A General and Efficient Synthesis of Azaindoles and Diazaindoles

Christian Harcken, Yancey Ward, David Thomson, Doris Riether*

Department of Medicinal Chemistry, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road/P.O. Box 368, Ridgefield, Connecticut 06877, USA
Fax +1(203)7916072; E-mail: driether@rdg.boehringer-ingelheim.com
Received 30 August 2005

Abstract: The DBU-mediated cyclization of *ortho*-(Boc-amino)alkynyl pyridines, -pyridazines, -pyrimidines and -pyrazines efficiently generates azaindoles and diazaindoles, respectively. The reaction proceeds under mild conditions and in high yields. A variety of functional groups are tolerated.

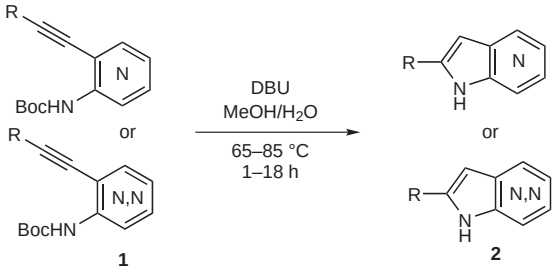
Key words: azaindole, diazaindoles, cyclization, heterocycles, alkynes

Azaindoles (pyrrolopyridines) and related heteroaromatic ring systems are common moieties in pharmaceutically important molecules. A limited number of synthetic routes to access azaindoles are described in the literature. The Madelung indole synthesis has been applied in the preparation of 4-, 5- and 6-azaindoles[1] as well as 4,6-diazaindoles (pyrrolopyrimidines).[2] The 4-, 5-, 6- and 7-azaindole isomers have been generated either by the cyclization of *ortho*-nitro-alkenylpyridines[3] or the palladium-catalyzed heteroannulation of internal alkynes with *ortho*-aminoiodopyridines.[4] Recently, the addition of the dianion of 3-amino-4-picoline to carboxylic esters has been reported for the synthesis of 6-azaindoles.[5]

However, the most general method used for the synthesis of azaindoles is the cyclization of *ortho*-amino-alkynyl pyridines. Historically, this transformation has been performed using either transition metal-mediated processes or strong bases. The first copper-mediated cyclization of *ortho*-amino-alkynyl anilines in the synthesis of an indole was described in 1963.[6] Since then, transition metal-mediated conditions have been applied to the synthesis of 5-azaindoles,[7,8] 6-azaindoles,[8] 7-azaindoles,[8,9] 4,5-diazaindoles (pyrrolopyridazines),[10] and 4,6-diazaindoles.[11] These reactions have typically been run at high temperatures (>100 °C) in DMF and generate product in moderate yields.

Alternatively, strong bases have been employed: cyclizations to give 4- or 5-azaindoles have been performed with NaOEt in EtOH;[12] 4-azaindoles have been generated using $NaNH_2$ in DMF,[13] and 4,7-diazaindoles have been cyclized using methylamine.[14] More recently, *t*-BuOK or KH in NMP has been used to synthesize various azaindoles and diazaindoles.[15,16] This last method has a more general scope regarding the pattern of ring substitution and functional group tolerability. However, in our hands, variable and moderate yields were observed. This is likely due to the difficult isolation of the polar azaindole products from the reaction mixture. For example, extraction with ethyl acetate or dichloromethane results in a large amount of NMP remaining in the organic layer, while other extraction circumvents this problem, but requires many extractions to isolate the product in good yield. Additionally, the strong basic conditions caused side reactions to occur when certain functional groups were present. Therefore, it was desirable to develop a synthetic method that enabled the cyclization of *ortho*-(Boc-amino)alkynyl pyridines and diazines using a milder base in a more convenient solvent.

