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Deprotonation and Regioselective Addition of 2*H*-Pyrazolo[3,4-*c*]quinolines to Electrophiles

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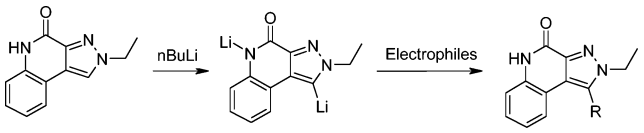


The deprotonation and regioselective reaction of 2*H*-pyrazolo[3,4-*c*]quinolines with a variety of electrophiles is described. Electrophiles include benzaldehyde, DMF, carbon dioxide, and iodine. This method provides a direct route to a class of pharmacologically interesting compounds.

Fused ring heterocyclic scaffolds are valuable building blocks for drug discovery. We recently reported that 1*H*-imidazo[4,5-*c*]quinolines act as immune response modifiers by inducing the production of interferon (IFN).[1]

Imiquimod, **1**, is a member of this class that has demonstrated clinical utility in treating genital warts, basal cell carcinoma, and actinic keratosis (Figure 1). In an effort to identify additional classes of compounds with similar activities, the 2*H*-pyrazolo-[3,4-*c*]quinoline fused ring system was targeted for synthesis and biological evaluation, **2**.

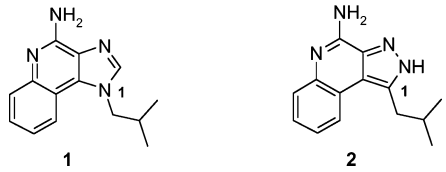
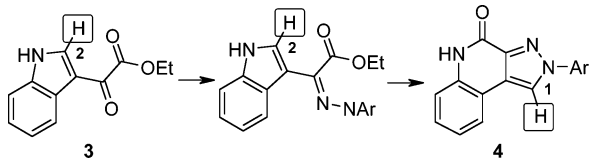


FIGURE 1. Imiquimod, **1**, a 1*H*-imidazo[4,5-*c*]quinoline, and **2**, a 2*H*-pyrazolo[3,4-*c*]quinoline.

Several reports on the synthesis and biological activity of the 2*H*-pyrazolo[3,4-*c*]quinoline ring system are known. Compounds from this class were reported to be glycine site *N*-methyl-D-aspartate receptor antagonists,[2] benzodiazepine antagonists,[3] and adenosine receptor antagonists.[4] All reports accessed this scaffold through a convenient hydrazone indole rearrangement (Scheme 1).[5]

SCHEME 1. Convenient Synthesis of 2*H*-Pyrazolo[3,4-*c*]quinolines

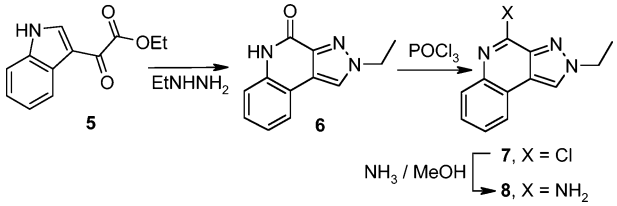


We knew from our previous imidazoquinoline work that the group at the N(1) position was vital to the pharmacological activity.[1] We therefore required a strategy that would allow functionalization at the analogous C(1) position of the pyrazoloquinoline core. A feature of the reaction shown in Scheme 1 is the transfer of the group at C(2) of indole **3** to the C(1) position of pyrazole **4**. We initially identified this as a convenient method for the installation of the required functionality at this position. Interestingly, the previously mentioned studies reported carrying only a small subset of functionality at C(2) of the indole (OH, Me, and aryl) through the rearrangement. This may be due to a lack of commercially available C(2) substituted indoles or the fact that sensitive functionality may not survive the rearrangement conditions. Our efforts using this synthetic approach to install diverse functionality at this site were met with limited success.

