A Regioselective and High-Yielding Method for Formaldehyde Inclusion in the 3CC Groebke–Blackburn–Bienaymé Reaction: One-Step Access to 3-Aminoimidazoazines

Anuj Sharma, Hong-yu Li*

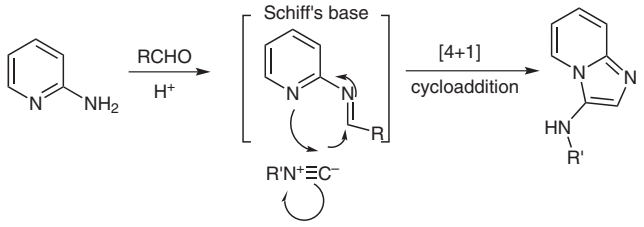
College of Pharmacy, Department of Pharmacoloy/Toxicology, The University of Arizona, Tucson, AZ 85721, USA
Fax +1(520)6260794; E-mail: hongyuli@pharmacy.arizona.edu

Received 27 January 2011

Abstract: A regioselective, mild, convenient, and effective condition is developed for the inclusion of glyoxylic acid as formaldehyde equivalent in the 3CC reaction towards synthesis of 3-aminoalkyl imidazo-azines. In general, formaldehydes do not perform well with Ugi-type multicomponent sequences, and the method reported here is a regioselective and high-yielding one for the HCHO variant of Groebke–Blackburn–Bienaymé reaction.

Key words: Groebke–Blackburn–Bienaymé, multicomponent reaction, aminoimidazoazines, formaldehyde, glyoxylic acid

In 1998, a new 3CC reaction involving isocyanide, aldehyde, and aminoazine was discovered by Groebke, Bienaymé, and Blackburn for the synthesis of imidazopyridines.[1] The reaction became immensely popular and in the last decade, countless reports have appeared covering wide scope of the reaction.[2] The reaction involves nonconcerted [4+1] cycloaddition between the iminium species and the isocyanide (Scheme 1) and gives direct access to various imidazoazines such as imidazopyridines, imidazopyrimidines, and imidazodiazines.



Scheme 1 Groebke–Blackburn–Bienaymé reaction

These compounds are of profound interest due to their functions as anxiolytics, calcium channel blockers, cytoprotective, and HIF-1α-prolyl hydroxylase inhibitors.[3] Well-known anxiolytic drugs such as alpidem, zolpidem, and saripidem are examples from this class of compounds.[4] The Groebke–Blackburn–Bienaymé reaction is compatible with a wide range of aryl/alkyl aldehydes, isonitriles, solvents like MeOH, toluene,[2f,k] water,[2n] PEG,[2o] and catalysts ranging from Brønsted acids as NH_4Cl,[2f] acetic acid,[1] perchloric acid,[1] tosylic acid,[2h] PTSA/*N*-hydroxysuccinamide,[2e] montmorillonite K-10,[2a] silica sulfuric acid,[2i] in addition to Lewis acids as $Sc(OTf)_3$,[1] $MgCl_2$,[2j] $InCl_3$,[2l] $ZnCl_2$.[2m] The reaction has also been reported under solid-phase,[2b] catalyst-free,[2n] and fluorous liquid-phase conditions.[2c]

Our interest in this scaffold emanated from our continued interest[5] in developing kinase inhibitors for cancer therapeutics, and recent reports of 2-unsubstituted 3-arylazine or 3-aminoazines used as putative kinase inhibitors or enzyme modulators (Figure 1).[6] Synthesis of such 2-unsubstituted 3-amino imidazoazine through Groebke–Blackburn–Bienaymé methodology would require formaldehyde as the aldehyde component. However, Ugi-type multicomponent reactions (MCR) have limited success with formaldehyde due to formation of unstable imines, thus resulting in poor yield of the final products.[7] Production of 2-unsubstituted-3-aminoimidazoazines through any other route typically results low yields and limited diversity.[9]

