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# Utilizing Solubility Differences to Achieve Regiocontrol in the Synthesis of Substituted Quinoline-4-carboxylic Acids

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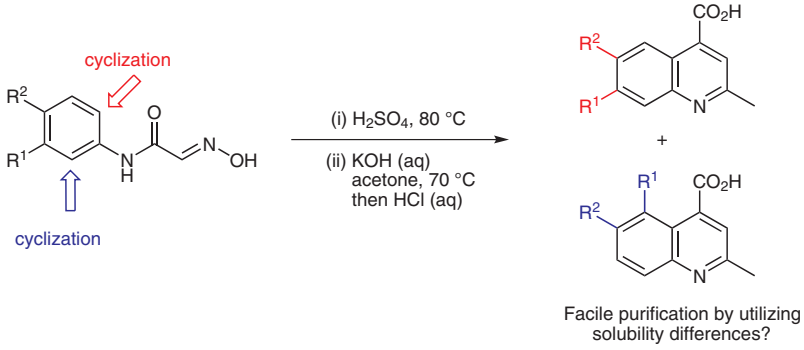


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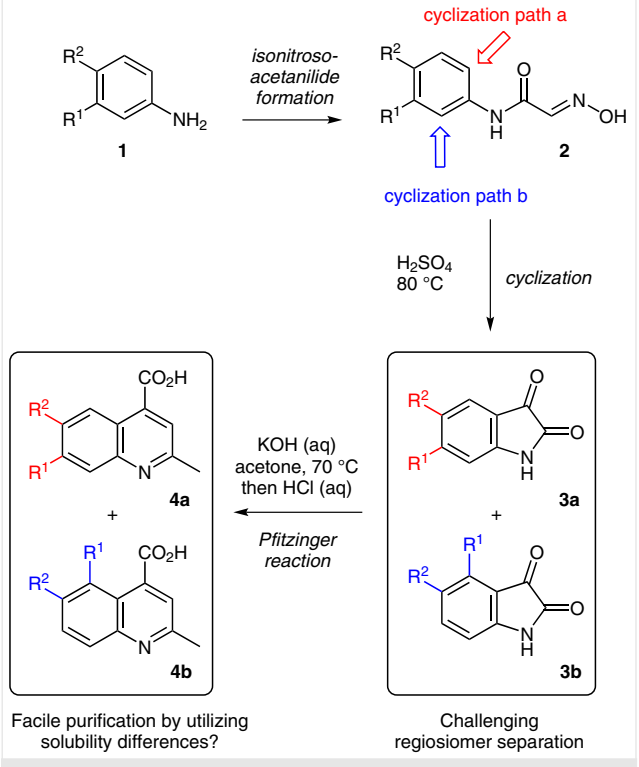
**Abstract** A practical method for the regiocontrolled synthesis of substituted quinoline-4-carboxylic acids is described. Solubility differences between the product quinoline regioisomers enable their facile separation, thus avoiding any challenging chromatographic purifications and allowing access to highly substituted quinoline compounds in three steps from commercially available anilines.

**Key words** heterocycles, quinolones, isatins, regioisomers, cyclization

Quinolines are an important class of heterocyclic compounds that have become a privileged structural motif in drug discovery, displaying widespread biological activity in numerous settings.[1] The classical synthetic approaches that have been developed for their construction from anilines fall broadly into two categories: (i) those methods that cyclize anilines (or their derivatives) onto a carbon atom adjacent to the nitrogen-bearing carbon of the benzene nucleus, typified by the Skraup[2] and Combes[3] methods – this approach can lead to mixtures of regioisomers if unsymmetrical aniline precursors are employed; (ii) those methods that pre-build the desired substitution into the starting aniline derivatives to avoid potential issues around the formation of regioisomeric mixtures, typified by the Friedlander[4] method. More modern synthetic approaches to build up quinoline scaffolds (including the use of catalytic metal complexes[5] and green chemistry[1a]) similarly have the potential to generate mixtures of regioisomers if they utilize the cyclization of unsymmetrical aniline precursors.[6] In contrast, the Pfitzinger method,[7] first discovered at the end of the 19th century, allows access to quinoline-4-carboxylic acids directly from isatin precursors, with the pre-built substitution of the isatins being transferred faithfully to the quinoline products. Therefore, to access substituted quinoline-4-carboxylic acids that bear substituents on the benzene ring (e.g., in the 5- or 7-positions), the Pfitzinger methodology requires isatin starting materials that have been synthesized in a regiocontrolled fashion. Many classical methods have been described for the synthesis of isatins,[8] including those of Gassman[9] and Stolle,[10] but perhaps the most widely adopted method for their construction was



