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Metal Free Formation of Various 3-Iodo-1*H*-pyrrolo[3′,2′:4,5]imidazo-[1,2-*a*]pyridines and [1,2-*b*]Pyridazines and Their Further Functionalization

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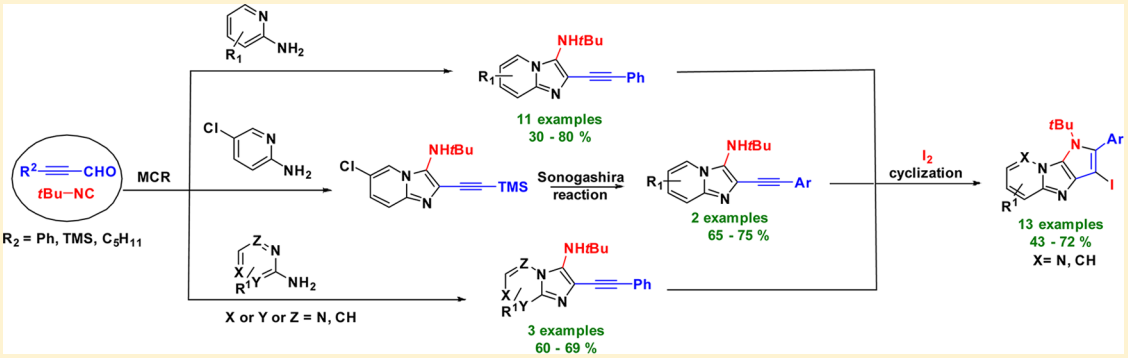
Supporting Information



ABSTRACT: 3-iodo-1*H*-pyrrolo[3′,2′:4,5]imidazo-[1,2-*a*]pyridines and [1,2-*b*]pyridazines were prepared following Groebke−Blackburn−Bienaymé MCR combined with I_2-promoted electrophilic cyclization. The flexibility of the method enables the introduction of diversity in the 2, 5, 6, and 7 positions on the resulting scaffold using commercially available starting materials. Furthermore, subsequent palladium-catalyzed reactions were successfully achieved using our iodinated derivatives.

INTRODUCTION

Because of their presence in biologically active natural products and pharmaceuticals, polycyclic scaffolds containing nitrogen arouse interest among industrial and academic communities. In this context, diversity-oriented synthesis (DOS) has emerged to efficiently create structurally diverse libraries of small molecules.[1] For many years, multicomponent reaction (MCR) was a method of choice to access relatively complex heterocyclic molecules in atom-economical ways by generating multiple bonds in a single step process.[2] To introduce further diversity, MCR and more particularly isocyanide-based multicomponent reaction (IMCR) are now associated with secondary transformations such as cyclization and functionalization, coupled with their great functional group tolerance.[3] Combining MCRs with post-modifications is therefore an efficient DOS strategy since it provides easy access to miscellaneous polyheterocyclic compounds in a small number of steps.

To orient the synthesis, the skeletons found in natural products and druglike molecules are usually good starting points.[4] Imidazo[1,2-*a*]pyridine is found in several commercialized drugs such as the sedative Zolpidem, the anxiolytics Alpidem, Saridipem, or Necopidem, the heart failure drug Olprinone, or the antiulcer drug Zolimidine (Figure 1).

Furthermore, imidazo[1,2-*a*]pyridines are known to exhibit a broad range of biological activities.[5] On the basis of our background in the synthesis and functionalization of imidazo[1,2-*a*]pyridines,[6] we investigated the formation of tri or tetracyclic fused imidazo[1,2-*a*]pyridines.[7] Apart from condensation or metal catalyzed amination, electrophilic cyclization on alkyne was recently investigated as a secondary transformation. Lately, Meng and Shen reported a Groebke−Blackburn−Bienaymé MCR[8] to synthesize unsaturated imidazo[1,2-*a*]pyridines **1** and **2** with 6-alkynyl-2-aminopyridines and 2-alkynylbenzaldehydes, respectively (Scheme 1).[9] Then, activation of the triple bond with a silver catalyst allowed intramolecular cyclization to obtain tri- and tetracyclic products.[9] We focused our effort on the use of linear propargylic aldehyde in the Groebke−Blackburn−Bienaymé MCR. Using this method, the formation of diverse 2-(alkynyl)imidazo[1,2-*a*]pyridine-3-arylamines **3** has been previously described, along with their cyclization under basic conditions to obtain original substituted pyrido[2′,1′:2,3]-imidazo[4,5-*b*]quinolones **4**.[10] We report herein the formation of 2-(alkynyl)imidazo[1,2-*a*]pyridin-3-alkylamines **5** followed by an iodine-catalyzed intramolecular cyclization. This two-step metal-free process gives access to original substituted 3-iodo-1*H*-pyrrolo[3′,2′:4,5]imidazo[1,2-*a*]-pyridines **6** from commercially available starting materials.

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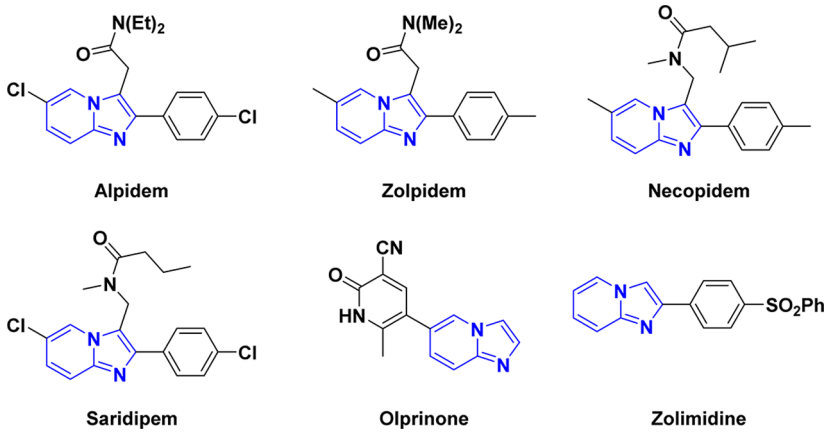
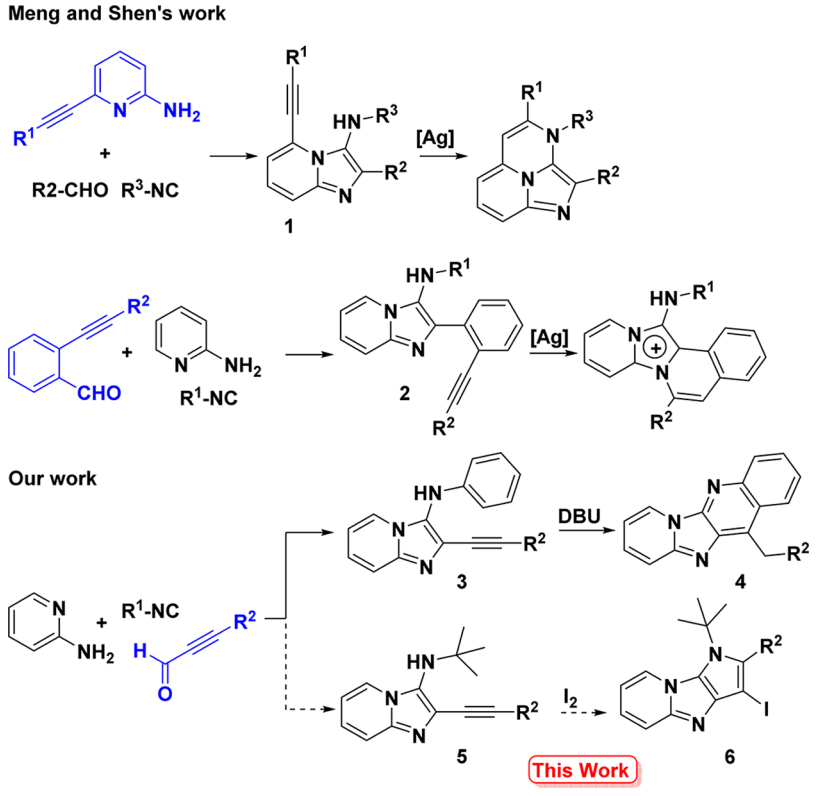
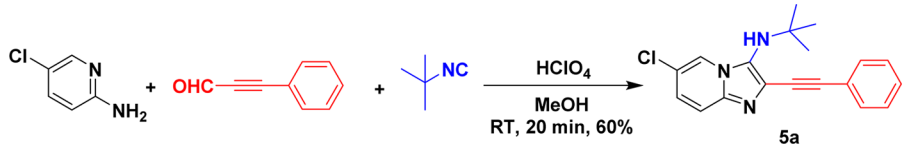


Figure 1. Therapeutic agents based on imidazo[1,2-*a*]pyridines.

