JOC*Note*

Rapid Synthesis of 3-Amino-imidazopyridines by a Microwave-Assisted Four-Component Coupling in One Pot

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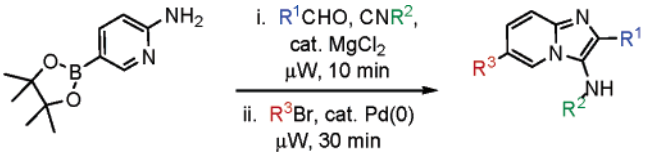
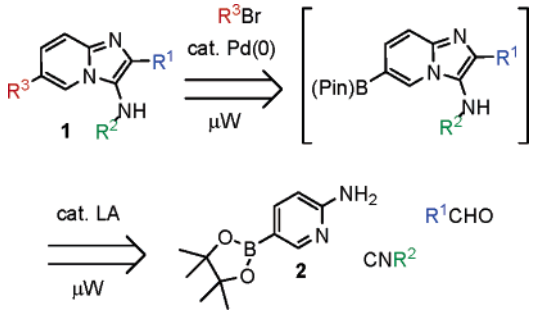


The rapid and efficient synthesis of various 2,6-disubstituted-3-amino-imidazopyridines using a microwave-assisted one-pot cyclization/Suzuki coupling approach is described. The utility of a 2-aminopyridine-5-boronic acid pinacol ester as a robust and versatile building block for the synthesis of diverse compound libraries is emphasized. The boronate functional group is remarkably tolerant to the Lewis acid catalyzed cyclizations, and the subsequent Pd(0)-catalyzed Suzuki coupling reactions proceed cleanly in the presence of magnesium salts. This work highlights the vast potential of microwave-assisted, metal-catalyzed, multicomponent reactions.

The substituted 5,6-fused heterocyclic core is prevalent in many synthetic and naturally occurring medicinal substances.[1] Efforts in our laboratory are focused on extending the scope and applications of microwave-assisted methods[2] for the rapid preparation of these ring systems from readily available, functionalized boronic esters.[3] The imidazo[1,2-*a*]pyridine framework is common to several diverse classes of compounds with medicinal value.[4] Accordingly, we set out to develop a convenient synthesis of 2,3,6-trisubstituted imidazo[1,2-*a*]pyridines (**1**) from commercially available 2-aminopyridine-5-boronic acid pinacol ester (**2**)[5] via an Ugi-type cyclization, Suzuki coupling sequence (Scheme 1). We hypothesized that a one-pot, microwave-assisted approach to this metal-catalyzed multicomponent reaction (MCR) could prove useful in focused library synthesis. Herein, we present a novel, divergent, and expedient method to prepare amino-imidazopyridine libraries from a common boronic ester building block. To the best of our knowledge, this is the first example of an Ugi-type cyclization of an aminopyridine in the presence of a boronate functional group.

SCHEME 1. Retrosynthetic Analysis of Target Compounds 1



Previously, we reported a microwave-assisted, one-pot, two-step cyclization/Suzuki coupling to access 2-substituted quinazoline imidazopyridines of general structure **3** (Scheme 2).[6] The tolerance of the boronic ester functionality in **2** to the acidic conditions at elevated temperature (130 °C) during the cyclization is noteworthy. These results prompted further investigation

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(1) (a) *Comprehensive Heterocyclic Chemistry II: Fused Five- and Six-Membered Rings with Ring Junction Heteroatom*; Jones, G., Ed.; Pergamon: Oxford, UK, 1996; Vol. 8. (b) *Comprehensive Heterocyclic Chemistry II: Fused Five- and Six-Membered Rings without Ring Junction Heteroatom*; Ramsden, C. A., Ed.; Pergamon: Oxford, UK, 1996; Vol. 7.

(2) For a comprehensive review of microwave-accelerated metal catalysis, see: Olofsson, K.; Larhed, M. In *Microwave Assisted Organic Synthesis*; Tierney, J. P., Lidström, P., Eds.; CRC Press: Boca Raton, FL, 2005; pp 23−43. For a comprehensive review of microwave-assisted heterocyclic chemistry, see: Besson, T.; Braun, C. T. In *Microwave Assisted Organic Synthesis*; Tierney, J. P., Lidström, P., Eds.; CRC Press: Boca Raton, FL, 2005; pp 44−74.