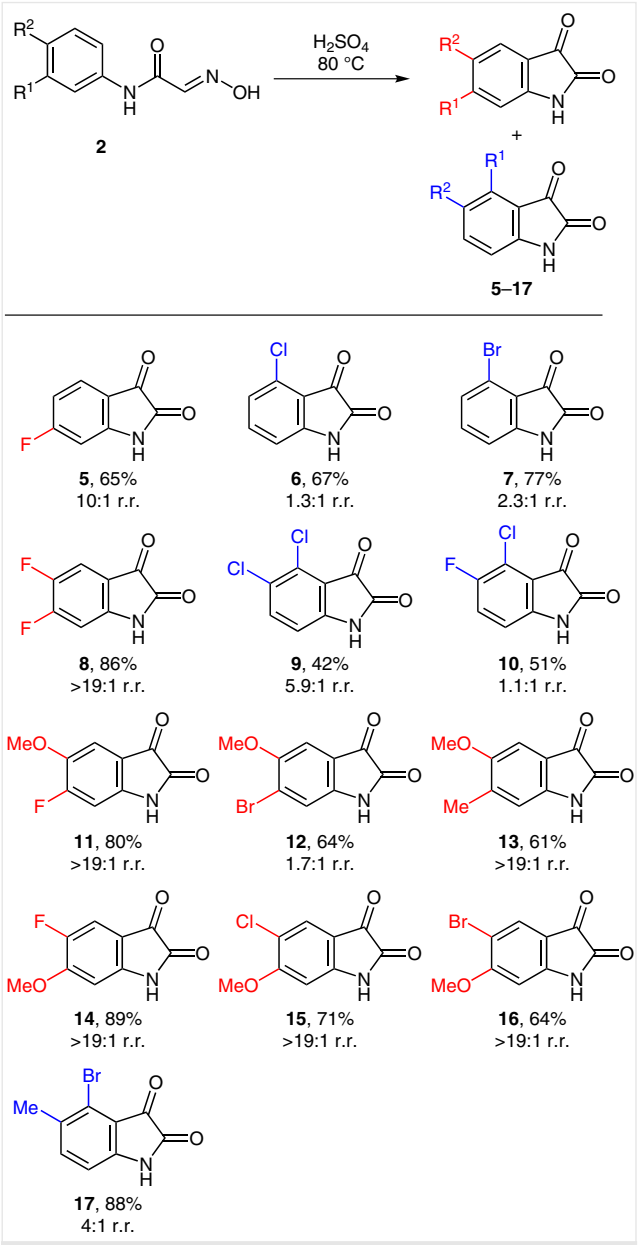

**Scheme 1** General route for the formation of quinolines **4a** and **4b** from anilines **1**

developed by Sandmeyer,[11] who showed that the cyclization of isonitrosoacetanilides **2** occurred at elevated temperatures in the presence of strong acid to give isatins **3** in a reliable fashion, with the requisite starting materials being readily prepared from the corresponding anilines **1** (see Scheme 1).

For symmetrical isonitrosoacetanilides (e.g., **2** when $R^1$ = H), isatins are formed as single regioisomers because cyclization can occur through two equivalent carbon atoms adjacent to the nitrogen-bearing carbon of the benzene nucleus. However, for unsymmetrical isonitrosoacetanilides (e.g., **2** when $R^1 \neq H$), the formation of two regioisomeric products is possible because cyclization can occur through two different carbon atoms (see 'cyclization path a' and 'cyclization path b' in Scheme 1), with the nature of the substituents $R^1$ and $R^2$ playing a key role in determining the ratio of isatin regioisomers. To tackle this problem, alternative methods for the synthesis of isatins have been reported in which the desired substitution has been pre-built into the starting materials to generate isatin products as single regioisomers, by utilizing $S_NAr$,[12] lithiation,[13] N-heteroannulation[14] and ylide-mediated carbonyl homologation methodologies.[15] More recently, a regioselective carbonylative approach was described by Lei and co-workers.[16] Despite these recent advances, the classical approaches for isatin synthesis are still widely employed and, as such, some limited methods for the separation of isatin regioisomers formed from unsymmetrical cyclization precursors have been reported,[17] including counter-current chromatography[18] and separation based on $pK_a$ differences,[19] with varying levels of success. Isatin regioisomer separations by traditional silica-gel chromatographic methods (which can be time-consuming and wasteful in terms of solvent consumption)[18] are hampered by the fact that isatins are often insoluble in common chromatography solvents.[12]