Scheme 1. Formation of Tri or Tetracyclic Fused Imidazo[1,2-*a*]pyridines by Electrophilic Cyclization on Alkyne



Scheme 2. Groebke–Blackburn–Bienaymé Reaction for the Synthesis of 5a



The reactivity of the resulting halogenated products was then evaluated in palladium catalyzed reactions to examine the scope of modulation.

RESULTS AND DISCUSSION

The cyclization was optimized with **5a**, which was obtained via a Groebke–Blackburn–Bienaymé MCR. An equimolar amount of 2-amino-5-chloropyridine, 3-phenylpropiolaldehyde, and 2-isocyano-2-methylpropane in methanol with perchloric acid as catalyst gave **5a** in good yield (Scheme 2).

This MCR reaction presumably proceeds via an intermediate imine, which is attacked by an isonitrile to give the nitrilium ion, which then undergoes intramolecular cyclization affording 3-aminoimidazo[1,2-*a*]pyridine (Scheme 3).

Once **5a** had been synthesized, several cyclization conditions were tried (Table 1). Iodine was first used since it has been reported to smoothly promote electrophilic cyclization.[11]

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J. Org. Chem. 2015, 80, 6564–6573

Scheme 3

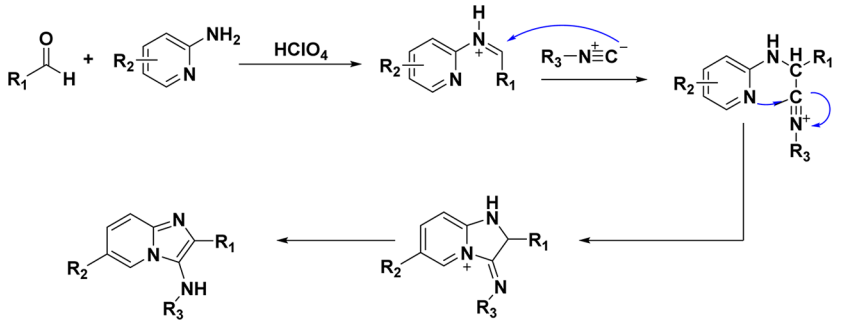
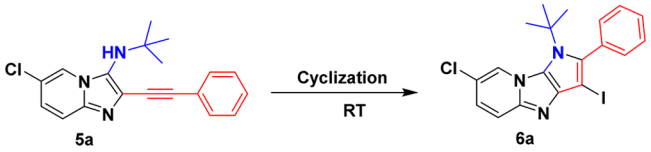


Table 1. Optimization of the Cyclization Conditions



5a 6a

entry	reagent	solvent	t	yield[a]
1	I_2 (1.5 equiv)	DCM	24 h	*b*,*c*
2	I_2 (3 equiv)	DCM	24 h	30%
3	NIS (3 equiv)	DCM	24 h	*b*
4	I_2 (6 equiv)	DCM	3 h	72%
5	I_2 (6 equiv)	DCE	3 h	49%
6	I_2 (6 equiv)	acetone/DCM	6 h	55%
7	I_2 (6 equiv)	MeCN/DCM	4 h	50%

[a]Isolated yield. [b]Complete degradation of the product. [c]Reaction repeated in the presence of K_2CO_3 (2 equiv).

However, while introducing 1.5 equiv of the reagent, a slow degradation of **5a** was observed. An addition of base produced no improvement (entry 1). It appeared that **5a** decomposed when the reaction time was prolonged. With a larger amount of iodine, the desired product was isolated with a promising 30% yield after 24 h. Surprisingly, *N*-iodosuccinimide gave only degradation (entry 3). We therefore decided to increase the amount of iodine and were pleased to observe the completion of the reaction after 3 h; **6a** was isolated in 72% yield. Different solvents were next examined but without any progress (entries 5−7). Because of the low solubility of **5a** in pure acetone and acetonitrile, additional dichloromethane was required to initiate the reaction. It was found that the optimal cyclization conditions were **5a** (1 equiv) with iodine (6 equiv) in DCM at room temperature for 3 h.

In an endeavor to expand the scope of the methodology, the reactivity of various *N*-(*tert*-butyl)-2-(phenylethylnyl)imidazo-[1,2-*a*]pyridin-3-amines was investigated (Table 2). The use of diverse 2-aminopyridines was first studied in the MCR. The expected products **5a−m** were exclusively afforded in yields ranging from 30 to 80%. Moderate steric and/or electronic effects of the substituents on the reactivity were observed for this first step. C5-substitutions seemed to have a neutral impact on the MCR (entry 3). Moderate electron donating, as well as moderate and strong electron withdrawing groups were well tolerated on C6, though sometimes requiring a longer reaction time (entries 4−8). However, a methyl group on C7 appeared to decrease the reactivity (entry 9). The substituents on C8 were the only ones to induce noticeable steric hindrance since the completion required a longer reaction time and gave **5m** in a lower yield (entry 11). Finally, a series of functional groups such as alkyl, cyano, halogen, nitroso, trifluoromethyl, and ester were compatible under these experimental conditions. Cyclization was next performed allowing the formation of **6a−m** as single products in moderate to good yields. No simple addition of the iodine to the triple bond was detected. A minor electronic effect was observed for electron withdrawing groups. Their presence induced a reduced loss of yield. However, the cyclization step appeared to be significantly sensitive to the presence of substituents on C5 since **5e** degraded slowly without a trace of the expected product. C8-substituents also tended to hinder cyclization, but the longer reaction time made it possible to isolate the desired product **6m** in 43% yield. Halide, ester, trifluoromethyle, and cyanide substituents were well tolerated under these mild conditions, which enabled further transformations. To obtain corresponding cyclized compounds **6**, the triple bond must be electron poor.

Other challenging 2-aminoheterocycles were next studied. Except for triazine, pyrimidine, pyrazine, and pyridazine scaffolds were successfully converted into the desired MCR products in good yields after 24 h (**5n−p**). Unfortunately, it was found that apart from **5n**, the other polynitrogen containing compounds did not cyclize even when the amount of iodine was increased or a cosolvent such as acetone or acetonitrile was added. Starting material along with degradation was recovered. The cyclization was found to be nevertheless widely applicable to pyridazine and pyridine scaffolds.

In addition to varying the 2-aminopyridine part, an overview of the influence of the substitution on the triple bond by using first commercially available propargyl aldehydes was considered. Oct-2-ynal and 3-(trimethylsilyl)propioaldehyde were successfully used in the MCR (**5b** and **5c**) (Table 2, entry 1). However, during the cyclization step, the optimized conditions previously found provided only starting material. Heating the reaction or increasing the reaction time favored only degradation without leading to the formation of the expected cyclized product. Our electrophilic cyclization using iodine is therefore restricted to aromatic ethynyl derivatives. In view of the lack of other easily available unsaturated aldehydes, we decided to examine the potent ability of *N*-*tert*-butyl-6-chloro-2-[2-(trimethylsilyl)-ethylnyl]imidazo[1,2-*a*]pyridin-3-amine **5c** to act as a useful precursor. Interestingly, Alagille et al. recently reported a Sonogashira reaction on pyridylethynyltrimethylsilyl derivatives.[12] Their experimental conditions were attempted on our substrate, and we were pleased to isolate **5q** and **5r** in good yield (Scheme 4). This cross-coupling reaction enabled the introduction of aryl-substituents bearing either electron withdrawing or electron donating groups. Then, the cyclization step proceeded smoothly to provide the desired products **6q** and **6r**, the only difference being that the synthesis of electron