(3) For recent reports of derivatization of functionalized boronic acids and esters, see: (a) Holland, R.; Spencer, J.; Deadman, J. J. *Synthesis* **2002**, 2379−2382. (b) Spencer, J.; Burd, A. P.; Goodwin, C. A.; Mérette, S. A. M.; Scully, M. F.; Adatia, T.; Deadman, J. J. *Tetrahedron* **2002**, *58*, 1551−1556. (c) Zenk, R.; Partzsch, S. *Chimica Oggi* **2003**, *21*, 70−73. (d) Tyrrell, E.; Brookes, P. *Synthesis* **2003**, *4*, 469−483. (e) McKiernan, G. J.; Hartley, R. C. *Org. Lett.* **2003**, *5*, 4389−4392. (f) Bois-Choussy, M.; Cristau, P.; Zhu, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4238−4241. (g) Kaiser, M.; Siciliano, C.; Assfalg-Machleidt, I.; Groll, M.; Milbradt, A. G.; Moroder, L. *Org. Lett.* **2003**, *5*, 3435−3437. (h) Schulz, M. J.; Coats, S. J.; Hlasta, D. J. *Org. Lett.* **2004**, *6*, 3265−3268. (i) Lautens, M.; Mancuso, J. *J. Org. Chem.* **2004**, *69*, 3478−3487. (j) Moore, J. E.; York, M.; Harrity, J. P. A. *Synlett* **2005**, 860−862. (k) Moore, J. E.; Davies, M. W.; Goodenough, K. M.; Wybrow, R. A. J.; York, M.; Johnson, C. N.; Harrity, J. P. A. *Tetrahedron* **2005**, *61*, 6706−6714. (l) Zhang, H.; Vogels, C. M.; Wheaton, S. L.; Baerlocher, F. J.; Decken, A.; Westcott, S. A. *Synthesis* **2005**, 2739−2743. (m) Gravel, M.; Thompson, K. A.; Zak, M.; Berube, C.; Hall, D. G. *J. Org. Chem.* **2002**, *67*, 3−15.

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(5) Available from Aldrich or Oakwood Products, Inc. Bulk quantities available.

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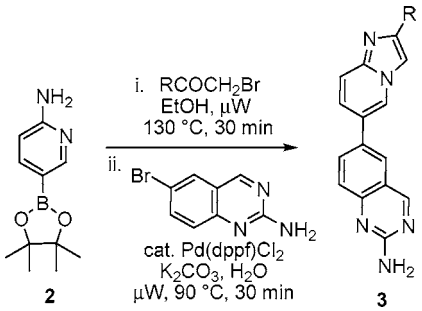
SCHEME 2. Microwave-Assisted Preparation of 2-Substituted Quinazoline Imidazopyridines 3

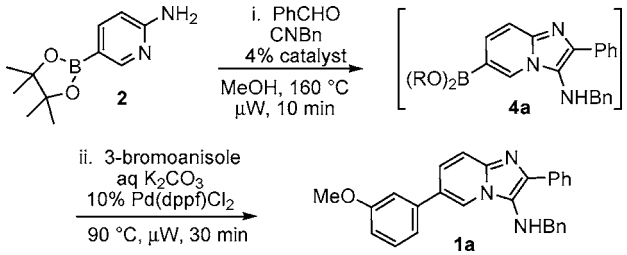


into the potential utility of **2** as a robust and versatile building block for the synthesis of diverse compound libraries.

The preparation of fused amino-imidazo[1,2-*a*]heterocycles via a Lewis or Brønsted acid catalyzed three-component Ugi-type cyclization was first reported in 1998.[7] Since then, few groups have contributed to the further development and application of this valuable methodology.[8] Varma and Kumar reported the montmorillonite K10-promoted three-component coupling (3-CC) under solvent-free conditions in a conventional microwave.[8c] Subsequently, Ireland et al. reported the microwave-assisted 3-CC using 4% $Sc(OTf)_3$ in MeOH at 160 °C for 10 min.[8d] More recently, Masquelin et al. used polymer-bound $Sc(OTf)_3$ to catalyze the microwave-mediated process, employing TMSCN as an isocyanide replacement.[8e] All three groups reported moderate to good yields over a range of substrates.