A recent report from the Kaila group showed that an inseparable mixture of isatin regioisomers (produced by the Sandmeyer method) could be converted into the corresponding quinoline-4-carboxylic acids using the Pfitzinger reaction and that the quinoline regioisomers displayed more marked differences in physical properties than their isatin counterparts, rendering them separable by column chromatography in some cases.[20] We were intrigued whether it would be possible to access substituted quinoline-4-carboxylic acids **4** as single regioisomers from mixtures of isatin regioisomers **3a** and **3b**, by exploiting this apparent greater difference in physical properties between the corresponding quinoline regioisomers (Scheme 1). This approach would avoid the tedious separation of isatin regioisomers and obviate the need to pre-build the desired substitution pattern into the starting anilines. Furthermore, we hypothesized that it might be possible to readily purify the quinoline-4-carboxylic acids by utilizing solubility differences between the regioisomers **4a** and **4b**, thus avoiding any chromatographic purifications. Consequently, this methodology might allow access to highly substituted quinolines as single regioisomers in a more facile manner.

Thus, a range of electronically and sterically diverse isonitrosoacetanilides **2** (prepared in one step from the corresponding commercially available anilines **1**; see the Supporting Information) were subjected to cyclization in sulfuric acid at 80 °C by following Sandmeyer's protocol to give isatin products **5**–**17** on multigram scale as mixtures of regioisomers (Scheme 2).[21] The effect of ring-substitution on the regioisomeric ratio of the product isatins was clearly

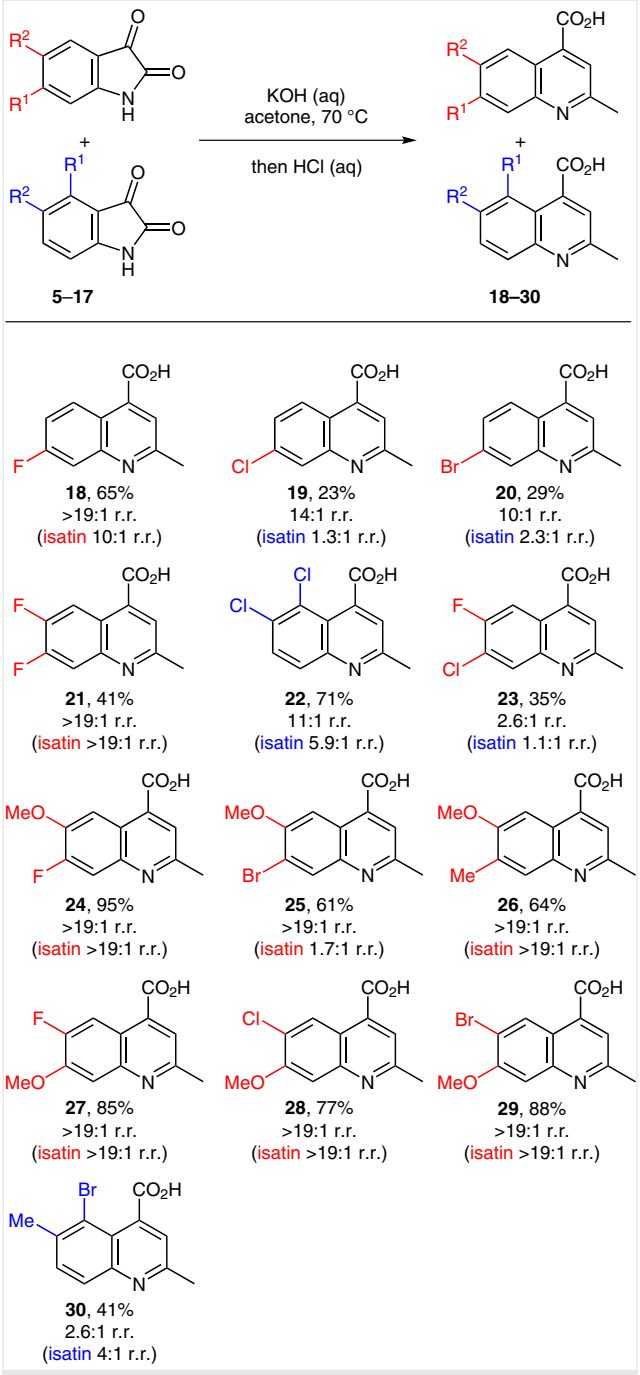



**Scheme 2** Formation of isatins **5**–**17** from isonitrosoacetanilides **2**; the structure of the major isatin regioisomer is depicted