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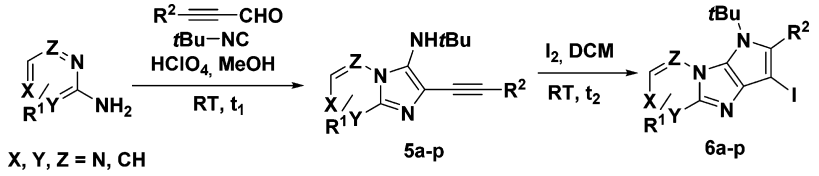
Table 2. Variation of the 2-Aminopyridines and Propargylic Aldehydes



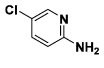
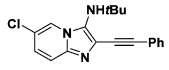
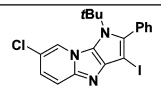
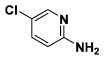
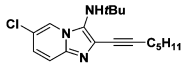
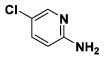
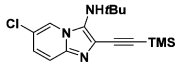
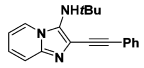
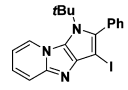
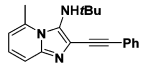
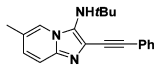
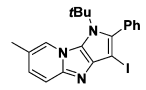
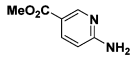
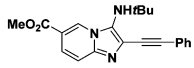
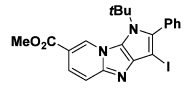
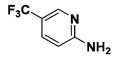
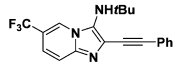
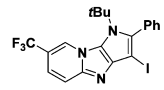
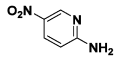
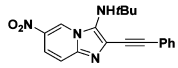
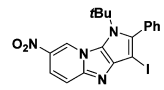
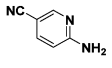
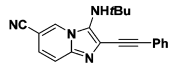
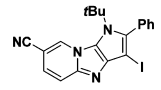
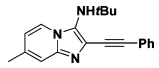
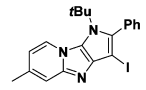
Entry	Amine	t_1(h)	Products 5[a]		Yields (%)	t_2(h)	Products 6[a]		Yields (%)
1		20 min		5a	60 %	3h		6a	72 %
2		18h		5b	63 %	24h	-		-
3		5h		5c	75 %	24h	-		-
4		4h		5d	67 %	3h		6d	68 %
5		8h		5e	60 %	24h	-		-
6		6h		5f	58 %	3h		6f	70 %
7		24h		5g	75 %	4h		6g	60 %
8		6h		5h	80 %	3h		6h	56 %
9		4h		5i	56 %	3h		6i	50 %
10		4h		5j	70 %	3h		6j	52 %
11		4h		5k	40 %	3h		6k	62 %

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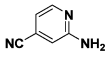
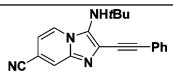
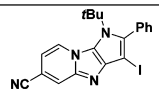
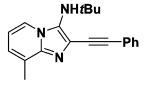
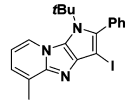
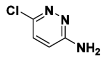
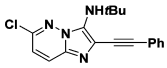
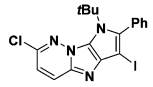
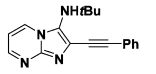
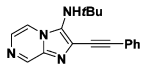
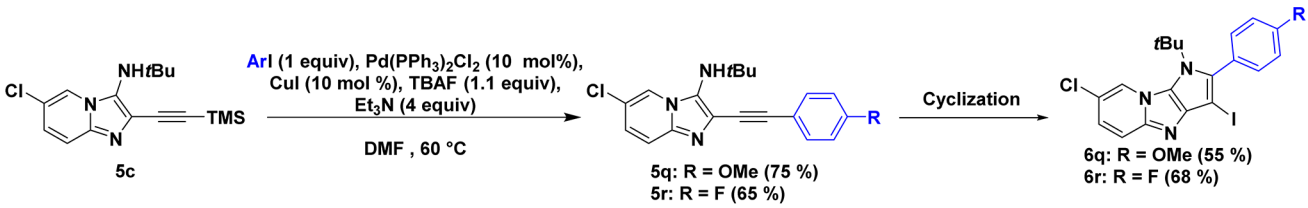
Table 2. continued

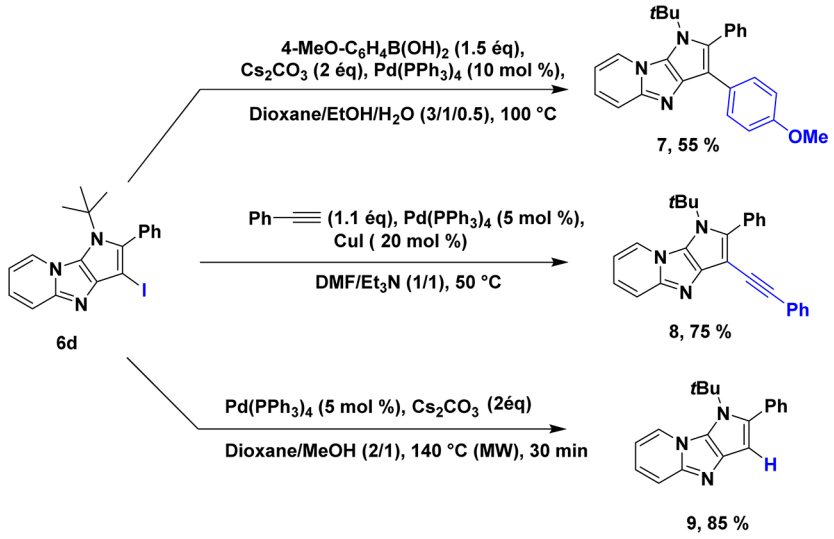
Entry	Amine	t_1(h)	Products 5[a]		Yields (%)	t_2(h)	Products 6[a]		Yields (%)
12		4h		5l	63 %	18h		6l	47 %
13		4h		5m	30 %	6h		6m	43%
14		24h		5n	69 %	26h		6n	58% [b]
15		24h		5o	65 %	24h	-		-
16		24h		5p	60 %	24h	-		-

[a]Isolated yield. [b]Yield after 26 h of reaction with 9 equiv of iodine and 8% of **5I**.

Scheme 4. Variation of the Substitution on the Triple Bond by Sonogashira Reaction



Scheme 5. Palladium-Catalyzed Reactions on 1-(*tert*-Butyl)-3-iodo-2-phenyl-1*H*-Pyrrolo[3′,2′:4,5]imidazo[1,2-*a*]pyridine 6d



withdrawing substituents required a longer reaction time (4 h vs 3 h).

Next we explored other strategies involving palladium-catalyzed coupling reactions to investigate the reactivity of our original iodinated scaffold (Scheme 5). Suzuki–Miyaura and Sonogashira reactions proceeded cleanly in good yields following known methodologies previously described.[13] Completion of the reaction was achieved by simply adjusting the temperature of the reaction to our system. Finally in the presence of a catalytic amount of $Pd(PPh_3)_4$ and Cs_2CO_3

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J. Org. Chem. 2015, 80, 6564–6573

in a mixture of dioxane/MeOH (2/1), a fast and complete dehalogenation was observed under microwave irradiation, and **9** was isolated in 85% yield.

CONCLUSIONS

In summary, we have described an efficient synthesis of the 3-iodo-1*H*-pyrrolo[3′,2′: 4,5]imidazo[1,2-*a*]pyridine and [1,2-*b*]pyridazine core by a two-step metal-free process from commercially available starting materials involving a Groebke−Blackburn−Bienaymé MCR and electrophilic cyclization. The salient features of our method are its modularity and simplicity. We were able to have diverse substituents in positions 5, 6, and 7 by simply choosing the desired 2-aminopyridine for the MCR. Next, we managed to overcome the lack of commercially available propargyl aldehydes by a straightforward Sonogashira reaction on *N-tert*-butyl-6-chloro-2-[2-(trimethylsilyl)ethylnyl]-imidazo[1,2-*a*]pyridin-3-amine **5c**. In this way, further diversities can be introduced in position 2. Finally, known palladium methodologies were successfully applied to the iodinated derivative 1-(*tert*-butyl)-3-iodo-2-phenyl-1*H*-pyrrolo[3′,2′:4,5]-imidazo[1,2-*a*]pyridine **6d**, thus widening the scope of substrates at position 3.