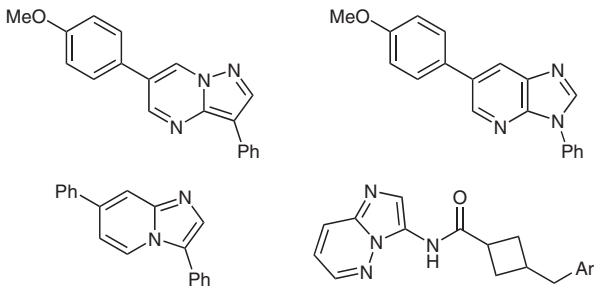


Figure 1

Alternatively, two excellent papers have utilized glyoxylic acid as a source of formaldehyde in Ugi-type MCR.[8] One of them by Kercher et al. exhibited successful application of either resin-bound or free glyoxylic acid, as a source of formaldehyde in Groebke–Blackburn–Bienaymé reaction.[8b] This protocol developed by Kercher was directly related to our intended studies and we, hence, sought to optimize the methodology and extend it to the synthesis of our target compounds. In this context, we disclose a mild and fairly general condition for the reaction of glyoxylic acid, 2-aminoazines, isocyanides, and $HClO_4$ used as catalyst to produce 2-unsubstituted imidazo[1,2-*a*]-annulated heterocycles in a single step.

SYNLETT 2011, No. 10, pp 1407–1412
Advanced online publication: 16.05.2011
DOI: 10.1055/s-0030-1260568; Art ID: S00811ST

A panel of potential formaldehyde equivalents and acid catalysts were screened in a reaction of 2-amino-5-bromopyridine (**1a**), and 1,1,3,3-tetramethylbutylisocyanide (**2a**) to form the product **3a** (Table 1). In a standard condition involving aqueous solution of formaldehyde and $Sc(OTf)_3$ as catalyst, the product was obtained in low yield (entry 1, Table 1). The side product, *N*,*N*'-bis(5-bromopyridin-2-yl)methanediamine was formed using silica gel (entry 2, Table 1).[7i] However, there was a moderate enhancement in the yield when acid catalysts were used, especially $HClO_4$ (entry 5, Table 1). Further, an attempt to replace MeOH with H_2O or toluene did not yield the desired result (entries 6 and 7, Table 1). After identification of the optimal catalyst and solvent, the goal was to find a suitable formaldehyde source. Three formaldehyde equivalents were tested (entries 8–10, Table 1) and glyoxylic acid provided a significant enhancement in the yield up to 88%. However, the yield dropped to 71% in the absence of $HClO_4$ (entry 11, Table 1) thus clearly underlying the importance of $HClO_4$ in this method. AcOH as an organocatalyst proved comparable to $HClO_4$ in terms of yield of **3a** (entry 12, Table 1).

After optimizing the conditions for this 3CC sequence, the scope and limitations of this protocol were tested with a series of aminoazines and isonitriles.[10]As delineated in Table 2, the method is high-yielding in most cases. In general, substitutions at the 4- or 5-position of the heterocyclic ring provided better yields than the unsubstituted ones. Similarly, all the isocyanides employed for this reaction demonstrated good to excellent reactivity. Unfortunately, 3-bromopyridine **1e** (entry 10, Table 2) and thiazole **1i** (entry 17, Table 2) resulted in poor yield of their respective products, and a majority of the starting material was recovered. There was no observable reaction with the use of oxazole **1j** (entry 18, Table 2). In the above three cases, poor imine formation likely resulted in low yield or failure to complete the reaction. Overall, the method worked well on the heterocyclic skeletons tested (pyridines, pyrimidines, pyrazines, and diazines) and a range of aryl/alkyl isocyanides.

It is worthwhile to mention that we did not find the regioisomeric product 2-aminoimidazoazine in any of the products,[11] which is otherwise a common occurrence to Groebke reaction, especially in polar protic solvents like MeOH.[2f,o,7,12] The regioselectivity was established

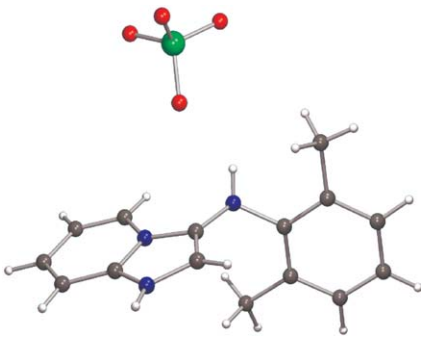
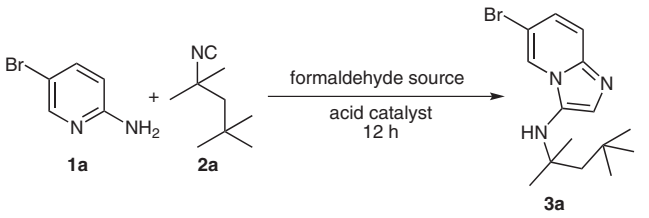


