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The synthesis of 3-pyrazinyl-imidazo[1,2-*a*]pyridines from a vinyl ether

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ABSTRACT

A new method has been developed for the synthesis of 3-pyrazinyl-imidazo[1,2-*a*]pyridines. 2-Chloro-6-[(*Z*)-2-ethoxyethenyl]pyrazine was treated with *N*-bromosuccinimide in dioxane–water to generate the 2-bromo-2-(6-chloropyrazin-2-yl)-1-ethoxyethanol intermediate. In a subsequent one-pot step, optional treatment with various 2-aminopyridines provided the cyclized 3-pyrazinyl-imidazo[1,2-*a*]pyridines in 31–76% yields.

Many biologically active compounds contain bicyclic heterocycles with a bridgehead nitrogen atom. Medicinal chemistry optimization required a method to prepare various 3-pyrazinyl-imidazo[1,2-*a*]pyridines as intermediates for synthesizing pharmaceutically active compounds.[1] The initial approach employed palladium-catalyzed direct arylation of imidazo[1,2-*a*]pyridines with 2,6-dichloropyrazine which gave 3-pyrazinyl-imidazo[1,2-*a*]pyridines (Scheme 1).[2]

Although this reaction was successful with imidazo[1,2-*a*]pyridine (entry 1), the direct arylation reaction gave low yields in the case of imidazo[1,2-*a*]pyridine-7-carbonitrile and 5-methylimidazo[1,2-*a*]pyridine (entries 2 and 3). Moreover, a diverse set of commercially available imidazo[1,2-*a*]pyridines is unavailable. Thus, a new method was required that would allow rapid and robust preparation of diverse 3-pyrazinyl-imidazo[1,2-*a*]pyridines.

Ethyl β-ethoxyacrylate **3** will react with *N*-bromosuccinimide (NBS) and water to form α-bromo-α-formylacetate hemiacetal **4**, which can then cyclize with thiourea to give ethyl 2-amino-1,3-thiazole-5-carboxylate **5** (Scheme 2).[3]

An analogous approach from the appropriately substituted vinyl ether was investigated to produce diverse imidazo[1,2-*a*]pyridines with the 3-position pyrazine installed. This Letter describes the synthesis of 2-chloro-6-[(*Z*)-2-ethoxyethenyl]pyrazine, the in situ generation of the hemiacetal, and subsequent cyclization with various 2-aminopyridines to give 3-pyrazinyl-imidazo[1,2-*a*]pyridines.

2-Chloro-6-[(*Z*)-2-ethoxyethenyl]pyrazine **9** was prepared from the nucleophilic *tele*-substitution on 2,3-dichlorpyrazine by the vinyl anion **7** (Scheme 3).[4] To prepare **7**, the *cis*-vinyl bromide **6** was dissolved in THF, cooled to −78 °C, and treated with *n*-BuLi. The vinyl anion was treated with 2,3-dichloropyrazine which gave only the *cis*-2,6-disubstituted pyrazine **9**.[5] The *trans*-2,6-disubstituted compound or the corresponding 2,3-disubstituted compounds were not observed in the crude reaction mixture. The regiochemistry of the reaction was confirmed by the proton NMR spectrum of compound **9**, which showed two singlets in the aromatic region and no coupling between the aromatic protons. A plausible mechanistic explanation for the nucleophilic *tele*-substitution is described by Edward McDonald.[4]

The synthesis of 3-pyrazinyl-imidazo[1,2-*a*]pyridines is shown in Scheme 4. The vinyl ether **9** was dissolved in a mixture of dioxane and water (3:1, respectively) and treated with NBS. The reaction mixture was stirred at room temperature for 10 min. Next, 2-aminopyridine **11** was added to the in situ-generated hemiacetal **10** and the reaction mixture was heated in a microwave for 10 min at 100 °C.[6] We believe that the endocyclic nitrogen of 2-aminopyridine **11** displaces the bromide of the hemiacetal **10** which generates a pyridinium ion and 1 equiv of HBr. The acid catalyzes the hydrolysis of the hemiacetal to the aldehyde and subsequent nucleophilic attack by the exocyclic nitrogen on the aldehydic carbon, followed by aromatization, to provide 3-pyrazinyl-imidazo[1,2-*a*]pyridines **12**.

The presence of **10** in the crude reaction mixture was not detected by LCMS. To confirm the formation of **10**, a separate

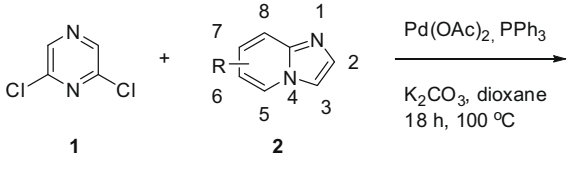
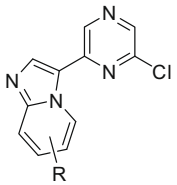


Table 1.

Entry	R	% Yield
1	H	40
2	7-CN	23
3	5-CH_3	3



Scheme 1. Palladium-catalyzed direct arylation.