EXPERIMENTAL SECTION

General Comments. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation. Flash column chromatography was performed on silica gel 60 (230−400.13 mesh, 0.040 0.063 mm). Melting points (mp [°C]) were taken on samples in open capillary tubes and are uncorrected. The infrared spectra of compounds are given in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded at 250 nm (^{13}C, 62.9 MHz) or at 400 nm (^{13}C, 100.62 MHz). Chemical shifts are given in parts per million using tetramethylsilane (TMS) as internal standard. Coupling constants (J) are reported in Hertz (Hz). High-resolution mass spectra (HRMS) were performed on a quadrupole analyzer.

General Procedure for the Preparation of 5a−p. Aldehyde (1.63 mmol, 1.05 equiv) and perchloric acid (1 M solution in methanol, 0.07 mmol, 0.05 equiv) were added to a solution of amine (1.55 mmol, 1 equiv), followed by *tert*-butylisonitrile (1.63 mmol, 1.05 equiv). The reaction mixture was stirred for the required time at room temperature. The product was recovered by filtration or purified by flash chromatography on silica gel.

*N-(tert-Butyl)-6-chloro-2-(phenylethynyl)imidazo[1,2-a]pyridin-3-amine (**5a**).* The general procedure with 5-chloroaminopyridine (200 mg, 1.55 mmol) was followed, and the crude product was washed with ethanol to provide 301 mg (60%) of **5a** as a yellow solid. mp 179−180 °C; NMR ^1H ($CDCl_3$, 250.13 MHz) δ 1.30 (s, 9H), 3.11 (s, 1H), 7.10 (dd, J = 9.6, 2.1 Hz, 1H), 7.31−7.39 (m, 3H), 7.41 (d, J = 9.5 Hz, 1H), 7.48−7.58 (m, 2H), 8.18−8.20 (m, 1H); NMR ^{13}C ($CDCl_3$, 62.9 MHz) δ 30.4 (3C), 56.9, 83.3, 93.6, 117.7, 120.8, 121.2, 122.9, 124.5, 126.5, 128.5 (2C), 128.6, 131.0, 131.5 (2C), 140.33. IR (neat): 755, 1222, 1485, 1545, 2974, 3211. HRMS (ESI): (m/z) calcd for $C_{19}H_{19}ClN_3$ $[M + H]^+$ 324.1266; found, 324.1262.

*N-(tert-Butyl)-6-chloro-2-(hept-1-yn-1-yl)imidazo[1,2-a]pyridin-3-amine (**5b**).* The general procedure with 2-amino-5-chloropyridine (200 mg, 1.55 mmol) and 2-octynal (231 μL, 1.62 mmol) was followed, and the crude product was purified by flash chromatography on silica gel (2:8 ethyl acetate/petroleum ether) to provide 312 mg (63%) of **5b** as a brick-red oil. NMR ^1H ($CDCl_3$, 400.13 MHz) δ 0.91 (t, J = 7.2 Hz, 3H), 1.24 (s, 9H), 1.28−1.40 (m, 2H), 1.38−1.53 (m, 2H), 1.58−1.66 (m, 2H), 2.46 (t, J = 7.1 Hz, 2H), 2.97 (s, 1H), 7.07 (dd, J = 9.5, 2.1 Hz, 1H), 7.36 (dd, J = 9.5, 0.9 Hz, 1H), 8.15 (dd, J = 2.1, 0.9 Hz, 1H); NMR ^{13}C ($CDCl_3$, 101 MHz) δ 14.1, 19.7, 22.4, 28.4, 30.4 (3C), 31.3, 57.0, 74.5, 95.0, 117.8, 120.4, 121.3, 125.6, 125.8, 140.2, 130.2. IR (neat): 793, 849, 1081, 1321, 1548, 2964, 3206. HRMS (ESI): (m/z) calcd for $C_{18}H_{25}ClN_3$ $[M + H]^+$ 318.1732; found, 318.1733.

*N-(tert-Butyl)-6-chloro-2-((trimethylsilyl)ethynyl)imidazo[1,2-a]-pyridin-3-amine (**5c**).* The general procedure with 2-amino-5-chloropyridine (200 mg, 1.55 mmol) and 3-(trimethylsilyl)-2-propynal (239 μL, 1.62 mmol) was followed, and the crude product was purified by flash chromatography on silica gel (3:7 ethyl acetate/petroleum ether) to provide 371 mg (75%) of **5c** as a yellow solid. mp: 126−127 °C; NMR ^1H ($CDCl_3$, 400.13 MHz) δ 0.23 (s, 9H), 1.22 (s, 9H), 3.00 (s, 1H), 7.06 (d, J = 9.4 Hz, 1H), 7.33 (d, J = 9.5 Hz, 1H), 8.12 (s, 1H); NMR ^{13}C ($CDCl_3$, 101 MHz) δ −0.1 (3C), 30.4 (3C), 57.2, 98.7, 99.3, 118.0, 120.7, 121.3, 124.7, 126.3, 131.5, 140.2. IR (neat): 759, 837, 1216, 1320, 1546, 2166, 2964, 3205. HRMS (ESI): (m/z) calcd for $C_{16}H_{23}ClN_3Si$ $[M + H]^+$ 320.1344; found, 320.1346.

*N-(tert-Butyl)-2-(phenylethynyl)imidazo[1,2-a]pyridin-3-amine (**5d**).* The general procedure with 2-aminopyridine (146 mg, 1.55 mmol) was followed, and the crude product was purified by flash chromatography on silica gel (2:8 ethyl acetate/petroleum ether) to provide 300 mg (67%) of **5d** as a brown solid. mp 167−168 °C; NMR ^1H ($CDCl_3$, 250.13 MHz) 1.30 (s, 9H), 3.08 (s, 1H), 6.78 (t, J = 6.8 Hz, 1H), 7.12−7.18 (m, 1H), 7.33−7.37 (m, 3H), 7.46 (d, J = 9.1 Hz, 1H), 7.56 (dd, J = 6.6, 3.0 Hz, 2H), 8.17 (d, J = 6.8 Hz, 1H); NMR ^{13}C ($CDCl_3$, 62,9 MHz) δ 30.5 (3C), 56.9, 84.1, 93.0, 112.0, 117.6, 123.3, 123.4, 123.8, 124.8, 128.4, 128.5 (2C), 130.8, 131.6 (2C), 142.3. IR (neat): 753, 964, 1362, 1551, 2975, 3209. HRMS (ESI): (m/z) calcd for $C_{19}H_{20}N_3$ $[M + H]^+$ 290.1652; found, 290.1655.

*N-(tert-Butyl)-5-methyl-2-(phenylethynyl)imidazo[1,2-a]pyridin-3-amine (**5e**).* The general procedure with 2-amino-6-picoline (168 mg, 1.55 mmol) was followed, and the crude product was purified by chromatography on silica gel (2:8 ethyl acetate/petroleum ether) to provide 282 mg (60%) of **5e** as a beige solid. mp 119−120 °C; NMR ^1H ($CDCl_3$, 400.13 MHz) δ 1.26 (s, 9H), 2.92 (s, 3H), 6.45 (d, J = 6.9 Hz, 1H), 7.03 (dd, J = 9.0, 6.8 Hz, 1H), 7.30−7.40 (m, 4H), 7.46−7.61 (m, 2H); NMR^{13}C ($CDCl_3$, 101 MHz) δ 20.5, 30.2 (3C), 56.7, 84.7, 92.9, 114.3, 115.8, 123.3, 125.0, 125.1, 128.2, 128.34 (2C), 131.4 (2C), 132.7, 136.7, 143.7. IR (neat): 774, 1029, 1213, 1361, 1550, 2968. HRMS (ESI): (m/z) calcd for $C_{20}H_{22}N_3$ $[M + H]^+$ 304.1808; found, 304.1812.