Recently, an example was described in the literature using DBU in the base-mediated cyclization of an *ortho*-(Boc-amino)alkynyl pyridine in the synthesis of a 5-azaindole.[17] In this example the reaction is run in DMF and the Boc group is retained on the indole nitrogen atom. This result inspired us to use DBU as a base. Furthermore, many azaindoles and diazaindoles can be precipitated from methanol–water mixtures. The presence of base in an aqueous medium should also lead to Boc-deprotection of the *N*-Boc-azaindole cyclization product. Therefore, we investigated the DBU-mediated cyclization of *ortho*-(Boc-amino)alkynyl pyridines and diazines **1** in MeOH–water (Scheme 1). To our delight, this reaction occurred smoothly yielding the desired N-deprotected azaindoles and diazaindoles **2** in good yield. Additionally, the work up consisted simply of removal of methanol and addition of water to precipitate the product with crude purities >95%.



Scheme 1 DBU-mediated cyclization of *ortho*-(Boc-amino)alkynyl pyridines, -pyridazines, -pyrimidines and -pyrazines (**1**) efficiently generates azaindoles and diazaindoles (**2**), respectively.

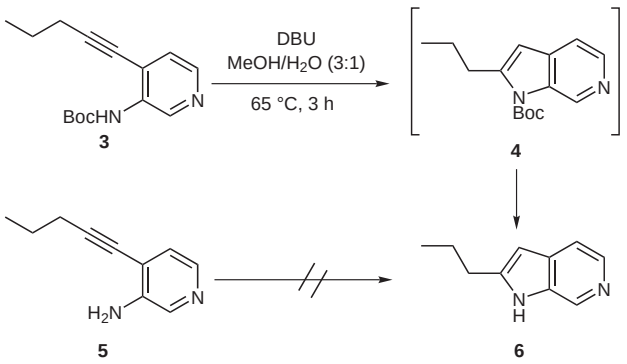
Mechanistically, the process likely involves the deprotonation of the carbamate nitrogen in **3**, cyclization to give *N*-Boc azaindole **4** and subsequent cleavage of the

SYNLETT 2005, No. 20, pp 3121–3125
Advanced online publication: 28.11.2005
DOI: 10.1055/s-2005-922753; Art ID: S08305ST

carbamate group with hydroxide ion to give azaindole **6**. This mechanism is supported by the fact that treatment of *N*-Boc azaindole **4** with aqueous DBU rapidly generates **6** (Scheme 2). Aniline **5** does not cyclize under these conditions, indicating that the carbamate is required for the cyclization step.

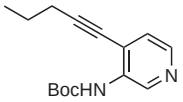
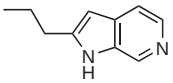
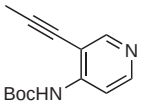
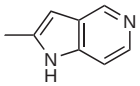
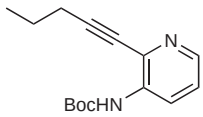
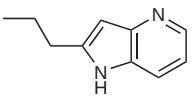
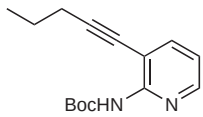
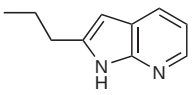
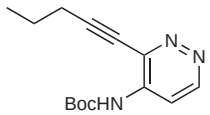
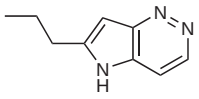
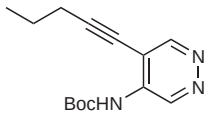
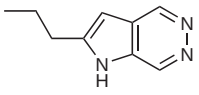
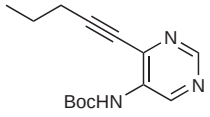
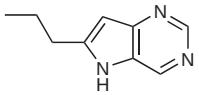
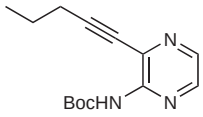
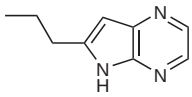
To evaluate the scope and limitations of this methodology, the synthesis of various heteroaromatic ring systems was investigated (Table 1).