We instead focused on the installation of functionality post-rearrangement, examples of which were not reported in the previously published work. In this note, we disclose our synthetic efforts toward this class of molecules, focusing on the post-rearrangement approach for building functionality at the C(1) position.

We were hopeful that we could take advantage of previously published work involving the deprotonation and reaction of non-fused ring pyrazoles.[6–9] We initially targeted the C(1)-H compounds **6** and **8** (Scheme 2). A route published by Cecchi et al.,[3] for the syntheses of similar compounds from indole **5**,

SCHEME 2. Synthesis of Pyrazoloquinolines 6 and 8



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(1) Gerster, J. F.; Lindstrom, K. J.; Miller, R. L.; Tomai, M. A.; Birmachu, W.; Bomersine, S. N.; Gibson, S. J.; Imbertson, L. M.; Jacobsen, J. R.; Knafla, R. T.; Maye, P. V.; Nikolaides, N.; Oneyemi, F. Y.; Parkhurst, G. J.; Pecore, S. E.; Reiter, M. J.; Scribner, L. S.; Testerman, T. L.; Thompson, N. J.; Wagner, T. L.; Weeks, C. E.; Andre, J.; Lagain, D.; Bastard, Y.; Lupu, M. *J. Med. Chem.* **2005**, *48*, 3481−3491.

(2) MacLeod, A. M.; Grimwood, S.; Barton, C.; Bristow, L.; Saywell, K. L.; Marshall, G. R.; Ball, R. G. *J. Med. Chem.* **1995**, *38*, 2239−2243.

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(4) Colotta, V.; Catarzi, D.; Varano, F.; Cecchi, L.; Filacchioni, G.; Martini, C.; Trincavelli, L.; Lucacchini, A. *J. Med. Chem.* **2000**, *43*, 3118−3124.

(5) For the first report of this rearrangement, see: Cusmano, G.; Macaluso, G.; Vivona, N.; Ruccia, M. *Heterocyles* **1986**, *24*, 3181−3186.

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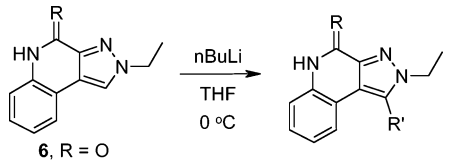
TABLE 1. Deprotonation of 6 and 8 and Addition of Electrophiles



6, R = O
8, R = NH

entry	R	electrophile	equiv[a]	R	yield[b] (%)
1	O	PhCHO	2.0	PhCHOH	71
2	O	DMF	2.5	CHO	74
3	O	CO_2		CO_2H	64
4	O	I_2	2.0	I	49[c]
5	NH	PhCHO	2.0	PhCHOH	57
6	NH	DMF	2.5	CHO	64[d]
7	NH	CO_2		CO_2H	90
8	NH	I_2	2.0	I	54

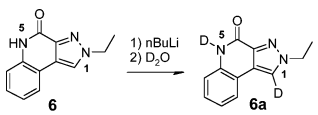
[a] Equivalents of electrophile. [b] Isolated yields. [c] Conditions: 1.4 equiv of TMEDA, 40 °C during the addition of I_2. [d] Conditions: 50 °C during the addition of DMF.

was followed and found to be applicable to our system. Both **6** and **8** were accessible from indole in two and four steps, respectively. This route provided **6** in kilogram quantities and allowed the utilization of different hydrazines to afford, in addition to ethyl, a diverse set of groups including methyl, propyl, butyl, and methoxyethyl at the N(2) position.[10]

We first attempted to deprotonate both the C(1) and the N(5) sites of the unprotected pyrazoloquinoline cores, **6** and **8**. We anticipated that we could then selectively react only the C(1) anion. Deprotonation of **6** with *n*-butyl lithium proceeded in a reproducible manner to provide, after a D_2O quench, the bis-deuterated material at C(1) and N(5).[11] Electrophiles that would provide useful functionality were examined next. Gratifyingly, in the reactions with benzaldehyde, DMF, and carbon dioxide, only the C(1) regioisomer was observed (Table 1).

