** (X=H): mp 111.5–112.5°C; ^{1}H NMR δ 2.40 (s, 3H), 2.67 (s, 3H), 2.75 (t, 2H, J=6.0 Hz), 3.04 (t, 2H, J=6.0 Hz), 7.79 (s, 1H); ^{13}C NMR δ 12.1, 16.9, 23.7, 36.7, 128.9, 130.4, 134.1, 134.8, 148.9, 159.0, 206.0; IR 1716, 1515, 1378, 1358, 1258, 1105 cm^{-1}. Anal. calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.24; H, 5.43; N, 6.77.

3.1.3. 5-Bromo-2,3-dihydro-4,7-dimethyl-6-nitro-1*H*-indene-1-one (12b, X=Br). Chromatography on Florisil™ (2:3 CH_2Cl_2/pentane) gave white solid (66% yield): mp (MeOH) 159–161°C; ^{1}H NMR δ 2.44 (s, 3H), 2.54 (s, 3H), 2.75 (br t, 2H, J=6.0 Hz), 3.08 (br t, 2H, J=6.0 Hz); ^{13}C NMR δ 11.9, 18.2, 25.1, 36.8, 120.6, 128.0, 133.5, 135.4, 152.2, 155.9, 205.7; IR (CH_2Cl_2) 1710, 1640, 1565, 1540, 1380, 1110 cm^{-1}. Anal. calcd for $C_{11}H_{10}BrNO_3$: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.48; H, 3.62; N, 4.88.

3.1.4. 2,3-Dihydro-4,7-dimethyl-6-nitro-1*H*-indene-1-ol (13a, X=H). A solution of **12a** (0.2196 g, 1.07 mmol) in MeOH (11 mL) was cooled in an ice bath and $NaBH_4$ (0.0607 g, 1.61 mmol) was added over 2 min with stirring. After 10 min the solvent was evaporated without heating and H_2O (10 mL) was added. The aqueous mixture was extracted with EtOAc and the combined organic layers were washed with brine and poured through a filter containing anhyd Na_2SO_4, decolorizing carbon, and silica gel. The filtrate was evaporated to give 0.2142 g (97% yield) of **13a** (X=H) as light yellow solid: mp 71–72°C; ^{1}H NMR δ 1.99 (bs, 1H), 2.09–2.18 (m, 1H), 2.28 (s, 3H), 2.35–2.49 (m, 1H), 2.56 (s, 3H), 2.81 (ddd, 1H, J=17.1, 9.7, 2.7 Hz), 3.03–3.14 (m, 1H), 5.36 (d, 1H, J=6.0 Hz), 7.68 (s, 1H); ^{13}C NMR δ 15.3, 18.4, 29.2, 34.6, 75.1, 125.7, 128.1, 132.6, 145.1, 148.5, 148.7; IR 3245br, 1518, 1442, 1346, 1047, 969 cm^{-1}.

3.1.5. 5-Bromo-2,3-dihydro-4,7-dimethyl-6-nitro-1*H*-indene-1-ol (13b, X=Br). Crude product was yellow solid (99% yield). Recrystallization (MeOH) gave large yellow hexagonal rods: mp 162–162.5°C; ^{1}H NMR δ 1.74 (s, 1H), 2.10 (qt, 1H, J=9.3, 3.4 Hz), 2.35 (s, 3H), 2.36 (s, 3H), 2.45 (d of sextets, 1H, J=7.1, 1.9 Hz), 2.85 (dq, 1H, J=9.0, 3.6 Hz), 3.13 (q, 1H, J=8.1 Hz), 5.31 (dd, 1H, J=6.9, 2.6 Hz); ^{1}H NMR (acetone-d_6) δ 1.95–2.10 (m, 1H), 2.30 (s, 3H), 2.33 (s, 3H), 2.35–2.50 (m, 1H), 2.77–2.90 (m, 1H), 3.03–3.17 (m, 1H), 2.90 (br d, 1H, J=4.3 Hz); ^{13}C NMR (acetone-d_6) δ 13.6, 19.6, 30.8, 35.4, 75.2, 114.0, 126.3, 134.1, 145.4, 146.7, 152.5, 206.5; IR (CH_2Cl_2) 3630, 2980, 1640, 1540, 1390, 1380 cm^{-1}.