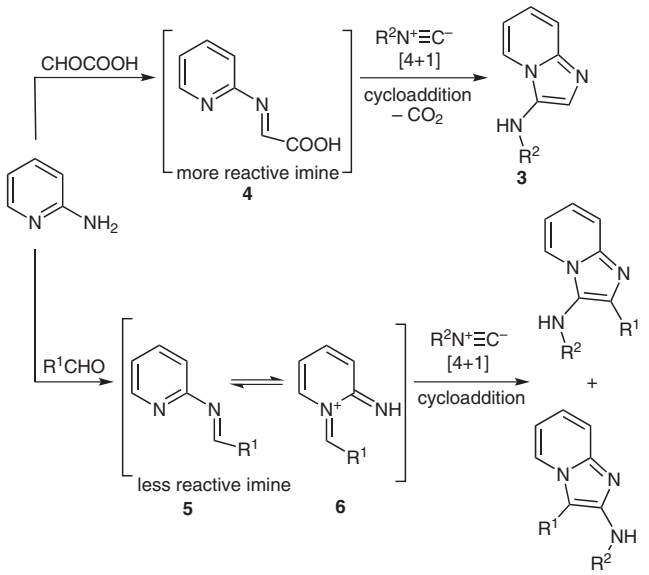
Figure 2 Compound **3b** crystallized as $[ClO_4]^-$ salt

Table 1 Optimization of a Formaldehyde-Based Groebke–Blackburn–Bienaymé Reaction[a]



Entry	Formaldehyde source	Acid catalyst	Solvent	Yield (%)[b]
1	HCHO aq (37%)	$Sc(OTf)_3$	MeOH	56
2	HCHO aq (37%)	silica gel	MeOH	0[c]
3	HCHO aq (37%)	AcOH	MeOH	67
4	HCHO aq (37%)	PTSA	MeOH	59
5	HCHO aq (37%)	$HClO_4$	MeOH	68
6	HCHO aq (37%)	$HClO_4$	H_2O	32
7	HCHO aq (37%)	$HClO_4$	toluene	38
8	paraformaldehyde	$HClO_4$	MeOH	52[d]
9	trimethyl orthoformate	$HClO_4$	MeOH	0
10	CHOCOOH aq (50%)	$HClO_4$	MeOH	88.2
11	CHOCOOH aq (50%)	–	MeOH	71
12	CHOCOOH aq (50%)	AcOH	MeOH	85

[a] Reactions were run on a 1.05 mmol scale of **1a**, 1.7 mmol of aldehyde, 10 mol% of catalyst followed by 1.05 mmol of **2a** in 1.5 mL of solvent and stirred at r.t. for 12 h.
[b] Yield after column purification.
[c] Some unresolved side product was formed.
[d] 17% of the regioisomer were isolated.



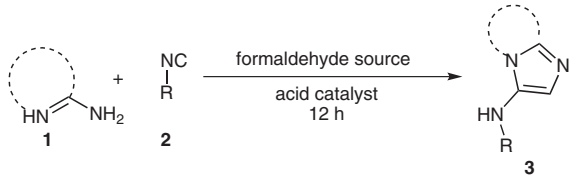
Scheme 2

through crystal structure confirmation of the product **3b** (Figure 2).[13]

It is possible that the glyoxylic acid derived imine **4** (Scheme 2) is more reactive and undergoes cycloaddition before isomerization resulting in a single regioisomer **3**. Imines derived from other aldehydes are not as reactive and may get isomerized (intermediates **5** and **6**) resulting in a mixture of regioisomers (Scheme 2).

We did not observe the cycloaddition product without decarboxylation and assume that removal of CO_2 from the intermediate **1** was concurrent during cycloaddition.