The general method involved treatment of **6** in THF with 3 equiv of *n*-butyl lithium[12] at 0 °C and stirring the resulting slurry for 30 min at rt. The electrophile was then added, and stirring was continued for 30 min at rt before quenching with acetic acid. For entries 1−3 in Table 1, this method provided greater than 90% conversion by HPLC of the starting material, and in all cases, the desired product was isolated in satisfactory yield. The reaction with I_2 under these conditions, entry 4, provided only 40% conversion and 30% isolated yield. Heating the dianion of **6** to 40 °C during the addition of I_2 resulted in a 60% conversion. A combination of heating and the use of TMEDA[9] increased the conversion to 70% and the isolated yield to 49%.

(6) Chenard, B. L. *J. Org. Chem.* **1984**, *49*, 1224−1227.
(7) Katritzky, A. R.; Lue, P.; Akutagawa, K. *Tetrahedron* **1989**, *45*, 4253−4262, and references cited therein.
(8) Diez-Barra, E.; Hoz, A.; Sanchez-Migallon, A.; Tejeda, J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1079−1083.
(9) Vedso, P.; Begtrup, M. *J. Org. Chem.* **1995**, *60*, 4995−4998, and references cited therein.
(10) Data not shown.
(11)



(12) An excess of *n*-butyl lithium was used to ensure reproducible bis-deprotonation.

We next extended this methodology to the unprotected 4-amino scaffold, **8**. When the general reaction conditions used in the 4-oxo case were applied, all but DMF provided product. The lack of reactivity in the DMF case was overcome by heating the dianion of **8** to 50 °C during the addition of DMF. This resulted in an increase from <5% conversion to >90% conversion and a 64% isolated yield.

The previous examples highlight the utility of this methodology. A diverse set of functionalizable groups was installed that would not have been accessible using the previously reported methods. The functionality was chosen so that further transformations could be performed on each of the newly installed groups (i.e., palladium mediated couplings, reductive aminations, etc.).

In summary, we have demonstrated a straightforward procedure for the deprotonation and subsequent reaction of an unprotected 2*H*-pyrazolo[3,4-*c*]quinoline ring system. The convenience of this new methodology combined with the facile two-step synthesis of the scaffold from indole provides the opportunity to quickly and efficiently synthesize very large numbers of compounds for biological evaluation. We are currently investigating this class of compounds for their ability to stimulate the production of IFN and tumor necrosis factors. We are also hopeful that this method will be useful for the synthesis of other fused oxo or amino substituted quionoline and pyridine ring systems.

Experimental Section

2-Ethyl-2,5-dihydro-pyrazolo[3,4-*c*]quinolin-4-one (6). To (1*H*-Indol-3-yl)-oxo-acetic acid ethyl ester (**5**)[3] (1000 g, 4.6 mol, 1.0 equiv) in a 22 L round-bottomed flask equipped with an overhead stirrer and a distillation apparatus was added hydrazine oxalate (1040 g, 6.90 mol, 1.5 equiv) and ethanol (15 L). The colorless slurry was treated with concentrated sulfuric acid (200 mL) and heated to reflux. A total of 1.5 L of solvent was removed over 4 h. The distillation apparatus was replaced with a reflux condenser, and the reaction was refluxed for 48 h at which point a colorless suspension was present in a yellow orange solution. The condenser was replaced with a distillation apparatus, and 9 L of solvent was removed. Acetonitrile (1 L) was added, and the reaction was cooled in an ice bath to 10 °C. The solid was filtered and washed with acetonitrile (3 L). The light yellow solid was placed in the original vessel, covered with water (3 L), stirred for 30 min, filtered, and washed with water (1 L). The material was dried overnight on the filter to obtain 856 g (87%) of the title compound as a light yellow crystalline solid: mp = 273−276 °C; ^{1}H NMR (300 MHz, DMSO) δ 11.30 (s, 1H), 8.70 (s, 1H), 7.85 (d, J = 7.1 Hz, 1H), 7.32−7.35 (m, 2H), 7.14−7.20 (m, 1H), 4.45 (q, J = 7.3 Hz, 2H), 1.51 (t, J = 7.3, 3H); ^{13}C NMR (75 MHz, DMSO) δ 157.3, 140.2, 136.3, 127.5, 125.2, 123.8, 122.3, 121.6, 116.3, 115.7, 48.3, 15.8; HRMS (ESI+) calcd for $C_{12}H_{11}N_3O$ $[M + H]^+$ 214.0980, found 214.0973 (error 3.6 ppm).