Boc-protection[18] of *ortho*-iodo-substituted and *ortho*-bromo-substituted aminopyridines and *ortho*-bromo-substituted or *ortho*-chloro-substituted aminopyridazines, -aminopyrimidines and -aminopyrazines followed by Sonogashira coupling[19] with terminal alkynes were performed as described in the literature. These substrates



Scheme 2 Reaction mechanism

Table 1 Synthesis of Azaindole and Diazaindole Isomers

Substrate	Product	Conditions (temp, time)	Isolated yield (%)[a]
 **7**	 **8**	65 °C, 3 h	91
 **9**	 **10**	65 °C, 12 h	86
 **11**	 **12**	65 °C, 3 h	85
 **13**	 **14**	85 °C, 14 h	62
 **15**	 **16**	65 °C, 1 h	98
 **17**	 **18**	65 °C, 1 h	86
 **19**	 **20**	65 °C, 1 h	97
 **21**	 **22**	65 °C, 1 h	90

[a] Yields are not optimized.

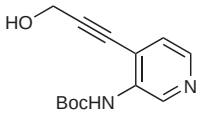
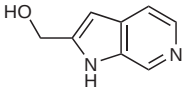
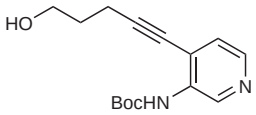
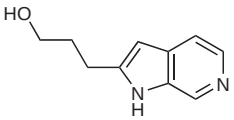
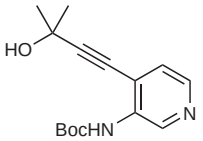
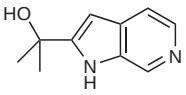
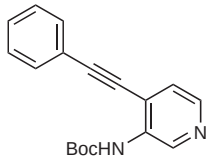
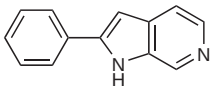
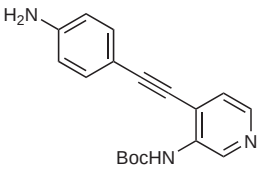
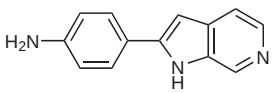
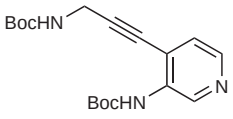
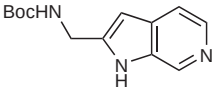
were then subjected to the cyclization conditions. The pyridine isomers **7**, **9**, and **11** cyclized readily giving 6-azaindole **8**, 5-azaindole **10**, and 4-azaindole **12** respectively, in good yields (85–91%).[20] The reactions were complete after 3–12 hours at 65 °C. 2-(Boc-amino)pyridine **13** required an extended reaction time (14 h) at a higher temperature (85 °C) to achieve complete conversion to 7-azaindole **14** (62% isolated yield). (Boc-amino)-substituted pyridazines **15** and **17**, pyrimidine **19**, and pyrazine **21** were subjected to the same conditions. The corresponding diazaindoles, pyrrolopyridazines **16** and **18**, pyrrolopyrimidine **20**, and pyrrolopyrazine **22**, were isolated in excellent yields (86–98%). It should be noted that various pyridines with additional substituents on the pyridine ring cyclize under the same conditions.[21]

To further assess the tolerance of functional groups to the reaction conditions, 3-(Boc-amino)-4-iodopyridine was coupled with selected terminal alkynes yielding functionalized substrates (Table 2). 3-(Boc-amino)-4-alkynyl pyridines such as **23**, **25**, and **27** containing an unprotected hydroxy group cyclized giving the hydroxyalkyl substituted azaindoles **24**, **26**, and **28** in good yields.

With an increase in steric demand, a slight decrease in reaction rate was observed, e.g. sterically demanding substrate **27** required a reaction time of 15 hours at 85 °C to afford complete conversion. The same was found for aryl-substituted alkynes **29** and **31**. Exploring additional functional groups, we also found that free amines are tolerated. Thus, aniline **31** was converted to azaindole **32** without any significant side reactions. We were also pleased to find, that in accordance with our mechanistic rationale, carbamate protecting groups on basic nitrogens such as in **33** are retained under the cyclization conditions.