*N-(tert-Butyl)-6-methyl-2-(phenylethynyl)imidazo[1,2-a]pyridin-3-amine (**5f**).* The general procedure with 2-amino-5-picoline (168 mg, 1.55 mmol) was followed, and the crude product was purified by flash chromatography on silica gel (2:8 ethyl acetate/petroleum ether) to provide 272 mg (58%) of **5f** as a brown solid. mp: 163−164 °C; NMR ^1H ($CDCl_3$, 250.13 MHz) δ 1.30 (s, 9H), 2.32 (s, 3H), 3.06 (s, 1H), 6.99 (dd, J = 9.3, 1.8 Hz, 1H), 7.32−7.38 (m, 4H), 7.54 (dd, J = 6.7, 3.0 Hz, 2H), 7.93 (d, J = 2.0 Hz, 1H); NMR ^{13}C ($CDCl_3$, 62,9 MHz) δ 18.4, 30.4 (3C), 57.0, 83.3, 93.6, 117.7, 120.8, 121.3, 122.9, 124.5, 126.5, 128.5 (2C), 128.6, 131.0, 131.5 (2C), 140.3. IR (neat): 794, 1197, 1547, 2974, 3209. HRMS (ESI): (m/z) calcd for $C_{20}H_{22}N_3$ $[M + H]^+$ 304.1808; found, 304.1810.

*Methyl 3-(tert-butylamino)-2-(phenylethynyl)imidazo[1,2-a]-pyridine-6-carboxylate (**5g**).* The general procedure with methyl 6-aminopyridine-3-carboxylate (235 mg, 1.55 mmol) was followed, and the crude product was filtered and washed with ethanol to provide 403 mg (75%) of **5g** as a beige solid. mp 212−213 °C; NMR ^1H ($CDCl_3$, 250.13 MHz) δ 1.31 (s, 9H), 3.21 (s, 1H), 3.96 (s, 3H), 7.33−7.36 (m, 3H), 7.45 (d, J = 9.4 Hz,1H), 7.52−7.56 (m, 2H), 7.69 (dd, J = 9.4, 1.5 Hz, 1H), 8.91 (s, 1H); NMR ^{13}C ($CDCl_3$, 62.9 MHz) δ 30.4 (3C), 52.5, 57.0, 83.3, 93.9, 116.2, 116.7, 122.8, 124.5, 125.2, 127.7, 128.5 (2C), 128.7, 131.6 (2C), 131.7, 142.5, 165.5. IR (neat): 755, 1072, 1128, 1288, 1715, 2967, 3210. HRMS (ESI): (m/z) calcd for $C_{21}H_{22}N_3O_2$ $[M + H]^+$ 348.1707; found, 348.1709.

*N-(tert-Butyl)-2-(phenylethynyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridin-3-amine (**5h**).* The general procedure with 2-amino-5-trifluoromethylpyridine (251 mg, 1.55 mmol) was followed, and the crude product was filtered and washed with (1:9 ethyl acetate/petroleum ether) to provide 440 mg (80%) of **5h** as a light yellow solid. mp: 196−197 °C; NMR ^1H ($CDCl_3$, 250.13 MHz) δ 1.31 (s, 9H), 3.17 (s, 1H), 7.29 (d, J = 9.9 Hz, 1H), 7.35−7.37 (m, 3H), 7.56−7.60 (m, 3H), 8.54 (s, 1H); NMR^{13}C ($CDCl_3$, 101 MHz): δ 30.4

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J. Org. Chem. 2015, 80, 6564−6573

(3C), 57.2, 83.1, 94.0, 116.9 (q, C_q, J_{C-F3} = 34.1 Hz), 118.2, 120.7 (q, CH_{ar}, J_{CF3} = 2.5 Hz), 122.6 (q, CH_{ar}, J_{CF3} = 6.02 Hz), 122.8, 123.8 (q, C_q, J_{C-F3} = 271.7 Hz), 125.6, 128.5 (2C), 128.80, 131.6 (2C), 131.8, 141.8; NMR ^{19}F ($CDCl_3$, 376 MHz) δ −62.53 (s). IR (neat): 759, 896, 1117, 1486, 1645, 2970. HRMS (ESI): (m/z) calcd for $C_{20}H_{19}F_3N_3$ $[M + H]^+$ 358.1526; found, 358.1532.

*N-(tert-Butyl)-6-nitro-2-(phenylethynyl)imidazo[1,2-a]pyridin-3-amine (**5i**).* The general procedure with 2- amino-5-nitropyridine (215 mg, 1.55 mmol) was followed, and the crude product was purified by flash chromatography on silica gel (2:8 ethyl acetate/petroleum ether) to provide 290 mg (56%) of **5i** as a yellow orange solid. mp: 203−205 °C; NMR ^{1}H ($CDCl_3$, 400.13 MHz) δ 1.34 (s, 9H), 3.23 (s, 1H), 7.34−7.42 (m, 3H), 7.52 (dd, J = 9.9, 0.9 Hz, 1H), 7.54−7.60 (m, 2H), 7.92 (dd, J = 9.8, 2.3 Hz, 1H), 9.29 (dd, J = 2.3 Hz, 0.8 Hz, 1H); NMR ^{13}C ($CDCl_3$, 101 MHz) δ 30.5 (3C), 57.8, 82.7, 94.9, 117.2, 119.0, 122.5, 123.7, 127.3, 128.6 (2C), 129.1, 131.7 (2C), 132.8, 137.4, 142.0. IR (neat): 750, 889, 1123, 1312, 1364, 1493, 1635, 2961. HRMS (ESI): (m/z) calcd for $C_{19}H_{19}N_4O_2$ $[M + H]^+$ 335.1503; found, 335.1505.

*3-(tert-Butylamino)-2-(phenylethynyl)imidazo[1,2-a]pyridine-6-carbonitrile (**5j**).* The general procedure with 2-amino-5-cyanopyridine (184 mg, 1.55 mmol) was followed, and the crude product was purified by flash chromatography on silica gel (1:9 ethyl acetate/petroleum ether) to provide 341 mg (70%) of **5j** as a yellow solid. mp: 205−206 °C; NMR ^{1}H ($CDCl_3$, 250.13 MHz) δ 1.31 (s, 9H), 3.16 (s, 1H), 7.24 (d, J = 10 Hz, 1H), 7.36−7.40 (m, 3H), 7.51−7.56 (m, 3H), 8.60 (s, 1H); NMR^{13}C ($CDCl_3$, 62.9 MHz) δ 30.5 (3C), 57.3, 82.7, 94.6, 98.4, 116.9, 118.5, 122.5, 124.5, 126.3, 128.6, 129.0 (2C), 129.8, 131.5, 131.7 (2C), 141.2. IR (neat): 749, 883, 1204, 1567, 2231, 3287. HRMS (ESI): (m/z) calcd for $C_{20}H_{19}N_4$ $[M + H]^+$ 315.1604; found, 315.1609.

*N-(tert-Butyl)-7-methyl-2-(phenylethynyl)imidazo[1,2-a]pyridin-3-amine (**5k**).* The general procedure with 2- amino-4-picoline (168 mg, 1.55 mmol) was followed, and the crude product was purified by flash chromatography on silica gel (2:8 ethyl acetate/petroleum ether) to provide 188 mg (40%) of **5k** as a yellow solid. mp 173−174 °C; NMR ^{1}H ($CDCl_3$, 250.13 MHz) δ 1.29 (s, 9H), 2.38 (s, 3H), 3.05 (s, 1H), 6.61 (dd, J = 7.1, 1.5 Hz, 1H), 7.21 (s, 1H), 7.31−7.40 (m, 3H), 7.50−7.59 (m, 2H), 8.04 (d, J = 7.0 Hz, 1H); NMR ^{13} C ($CDCl_3$, 101 MHz) δ 21.4, 30.4 (3C), 56.8, 84.2, 92.8, 114.7, 115.7, 122.7, 123.1, 123.4, 128.3, 128.4 (2C), 130.4, 131.5 (2C), 135.9, 142.7. IR (neat): 755, 1200, 1226, 1361, 1596, 2972. HRMS (ESI): (m/z) calcd for $C_{20}H_{22}N_3$ $[M + H]^+$ 304.1808; found, 304.1813.

*3-(tert-Butylamino)-2-(phenylethynyl)imidazo[1,2-a]pyridine-7-carbonitrile(**5l**).* The general procedure with 2-amino-4-cyanopyridine (184 mg, 1.55 mmol) was followed, and the crude product was filtered and washed with cold ethanol to provide 306 mg (63%) of **5l** as a yellow solid. mp: 254−255 °C; NMR ^{1}H ($CDCl_3$, 250.13 MHz) δ 1.31 (s, 9H), 3.17 (s, 1H), 6.92 (dd, J = 7.2, 1.6 Hz, 1H), 7.36−7.39 (m, 3H), 7.54−7.58 (m, 2H), 7.86 (dd, J = 1.5, 1.0 Hz, 1H), 8.25 (dd, J = 7.2, 0.9 Hz, 1H); NMR ^{13}C ($CDCl_3$, 101 MHz) δ 30.5 (3C), 57.6, 82.7, 94.7, 107.4, 112.2, 117.8, 122.6, 123.7, 124.2, 127.4, 128.6 (2C), 129.1, 131.7 (2C), 132.6, 139.9. IR (neat): 755, 1200, 1346, 1538, 2228, 2968, 3218. HRMS (ESI): (m/z) calcd for $C_{20}H_{19}N_4$ $[M + H]^+$ 315.1604; found, 315.1607.