4-Chloro-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinoline (7).[13] To a solution of **6** (10.0 g, 46.9 mmol) and dichloromethane (234 mL) at 0 °C was added a premixed solution of DMF (23 mL) and thionyl chloride (23 mL) dropwise. The reaction was stirred 30 min at 0 °C and 18 h at rt. The resulting light yellow suspension was concentrated under reduced pressure to a volume of ∼150 mL. Acetonitrile (150 mL) was added, and the resulting suspension was stirred for 10 min at rt before filtering to obtain 8.9 g (82%) of the title compound as a tan crystalline solid: mp = 98−100 °C; ^{1}HNMR (300 MHz, DMSO) δ 9.10 (s, 1H), 8.21−8.24 (m, 1H), 7.98−8.05 (m, 1H), 7.63−7.72 (m, 2H), 4.64 (q, J = 7.3 Hz, 2H), 1.65 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, DMSO) δ 142.6,

(13) This chlorination procedure was taken from: Hernandez, S.; Ford, H., Jr.; Marquez, V. E. *Bioorg. Med. Chem.* **2002**, *10*, 2723−2730.

141.6, 140.4, 129.0, 127.9, 127.5, 125.7, 123.9, 122.2, 122.2, 49.0, 15.8; HRMS (ESI+) calcd for $C_{12}H_{10}ClN_3$ $[M + H]^+$ 232.0642, found 232.0640 (error 0.9 ppm).

2-Ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (8). A 200 mL stainless steel pressure vessel was charged with **7** (5.0 g, 23 mmol) and 7 N ammonia in methanol (50 mL). The container was sealed and placed in a 150 °C oven for 24 h. The vessel was removed from the oven, cooled to rt, and aged for 18 h. Colorless crystals were present. Filtration and drying on a funnel provided 3.4 g (68%) of the title compound as light tan crystals: mp = 241−244 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.72 (s, 1H), 7.89 (dd, J = 1.6, 8.1 Hz, 1H), 7.47 (dd, J = 0.9, 8.3 Hz, 1H), 7.32 (ddd, J = 1.6, 7.2, 8.6 Hz, 1H), 7.16 (ddd, J = 1.4, 7.3, 8.4 Hz, 1H), 6.72 (bs, 2H), 4.46 (q, J = 7.3 Hz, 2H), 1.54 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 150.9, 144.0, 136.7, 126.7, 125.7, 124.2, 123.4, 121.8, 120.9, 119.2, 48.2, 16.0; HRMS (ESI+) calcd for $C_{12}H_{12}N_4$ $[M + H]^+$ 213.1140, found 213.1141 (error 0.3 ppm).