In conclusion, we have developed a simple, efficient, and general synthesis of all azaindole isomers and numerous diazaindole isomers via the cyclization of *ortho*-(Boc-amino)alkynyl pyridines and diazines using DBU in aqueous methanol. In general, the reaction has proceeded to

Table 2 Synthesis of 2-Substituted 6-Azaindoles

Substrate	Product	Condition (temp, time)	Isolated yield (%)[a]
 **23**	 **24**	65 °C, 4 h	79
 **25**	 **26**	65 °C, 4 h	72
 **27**	 **28**	85 °C, 15 h	71
 **29**	 **30**	85 °C, 12 h	66
 **31**	 **32**	85 °C, 18 h	88
 **33**	 **34**	65 °C, 1 h	78

[a] Yields are not optimized.

completion in high yield at 65 °C within a few hours. The cyclization products have been precipitated from the reaction mixture and the products have not required purification by chromatography. Furthermore, we have shown that various functional groups are tolerated.

This methodology represents the most general method for the synthesis of azaindoles and diazaindoles described in the literature to date. We believe that this methodology will find many applications in the synthesis of compounds containing this class of heterocycles.

References

(1) Hands, D.; Sishop, B.; Cameron, M.; Edwards, J. S.; Cottrell, I. F.; Wright, S. H. B. *Synthesis* **1996**, 877.
(2) Modnikova, G. A.; Titkova, R. M.; Glushkov, R. G.; Sokolova, A. S.; Silin, V. A.; Chernov, V. A. *Pharm. Chem. J.* **1988**, *22*, 135.
(3) Kuzmich, D.; Mulrooney, C. *Synthesis* **2003**, 1671.
(4) Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 5355.
(5) Song, J. J.; Tan, Z.; Gallou, F.; Xu, J.; Yee, N. K.; Senanayake, C. H. *J. Org. Chem.* **2005**, *70*, 6512.
(6) Castro, C. E.; Stevens, R. D. *J. Org. Chem.* **1963**, *28*, 2163.
(7) Xu, L.; Lewis, I. R.; Davidsen, S. K.; Summers, J. B. *Tetrahedron Lett.* **1998**, *39*, 5159.
(8) Mazéas, D.; Guillaumet, G.; Viaud, M.-C. *Heterocycles* **1999**, *50*, 1065.
(9) Kumar, V.; Dority, J. A.; Bacon, E. R.; Singh, B.; Lesher, G. Y. *J. Org. Chem.* **1992**, *57*, 6995.
(10) Ames, D. E.; Bull, D. *Tetrahedron* **1982**, *38*, 383.
(11) Norman, M. H.; Chen, N.; Chen, Z.; Fotsch, C.; Hale, C.; Han, N.; Hurt, R.; Jenkins, T.; Kincaid, J.; Liu, L.; Lu, Y.; Moreno, O.; Santora, V. J.; Sonnenberg, J. D.; Karbon, W. *J. Med. Chem.* **2000**, *43*, 4288.
(12) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 1823.
(13) Brière, J.-F.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Heterocycles* **2000**, *52*, 1371.
(14) Ames, D. E.; Brohi, M. I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1384.
(15) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571.
(16) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 2488.
(17) Choi-Sledeski, Y. M.; Kearney, R.; Poli, G.; Pauls, H.; Gardner, C.; Gong, D.; Becker, M.; Davis, R.; Spada, A.; Liang, G.; Chu, V.; Brown, K.; Collussi, D.; Leadley, R. Jr.; Rebello, S.; Moxey, P.; Morgan, S.; Bentley, R.; Kasiewski, C.; Maignan, S.; Guilloteau, J.-P.; Mikol, V. *J. Med. Chem.* **2003**, *46*, 681.
(18) Kelly, T. A.; Patel, U. R. *J. Org. Chem.* **1995**, *60*, 1875.
(19) **General Procedure for the Sonogashira Coupling.**
To a solution of *ortho*-(Boc-amino)halogeno pyridine or diazine (1 mmol) in anhyd DMF (1 mL) and Et_3N (3 mL) was added copper iodide (0.10 mmol), $Pd(PPh_3)_2Cl_2$ (0.05 mmol) and the alkyne (1 mmol) under argon and the reaction stirred at r.t. for 15 h. The reaction was diluted with EtOAc (10 mL), washed with sat. aq NH_4Cl solution (2 × 5 mL) and the combined aqueous layers were extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated. Column chromatography (hexane–EtOAc) yielded *ortho*-(Boc-amino)alkynyl pyridines or diazines in 37–99% yield.