*N-(tert-Butyl)-8-methyl-2-(phenylethynyl)imidazo[1,2-a]pyridin-3-amine (**5m**).* The general procedure with 2- amino-3-picoline (156 μL, 1.55 mmol) was followed, and the crude product was purified by flash chromatography on silica gel (3:7 ethyl acetate/petroleum ether) to provide 141 mg (30%) of **5m** as a brown solid. mp 128−129 °C; NMR ^{1}H ($CDCl_3$, 250.13 MHz) δ 1.29 (s, 9H), 2.59 (s, 3H), 3.09 (s, 1H), 6.69 (t, J = 6.8 Hz, 1H), 6.94 (d, J = 6.8 Hz, 1H), 7.32−7.37 (m, 3H), 7.56 (dd, J = 6.6, 3.2 Hz, 2H), 8.04 (d, J = 6.9 Hz, 1H); NMR ^{13}C ($CDCl_3$, 101 MHz) δ 16.7, 30.5 (3C), 56.9, 84.3, 92.9, 112.0, 121.4, 123.1, 123.4, 123.6, 127.3, 128.4, 128.4 (2C), 131.3, 131.6 (2C), 142.7. IR (neat): 750, 1200, 1223, 1363, 1543, 2967. HRMS (ESI): (m/z) calcd for $C_{20}H_{22}N_3$ $[M + H]^+$ 304.1808; found, 304.1812.

*N-(tert-Butyl)-6-chloro-2-(phenylethynyl)imidazo[1,2-b]-pyridazin-3-amine (**5n**).* The general procedure with 6-chloropyridazin-3-amine (200 mg, 1.55 mmol) was followed, and the crude product was purified by flash chromatography on silica gel (2:8 ethyl acetate/petroleum ether) to provide 347 mg (69%) of **5n** as an orange-yellow solid. mp: 162−164 °C; NMR ^{1}H ($CDCl_3$, 400.13 MHz) δ 1.48 (s, 9H), 4.13 (s, 1H), 6.91 (d, J = 9.4 Hz, 1H), 7.33−7.37 (m, 3H), 7.50−7.60 (m, 2H), 7.70 (d, J = 9.3 Hz, 1H); NMR ^{13} C ($CDCl_3$, 101 MHz) δ 30.7 (3C), 55.4, 84.7, 94.2, 117.5, 118.0, 123.2, 126.5, 128.5 (2C), 128.6, 131.5 (2C), 133.3, 135.5, 147.1. IR (neat): 764, 1448, 1472, 2326, 3212. HRMS (ESI): (m/z) calcd for $C_{18}H_{18}ClN_4$ $[M + H]^+$ 325.1215; found, 325.1214.

*N-(tert-Butyl)-2-(phenylethynyl)imidazo[1,2-a]pyrimidin-3-amine (**5o**).* The general procedure with aminopydazine (147 mg, 1.55 mmol) was followed, and the crude product was purified by flash chromatography on silica gel (4:6 ethyl acetate/petroleum ether) to provide 351 mg (65%) of **5o** as a yellow solid. mp: 206−207 °C; NMR ^{1}H (acetone-d_6, 250.13 MHz): δ 1.44 (s, 9H), 5.05 (s, 1H), 7.44−7.59 (m, 3H), 7.65−7.71 (m, 2H), 7.81−7.85 (m, 1H), 9.15 (dd, J = 4.4, 1.8 Hz, 1H), 9.41 (dd, J = 6.9, 1.8 Hz, 1H); NMR ^{13}C (DMSO, 62.9 MHz): δ 29.7 (3C), 56.5, 78.4, 97.6, 112.6, 112.7, 120.7, 129.1 (2C), 130.1, 131.3 (2C), 131.4, 134.3, 141.0, 156.9. IR(neat): 753, 1053, 1114, 1528, 1636, 2229, 3317. HRMS (ESI): (m/z) calcd for $C_{18}H_{19}N_4$ $[M + H]^+$ 291.1604; found, 291.1607.

*N-(tert-Butyl)-2-(phenylethynyl)imidazo[1,2-a]pyrazin-3-amine (**5p**).* The general procedure with 2-aminopyrazine (147 mg, 1.55 mmol) was followed, and the crude product was purified by flash chromatography on silica gel (3:7 ethyl acetate/petroleum ether) to provide 270 mg (60%) of **5p** as a beige solid. mp: 145−146 °C; NMR ^{1}H ($CDCl_3$, 250.13 MHz) δ 1.31 (s, 9H), 3.15 (s, 1H), 7.35−7.42 (m, 3H), 7.54−7.60 (m, 2H), 7.86 (d, J = 4.7 Hz, 1H), 8.08 (dd, J = 4.6, 0.8 Hz, 1H), 8.94 (s, 1H); NMR ^{13}C ($CDCl_3$, 62.9 MHz) δ 30.4 (3C), 57.3, 82.8, 93.9, 116.2, 122.5, 126.3, 128.5 (2C), 128.9, 129.2, 131.6 (2C), 137.3 (2C), 143.6. IR(neat): 755, 1200, 1346, 1538, 2228, 2968, 3218. HRMS (ESI): (m/z) calcd for $C_{18}H_{19}N_4$ $[M + H]^+$ 291.1604; found, 291.1610.

General Procedure for the Preparation of 5q−r. To a solution of **5c** (1 equiv) in DMF (0,17M) was successively added Et_3N (4 equiv), aryl iodide (1 equiv), CuI (10 mol %), and *trans*-dichlorobis(triphenylphosphine)palladium (10 mol %). The resulting mixture was warmed up to 60 °C, and 1 M TBAF in THF (1.1 equiv) was added dropwise. After completion, the mixture was hydrolyzed with H_2O and extracted with AcOEt. The organic layer was washed with a saturated solution of NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography.

*N-(tert-Butyl)-6-chloro-2-((4-methoxyphenyl)ethynyl)imidazo-[1,2-a]pyridin-3-amine (**5q**).* The general procedure with **5c** (100 mg, 0.314 mmol) was followed, and the crude product was purified by flash chromatography on silica gel (2:8 ethyl acetate/petroleum ether) to provide 83 mg (75%) of **5q** as a brown solid. mp: 158−159 °C; NMR ^{1}H ($CDCl_3$, 400.13 MHz) δ 1.30 (s, 9H), 3.07 (s, 1H), 3.83 (s, 3H), 6.88 (d, J = 8.7 Hz, 2H), 7.10 (dd, J = 9.5, 2.0 Hz, 1H), 7.39 (d, J = 9.5 Hz, 1H), 7.48 (d, J = 8.3 Hz, 2H), 8.19 (d, J = 2.0 Hz, 1H); NMR ^{13}C ($CDCl_3$, 100,9 MHz) δ 30.6 (3C), 55.6, 57.2, 82.3, 93.6, 114.3 (2c), 115.3, 118.1, 120.7, 121.4, 125.4, 126.3, 130.7, 133.2 (2C), 140.6, 160.1 IR (neat): 708, 792, 833, 1036, 1243, 1323, 1507, 2971, 3209. HRMS (ESI): (m/z) calcd for $C_{20}H_{21}ClN_3O$ $[M + H]^+$ 354.1368; found, 354.1370.