2-Ethyl-1-(hydroxy-phenyl-methyl)-2,5-dihydro-pyrazolo[3,4-*c*]quinolin-4-one (Table 1, Entry 1). To a suspension of **6** (426 mg, 2.00 mmol, 1.0 equiv) in THF (20 mL) at 0 °C was added *n*-butyl lithium (2.4 mL, 2.5 M in hexanes, 6.0 mmol, 3.0 equiv) dropwise. During the addition of *n*-butyl lithium, the suspension dissolved and then reappeared. The resulting suspension was stirred for 30 min at rt. Benzaldehyde (420 mg, 4.0 mmol, 2.0 equiv) was then added at rt, and the reaction was stirred for 10 min at which point HPLC showed completion. The reaction was quenched with glacial acetic acid (0.25 mL) and concentrated. Dichloromethane and MeOH were added to dissolve all solids. Silica gel (2 g) was added, and the suspension was evaporated under reduced pressure and purified via automated flash chromatography (3% MeOH to 25% MeOH in $CHCl_3$) to obtain 451 mg (71%) of the title compound as a white powder: mp > 300 °C; ^{1}H NMR (300 MHz, DMSO) δ 11.35 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.23−7.36 (m, 7H), 7.01 (ddd, J = 1.6, 6.9, 8.1 Hz, 1H), 6.73 (d, J = 4.0 Hz, 1H), 6.65 (d, J = 3.9 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (DMSO, 75 MHz) δ 157.2, 141.6, 140.4, 140.0, 136.5, 128.8, 127.7, 127.2, 126.0, 125.4, 122.1, 118.4, 116.3, 115.9, 65.6, 46.8, 15.9; HRMS (ESI+) calcd for $C_{19}H_{17}N_3O_2$ $[M + H]^+$ 320.1399, found 320.1393 (error 1.7 ppm).

2-Ethyl-4-oxo-4,5-dihydro-2*H*-pyrazolo[3,4-*c*]quinoline-1-carbaldehyde (Table 1, Entry 2). The reaction of **6** with DMF (0.39 mL, 5.0 mmol, 2.5 equiv) was performed as described previously for entry 1 using 0% CMA[14] to 30% CMA in $CHCl_3$ for chromatography to obtain 360 mg (74%) of the title compound as a pale yellow powder: mp = 265−267 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.63 (s, 1H), 10.51 (s, 1H), 8.69 (dd, J = 1.2, 8.2 Hz, 1H), 7.48 (ddd, J = 1.2, 7.2, 8.2 Hz, 1H), 7.40 (dd, J = 0.9, 8.2 Hz, 1H), 7.23 (ddd, J = 1.2, 6.9, 8.2 Hz, 1H), 4.82 (q, J = 7.2 Hz, 2H), 1.53 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO) δ 181.4, 155.9, 139.3, 137.3, 134.0, 129.3, 126.5, 123.8, 122.1, 116.2, 114.0, 48.1, 15.5; HRMS (ESI+) calcd for $C_{13}H_{11}N_3O$ $[M + H]^+$ 242.0930, found 242.0928 (error 0.5 ppm).

2-Ethyl-4-oxo-4,5-dihydro-2*H*-pyrazolo[3,4-*c*]quinoline-1-carboxylic acid (Table 1, Entry 3). The lithiation of **6** was performed as described above for entry 1, and the resulting suspension was then poured into a second flask containing a suspension of frozen carbon dioxide (440 mg) in THF (5 mL). The resulting suspension was stirred for 30 min at rt. The reaction was quenched with water (30 mL), and the layers were separated. The aqueous layer was washed with dichloromethane (2 × 25 mL). The aqueous layer was made acidic (pH = 3) with 6 N HCl and stirred for 2 h at rt. The resulting suspension was then filtered to obtain 353 mg (69%) of the title compound as a white solid: mp = 228−229 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.56 (s, 1H), 8.67 (d, J = 8.5 Hz, 1H), 7.41 (t, J = 6.9 Hz, 1H), 7.36 (d, J = 6.9 Hz, 1H), 7.20 (t, J = 7.9 Hz, 1H), 4.69 (q, J = 7.2 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H) (CO_2H not observed). ^{13}C NMR (DMSO, 125 MHz) δ 161.8, 156.5, 139.7, 137.3, 129.4, 128.8, 126.1, 122.3, 122.1, 116.6, 114.7, 49.3, 16.1; HRMS (ESI+) calcd for $C_{13}H_{11}N_3O_3$ $[M + H]^+$ 258.0879, found 258.0888 (error 3.6 ppm).