evident. Thus, the 6-substituted fluoroisatin **5** was formed over its 4-substituted counterpart in a 10:1 ratio, whereas the formation of chloro- and bromoisatins **6** and **7** was less selective, in agreement with reported data.[17] The majority of the disubstituted isatins investigated were formed with a preference for the 5,6-regioisomer (through cyclization path a), with selectivities over the 4,5-regioisomer ranging from a modest 1.7:1 for isatin **12** up to >19:1 for isatins **8**, **11**, and **13**–**16**. Of the disubstituted compounds tested, only the dichloroisatin **9** and the bromo-methyl compound **17** showed a marked preference for the formation of the 4,5-regioisomer (through cyclization path b), whereas chloro fluoroisatin **10** was formed as a 1.1:1 mixture. During the course of this study, we found that the isatin mixtures could be readily purified from minor impurities by triturating them in isopropanol, although the crude regioisomer ratios were preserved during this process.

With a range of isatins **5**–**17** in hand, we subjected these regioisomeric mixtures to the Pfitzinger reaction conditions on a multigram scale, utilizing acetone in aqueous potassium hydroxide at 70 °C (Scheme 3).[22] Upon cooling and neutralization of these reactions mixtures, the product quinoline-4-carboxylic acids **4** precipitated from the reaction mixtures and were readily isolated by filtration. These could be further purified by trituration to remove minor impurities (see the Supporting Information), with little change in the regioisomer ratio. Interestingly, quinolines **18**–**20** were all isolated as predominantly the 7-substituted quinoline regioisomer. This selectivity was remarkable, considering the starting chloro- and bromoisatins **6** and **7** had been enriched in the 4-substituted isomers; LCMS analysis revealed that the mother liquors had been correspondingly enriched in the 5-substituted quinoline regioisomers during the precipitations. Likewise, quinolines **21** and **23**–**29** were all isolated as predominantly the 6,7-disubstituted regioisomers. Whereas the high ratios of isatin regioisomers were preserved in the formation and isolation of quinolines **21**, **24**, and **26**–**29**, the chloro-fluoro compound **23**, bromo-methoxy compound **25** and bromomethyl compound **30** all showed some rejection of the corresponding 5,6-disubstituted quinoline regioisomers into the mother liquors to varying extents during their respective precipitations. Only the dichloroquinoline **22** was further enriched in the 5,6-regioisomer after the Pfitzinger reaction and trituration process.

We hypothesize that the marked solubility differences exhibited by the quinoline regioisomers may be due, in part, to their different packing in the solid state. A crystal structure of quinoline-4-carboxylic acid has been reported by Dobson and Gerkin, in which various hydrogen-bonding interactions were proposed.[23] Substituents on the quinoline ring in the 5-position might disrupt these interactions to a greater extent than those in the 7-position, leading to less effective packing and a lower tendency towards precipitation for the 5-substituted regioisomers, allowing them to be washed into the mother liquors more readily upon neutralization from the Pfitzinger reaction. During the course of our studies, we observed that the isatin regioisomers typically showed small differences in retention time of 0.03–0.06 minutes during a standard 2-minute LCMS meth-




**Scheme 3** Conversion of isatins **5**–**17** into quinolines **18**–**30**; the structure of the major quinoline regioisomer is depicted

od, whereas the corresponding quinoline regioisomers showed larger differences in retention time of 0.12–0.25 minutes on the same LCMS method. This LCMS data is therefore consistent with the challenging separation of isatin regioisomers that has been reported previously and the more facile separation of the corresponding quinoline regioisomers that we observed was due to their greater differences in physical properties.[20]

In summary, we have developed a simple three-step process for the practical synthesis of substituted quinoline-4-carboxylic acids from anilines in a regiocontrolled fashion, avoiding any challenging separations of regioisomers by chromatographic methods. Thus, the Sandmeyer isatin synthesis was employed to generate mixtures of isatin regioisomers, which were subjected to the Pfitzinger reaction with acetone. Solubility differences in the product quinoline-4-carboxylic acids were sufficient in many cases to allow the preferential precipitation of 7- and 6,7-substituted quinoline regioisomers (even when only present as the minor regioisomer), while rejecting 5- and 5,6-substituted quinolines into the mother liquors. This method therefore provides efficient access to these substituted quinoline-4-carboxylic acids and is likely to find applications in the synthesis of pharmacologically relevant molecules as a result.