*N-(tert-Butyl)-6-chloro-2-((4-fluorophenyl)ethynyl)imidazo[1,2-a]pyridin-3-amine (**5r**).* The general procedure with **5c** (100 mg, 0.314 mmol) was followed, and the crude product was purified by flash chromatography on silica gel (3:7 ethyl acetate/petroleum ether) to provide 69 mg (65%) of **5r** as brown solid. mp: 180−181 °C ; NMR ^{1}H ($CDCl_3$, 400.13 MHz) δ 1.30 (s, 9H), 3.07 (s, 1H), 7.01−7.09 (m, 2H), 7.12 (dd, J = 9.5, 1.9 Hz, 1H), 7.40 (d, J = 9.5 Hz, 1H), 7.52 (dd, J = 8.6, 5.4 Hz, 2H), 8.16 (d, J = 1.2 Hz, 1H); NMR ^{13}C ($CDCl_3$, 100,9 MHz) δ 30.5 (3C), 57.0, 83.3, 92.3, 115.9 (d, J = 22.2 Hz, 2C), 118.0, 119.2 (d, J = 3.5 Hz), 120.8, 121.3, 124.8, 126.4, 131.0, 133.52 (d, J = 8.4 Hz, 2C), 140.6, 162.8 (d, J = 250.13.1 Hz, C_q-F). NMR ^{19}F ($CDCl_3$, 376 MHz) δ −110.37. IR (neat): 837, 1053, 1153, 1197, 1321, 1505, 1546, 2987, 3213. HRMS (ESI): (m/z) calcd for $C_{19}H_{18}ClFN_3$ $[M + H]^+$ 342.1168; found, 342.1172.

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General Procedure for the Preparation of 6a−r. Under argon atmosphere, iodine (1.8 mmol) was added to a solution of **5** (0.30 mmol) in 5 mL of dichloromethane. The mixture was stirred at room temperature for the required time. Then, the reaction mixture was concentrated under reduced pressure. The residue was diluted in DCM (20 mL) and washed successively with a 10% solution of sodium hydroxide (10 mL), a saturated solution of sodium thiosulfate (10 mL), and then with water (10 mL). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether).

*1-(tert-Butyl)-7-chloro-3-iodo-2-phenyl-1H-pyrrolo[3′,2′:4,5]-imidazo[1,2-a]pyridine (**6a**).* Following the general procedure with **5a** (100 mg, 0.3 mmol), the crude product was purified by flash chromatography on silica gel (2:8 ethyl acetate/petroleum ether) to provide 96 mg (72%) of **6a** as a yellow solid. mp: 207−208 °C; NMR ^{1}H ($CDCl_3$, 250.13 MHz) δ 1.56 (s, 9H), 7.12 (dd, J = 9.7, 1.9 Hz, 1H), 7.33−7.41 (m, 2H), 7.48−7.42 (m, 3H), 7.69 (dd, J = 9.7, 0.7 Hz, 1H), 8.49 (d, J = 1.2 Hz, 1H); NMR ^{13}C ($CDCl_3$, 62.9 MHz) δ 33.0 (3C), 59.7, 118.6, 118.9, 121.4, 123.4, 127.2, 128.1 (2C), 128.8, 131.7 (2C), 136.14 (2C), 141.0, 141.4, 144.5. IR (neat): 759, 1221, 1473, 1552, 2968. HRMS (ESI): (m/z) calcd for $C_{19}H_{17}ClIN_3$ $[M + H]^+$ 450.0228; found, 450.0230.

*1-(tert-Butyl)-3-iodo-2-phenyl-1H-pyrrolo[3′,2′:4,5]imidazo[1,2-a]pyridine (**6d**).* Following the general procedure with **5d** (87 mg, 0.3 mmol), the crude product was purified by flash chromatography on silica gel (3:7 ethyl acetate/petroleum ether) to provide 85 mg (68%) of **6d** as a brown solid. mp: 187−188 °C; NMR ^{1}H ($CDCl_3$, 400.13 MHz) δ 1.57 (s, 9H), 6.81 (t, J = 7.0 Hz, 1H), 7.10−7.19 (m, 1H), 7.39 (dd, J = 7.0, 3.0 Hz, 2H), 7.41−7.46 (m, 3H), 7.44 (d, J = 9.1 Hz, 1H), 8.17 (d, J = 7.1, 1H); NMR ^{13}C ($CDCl_3$, 101 MHz) δ 32.9 (3C), 56.0, 59.4, 110.5, 118.7, 122.2, 123.7, 127.0, 127.90 (2C), 128.4, 131.7 (2C), 136.3, 139.9, 140.2, 146.1. IR (neat): 702, 1023, 1131, 1214, 1371, 1514, 3200. HRMS (ESI): (m/z) calcd for $C_{19}H_{19}IN_3$ $[M + H]^+$ 416.0618; found, 416.0621.

*1-(tert-Butyl)-3-iodo-7-methyl-2-phenyl-1H-pyrrolo[3′,2′:4,5]-imidazo[1,2-a]pyridine (**6f**).* Following the general procedure with **5f** (91 mg, 0.3 mmol), the crude product was purified by flash chromatography on silica gel (1:9 ethyl acetate/petroleum ether) to provide 90 mg (70%) of **6f** as a beige solid. mp: 164−165 °C; NMR ^{1}H ($CDCl_3$, 250.13 MHz) δ 1.56 (s, 9H), 2.42 (s, 3H), 7.01 (d, J = 9.4 Hz, 1H), 7.30−7.52 (m, 5H), 7.65 (d, J = 9.4 Hz, 1H), 8.23 (s, 1H); NMR ^{13}C ($CDCl_3$, 62.9 MHz) δ 19.0, 33.0 (3C), 56.2, 59.4, 118.2, 120.1, 121.5, 125.5, 127.2, 128.0 (2C), 128.5, 131.8 (2C), 136.5, 139.9, 140.4, 145.5. IR (neat): 712, 785, 1109, 1248, 1371, 1504, 2977. HRMS (ESI): (m/z) calcd for $C_{20}H_{21}IN_3$ $[M + H]^+$ 430.0775; found, 430.0778.

*Methyl 1-(tert-butyl)-3-iodo-2-phenyl-1H-pyrrolo[3′,2′:4,5]-imidazo[1,2-a]pyridine-7 carboxy-late (**6g**).* Following the general procedure with **5g** (104 mg, 0.3 mmol), the crude product was purified by flash chromatography on silica gel (2:8 ethyl acetate/petroleum ether) to provide 85 mg (60%) of **6g** as a yellow solid. mp: 216−217 °C; NMR ^{1}H ($CDCl_3$, 250.13 MHz) δ 1.59 (s, 9H), 3.97 (s, 3H), 7.35−7.39 (m, 2H), 7.41−7.45 (m, 3H), 7.69 (d, J = 1.1 Hz, 2H), 9.31 (s, 1H); NMR ^{13}C ($CDCl_3$, 62.9 MHz) δ 32.8 (3C), 52.6, 56.3, 59.9, 114.3, 117.5, 121.8, 126.9, 128.1, 128.1 (2C), 128.8, 131.8 (2C), 136.1, 140.8, 141.7, 146.5, 165.9. IR (neat): 701, 755, 1105, 1255, 1709, 2234. HRMS (ESI): (m/z) calcd for $C_{21}H_{21}IN_3O_2$ $[M + H]^+$ 474,0673; found, 474.0677.

*1-(tert-Butyl)-3-iodo-2-phenyl-7-(trifluoromethyl)-1H-pyrrolo-[3′,2′:4,5]imidazo[1,2-a]pyridine (**6h**).* Following the general procedure with **5h** (107 mg, 0.3 mmol), the crude product was purified by flash chromatography on silica gel (1:9 ethyl acetate/petroleum ether) to provide 79 mg (56%) of **6h** as a brown solid. mp: 182−183 °C; NMR ^{1}H ($CDCl_3$, 400.13 MHz) δ 1.58 (s, 9H), 7.30 (dd, J = 9.6, 1.3 Hz, 1H), 7.37−7.40 (m, 2H), 7.45−7.49 (m, 3H), 7.83 (d, J = 9.5 Hz, 1H), 8.84 (s, 1H). NMR ^{13}C ($CDCl_3$, 101 MHz) δ 33.0 (3C), 56.3, 59.9, 114.7 (q, C_q, J_{C-F3} = 33.3 Hz), 117.9 (q, CH_{ar}, J_{CF3} = 2.5 Hz), 119.1, 122.4 (q, CH_{ar}, J_{CF3} = 6.06 Hz), 124.0 (q, C_q, J_{C-F3} = 272.0 Hz), 127.1, 128.17 (2C), 128.9, 131.7 (2C), 135.9, 141.3, 141.8, 145.6. NMR ^{19}F ($CDCl_3$, 376 MHz) δ −61.71 (s). IR (neat): 701, 849, 1047, 1121, 1312, 1517, 2924. HRMS (ESI): (m/z) calcd for $C_{20}H_{18}F_3IN_3$ $[M + H]^+$ 484.0492; found, 484.0491.