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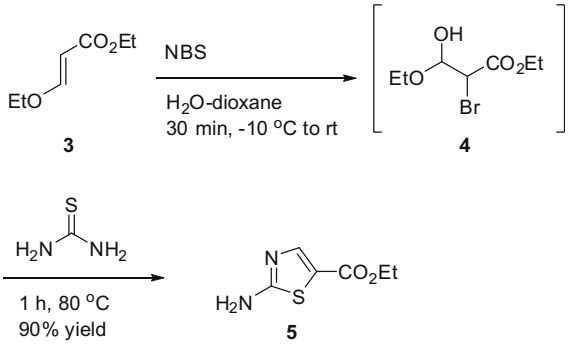
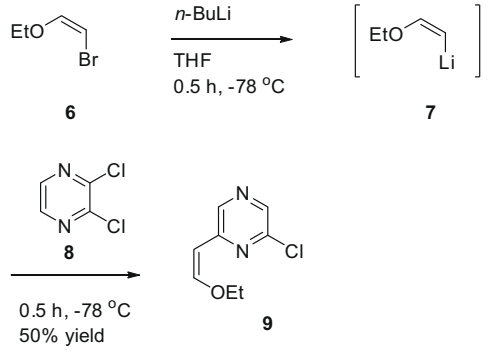


Scheme 2. Synthesis of aminothiazole.

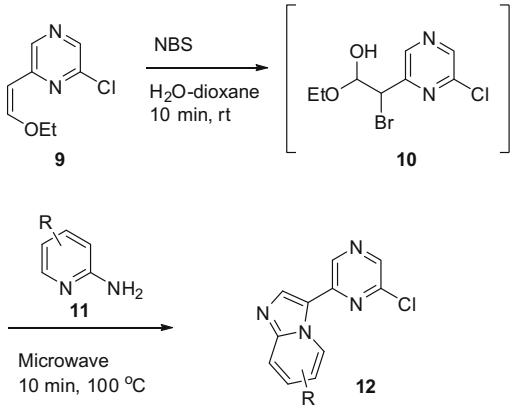


Scheme 3. *Tele* substitution.

experiment was conducted where the vinyl ether **9** was dissolved in D_2O and 1,4-dioxane-d_8 and treated with NBS. The ^1H NMR spectrum of the crude reaction mixture confirmed the clean conversion of the vinyl ether **9** to the hemiacetal **10**.[7]

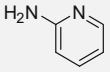
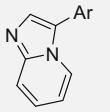
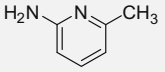
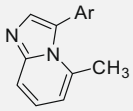
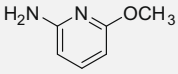
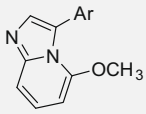
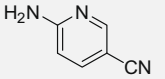
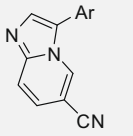
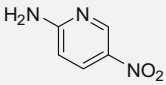
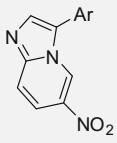
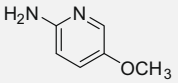
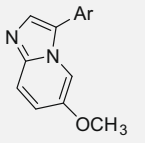
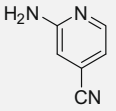
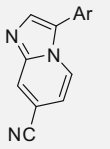
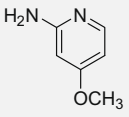
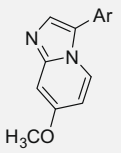
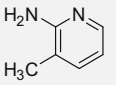
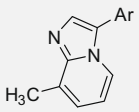
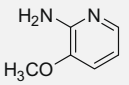
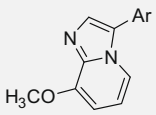
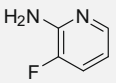
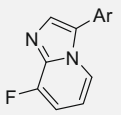
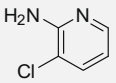
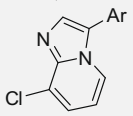
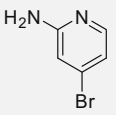
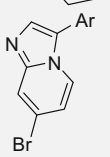
The scope of the reaction was investigated and the results are summarized in Table 2.

The cyclization of the hemiacetal **10** with 2-aminopyridine gave a 62% yield of the 3-(6-chloropyrazin-2-yl)imidazo[1,2-*a*]pyridine (entry 1 of Table 2). The ^1H NMR spectrum was identical to that of the product obtained in the direct arylation reaction (entry 1 of Table 1). The scope of this method is broad, with only moderate variation in yields observed. The presence of a methyl or methoxy group at the 6-position of the 2-aminopyridine reactant provided slightly lower yields than that of the unsubstituted 2-aminopyri-



Scheme 4. Synthesis of imidazo[1,2-*a*]pyridines.

Table 2
Cyclization of hemiacetal **10** with 2-aminopyridines **11**

Entry	2-Aminopyridine	Product	% Yield
1			62 (40)[a]
2			46 (3)[a]
3			31
4			62
5			44
6			63
7			60 (23)[a]
8			49
9			46
10			56
11			48
12			61
13			76

[a] Yield for the direct arylation method.

dine (entries 2 and 3, 46% and 31%, respectively), suggesting that steric congestion of the endocyclic nitrogen has a moderate negative impact on a key step in this cyclization reaction.