Table 2 Scope and Limitations of the Formaldehyde-Based Groebke–Blackburn–Bienaymé Reaction[a]



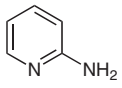
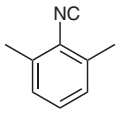
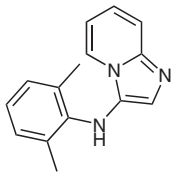
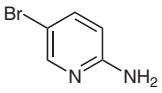
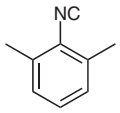
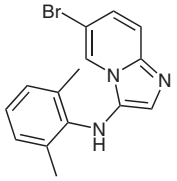
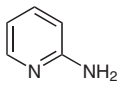
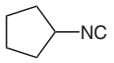
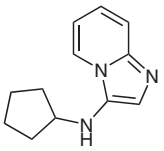
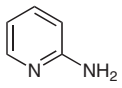
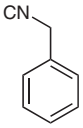
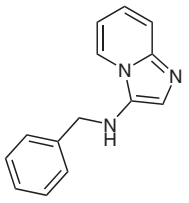
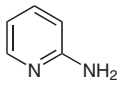
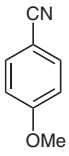
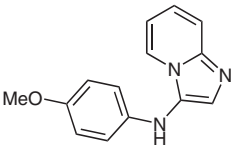
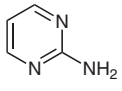
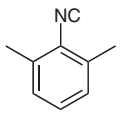
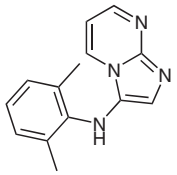
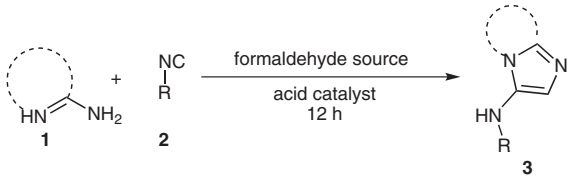
Entry	Aminoazine	Isonitrile	Product	Yield (%)[b]
1	 **1b**	 **2b**	 **3b**	77
2	 **1a**	 **2b**	 **3c**	85
3	 **1b**	 **2c**	 **3d**	61
4	 **1b**	 **2d**	 **3e**	71
5	 **1b**	 **2e**	 **3f**	61
6	 **1c**	 **2b**	 **3g**	61

Table 2 Scope and Limitations of the Formaldehyde-Based Groebke–Blackburn–Bienaymé Reaction[a] (continued)



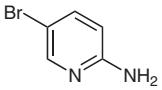
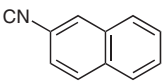
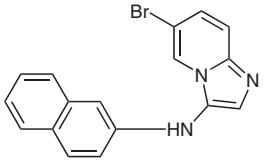
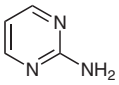
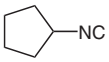
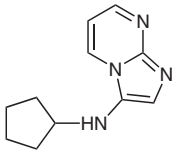
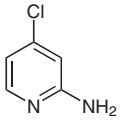
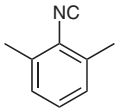
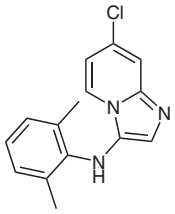
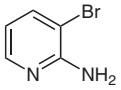
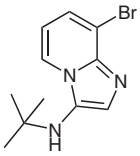
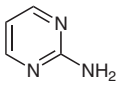
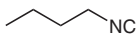
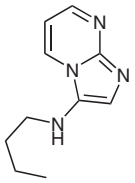
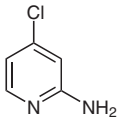
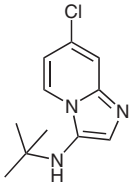
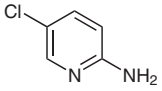
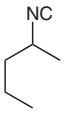
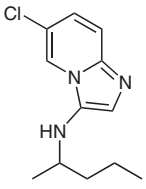
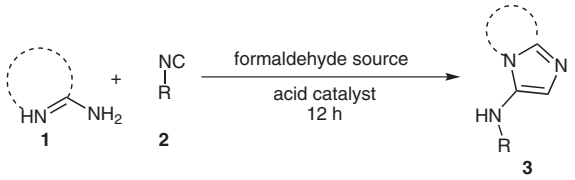
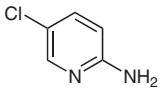
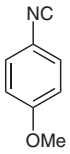
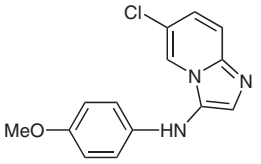
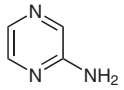
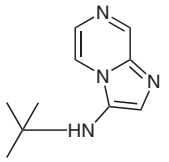
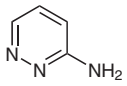
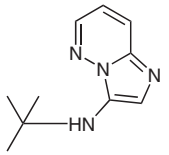
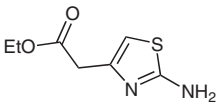
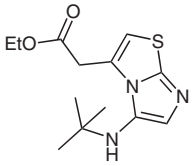
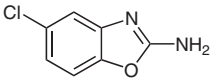
Entry	Aminoazine	Isonitrile	Product	Yield (%)[b]
7	 **1a**	 **2f**	 **3h**	71
8	 **1c**	 **2c**	 **3i**	57
9	 **1d**	 **2b**	 **3j**	66
10	 **1e**	 **2g**	 **3k**	39
11	 **1c**	 **2h**	 **3l**	80
12	 **1d**	 **2g**	 **3m**	93
13	 **1f**	 **2l**	 **3n**	92