2-Ethyl-1-iodo-2,5-dihydro-pyrazolo[3,4-*c*]quinolin-4-one (Table 1, Entry 4). To a suspension of **6** (426 mg, 2.00 mmol, 1.0 equiv) and TMEDA (280 mg, 2.4 mmol, 1.2 equiv) in THF (20 mL) at 0 °C was added *n*-butyl lithium (2.4 mL, 2.5 M in hexanes, 6.0 mmol, 3.0 equiv) dropwise. During the addition of *n*-butyl lithium, the suspension dissolved and then reappeared. The resulting suspension was stirred for 30 min at 40 °C. Iodine (1.0 g, 4.0 mmol, 2.0 equiv), dissolved in THF (2.0 mL), was added dropwise to the reaction, and stirring was continued for 10 min at 40 °C at which point HPLC showed completion. The reaction was quenched with glacial acetic acid (0.25 mL) and methanol (10 mL). The reaction was then concentrated to dryness. The resulting brown solid was slurried in 1% aqueous sodium carbonate (20 mL) and saturated aqueous sodium bisulfite (10 mL) for 30 min. The mixture was filtered to obtain the crude product as an off-white solid. This material was dissolved in chloroform (20 mL) and methanol (20 mL). Silica gel (2 g) was added to the crude solution, and the suspension was evaporated under reduced pressure and purified via automated flash chromatography (0% CMA[14] to 20% CMA in $CHCl_3$) to obtain 330 mg (49%) of the title compound as an off-white solid: mp = 280−282 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.42 (s, 1H), 8.62 (d, J = 7.9 Hz, 1H), 7.36−7.43 (m, 2H), 7.28 (ddd, J = 1.6, 6.9, 8.2 Hz, 1H), 4.48 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H). ^{13}C NMR (DMSO, 125 MHz) δ 156.5, 141.4, 136.7, 128.2, 123.0, 122.0, 120.8, 116.7, 115.3, 80.1, 48.6, 15.5; HRMS (ESI+) calcd for $C_{12}H_{10}IN_3O$ $[M + H]^+$ 339.9947, found 339.9954 (error 2.0 ppm).

(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-phenyl-methanol (Table 1, Entry 5). The reaction of **8** (426 mg, 2.00 mmol, 1.0 equiv) with benzaldehyde (424 mg, 4.00 mmol, 2.0 equiv) was performed as described previously for entry 1 using 3% 1 M ammonia/MeOH to 25% 1 M ammonia/MeOH in $CHCl_3$ for chromatography to obtain 365 mg (57%) of the title compound as a light yellow solid: mp 252−255 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.08 (d, J = 8.0 Hz, 1H), 7.47 (dd, J = 1.1, 8.1 Hz, 1H), 7.22−7.35 (m, 6H), 7.03 (ddd, J = 1.4, 7.2, 8.1 Hz, 1H), 7.70−6.75 (m, 3H), 4.46 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (DMSO, 75 MHz) δ 150.9, 144.6, 141.9, 139.5, 136.1, 128.7, 127.6, 126.4, 126.0, 125.9, 124.6, 121.6, 119.5, 117.7, 65.8, 46.7, 16.0; HRMS (ESI+) calcd for $C_{19}H_{17}N_3O_2$ $[M + H]^+$ 320.1399, found 320.1393 (error 1.7 ppm).