The yields for the cyclization were unaffected by the electronics of the pyridine ring as demonstrated by the similar results for electron-withdrawing or electron-donating groups at the 5 or 4 positions of the 2-aminopyridine reactant (entries 4–8 in Table 2).

The entries 9–12 in Table 2 demonstrate that substitution of 2-aminopyridine at the 3-position with a chloro, fluoro, methyl, or methoxy group gave the desired products in 46–61% yields. The synthesis of the brominated compound shown in entry 13 of Table 2 may be difficult using the palladium-catalyzed direct arylation conditions shown in Scheme 1, however, 7-bromo-3-(6-chloropyrazin-2-yl)imidazo[1,2-*a*]pyridine was readily prepared using the vinyl ether chemistry (76% yield).

Compared with the direct arylation method, the vinyl ether chemistry provided higher yields across three direct pairs as shown in entries 1, 2, and 7 of Table 2.

In conclusion, a new and robust synthesis of 3-pyrazinyl-imidazo[1,2-*a*]pyridines has been developed. This procedure provides higher yields than the palladium-catalyzed direct arylation procedure and provides access to a diverse set of 3-pyrazinyl-imidazo[1,2-*a*]pyridines from readily available 2-aminopyridines.

Acknowledgment

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References and notes

1. Ninkovic, S.; Braganza, J. F.; Collins, M. R.; Kath, J. C.; Li, H.; Richter, D. T. World Intellectual Property Organization, WO 2010/016005 A1.
2. Koubachi, J.; El Kazzouli, S.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Synlett* **2006**, 3237–3242.
3. Zhao, R.; Gove, S.; Sundeen, J. E.; Chen, B. C. *Tetrahedron Lett.* **2001**, *42*, 2101–2102.
4. Torr, J. E.; Large, J. M.; Horton, P. N.; Hursthouse, M. B.; McDonald, E. *Tetrahedron Lett.* **2006**, *47*, 31–34.
5. 2-Chloro-6-[(*Z*)-2-ethoxyethenyl]pyrazine **9**: To a solution of (*Z*)-1-bromo-2-ethoxyethene (11.6 mL, 92.6 mmol, 1.1 equiv) in THF (150 mL) at −78 °C was added *n*-BuLi (37 mL, 2.5 M in hexane, 92.6 mmol, 1.1 equiv). The mixture was stirred at −78 °C for 30 min yielding a colorless solution. A solution of 2,3-dichloropyrazine (12.8 g, 84 mmol, 1.0 equiv) in THF (50 mL) was added slowly to the vinyl anion. The resulting brown solution was stirred at −78 °C for 30 min. The reaction was quenched with water and the reaction mixture was warmed to room temperature. The mixture was diluted with EtOAc and the organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified over silica gel (flash chromatography, 15–30% ethyl acetate–heptane) affording 8.0 g of the desired product as a brown oil (50% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.01 (s, 1H), 8.44 (s, 1H), 6.91 (d, J = 7.1 Hz, 1H), 5.36 (d, J = 7.1 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 154.6, 151.7, 147.6, 142.6, 139.8, 101.9, 70.5, 15.8. LCMS (APCI) m/z 185 $(M+H)^+$.
6. (3-(6-Chloropyrazin-2-yl)imidazo[1,2-*a*]pyridine): To a solution of 2-chloro-6-[(*Z*)-2-ethoxyethenyl]pyrazine **9** (200 mg, 1.08 mmol, 1.05 equiv) in a mixture of water (2.5 mL) and dioxane (7 mL) was added NBS (183 mg, 1.05 mmol, 1.0 equiv). The heterogeneous mixture became homogeneous after several minutes. The homogeneous solution was stirred at room temperature for 10 min. 2-Aminopyridine (102 mg, 1.08 mmol, 1.05 equiv) was added and the reaction mixture was heated in a microwave for 10 min at 100 °C. The crude product was poured into 50% saturated $NaHCO_3$ (70 mL) and the aqueous layer was extracted with EtOAc (2 × 50 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified over silica gel (Biotage 25S cartridge, 0–10% methanol–ethyl acetate) furnishing 154 mg of the desired product as a beige solid (62% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.57 (d, J = 6.8 Hz, 1H), 9.32 (s, 1H), 8.69 (s, 1H), 8.57 (s, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.24 (t, J = 6.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 147.7, 146.5, 145.7, 140.3, 139.2, 137.8, 127.2, 127.1, 119.1, 117.5, 114.3. LCMS (APCI) m/z 231 $(M+H)^+$.
7. 2-Bromo-2-(6-chloropyrazin-2-yl)-1-ethoxyethanol **10**: ^{1}H NMR (400 MHz, dioxane-d_8—D_2O) δ ppm 8.52 (s, 1H), 8.44 (s, 1H), 5.03 (d, J = 6.6 Hz, 1H), 4.84 (d, J = 6.6 Hz, 1H), 3.54–3.59 (m, 1H), 3.27–3.33 (m, 1H), 0.85 (t, J = 7.1 Hz, 3H).