Data for Alkynes.
Compound **7**: prepared from (4-iodopyridin-3-yl)carbamic acid *tert*-butyl ester.[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (s, 1 H), 8.20 (d, *J* = 5.06 Hz, 1 H), 7.19 (d, *J* = 5.06 Hz, 1 H), 7.06 (s, 1 H), 2.51 (t, *J* = 7.07 Hz, 2 H), 1.72 (qt, *J* = 7.07 Hz, *J* = 7.33 Hz, 2 H), 1.55 (s, 9 H), 1.09 (t, *J* = 7.33 Hz, 3 H).
Compound **9**: ^{1}H NMR data are in accordance with data reported in the literature.[7]
Compound **11**: prepared from (2-bromopyridin-3-yl)carbamic acid *tert*-butyl ester.[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 9.08 Hz, 1 H), 8.19 (dd *J* = 1.39 Hz, *J* = 4.67 Hz, 1 H), 7.18 (dd, *J* = 4.67 Hz, *J* = 8.57 Hz, 1 H), 2.53 (t, *J* = 7.08 Hz, 2 H), 1.74 (qt, *J* = 7.33 Hz, *J* = 7.08 Hz, 2 H), 1.54 (s, 9 H), 1.10 (t, *J* = 7.33 Hz, 3 H).
Compound **13**: prepared from (3-iodopyridin-2-yl)carbamic acid *tert*-butyl ester.[24] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (dd, *J* = 5.05 Hz, *J* = 1.77 Hz, 1 H), 7.60 (dd, *J* = 7.58 Hz, 1.77 Hz, 1 H), 7.57 (s, 1 H), 6.90 (dd, *J* = 7.58 Hz, *J* = 5.05 Hz, 1 H), 2.49 (t, *J* = 7.07 Hz, 2 H), 1.69 (qt, *J* = 7.33 Hz, *J* = 7.07 Hz, 2 H), 1.54 (s, 9 H), 1.09 (t, *J* = 7.33 Hz, 3 H).
Compound **15**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (br s, 1 H), 9.29 (br s, 1 H), 6.90 (s, 1 H), 2.99 (t, *J* = 7.58 Hz, 2 H), 1.69 (m, 11 H), 0.99 (t, *J* = 7.33 Hz, 3 H).
Compound **17**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.97 (br s, 1 H), 7.92 (br s, 1 H), 6.74 (s, 1 H), 2.99 (t, *J* = 7.58 Hz, 2 H), 1.69 (qt, *J* = 7.58 Hz, *J* = 7.58 Hz, 2 H), 1.63 (s, 9 H), 1.01 (t, *J* = 7.58 Hz, 3 H).
Compound **19**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.41 (s, 1 H), 8.73 (s, 1 H), 6.96 (br s, 1 H), 2.49 (t, *J* = 7.08 Hz, 2 H), 1.66 (qt, *J* = 7.33 Hz, *J* = 7.08 Hz, 2 H), 1.48 (s, 9 H), 1.03 (t, *J* = 7.33 Hz, 3 H).
Compound **21**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (br s, 1 H), 8.24 (br s, 1 H), 6.46 (br s, 1 H), 2.96 (t, *J* = 7.58 Hz, 2 H), 1.69 (qt, *J* = 7.58 Hz, *J* = 7.34 Hz, 2 H), 1.62 (s, 9 H), 0.99 (t, *J* = 7.34 Hz, 3 H).
Compound **23**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (s, 1 H), 8.14 (d, *J* = 5.03 Hz, 1 H), 7.16 (d, *J* = 4.80 Hz, 1 H), 6.97 (s, 1 H), 4.53 (s, 2 H), 1.46 (s, 9 H).
Compound **25**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.26 (br s, 1 H), 8.12 (d, *J* = 5.05 Hz, 1 H), 7.25 (s, 1 H), 7.11 (d, *J* = 5.05 Hz, 1 H), 3.79 (t, *J* = 5.71 Hz, 2 H), 2.60 (t, *J* = 6.95 Hz, 2 H), 1.85 (tt, *J* = 6.95 Hz, *J* = 5.71 Hz, 2 H), 1.48 (s, 9 H).
Compound **27**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.28 (s, 1 H), 8.14 (d, *J* = 5.05 Hz, 1 H), 7.13 (d, *J* = 5.05 Hz, 1 H), 6.98 (s, 1 H), 3.41 (s, 1 H), 1.60 (s, 6 H), 1.46 (s, 9 H).
Compound **29**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (s, 1 H), 8.21 (d, *J* = 5.05 Hz, 1 H), 7.25–7.52 (m, 6 H), 7.04 (br s, 1 H), 1.49 (s, 9 H).
Compound **31**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (s, 1 H), 8.10 (d, *J* = 5.05 Hz, 1 H), 7.32 (d, *J* = 5.05 Hz, 1 H), 7.23 (d, *J* = 8.85 Hz, 2 H), 6.57 (s, *J* = 8.85 Hz, 2 H), 1.45 (s, 9 H).
Compound **33**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.41 (s, 1 H), 8.22 (d, *J* = 5.06 Hz, 1 H), 7.20 (d, *J* = 5.06 Hz, 1 H), 7.04 (s, 1 H), 4.86 (s, 1 H), 4.22 (d, *J* = 5.56 Hz, 2 H), 1.56 (s, 9 H), 1.48 (s, 9 H).