3.1.6. 4,7-Dimethyl-5-nitro-1*H*-indene (14a, X=H). A solution of **13a** (0.2142 g, 1.03 mmol) in benzene (2.5 mL) containing *p*-TsOH (0.0026 g, 0.01 mmol) was heated to reflux, and the condensate was returned through a Dean–Stark trap containing anhyd $CaCl_2$ pellets. After 16 h, the reaction mixture was allowed to cool, and EtOAc (15 mL) and H_2O (15 mL) were added. The organic layer was washed with brine and evaporated to a light brown solid. Chromatography on silica gel (1:4 EtOAc/petroleum ether) gave 0.1895 g (97% yield) of **14a** (X=H) as light yellow solid. Recrystallization (heptane) gave fluffy yellow needles: mp 62.5–63.5°C; ^{1}H NMR δ 2.37 (s, 3H), 2.59 (s, 3H), 3.36 (t, 2H, J=2.0 Hz), 6.70 (dt, 1H, J=5.7, 2.0 Hz), 7.03 (dt, 1H, J=5.7, 2.0 Hz), 7.61 (s, 1H); ^{13}C NMR δ 15.6, 18.2, 38.7, 122.0, 123.0, 130.2, 131.0, 135.6, 145.6, 147.2, 148.8; IR 1514, 1382, 1337br, 866, 755, 691 cm^{-1}. Anal. calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.62; H, 5.86; N, 7.41.

3.1.7. 6-Bromo-4,7-dimethyl-5-nitro-1*H*-indene (14b, X=Br). Chromatography on Florisil™ (2:3 CH_2Cl_2/pentane) gave white solid (86% yield): mp (MeOH) 134–135°C; ^{1}H NMR δ 2.33 (s, 3H), 2.40 (s, 3H), 3.36 (br s, 2H), 6.69 (br d, 1H, J=3.6 Hz), 6.90 (br d, 1H, J=3.9 Hz); ^{13}C NMR δ 13.9, 19.3, 39.7, 110.8, 120.3, 129.6, 132.0, 136.2, 143.4, 144.3, 151.5; IR (CH_2Cl_2) 2940, 1535, 1385, 950, 880 cm^{-1}. Anal. calcd for $C_{11}H_{10}BrNO_2$: C, 49.23; H, 3.76; N, 5.22. Found: C, 49.09; H, 3.85; N, 5.25.

3.1.8. 5,8-Dimethyl-7-nitroisoquinoline (15a, X=H). A solution of **14a** (6.3083 g, 33.3 mmol) in MeOH (167 mL) and CH_2Cl_2 (167 mL) was cooled to −78°C and treated with ozone until the solution turned blue. The solution was purged with oxygen until the blue color disappeared, then added to Me_2S (16.7 mL) and $NaHCO_3$ (3.33 g), and the sealed flask was stirred for 4 h at room temperature. Conc. NH_4OH (167 mL) was added and the resealed flask was stirred overnight. The mixture was mostly evaporated and the remaining aqueous suspension was extracted with $CHCl_3$ and the combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to give 6.3196 g (94% yield) of orange–yellow solid. Recrystallization (EtOAc) gave **15a** (X=H) as bright yellow needles: mp 161–162°C; ^{1}H NMR δ 2.69 (s, 3H), 2.88 (s, 3H), 7.79 (m, 2H), 8.73 (d, 1H, J=6.0 Hz), 9.63 (d, 1H, J=0.6 Hz); ^{13}C NMR δ 13.4, 18.3, 117.1, 124.3, 127.3, 128.6, 133.8, 136.8, 145.4, 147.7, 151.0; IR 1521, 1386, 1365, 1348, 879, 824 cm^{-1}. Anal. calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.37; H, 4.97; N, 13.87.