We began our investigation with a microwave-assisted, one-pot, two-step cyclization/Suzuki coupling to access amino-imidazopyridine **1a**. First, we conducted a brief Ugi−catalyst screen (Table 1), using the catalysts reported by Varma (entry 2), Ireland (entry 4), and Masquelin (entry 5), as well as other conventional Brønsted (HA) and Lewis acids (LA). Although the cyclization generally proceeded to near completion with all of the catalysts tested, the subsequent Suzuki reaction was apparently perturbed by the presence of certain HA or LA additives in the pot. We were delighted to find that the isolated yield of **1a** was highest with inexpensive LA catalysts $AlCl_3$ and $MgCl_2$ (entries 6 and 8). With both catalysts, the cyclization[9] was very clean and the two minor byproducts observed in the Suzuki reaction resulted from protodeboronation and coupling of remaining **2** to 3-bromoanisole. Interestingly, an attempt to promote the Ugi reaction with Suzuki catalyst $Pd(dppf)Cl_2$ was not successful. In fact, the cyclization was almost completely suppressed. At this time, we are unable to explain the lack of cyclization in the presence of catalytic (10%) palladium.

TABLE 1. Lewis/Brønsted Acid Catalyst Screen



entry	catalyst	cyclization (% conversion to **4a**)[d]	yield of **1a** (%)
1	none	61	32
2	montmorillonite K10[c]	67	35
3	*p*-TsOH	84	33
4	$Sc(OTf)_3$	85	62
5	PS-$Sc(OTf)_3$	80	46
6	$AlCl_3$	88	65
7	Si-$AlCl_3$	83	54
8	$MgCl_2$	80	65
9[a]	$MgCl_2$	80	60
10[b]	$Pd(dppf)Cl_2$	0	−

[a] CH_3CN was used instead of MeOH. [b] 10% catalyst was used. [c] 30 wt %. [d] % conversion determined by LCMS (ratio **4a**/**2**).

TABLE 2. Suzuki Screen (One-Pot Conversion of 2 to 1a)[a]

entry	catalyst	base	*T* (°C)[d]	*t* (min)[d]	yield of **1a** (%)
1	$Pd(dppf)Cl_2$	none	90	30	0
2	$Pd(dppf)Cl_2$	CsF	90	30	30
3	$Pd(dppf)Cl_2$	K_2CO_3[c]	90	30	65
4	$Pd(dppf)Cl_2$	K_2CO_3[c]	90	60	60
5	$Pd(dppf)Cl_2$	K_2CO_3[c]	120	30	59
6[b]	$Pd(dppf)Cl_2$	K_2CO_3[c]	90	30	54
7	$Pd(PPh_3)_2Cl_2$	K_2CO_3[c]	90	30	40
8	$Pd(PPh_3)_4$	K_2CO_3[c]	90	30	0

[a] Step 1: 1.0 equiv of **2**, 1.0 equiv of BnNC, 1.0 equiv of PhCHO, 0.04 equiv of $MgCl_2$, 160 °C, 10 min, μW. Step 2: 1.0 equiv of 3-bromoanisole, 0.10 equiv of catalyst, 2.5 equiv of base, μW. [b] 1.3 equiv of 3-bromoanisole. [c] 2.0 M aqueous solution. [d] *T* and *t* for step 2.

To examine the Suzuki reaction in more detail, we conducted a brief screen of palladium catalysts and reaction conditions (Table 2). The aqueous carbonate base proved superior to fluoride for activation of the boronate (entry 3 vs entry 2). Increasing the reaction time (entry 4) or temperature (entry 5) did not improve the yield of **1a**. Because the minor product resulting from Suzuki coupling of uncyclized **2** and 3-bromoanisole was frequently observed, we attempted the reaction using excess 3-bromoanisole (entry 6); no improvement was observed under these conditions. The use of $Pd(PPh_3)_2Cl_2$ (entry 7) or $Pd(PPh_3)_4$ (entry 8) as the catalyst led to a significant decrease in turnover and yield.

Having identified suitable conditions for cyclization and Suzuki coupling, we conducted an extensive substrate scope study (Table 3). The reaction scope is quite broad with respect to the aldehyde (R^1) and bromide (R^3) components. Electron-rich, electron-poor, aromatic, aliphatic, and sterically encumbered substrates were all well tolerated. Furthermore, to the best of our knowledge, the isolation of **1i**, **1k**, and **1o** represents the first successful inclusion of paraformaldehyde as the aldehyde component in the Ugi-type cyclization of an amino-pyridine, providing convenient access to 3,6-disubstituted imidazo[1,2-*a*]pyridines.