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## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561395.

## References and Notes

(1) (a) Chung, P.-Y.; Bian, Z.-X.; Pun, H.-Y.; Chan, D.; Chan, A. S.-C.; Chui, C. H.; Tang, J. C.-O.; Lam, K.-H. *Future Med. Chem.* **2015**, *7*, 947. (b) Foley, M.; Tilley, L. *Pharmacol. Ther.* **1998**, *79*, 55. (c) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627.
(2) Denmark, S. E.; Venkatraman, S. *J. Org. Chem.* **2006**, *71*, 1668.
(3) Yamashkin, S. A.; Yudin, L. G.; Kost, A. N. *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **1992**, *28*, 845.
(4) Muchowski, J. M.; Maddox, M. L. *Can. J. Chem.* **2004**, *82*, 461.
(5) Khusnutdinov, R. I.; Bayguzina, A. R.; Dzhemilev, U. M. *J. Organomet. Chem.* **2014**, *768*, 75.
(6) (a) Prajapati, S. M.; Patel, K. D.; Vekariya, R. H.; Panchala, S. N.; Patel, H. D. *RSC Adv.* **2014**, *4*, 24463. (b) Kouznetsov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M. *Curr. Org. Chem.* **2005**, *9*, 141.
(7) Sangshetti, J. N.; Zambare, A. S.; Gonjari, I.; Shinde, D. B. *Mini-Rev. Org. Chem.* **2014**, *11*, 1.
(8) da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273.
(9) Gassman, P. G.; Cue, B. W. Jr.; Luh, T.-Y. *J. Org. Chem.* **1977**, *42*, 1344.
(10) Stolle, R.; Bergdoll, R.; Luther, M.; Auerhahn, A.; Wacker, W. *J. Prakt. Chem.* **1930**, *128*, 1.
(11) Sandmeyer, T. *Helv. Chim. Acta* **1919**, *2*, 234.
(12) Kraynack, E. A.; Dalgard, J. E.; Gaeta, F. C. A. *Tetrahedron Lett.* **1998**, *39*, 7679.
(13) Hewawasam, P.; Meanwell, N. A. *Tetrahedron Lett.* **1994**, *35*, 7303.
(14) Söderberg, B. C. G.; Gorugantula, S. P.; Howerton, C. R.; Petersen, J. L.; Dantale, S. W. *Tetrahedron* **2009**, *65*, 7357.
(15) Lollar, C. T.; Krenek, K. M.; Bruemmer, K. J.; Lippert, A. R. *Org. Biomol. Chem.* **2014**, *12*, 406.
(16) Li, W.; Duan, Z.; Zhang, X.; Zhang, H.; Wang, M.; Jiang, R.; Zeng, H.; Liu, C.; Lei, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 1893.
(17) Sadler, P. W. *J. Org. Chem.* **1956**, *21*, 169.
(18) Almeida, M. R.; Leitão, G. G.; Silva, B. V.; Barbosa, J. P.; Pinto, A. C. *J. Braz. Chem. Soc.* **2010**, *21*, 764.
(19) Varma, R. S.; Singh, A. P. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1990**, *29*, 578.
(20) Kaila, N.; Janz, K.; DeBernardo, S.; Bedard, P. W.; Camphausen, R. T.; Tam, S.; Tsao, D. H. H.; Keith, J. C. Jr.; Nickerson-Nutter, C.; Shilling, A.; Young-Sciame, R.; Wang, Q. *J. Med. Chem.* **2007**, *50*, 21.
(21) **4-Bromo-5-methylindoline-2,3-dione (17); Typical Procedure:** To a stirred solution of aqueous sulfuric acid (18.1 M, 42.0 mL) at 60 °C, was added (2*E*)-*N*-(3-bromo-4-methylphenyl)-2-(hydroxyimino)acetamide (15.8 g, 61.8 mmol) portionwise. The reaction mixture was stirred in a heating block for 30 min at an internal temperature of 80 °C, then the mixture was cooled to room temperature. The solution was added slowly to a saturated water/ice mixture (79.5 mL) and stirred for 10 min at room temperature, then filtered. The resultant solid was dried under vacuum at 40 °C for 40 h, then added to isopropyl alcohol (10 mL), stirred at room temperature for 15 min, filtered and dried under vacuum at 40 °C for 16 h to give isatin **17** (13.0 g, 54.4 mmol, 88% yield, 4:1 r.r. in favor of the 4-bromo-5-methyl isomer over the 5-methyl-6-bromo isomer) as an orange solid. Data listed for both regioisomers: mp 236–238 °C. IR (thin film): 3289, 1728, 1605, 1458, 1273, 1211, 1152, 1042, 995, 980, 824, 635 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 11.07 (s, 0.8 H), 11.04 (s, 0.2 H), 7.53–7.51 (m, 2 H), 7.11 (s, 0.2 H), 6.81 (d, *J* = 8.0 Hz, 0.8 H), 2.30 (s, 0.6 H), 2.29 (s, 2.4 H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 183.6, 182.0, 159.4, 158.6, 150.6, 149.2, 139.3, 133.9, 132.1, 131.6, 126.3, 121.7, 117.4, 116.6, 115.6, 111.2, 21.7, 20.7. HRMS (ESI$^+$): *m*/*z* [M]$^+$ calcd for $C_9H_6BrNO_2^+$: 238.9582; found: 238.9575 (+2.99 ppm).
(22) **5-Bromo-2,6-dimethylquinoline-4-carboxylic Acid (30); Typical Procedure:** To a stirred solution of KOH (15.3 g, 272 mmol) in $H_2O$ (52.2 mL) in an ice-water bath was added isatin **17** (13.0 g, 54.4 mmol, 4:1 r.r. in favor of the 4-bromo-5-methyl isomer over the 5-methyl-6-bromo isomer) portionwise. The reaction mixture was stirred at room temperature for 10 min, then cooled in an ice-water bath and acetone (52.2 mL) was added dropwise. The reaction mixture was stirred in a 70 °C heating block for 5 h, then cooled in an ice-water bath and a solution of aqueous HCl (5 M, 49.0 mL, 245 mmol) was added dropwise until the mixture reached pH 5–6. The reaction mixture was stirred at room temperature for 10 min and then filtered. The resultant solid was dried under vacuum at 40 °C for 16 h, then added to isopropyl alcohol (10 mL), stirred at room temperature for 15 min, filtered, and dried under vacuum at 40 °C for 16 h. The solid was then added to ethyl acetate (10 mL), stirred at room temperature for 15 min, filtered, and dried under vacuum at 40 °C for 6 h to give quinoline **30** (6.26 g, 22.3