Table 2 Scope and Limitations of the Formaldehyde-Based Groebke–Blackburn–Bienaymé Reaction[a] (continued)



Entry	Aminoazine	Isonitrile	Product	Yield (%)[b]
14	 **1f**	 **2e**	 **3o**	88
15	 **1g**	 **2g**	 **3p**	65
16	 **1h**	 **2g**	 **3q**	50[c]
17	 **1i**	 **2g**	 **3r**	29[c]
18	 **1j**	 **2g**	no product	–

[a] Reactions were run on a 1.05 mmol scale of **1** in MeOH (1.5 mL) containing 1.78 mmol of CHOCOOH, 10 mol% of $HClO_4$ followed by 1.05 mmol of **2** at r.t. for 12 h.
[b] Isolated yields.
[c] Yields based on LC-MS.

In conclusion, we have successfully demonstrated a mild, convenient, and effective method for the use of glyoxylic acid as a formaldehyde equivalent in the 3CC reaction for the synthesis of 2-aminoalkyl imidazo-azines. This regioselective methodology is superior to previous methods in terms of yield and simplicity. The main advantages of the protocol include complete regioselectivity, use of inexpensive formaldehyde source, and an inexpensive catalyst, high yields, and broad applicability. Extension of this formaldehyde inclusion methodology to other MCR sequences is presently under way.

Acknowledgment

We would like to thank the University of Arizona for funding. We also acknowledge Dr. C. Hulme for suggestions and discussions.

References and Notes

(1) (a) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661. (b) Bienaymé, H.; Bouzid, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 2234. (c) Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. *Tetrahedron Lett.* **1998**, *39*, 3635.
(2) (a) Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 7665. (b) Chen, J. J.; Golebiowski, A.; McClenaghan, J.; Klopfenstein, S. R.; West, L. *Tetrahedron Lett.* **2001**, *42*, 2269. (c) Lu, Y.; Zhang, W. *QSAR Comb. Sci.* **2004**, *23*, 827. (d) Gudmundsson, K. S.; Masquelin, T.; Perun, T.; Hulme, C. *Tetrahedron Lett.* **2005**, *46*, 8355. (e) Mironov, M. A.; Tokareva, M. I.; Ivantsova, M. N.; Mokruskin, V. S. *Russ. Chem. Bull. Int. Ed.* **2006**, *55*, 1835. (f) Parchinsky, V. Z.; Schuvalova, O.; Ushalova, O.; Krachenko, D. V.; Krasavin, M. *Tetrahedron Lett.* **2006**, *47*, 947. (g) Masquelin, T.; Baui, H.; Brickley, B.; Stephenson, G.; Schwerkoske, J.; Hulme, C. *Tetrahedron Lett.* **2006**, *47*,