4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinoline-1-carbaldehyde (Table 1, Entry 6). The lithiation of **8** was performed as described previously for entry 1, and the resulting suspension was warmed to 50 °C and stirred for 10 min. DMF (0.39 mL, 5.0 mmol, 2.5 equiv) was then added at the same temperature, and the reaction was stirred for 10 min at which point HPLC showed completion. The reaction was cooled to rt. Workup and purification were performed as described for entry 1 using 0% CMA[14] to 30% CMA in $CHCl_3$ for chromatography to obtain 310 mg (64%) of the title compound as a pale yellow powder: mp = 199−202 °C; ^{1}H NMR (300 MHz, DMSO) δ 10.59 (s, 1H), 8.75 (dd, J = 1.2, 8.1 Hz, 1H), 7.45−7.56 (m, 2H), 7.24 (ddd, J = 1.4, 6.9, 8.1 Hz, 1H), 7.00 (bs, 2H), 4.88 (q, J = 7.3 Hz, 2H), 1.55 (t, J = 7.3 Hz, 3H); ^{13}C NMR (DMSO, 125 MHz) δ 181.2, 150.3, 145.8, 135.2, 133.3, 128.5, 126.0, 125.8, 122.8, 121.6, 117.4, 48.0, 15.8; HRMS (ESI+) calcd for $C_{13}H_{12}N_4O$ $[M + H]^+$ 241.1089, found 241.1090 (error 0.3 ppm).

4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinoline-1-carboxylic Acid (Table 1, Entry 7). The lithiation of **8** was performed as described previously for entry 1, and the resulting suspension was stirred for 30 min at rt. A frozen piece of carbon dioxide (800 mg) was added. The resulting suspension was stirred for 30 min at rt. Workup and

(14) CMA refers to a 80:18:2 ratio of chloroform/MeOH/concentrated aqueous ammonium hydroxide.

purification were performed as described previously for entry 3 to obtain 451 mg (64%) of the title compound as a pale yellow solid: mp = 260−264 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.1 (s, 2H), 8.10 (d, J = 8.1 Hz, 1H), 7.55 (t, J = 8.3 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 4.82 (q, J = 7.2 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H) (CO_2H not observed). ^{13}C NMR (DMSO, 125 MHz) δ 153.1, 136.2, 129.4, 123.1, 121.8, 116.5, 115.8, 114.0, 112.7, 106.2, 47.5, 15.3 (CO_2H not observed); HRMS (ESI+) calcd for $C_{13}H_{12}N_4O_2$ $[M + H]^+$ 257.1039, found 257.1039 (error 2.6 ppm).

2-Ethyl-1-iodo-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylamine (Table 1, Entry 8). To a suspension of **8** (426 mg, 2.00 mmol, 1.0 equiv) and TMEDA (280 mg, 2.4 mmol, 1.2 equiv) in THF (20 mL) at 0 °C was added *n*-butyl lithium (2.4 mL, 2.5 M in hexanes, 6.0 mmol, 3.0 equiv) dropwise. During the addition of *n*-butyl lithium, the suspension dissolved and then reappeared. The resulting suspension was stirred for 30 min at rt. Iodine (1.0 g, 4.0 mmol, 2.0 equiv) dissolved in THF (2.0 mL) was added dropwise to the reaction, and stirring was continued for 10 min at rt at which point HPLC showed completion. Quenching, workup, and purification were performed as described previously for entry 4 using 0% CMA[14] to 20% CMA in $CHCl_3$ for chromatography to obtain 437 mg (65%) of the title compound as a brown solid: mp = 210−213 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.67 (d, J = 7.9 Hz, 1H), 7.51 (dd, J = 1.2, 8.2 Hz, 1H), 7.40 (ddd, J = 1.5, 7.2, 8.5 Hz, 1H), 7.27 (ddd, J = 1.2, 6.9, 8.2 Hz, 1H), 6.80 (bs, 2H), 4.53 (q, J = 7.3 Hz, 2H), 1.48 (t, J = 7.3 Hz, 3H). ^{13}C NMR (DMSO, 125 MHz) δ 150.6, 144.5, 137.4, 127.3, 126.1, 122.4, 121.5, 120.1, 118.7, 78.7, 48.5, 15.7; HRMS (ESI+) calcd for $C_{12}H_{11}IN_4$ $[M + H]^+$ 339.0107, found 339.0109 (error 0.7 ppm).

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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