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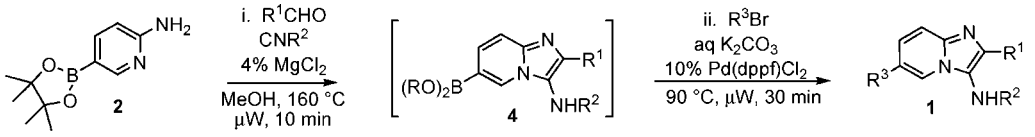
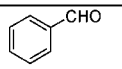
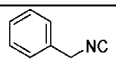
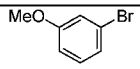
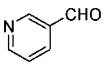
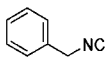
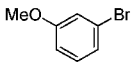
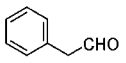
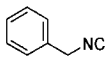
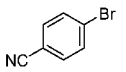
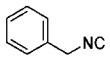
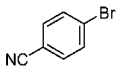
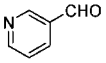
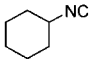
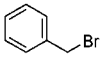
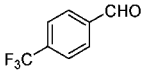
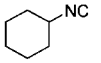
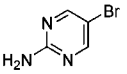
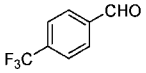
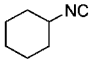
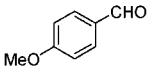
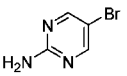
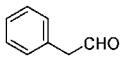
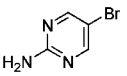
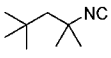
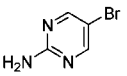
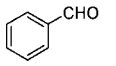
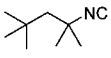
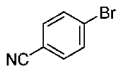
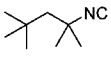
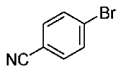
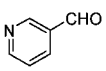
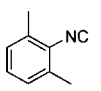
(8) (a) For, a review of isocyanide-based MCRs, see: Doemling, A. *Chem. Rev.* **2006**, *106*, 17−89. (b) For a review of Ugi MCRs, see: Tempest, P. A. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 776−788. For microwave-promoted adaptations, see: (c) Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 7665−7669. (d) Ireland, S. M.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2003**, *44*, 4369−4371. (e) Masquelin, T.; Bui, H.; Brickley, B.; Stephenson, G.; Schwerkoske, J.; Hulme, C. *Tetrahedron Lett.* **2006**, *47*, 2989−2991. (f) Lu, Y.; Zhang, W. *QSAR Comb. Sci.* **2004**, *23*, 827−835. For solid-supported adaptations, see: (g) Blackburn, C.; Guan, B. *Tetrahedron Lett.* **2000**, *41*, 1495−1500. (h) Chen, J. J.; Golebiowski, A.; McClenaghan, J.; Klopfenstein, S. R.; West, L. *Tetrahedron Lett.* **2001**, *42*, 2269−2271. (i) Lyon, M. A.; Kercher, T. S. *Org. Lett.* **2004**, *6*, 4989−4992.

(9) Extending the reaction time for the cyclization to 20 min did not improve the conversion to **4a**.

TABLE 3. Substrate Scope

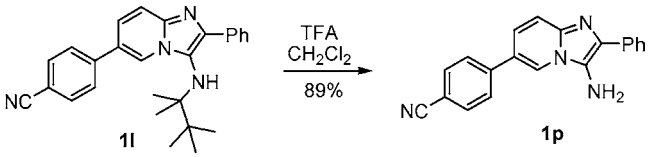


entry	1	R^1CHO	R^2NC	R^3Br	cyclization (% conv. to **4**)[d]	yield **1** (%)
1	**1a**[a]				74	58
2	**1b**				67	54
3	**1c**				72	61
4	**1d**				66	52
5	**1e**[b]				78	46
6	**1f**				72	44
7	**1g**				89	55
8	**1h**				71	44
9	**1i**[c]	HCHO			77	58
10	**1j**				69	68
11	**1k**[c]	HCHO			78	65
12	**1l**				88	42
13	**1m**				56	57
14	**1n**				72	0
15	**1o**[c]	HCHO			64	60

[a] Average of three reactions. [b] Average of two reactions. [c] Paraformaldehyde; cyclization $t = 20$ min. [d] % conversion determined by LCMS (ratio **4**/**2**).

The one-pot, two-step process is quite general for alkyl isocyanides, and moderate yields are consistently obtained (**1a**−**m**). Importantly, the reaction proceeds well with 1,1,3,3-tetramethylbutylisocyanide, which has previously been demonstrated to be a surrogate for the cyanide anion because the tetramethylbutylamine products, such as **1k**−**m**, can be readily

SCHEME 3. Example of Facile Deprotection of Tetramethylbutylamine Products: Preparation of 1p



converted to the primary amines upon treatment with TFA.[8g] For example, **1l** was converted to the corresponding primary amine (**1p**, R^2 = H) in 89% yield, using 1:1 CH_2Cl_2/TFA (Scheme 3).