3.1.9. 6-Bromo-5,8-dimethyl-7-nitroisoquinoline (15b, X=Br). Chromatography on basic alumina (9:1 CH_2Cl_2/petroleum ether) gave yellow-tan solid (89% yield). Recrystallization (EtOAc) followed by sublimation gave **15b** (X=Br) as a pale yellow solid: mp 194–197°C; ^{1}H NMR δ 2.65 (s, 3H), 2.76 (s, 3H), 7.78 (d, 1H, J=5.9 Hz), 8.70 (d, 1H, J=6.0 Hz), 9.42 (s, 1H); ^{13}C NMR δ 13.2, 18.6, 115.8, 117.2, 125.4, 125.8, 134.5, 135.3, 145.6, 150.2, 157.4; IR 1604, 1532, 1387, 835 cm^{-1}. Anal. calcd for $C_{11}H_9BrN_2O_2$: C, 47.17; H, 2.88; N, 10.00. Found: C, 46.84; H, 3.09; N, 9.72.

3.1.10. 5,8-Dimethyl-7-nitro-6-(phenylthio)isoquinoline (15c, X=SPh). A solution of **15b** (141 mg, 0.500 mmol), thiophenol (111 mg, 1.01 mmol), NaOMe (28.5 mg, 0.528 mmol) and DMF (3 mL) were heated on a steam bath for 6 h. The cooled mixture was diluted with H_2O (25 mL) and extracted with Et_2O. The combined extracts were washed with saturated $NaHCO_3$, H_2O, and brine, dried and evaporated to a tan solid. Chromatography on basic alumina (8:1 CH_2Cl_2/hexanes) gave 146 mg (94% yield) of yellow-beige solid. Recrystallization (MeOH) gave **15c** (X=SPh) as light yellow needles: mp 155.5–156.5°C; ^{1}H NMR δ 2.69 (s, 3H), 2.76 (s, 3H), 7.1–7.3 (m, 5H), 7.83 (d, 1H, J=6.6 Hz), 8.72 (d, 1H, J=5.7 Hz) and 9.53 (s, 1H); ^{13}C NMR δ: 13.1, 16.7, 117.6, 124.6, 125.0, 126.5, 126.7, 128.0, 129.1, 135.2, 135.5, 140.9, 145.3, 150.2, 153.6; IR 1533, 1440, 1361, 837, 739, 684 cm^{-1}. Anal. calcd for $C_{17}H_{14}N_2O_2S$: C, 65.69; H, 4.49; N, 8.97. Found: C, 65.79; H, 4.55; N, 9.03.

3.1.11. 7-Amino-5,8-dimethylisoquinoline (5a, X=H). A mixture of **15a** (2.5535 g, 12.54 mmol), hydrazine monohydrate (3.77 g, 75 mmol), and 80% Raney nickel in H_2O (1.13 g, 15 mmol) in EtOH (75 mL) was refluxed for 2 h, by which time the reaction was confirmed to be complete by TLC. Most of the EtOH was boiled away, and the cooled mixture was diluted with EtOAc and filtered through celite. The filtrate was extracted with dilute HCl and the combined aqueous layers were basified with $NaHCO_3$. The aqueous mixture was extracted with EtOAc, dried (Na_2SO_4) and evaporated to give 1.9979 g (92% yield) of orange solid. Recrystallization (MeOH) gave **5a** (X=H) as flat orange rods: mp 201.5–202.5°C; ^{1}H NMR δ 2.45 (s, 3H), 2.56 (s, 3H), 3.88 (bs, 2H), 6.98 (s, 1H), 7.60 (d, 1H, J=5.7 Hz), 8.35 (d, 1H, J=5.7 Hz), 9.31 (s, 1H); ^{13}C NMR δ 10.6, 18.3, 110.6, 117.1, 123.0, 128.9, 130.3, 132.2, 139.4, 142.0, 147.8; IR 3197br, 1645, 1609, 1386, 874, 809 cm^{-1}. Anal. calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.55; H, 6.97; N, 16.23.