2989. (h) Che, C.; Xiang, J.; Wang, G.-X.; Fathi, R.; Quan, J.-M.; Yang, Z. *J. Comb. Chem.* **2007**, *9*, 982. (i) Shaabani, A.; Soleeimani, E.; Maleki, A. *Monatsh. Chem.* **2007**, *138*, 73. (j) DiMauro, E. F.; Kennedy, J. M. *J. Org. Chem.* **2007**, *72*, 1013. (k) Nenadjenko, V. G.; Reznichenko, A. L.; Balenkova, E. S. *Russ. Chem. Bull. Int. Ed.* **2007**, *56*, 560. (l) Umkehrer, M.; Ross, G.; Jager, N.; Burdack, C.; Kolb, J.; Hu, H.; Alvim-Gaston, M.; Hulme, C. *Tetrahedron Lett.* **2007**, *48*, 2213. (m) Rousseau, A. L.; Matlaba, P.; Parkinson, C. J. *Tetrahedron Lett.* **2007**, *48*, 4079. (n) Adib, M.; Madhavi, M.; Noghani, M. A.; Mirzaei, P. *Tetrahedron Lett.* **2007**, *48*, 7263. (o) Guchhait, S. K.; Madaan, C. *Synlett* **2009**, 628.

(3) (a) Sablayrolles, C.; Cros, G. H.; Milhavet, J. C.; Rechenq, E.; Chapat, J.-P.; Boucard, M.; Serrano, J. J.; McNeill, J. H. *J. Med. Chem.* **1984**, *27*, 206. (b) Kaminski, J. J.; Bristol, J. A.; Puchalski, C.; Lovey, R. G.; Elliott, A. J.; Guzik, H.; Solomon, D. M.; Conn, D. J.; Domalski, M. S.; Wong, S. C.; Gold, E. H.; Long, J. F.; Chiu, P. J. S.; Steinberg, M.; Mc Phail, A. T. *J. Med. Chem.* **1985**, *28*, 876. (c) Clements-Jewery, S.; Danswan, G.; Gardner, C. R.; Matharu, S. S.; Murdoch, R.; Tully, W. R.; Westwood, R. *J. Med. Chem.* **1988**, *31*, 1220. (d) Kaminski, J. J.; Wallmark, B.; Briving, C.; Andersson, B.-M. *J. Med. Chem.* **1991**, *34*, 533. (e) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170. (f) Meurer, L.; Tolman, R. L.; Chapin, E. W.; Saperstein, R.; Vicario, P. P.; Zrada, M.; MacCoss, M. M. *J. Med. Chem.* **1992**, *35*, 3845. (g) Lober, S.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 97. (h) Lhassani, M.; Chavignon, O.; Chezal, J.-M.; Teulade, J.-C.; Chapat, J.-P.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clerque, E.; Gueiffier, A. *Eur. J. Med. Chem.* **1999**, 271. (i) Hamdouchi, C.; de Blas, J.; del Prado, M.; Gruber, J.; Heinz, B. A.; Vance, L. *J. Med. Chem.* **1999**, *42*, 50. (j) Trapini, G.; Franco, M.; Latrofa, A.; Ricciardi, L.; Carotti, A.; Serra, M.; Sanna, E.; Biggio, G.; Liso, G. *J. Med. Chem.* **1999**, *42*, 3934. (k) Warshakoon, N. C.; Wu, S.; Boyer, A.; Kawamoto, R.; Sheville, J.; Renock, S.; Xu, K.; Pokross, M.; Evdokimov, A. G.; Walter, R.; Mekel, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5598.

(4) (a) Georges, G.; Vercauteren, D. P.; Vanderveken, D. J.; Horion, R.; Evrard, G. H.; Durant, F. V.; George, P.; Wick, A. E. *Eur. J. Med. Chem.* **1993**, 323. (b) Jain, A. K. *J. Med. Chem.* **2004**, *47*, 947. (c) Swainston Harrison, T.; Keating, G. M. *CNS Drugs* **2005**, *19*, 65. (d) Wiegand, M. H. *Drugs* **2008**, *68*, 2411. (e) Hanson, S. M.; Morlock, E. V.; Satyshur, K. A.; Czajkowski, C. *J. Med. Chem.* **2008**, *51*, 7243. (f) Chernyak, N.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2010**, *49*, 2743.

(5) Li, H. Y.; McMillen, T.; Heap, C. R.; McCann, D. J.; Yan, L.; Campbell, R. M.; Mundla, S. R.; King, C. R.; Dierks, E. A.; Anderson, B. D.; Britt, K. S.; Huss, K. L.; Voss, M. D.; Wang, Y.; Clawson, D. K.; Yingling, J. M.; Sawyer, J. S. *J. Med. Chem.* **2008**, *51*, 2302.