(20) **Typical Procedure for the Cyclization.**
To a solution of *ortho*-(Boc-amino)alkynyl pyridine or diazine (1 mmol) in MeOH–H_2O (5 mL, 3:1) was added DBU (5 mmol) and the reaction heated to 65–85 °C for 1–14 h. Then, MeOH was removed under vacuum and the solution cooled in an ice-water bath; H_2O was added dropwise to precipitate the azaindole or diazaindole. Compounds **16**, **18**, **28**, and **30** did not solidify from aqueous solution. In these cases the H_2O–DBU mixture was decanted from the oil. The

oil is then dissolved in MeOH and the precipitation procedure repeated. Compound **28** was purified by chromatography. The precipitate was collected by filtration, washed with H_2O and dried to give the desired products (>95% purity). Yields 62%–97%.

Data for Azaindoles and Diazaindoles.

Compound **8**: mp (MeOH–H_2O) 158 °C. ^{1}H NMR (400 MHz $CDCl_3$): δ = 8.71 (s, 1 H), 8.20 (d, *J* = 5.31 Hz, 1 H), 7.43 (d, *J* = 5.31 Hz, 1 H), 6.28 (s, 1 H), 2.80 (t, *J* = 7.58 Hz, 2 H), 1.81 (qt, *J* = 7.58 Hz, *J* = 7.33 Hz, 2 H), 1.03 (t, *J* = 7.33 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.22, 137.99, 134.03, 133.50, 132.73, 99.02, 30.45, 22.36, 13.90. HRMS (APCI): *m/z* calcd for $C_{10}H_{13}N_2$ [M + 1]: 161.1073; found: 161.1075.

Compound **10**: ^{1}H NMR data are in accordance with data reported in the literature.[25]

Compound **12**: mp (MeOH–H_2O) 123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.43 (s, 1 H), 8.40 (dd, *J* = 1.26 Hz, 4.80 Hz, 1 H), 7.59 (d *J* = 8.08 Hz, 1 H), 7.02 (dd, *J* = 4.80 Hz, 8.08 Hz, 1 H), 6.44 (s, 1 H), 2.80 (t, *J* = 7.58 Hz, 2 H), 1.76 (qt, *J* = 7.33 Hz, *J* = 7.58 Hz, 2 H), 0.98 (t, *J* = 7.33 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.27, 145.08, 141.98, 129.39, 117.72, 115.63, 99.68, 30.70, 22.37, 13.85. HRMS (APCI): *m/z* calcd for $C_{10}H_{13}N_2$ [M + 1]: 161.1073; found: 161.1076.