3.1.12. 7-Amino-6-bromo-5,8-dimethylisoquinoline (5b, X=Br). Chromatography on silica gel (2% MeOH/$CHCl_3$) gave yellow solid (82% yield). Recrystallization (CH_3CN) gave fluffy white clumps: mp 163–164°C; ^{1}H NMR δ 2.49 (s, 3H), 2.70 (s, 3H), 4.48 (bs, 2H), 7.60 (dd, 1H, J=5.9, 0.6 Hz), 8.33 (d, 1H, J=5.9 Hz), 9.28 (d, 1H, J=0.6 Hz); ^{13}C NMR δ 12.0, 18.9, 111.9, 117.1, 120.6, 127.2, 129.4, 131.7, 139.9, 140.1, 148.0; IR 3328br, 1627, 1381, 1235, 1005, 805 cm^{-1}. Anal. calcd for $C_{11}H_{11}BrN_2$: C, 52.61; H, 4.41; N, 11.16. Found: C, 52.96; H, 4.28; N, 11.42.

3.1.13. 7-Amino-5,8-dimethyl-6-(phenylthio)isoquinoline (5c, X=SPh). Crude product (82% yield) was recrystallized (*i*-PrOH) to give dark yellow needles: mp 141–141.5°C; ^{1}H NMR δ 2.51 (s, 3H), 2.83 (s, 3H), 4.78 (bs, 2H), 7.00 (d, 2H, J=8.1 Hz), 7.11 (t, 1H, J=7.2 Hz), 7.20 (t, 2H, J=7.2 Hz), 7.69 (d, 1H, J=6.0 Hz), 8.36 (d, 1H, J=6.0 Hz), 9.37 (s, 1H); ^{13}C NMR δ 11.8, 17.1, 111.0, 117.8, 123.0, 125.6, 126.2, 128.8, 129.2, 129.3, 135.6, 139.1, 139.6, 144.2, 148.2; IR 3312, 1631, 1563, 1477, 1375, 738 cm^{-1}. Anal. calcd for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99. Found: C, 72.85; H, 5.93; N, 9.96.

3.1.14. 5-Methyl-3*H*-pyrazolo[3,4-*h*]isoquinoline (6a, X=H, R=CH_3). A stirring solution of **5a** (0.4516 g, 2.62 mmol) in AcOH (20.7 mL) was placed in an ice bath. After 2 min a solution of $NaNO_2$ (0.199 g, 2.88 mmol) in H_2O (2.62 mL) was added over 4 min. The ice bath was allowed to warm to room temperature overnight. The dark red solution was diluted with H_2O (50 mL) and basified using dilute NH_4OH. Once cool, the mixture was extracted with CH_2Cl_2 and the organic layer was dried (Na_2SO_4) and directly chromatographed on silica gel (0–5% MeOH/$CHCl_3$) to give 18 mg (4% recovery) of starting material and 0.401 g (83% conversion, 87% yield based on recovered starting material) of product. Recrystallization ($CHCl_3$, then MeOH) gave light brown needles of **6a** (X=H, R=CH_3) which were further purified by sublimation at 155°C under high vacuum: mp 292–293°C (dec.); ^{1}H NMR (Me_2SO-d_6) δ 2.66 (s, 3H), 7.76 (s, 1H), 7.86 (d, 1H, J=5.7 Hz), 8.57 (d, 1H, J=5.7 Hz), 8.70 (s, 1H), 9.70 (s, 1H), 13.50 (bs, 1H); ^{1}H NMR (CD_3CO_2D) δ 2.58 (s, 3H), 7.76 (s, 1H), 8.08 (d, 1H, J=6.4 Hz), 8.51 (s, 1H), 8.58 (d, 1H, J=6.4 Hz), 9.55 (s,

1H); ^{13}C NMR (CD_3CO_2D) δ 20.0, 116.8, 122.5, 123.1, 124.0, 132.8, 135.2, 136.0, 138.2, 141.2, 142.5; IR 3118br, 2901, 1611, 1260, 936, 848 cm^{-1}. Anal. calcd for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 72.21; H, 4.91; N, 23.12.