Although the Ugi cyclization with 2,6-dimethylphenylisocyanide and nicotinaldehyde proceeded relatively cleanly, the boronate intermediate failed to couple with a variety of aryl bromides under the usual Suzuki conditions (entry 14).[10] We reasoned that the bulky 2,6-dimethylphenyl group at R^2 was conformationally biased by proximity to the pyridine at R^1 and therefore posed a steric hindrance to the Suzuki reaction. With paraformaldehyde as the aldehyde component, 2,6-dimethylphenylisocyanide underwent clean Ugi-type cyclization and subsequent Suzuki coupling to afford **1o** in 60% yield (entry 15).

Attempts to perform the 4-CC in one step were not successful. Reaction of **2**, benzaldehyde, benzylisocyanide, and 3-bromoanisole in the presence of aq K_2CO_3, 10% Pd(dppf)Cl_2, and 4% $MgCl_2$ (160 °C, 30 min, μW) resulted in the formation of multiple products. The alternative one-pot, sequential reaction sequence (i.e., Suzuki then cyclization) was not feasible. Although the Suzuki reaction was very clean and proceeded to completion, no cyclized product was observed after subjecting the crude 5-(3-methoxyphenyl)pyridin-2-amine to the typical Ugi conditions (benzaldehyde, benzylisocyanide, 4% $MgCl_2$, 30 min, μW). For these reactions, we speculate that the presence of aqueous base in the reaction pot severely retards the cyclization, presumably by inactivating the Lewis acid catalyst.

In conclusion, we have demonstrated the utility of the 2-aminopyridine-5-boronic acid pinacol ester (**2**) as a robust and versatile building block for the synthesis of a diverse aminoimidazo[1,2-*a*]pyridine library (**1**). This highly practical and operationally simple method underscores the enormous potential of microwave-assisted, metal-catalyzed, multicomponent reactions.

(10) Similarly, no Suzuki coupling is observed using 4-bromopyridine or 5-bromopyrimidin-2-amine instead of 1-bromo-3-methoxybenzene. No coupling is observed when excess base (5 equiv of K_2CO_3) is used.

Experimental Section

General Method for the Preparation of 1a−m and 1o. To a 2−5 mL microwave reaction vessel were added 2-aminopyridine-5-boronic acid pinacol ester (**2**) (200 mg, 0.91 mmol), isocyanide (0.91 mmol), aldehyde (0.91 mmol), $MgCl_2$ (3.4 mg, 0.036 mmol), and anhydrous MeOH (3.5 mL). The vessel was sealed and purged with N_2. The mixture was heated in a laboratory microwave at 160 °C for 10 min (20 min for **1l** and **1o**) then allowed to cool to room temperature. The vessel was opened, and bromide (0.91 mmol), 2.0 M K_2CO_3 (1.14 mL, 2.28 mmol), and Pd(dppf)Cl_2 (73 mg, 0.09 mmol) were added to it. The vessel was resealed and purged with N_2. The mixture was heated in the microwave for 30 min at 90 °C then allowed to cool to room temperature. The contents of the vessel were filtered through celite and washed with CH_2Cl_2. Organic solvents were evaporated, and the crude solid was purified on preparative HPLC (eluent: 0.1% TFA in aqueous solution and 0.1% TFA in acetonitrile). The product fractions were combined and washed with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. Organic solvents were evaporated to yield the title compound.

***N*-Benzyl-6-(3-methoxyphenyl)-2-phenyl-imidazo[1,2-*a*]pyridin-3-amine (1a):** 0.214 g (58.0%), brown solid; HPLC 100.0%; HRMS calcd for $[C_{27}H_{24}N_3O]^+$ 406.19139, found 406.19255; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.23 (d, J = 7.2 Hz, 2H), 7.53−7.39 (m, 5H), 7.33−7.15 (m, 8H), 6.97 (dd, J = 8.1, 2.4 Hz, 1H), 5.50 (t, J = 6.4 Hz, 1H), 4.15 (d, J = 6.3 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.8, 140.0, 139.7, 138.4, 134.5, 134.3, 130.1, 128.4, 128.2, 128.1, 127.3, 127.1, 126.9, 126.4, 124.0, 123.7, 120.3, 118.7, 116.7, 112.9, 112.0, 55.2, 51.5.

Acknowledgment. J.M.K. thanks Amgen Inc. for a summer internship.

Supporting Information Available: Experimental details for the preparation of **1p** and characterization of all new compounds including analytical data for **1a**−**m** and **1o**,**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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