Compound **14**: mp (MeOH–H_2O) 65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.37 (s, 1 H), 8.21 (d, *J* = 4.55 Hz, 1 H), 7.83 (dd, *J* = 7.83 Hz, *J* = 1.26 Hz, 1 H), 7.03 (dd, *J* = 7.83 Hz, *J* = 4.80 Hz, 1 H), 6.20 (s, 1 H), 2.86 (t, *J* = 7.58 Hz, 2 H), 1.86 (qt, *J* = 7.58 Hz, *J* = 7.33 Hz, 2 H), 1.04 (t, *J* = 7.33 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.33, 141.78, 140.18, 127.63, 122.00, 115.38, 97.17, 30.84, 22.46, 13.99. HRMS (APCI): *m/z* calcd for $C_{10}H_{13}N_2$ [M + 1]: 161.1073; found: 161.1073.

Compound **16**: mp (MeOH–H_2O) 154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.46 (br s, 1 H), 9.28 (br s, 1 H), 6.35 (s, 1 H), 2.89 (t, *J* = 7.46 Hz, 2 H), 1.81 (qt, *J* = 7.45 Hz, *J* = 7.33 Hz, 2 H), 0.95 (t, *J* = 7.33 Hz, 3 H). ^{13}C NMR (100 MHz, MeOH-d_4): δ = 148.43, 145.51, 137.86, 133.96, 126.91, 99.78, 30.95, 23.37, 14.09. HRMS (APCI): *m/z* calcd for $C_9H_{12}N_3$ [M + 1]: 162.1025; found: 162.1032.

Compound **18**: mp (MeOH–H_2O) 177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.02 (br s, 1 H), 8.83 (br s, 1 H), 7.44 (br s, 1 H), 6.64 (s, 1 H), 2.81 (t, *J* = 7.46 Hz, 2 H), 1.79 (qt, *J* = 7.46 Hz, *J* = 7.34 Hz, 2 H), 0.97 (t, *J* = 7.34 Hz, 3 H). ^{13}C NMR (100 MHz, MeOH-d_4): δ = 151.68, 149.60, 130.76, 107.23, 97.11, 29.69, 21.40, 12.47. HRMS (APCI): *m/z* calcd for $C_9H_{12}N_3$ [M + 1]: 162.1025; found: 162.1032.

Compound **20**: mp (MeOH–H_2O) 176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.87 (s, 1 H), 8.63 (s, 1 H), 6.39 (s, 1 H), 2.79 (t, *J* = 7.46 Hz, 2 H), 1.75 (qt, *J* = 7.46 Hz, *J* = 7.46 Hz, 2 H), 0.95 (t, *J* = 7.46 Hz, 3 H). ^{13}C NMR (100 MHz, MeOH-d_4): δ = 151.10, 150.11, 148.43, 137.04, 127.43, 98.08, 29.75, 21.46, 12.33. HRMS (APCI): *m/z* calcd for $C_9H_{12}N_3$ [M + 1]: 162.1025; found: 162.1031.

Compound **22**: mp (MeOH–H_2O) 156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.26 (br s, 1 H), 8.36 (br s, 1 H), 8.08 (br s, 1 H), 6.40 (s, 1 H), 2.81 (t, *J* = 7.58 Hz, 2 H), 1.79 (qt, *J* = 7.58 Hz, *J* = 7.34 Hz, 2 H), 0.99 (t, *J* = 7.34 Hz, 3 H). ^{13}C NMR (100 MHz, MeOH-d_4): δ = 149.67, 143.79, 141.70, 137.77, 136.53, 98.67, 31.67, 23.26, 14.09. HRMS (APCI): *m/z* calcd for $C_9H_{12}N_3$ [M + 1]: 162.1025; found: 162.1031.