3.1.15. 6-Bromo-5-methyl-3*H*-pyrazolo[3,4-*h*]isoquinoline (6b, X=Br, R=CH_3). Chromatography on silica gel (0–7% MeOH/1% Et_3N/$CHCl_3$) gave **6b** (X=Br, R=CH_3) as yellow solid (66% yield). Recrystallization ($CHCl_3$) gave yellow needles: mp >300°C; ^{1}H NMR (Me_2SO-d_6) δ 2.70 (s, 3H), 7.89 (d, 1H, *J*=5.7 Hz), 8.57 (d, 1H, *J*=5.7 Hz), 8.85 (bs, 1H), 9.66 (s, 1H), 13.84 (bs, 1H); ^{1}H NMR (CD_3CO_2D) δ 2.84 (s, 3H), 8.41 (d, 1H, *J*=6.5 Hz), 8.77 (d, 1H, *J*=6.5 Hz), 8.91 (s, 1H), 9.84 (s, 1H); ^{13}C NMR (CD_3CO_2D) δ 19.1, 117.1, 120.5, 123.8, 124.0, 132.9, 134.6, 137.2, 139.0, 143.1, 143.2; IR 1596, 1446, 1208, 936, 821, 716 cm^{-1}. Anal. calcd for $C_{11}H_8BrN_3$: C, 50.41; H, 3.08; N, 16.03. Found: C, 50.54; H, 3.04; N, 15.78.

3.1.16. 5-Methyl-6-phenylthio-3*H*-pyrazolo[3,4-*h*]isoquinoline (6c, X=SPh, R=CH_3) and 6-thiaellipticine (18). Chromatography on activity I basic alumina (CH_2Cl_2) gave 6-thiaellipticine (**18**) side product (34% yield). Further elution with methanol gave product **6c** (41% yield). Recrystallization ($CHCl_3$) of **6c** gave yellow prisms: mp 219.5–220.5°C; ^{1}H NMR δ 2.90 (s, 3H), 7.05–7.25 (m, 5H), 7.88 (d, 1H, *J*=6.0 Hz), 8.52 (s, 1H), 8.70 (d, 1H, *J*=5.7 Hz), 9.62 (s, 1H), 11.35 (bs, 1H); ^{13}C NMR δ 16.3, 102.9, 116.1, 118.8, 122.3, 126.5, 127.4, 129.5, 133.4, 133.6, 134.7, 138.6, 140.4, 143.7, 147.6; IR 1582, 1477, 1439, 931, 817, 736 cm^{-1}. The structure was verified by single crystal X-ray analysis.

3.2. Measurement of azide formation for 7-amino-5,8-dimethyl-6-(phenylthio)isoquinoline

Four reactions of equivalent scale were set up and each was designated a letter A, B, C, or D. In each of reactions A and B, a solution of **5c** (11.0 mg, 0.039 mmol) was prepared in H_2O (1 drop) and AcOH (0.31 mL). In reactions C and D, the same amount of amine was dissolved in H_2O (1 mL) and conc. HCl (0.3 mL). All four solutions were cooled in an ice bath and then an aqueous solution (44 μL) of $NaNO_2$ (2.98 mg, 0.043 mmol) was injected in one portion into each one. After 10 min, an aqueous solution (56 μL) of NaN_3 (5.61 mg, 0.086 mmol) was injected into each of reactions B and D. At the same time, H_2O (56 μL) was injected into reactions A and C as a control. All flasks were wrapped in aluminum foil to protect them from light and the ice bath was allowed to warm to room temperature overnight. Each reaction mixture was separately poured into dilute NH_4OH and confirmed to be basic before being extracted with $CHCl_3$. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. The composition of each product mixture was measured using the integrations of the most cleanly integrated peaks on the NMR spectrum.