(6) (a) Wu, Z.; Fraley, M. E.; Bilodeau, M. T.; Kaufman, M. L.; Tasber, E. S.; Balitza, A. E.; Hartman, G. D.; Coll, K. E.; Rickert, K.; Shipman, J.; Shi, B.; Sepp-Lerenzino, L.; Thomas, K. A. *Bioorg. Med. Chem.* **2004**, *14*, 909. (b) Breitenbucher, G. J.; Tichenor, M. S.; Merit, J. E.; Hawryluk, N. A.; Chambers, A. L.; Keith, J. M. .

(7) (a) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (b) Hulme, C.; Nixey, T. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 921. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (d) Rivera, D. G.; Pando, O.; Coll, F. *Tetrahedron* **2006**, *62*, 8327. (e) Rivera, D. G.; Wessjohann, L. A. *Molecules* **2007**, *12*, 1890. (f) Banfi, L.; Basso, A.; Cerulli, V.; Guanti, G.; Riva, R. *J. Org. Chem.* **2008**, *73*, 1608. (g) Hulme, C.; Lee, Y.-S. *Mol. Diversity* **2008**, *12*, 1. (h) Banfi, L.; Riva, R.; Basso, A. *Synlett* **2010**, 23. (i) Nichol, G. S.; Sharma, A.; Li, H.-Y. *Acta Crystallogr.* **2011**, *E67*, o833.

(8) (a) Sisko, J.; Kassik, A. J.; Mellinger, M.; Filan, J. J.; Allen, A.; Olsen, M. A. *J. Org. Chem.* **2000**, *65*, 1516. (b) Lyon, M. A.; Kercher, T. S. *Org. Lett.* **2004**, *6*, 4989.

(9) (a) Kaminski, J. J.; Hilbert, J. M.; Pramanik, B. N.; Solomon, D. M.; Conn, D. J.; Rizvi, R. K.; Elliott, A. J.; Guzik, H.; Lovey, R. G.; Domalski, M. S.; Wong, S.-C.; Puchalski, C.; Gold, E. H.; Long, J. F.; Chiu, P. J. S.; McPhailt, A. T. *J. Med. Chem.* **1987**, *30*, 2031. (b) Groziak, M. P.; Wilson, S. R.; Clauson, G. L.; Leonard, N. J. *J. Am. Chem. Soc.* **1986**, *108*, 8002. (c) Katritzky, A. R.; Xu, Y.-J.; Tu, H. *J. Org. Chem.* **2003**, *68*, 4935.

(10) **Representative Procedure for the Synthesis of *N*-(2,6-dimethylphenyl)imidazo[1,2-*a*]pyridin-3-amine (3b, Table 2)**
To a solution of 2-aminopyridine (**1b**, 1.05 mmol) in MeOH (1.5 mL), was added glyoxylic acid (1.78 mmol) followed by $HClO_4$ (0.105 mmol), and the solution was stirred for 10 min. 2-Isocyano-1,3-dimethylbenzene (1.05 mmol) was added to this mixture, and the solution was stirred for 12 h. MeOH was evaporated from the reaction mixture, and the crude was purified through silica gel chromatography to provide **3b** in 77% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.72 (d, *J* = 8 Hz, 1 H), 7.81 (d, *J* = 4 Hz, 2 H), 7.60 (s, 1 H), 7.52–7.48 (m, 1 H), 7.11 (d, *J* = 8 Hz, 2 H), 7.05–7.02 (m, 3 H), 2.09 (s, 6 H). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 138.5, 136.4, 135.8, 133.4, 132.0, 131.7, 129.3, 128.0, 125.8, 125.3, 116.6, 112.9, 106.3, 18.1. HRMS: *m/z* calcd for $C_{15}H_{16}N_3$: 238.13387; found: 238.13377. LC-MS (ES): 98.6% (λ = 214 nm).

(11) Formation of regioisomer was observed during optimization studies using paraformaldehyde as formaldehyde source (entry 8, Table 1).

(12) Mandair, G. S.; Light, M.; Russell, A.; Hursthouse, M.; Bradley, M. *Tetrahedron Lett.* **2002**, *43*, 4267.

(13) Nichol, G. S.; Sharma, A.; Li, H. Y. *unpublished results*.