Compound **24**: mp (MeOH–H_2O) 185 °C. ^{1}H NMR (400 MHz, MeOH-d_4): δ = 8.60 (s, 1 H), 8.00 (d, *J* = 5.56 Hz, 1 H), 7.43 (d, *J* = 5.81 Hz, 1 H), 6.44 (s, 1 H), 4.79 (s, 2 H). HRMS (APCI): *m/z* calcd for $C_8H_9N_2O$ [M + 1]: 149.0709; found: 149.0711.

Compound **26**: mp (MeOH–H_2O) 161 °C. ^{1}H NMR (400 MHz, MeOH-d_4): δ = 8.52 (s, 1 H), 7.96 (d, *J* = 5.56 Hz, 1 H), 7.44 (d, *J* = 5.56 Hz, 1 H), 6.29 (s, 1 H), 3.62 (t, *J* = 6.32 Hz, 2 H), 2.90 (t, *J* = 7.71 Hz, 2 H), 1.98 (tt, *J* = 6.32 Hz, *J* = 7.71 Hz, 2 H). HRMS (APCI): *m/z* calcd for $C_{10}H_{13}N_2O$ [M + 1]: 177.1022; found: 177.1026.

Compound **28**: oil. ^{1}H NMR (400 MHz, MeOH-d_4): δ = 8.60 (s, 1 H), 8.01 (d, *J* = 5.56 Hz, 1 H), 7.50 (d, *J* = 5.65 Hz, 1 H), 6.43 (s, 1 H), 1.57 (s, 6 H). HRMS (APCI): *m/z* calcd for $C_{10}H_{11}N_2$ [M – H_2O + 1]: 159.0916; found: 159.0917.

Compound **30**: mp (MeOH–H_2O) 205 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (s, 1 H), 8.14 (d, *J* = 5.56 Hz, 1 H), 7.80 (d, *J* = 7.96 Hz, 2 H), 7.50 (d, *J* = 5.31 Hz, 1 H), 7.41 (dd, *J* = 7.58 Hz, *J* = 7.58 Hz, 2 H), 7.33 (dd, *J* = 6.81 Hz, *J* = 6.81 Hz, 2 H), 6.79 (s, 1 H). HRMS (APCI): *m/z* calcd for $C_{13}H_{11}N_2$ [M + 1]: 195.0916; found: 195.0921.

Compound **32**: mp (MeOH–H_2O) 188 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (s, 1 H), 8.22 (d, *J* = 5.56 Hz, 1 H), 7.53 (d, *J* = 8.59 Hz, 2 H), 7.46 (d, *J* = 5.30 Hz, 1 H), 6.77 (d, *J* = 8.33 Hz, 2 H), 6.65 (s, 1 H), 3.49 (br s, 2 H). HRMS (APCI): *m/z* calcd for $C_{13}H_{12}N_3$ [M + 1]: 210.1031; found: 210.1034.

Compound **34**: mp (MeOH–H_2O) 64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (s, 1 H), 8.22 (d, *J* = 5.56 Hz, 1 H), 7.45 (dd, *J* = 5.56 Hz, *J* = 1.01 Hz, 1 H), 6.33 (s, 1 H), 5.15 (s, 1 H), 4.41 (d, *J* = 6.06 Hz, 2 H), 1.49 (s, 9 H). HRMS (APCI): *m/z* calcd for $C_{13}H_{18}N_3O_2$ [M + 1]: 248.1393; found: 248.1384.

(21) Unpublished results: pyridines and diazines with substituents such as NMe_2, OMe, or CN are well tolerated in this reaction.

(22) Venuti, M. C.; Stephenson, R. A.; Alvarez, R.; Bruno, J. J.; Strosberg, A. M. *J. Med. Chem.* **1988**, *31*, 2136.

(23) Crous, R.; Dywer, C.; Holzapfel, C. W. *Heterocycles* **1999**, *51*, 721.

(24) Park, S. S.; Choi, J.-K.; Yum, E. K.; Ha, D.-C. *Tetrahedron Lett.* **1998**, *39*, 627.

(25) Estel, L.; Marsais, F.; Queguiner, G. *J. Org. Chem.* **1988**, *53*, 2740.