3.2.1. 7-Azido-5,8-dimethyl-6-(phenylthio)isoquinoline (8). A stirred solution of **5c** (20.0 mg, 0.071 mmol) in H_2O (36 mL) and conc. HCl (0.46 mL) was cooled to 4°C and $NaNO_2$ (7.4 mg, 0.107 mmol) was added. After 10 min, NaN_3 (93 mg, 1.43 mmol) was added and the flask was wrapped in aluminum foil. The ice bath was allowed to warm to room temperature overnight. EtOAc (40 mL) was added to the clear yellow solution and the aqueous layer was basified by adding aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated. Chromatography on silica gel (1:1 EtOAc/petroleum ether) followed by recrystallization (EtOAc) gave 14.3 mg (65% yield) of **8** as long yellow needles: mp 114–114.5°C; ^{1}H NMR δ 2.78 (s, 3H), 2.87 (s, 3H), 7.05 (d, 2H, *J*=7.0 Hz), 7.15 (t, 1H, *J*=7.3 Hz), 7.22 (t, 2H, *J*=7.4 Hz), 7.80 (dd, 1H, *J*=5.9, 0.6 Hz), 8.62 (d, 1H, *J*=5.9 Hz), 9.48 (s, 1H); ^{13}C NMR δ 13.4, 17.1, 117.7, 126.0, 126.9, 127.0, 128.0, 129.2, 131.3, 133.8, 136.4, 138.7, 139.6, 143.4, 149.8; IR 2112, 1478, 1439, 1363, 1334, 741 cm^{-1}.

3.2.2. 3-(2,2-Diethoxyethyliminomethyl)-2-methylacetanilide (17). A stirring mixture of 3-acetamido-2-methylbenzaldehyde (**16**) (0.2249 g, 1.27 mmol) and aminoacetaldehyde diethyl acetal (0.369 mL, 2.54 mmol) was placed in a 160°C oil bath under a reflux condenser. After 90 min the flask was allowed to cool and a stream of air was used to remove remaining acetal. The solid recrystallized (*i*-PrOH) to give 0.2892 g (78% yield) of **17** as a bulky white fluff: mp 130.5–131°C; ^{1}H NMR δ 1.20 (t, 6H, *J*=7.0 Hz), 2.08 (s, 3H), 2.23 (s, 3H), 3.58 (dq, 2H, *J*=9.3, 7.0 Hz), 3.73 (dq, 2H, *J*=9.3, 7.0 Hz), 3.77 (d, 2H, *J*=5.3 Hz), 4.79 (t, 1H, *J*=5.3 Hz), 7.12 (t, 1H, *J*=7.8 Hz), 7.36 (d, 1H, *J*=7.7 Hz), 7.64 (d, 1H, *J*=7.6 Hz), 8.08 (s, 1H), 8.50 (s, 1H); ^{13}C NMR δ 13.0, 15.1, 23.3, 62.5, 64.7, 101.8, 125.4, 125.8, 127.4, 131.8, 135.1, 135.8, 162.1, 169.1; IR 3268br, 2974, 1648, 1541, 1371, 1073 cm^{-1}.

3.2.3. 7-Amino-8-methylisoquinoline (5d, X=H, R=H). A stirring mixture of P_2O_5 (8.94 g) and conc. H_2SO_4 (5 mL) was heated in a 160°C oil bath. Portions of conc. H_2SO_4 (45 mL) were used to dissolve **17** (1.30 g, 4.5 mmol) as rapidly as possible (about 25 min) and then added through a reflux condenser to the reaction mixture. The solution was allowed to react until 30 min after the addition was started. The cooled black mire was poured onto ice (300 mL) and basified using Na_2CO_3. The mixture was extracted with $CHCl_3$ and the combined organic layers were extracted with 2% HCl. The combined aqueous layers were basified with aqueous Na_2CO_3 and the resulting mixture was extracted with $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and evaporated to a brown residue. Chromatography on silica gel (0.5% conc. NH_4OH/2% MeOH/$CHCl_3$) gave 0.060 g (8.5% yield) of **5d** (X=H, R=H) as a yellow solid: mp 170–172°C; ^{1}H NMR δ 2.49 (s, 3H), 3.90 (bs, 2H), 7.15 (d, 1H, *J*=8.7 Hz), 7.50 (d, 1H, *J*=5.6 Hz), 7.54 (d, 1H, *J*=8.8 Hz), 8.32 (d, 1H, *J*=5.6 Hz), 9.34 (s, 1H); ^{13}C NMR δ 10.9, 112.9, 120.7, 122.5, 125.5, 128.7, 130.7, 139.4, 142.6, 147.4; IR 3361, 3188br, 1617, 1598, 1404, 833 cm^{-1}; HRMS calcd for $C_{10}H_{10}N_2$ 158.0844, found 158.0845.