mmol, 41% yield, 2.6:1 r.r. in favor of the 5-bromo-6-methyl isomer over the 6-methyl-7-bromo isomer) as a golden brown solid. Data listed for both regioisomers: mp 245–251 °C (decomp.). IR (thin film): 1705, 1587, 1558, 1458, 1333, 1256, 1188, 1149, 1036, 910, 880, 826, 785, 733, 689 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 13.80 (br. s, 1 H), 8.59 (s, 0.3 H), 8.25 (s, 0.3 H), 7.94 (d, *J* = 8.6 Hz, 0.7 H), 7.86 (s, 0.3 H), 7.78 (d, *J* = 8.6 Hz, 0.7 H), 7.52 (s, 0.7 H), 2.70 (s, 0.8 H), 2.68 (s, 2.2 H), 2.57 (s, 2.2 H), 2.55 (s, 0.8 H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 169.9, 167.2, 159.3, 158.2, 147.4, 147.4, 141.2, 137.6, 135.9, 135.6, 132.5, 131.3, 128.5, 126.6, 126.1, 123.5, 122.1, 121.9, 121.3, 119.5, 24.6, 24.1, 24.0, 23.0. HRMS (ESI$^+$): *m*/*z* [M]$^+$ calcd for $C_{12}H_{10}BrNO_2^+$: 278.9895; found: 278.9901 (−2.09 ppm).

(23) Dobson, A. J.; Gerkin, R. E. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1998**, *54*, 1883.