3.2.4. 3*H*-Pyrazolo[3,4-*h*]isoquinoline (6d, X=H, R=H). Chromatography on silica gel (0.5% conc. NH_4OH/3–5% MeOH/CH_2Cl_2) gave off-white solid (96% yield): mp 244–244.5°C; ^{1}H NMR (CD_3CO_2D) δ 7.92 (d, 1H, *J*=9.3 Hz), 8.23 (d, 1H, *J*=9.3 Hz), 8.28 (d, 1H, *J*=6.3 Hz), 8.71 (d, 1H,

J=6.3 Hz), 8.81 (s, 1H), 9.86 (s, 1H); ^{13}C NMR (CD_3CO_2D) δ 117.7, 123.8, 123.9, 126.3, 127.5, 132.8, 135.4, 138.6, 141.4, 142.5; IR 3122br, 2937br, 2855br, 2788br, 938, 828 cm^{-1}. Anal. calcd for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 70.94; H, 4.12; N, 24.79.

3.3. Supplementary material

Crystallographic data (excluding structure factors) for 5-methyl-6-phenylthio-3*H*-pyrazolo[3,4-*h*]isoquinoline (**6c**, R=CH_3, X=SPh) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 182/288. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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References

1. (a) Bamberger, E. *Ann. Chim.* **1899**, *305*, 289–379. (b) Porter, H. D.; Peterson, W. D. *Organic Syntheses*, Collect. Vol. 3; Wiley: New York, 1955 pp 660–661. (c) Noelting, E. *Chem. Ber.* **1904**, *37*, 2556–2597. (d) Huisgen, R.; Nakaten, H. *Ann. Chim.* **1951**, *573*, 181.
2. Zollinger, H. *Diazo Chemistry I: Aromatic and Heteroaromatic Compounds*; VCH: New York, 1994 pp 137–141.
3. (a) Foster, H. E.; Hurst, J. *J. Chem. Soc., Perkin Trans. 1* **1973**, *3*, 2901–2907. (b) Chapman, D.; Hurst, J. *J. Chem. Soc, Perkin Trans. 1* **1980**, *11*, 2398–2404.
4. Bailey, R. J.; Card, P. J.; Shechter, H. *J. Am. Chem. Soc.* **1983**, *105*, 6096–6103.
5. Ockenden, D. W.; Schofield, K. *J. Chem. Soc.* **1953**, 1915–1919.
6. Miller, R. B.; Stowell, J. G.; Jenks, C. W.; Farmer, S. C.; Wujcik, C. E.; Olmstead, M. M. *J. Chem. Soc., Chem. Commun.* **1996**, *24*, 2711–2712.
7. Cruz, R.; Arias, M. S.; Arias, M. E.; Soliveri, J. *J. Antibiot.* **1996**, *49* (7), 700–702.
8. Hassan, A. A.; Mekheimer, R.; Mohamed, N. K. *Pharmazie* **1997**, *52* (8), 589–593.
9. Cecchi, L.; Colotta, V.; Melani, F.; Palazzino, G.; Filacchioni, G.; Martini, C.; Giannaccini, G.; Lucacchini, A. *J. Pharm. Sci.* **1989**, *78*, 437.
10. (a) Ducrocq, C.; Bisagni, E.; Rivalle, C.; Lhoste, J. M. *J. Chem. Soc., Perkin Trans. 1* **1979**, *1*, 142–145. (b) Rivalle, C.; Ducrocq, C.; Lhoste, J. M.; Bisagni, E. *J. Org. Chem.* **1980**, *45* (11), 2176–2180.
11. (a) Gensler, W. J. *Org. React.* **1951**, *6*, 191–206. (b) Sengupta, D.; Anand, N. *Indian J. Chem.* **1986**, *25B*, 72–75. (c) Balkau, F.; Elmes, B. C.; Loder, J. W. *Aust. J. Chem.* **1969**, *22*, 2489–2492.
12. Fujiwara, A. N.; Acton, E. M.; Goodman, L. *J. Heterocycl. Chem.* **1968**, *5* (6), 853–858.
13. Hart, R. T.; Tebbe, R. F. *J. Am. Chem. Soc.* **1950**, *72* (7), 3286–3287.