*1-(tert-Butyl)-3-iodo-7-nitro-2-phenyl-1H-pyrrolo[3′,2′: 4,5]-imidazo[1,2-a]pyridine (**6i**).* Following the general procedure with **5i** (100 mg, 0.3 mmol), the crude product was purified by flash chromatography on silica gel (3:7 ethyl acetate/petroleum ether) to provide 69 mg (50%) of **6i** as a brown solid. mp: 192−193 °C. NMR ^{1}H ($CDCl_3$, 250.13 MHz) δ 1.62 (s, 9H), 7.37−7.43 (m, 2H), 7.46−749 (m, 3H), 7.76 (d, J = 10.1 Hz, 1H), 7.96 (dd, J = 10.1, 2.2 Hz, 1H), 9.69 (d, J = 1.8 Hz, 1H); NMR ^{13}C ($CDCl_3$, 62.9 MHz) δ 32.8 (3C), 56.6, 60.3, 116.3, 117.3, 123.8, 127.1, 128.3 (2C), 129.2, 131.7 (2C), 135.3, 135.6, 142.3, 145.8, 143.3. IR (neat): 705, 808, 1023, 1069, 1116, 1331, 1500, 1638, 2163. HRMS (ESI): (m/z) calcd for $C_{19}H_{18}IN_4O_2$ $[M + H]^+$ 461.0469; found, 461.0469.

*1-(tert-Butyl)-3-iodo-2-phenyl-1H-pyrrolo[3′,2′:4,5]imidazo[1,2-a]pyridine-7-carbonitrile (**6j**).* Following the general procedure **5j** (94 mg, 0.3 mmol), the crude product was purified by chromatography on silica gel (2:8 ethyl acetate/petroleum ether) to provide 70 mg (52%) of **6j** as a beige solid. mp: 217−218 °C; NMR ^{1}H ($CDCl_3$, 250.13 MHz) δ 1.58 (s, 9H), 7.23−7.28 (d, J = 8.8 Hz, 1H), 7.36−7.40 (m, 2H), 7.44−7.48 (m, 3H), 7.79 (d, J = 9.4 Hz, 1H), 8.89 (s, 1H); NMR ^{13} C ($CDCl_3$, 62.9 MHz) δ 32.9 (3C), 56.3, 60.1, 96.4, 117.5, 119.3, 121.7, 126.6, 128.2 (2C), 129.1, 129.4, 131.7 (2C), 135.7, 141.9, 142.2, 145.0. IR (neat): 759, 1221, 1472, 1573, 2968. HRMS (ESI): (m/z) calcd for $C_{20}H_{18}IN_4$ $[M + H]^+$ 441.0571; found, 441.0573.

*1-(tert-Butyl)-3-iodo-6-methyl-2-phenyl-1H-pyrrolo[3′,2′:4,5]-imidazo[1,2-a]pyridine (**6k**).* Following the general procedure with **5k** (91 mg, 0.3 mmol), the crude product was purified by flash chromatography on silica gel (1:9 ethyl acetate/petroleum ether) to provide 79 mg (62%) of **6k** as a greenish solid. mp: 170−171 °C. NMR ^{1}H ($CDCl_3$, 250.13 MHz) δ 1.55 (s, 9H), 2.43 (s, 3H), 6.63 (dd, J = 7.3, 1.8 Hz, 1H), 7.34−7.46 (m, 5H), 7.48 (s, 1H), 8.34 (d, J = 7.3 Hz, 1H); NMR ^{13} C ($CDCl_3$, 101 MHz) δ 21.4, 32.9 (3C), 56.1, 59.4, 113.2, 117.5, 123.1, 126.8, 128.0 (2C), 128.8, 131.9 (2C), 133.2, 136.6, 139.2, 140.2, 146.8. IR (neat): 733, 804, 1150, 1375, 1461, 2226. HRMS (ESI): (m/z) calcd for $C_{20}H_{21}IN_3$ $[M + H]^+$ 430.0779; found, 430.0775.

*1-(tert-Butyl)-3-iodo-2-phenyl-1H-pyrrolo[3′,2′:4,5]imidazo[1,2-a]pyridine-6-carbonitrile (**6l**).* Following the general procedure with **5l** (94 mg, 0.3 mmol), the crude product was purified by flash chromatography on silica gel (1:9 ethyl acetate/petroleum ether) to provide 62 mg (47%) of **6l** as a yellow solid. mp: 206−207 °C; NMR ^{1}H ($CDCl_3$, 250.13 MHz) δ 1.58 (s, 9H), 6.97 (dd, J = 7.4, 1.5 Hz, 1H), 7.36−7.38 (m, 2H), 7.46−7.48 (m, 3H), 8.13 (s, 1H), 8.53 (d, J = 7.4 Hz, 1H); NMR ^{13}C ($CDCl_3$, 62.9 MHz) δ 33.0 (3C), 56.2, 60.1, 103.9, 110.8, 118.3 (2C), 123.9, 124.5, 128.2 (2C), 129.1, 131.52 (2C), 135.7 (2C), 143.2, 143.8. IR (neat): 710, 1114, 1184, 1327, 1527, 2214. HRMS (ESI): (m/z) d for $C_{20}H_{18}IN_4$ $[M + H]^+$ 441.0571; found, 441.0573.

*1-(tert-Butyl)-3-iodo-5-methyl-2-phenyl-1H-pyrrolo[3′,2′:4,5]-imidazo[1,2-a]pyridine (**6m**).* Following the general procedure with **5m** (91 mg, 0.3 mmol), the crude product was purified by flash chromatography on silica gel (2:8 ethyl acetate/petroleum ether) to provide 54 mg (43%) of **6m** as a yellow solid. mp 135−136 °C; NMR ^{1}H ($CDCl_3$, 250.13 MHz) δ 1.56 (s, 9H), 2.73 (s, 3H), 6.72 (t, J = 6.9 Hz, 1H), 6.96 (d, J = 6.6 Hz, 1H), 7.34−7.46 (m, 5H), 8.37 (d, J = 7.3 Hz, 1H). NMR ^{13}C ($CDCl_3$, 62.9 MHz): δ 18.3, 33.0 (3C), 56.4, 59.5, 110.4, 121.4 (2C), 121.9, 128.0 (2C), 128.5, 128.6, 131.9 (2C), 136.7, 139.7, 139.9, 146.7. IR (neat): 710, 1115, 1338, 1442, 2992. HRMS (ESI): (m/z) calcd for $C_{20}H_{21}IN_3$ $[M + H]^+$ 430.0775; found, 430.0777.

*1-(tert-Butyl)-7-chloro-3-iodo-2-phenyl-1H-pyrrolo[3′,2′:4,5]-imidazo[1,2-b]pyridazine (**6n**).* Following the general procedure with **5n** (100.mg, 0.3 mmol), the crude product was purified by chromatography on silica gel (1:9 ethyl acetate/petroleum ether) to provide 85 mg (58%) of **6n** as a brown solid. mp: 194−195 °C; NMR ^{1}H ($CDCl_3$, 400.13 MHz) δ 1.62 (s, 9H), 7.02 (d, J = 9.5 Hz, 1H), 7.37−7.40 (m, 2H), 7.42−7.48 (m, 3H), 7.98 (d, J = 9.5 Hz, 1H).

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NMR ^{13}C ($CDCl_3$, 101 MHz): δ 32.3 (3C), 55.4, 61.5, 116.1, 126.7, 128.1 (2C), 128.5, 128.9, 131.7 (2C), 135.8, 138.4, 141.3, 142.4, 143.0. IR (neat): 700, 1073, 1263, 1275, 1515, 1615, 2979. HRMS (ESI): (m/z) calcd for $C_{18}H_{17}ClIN_4$ $[M + H]^+$ 451,0181; found, 451,0183.

*1-(tert-Butyl)-7-chloro-3-iodo-2-(4-methoxyphenyl)-1H-pyrrolo-[3′,2′:4,5]imidazo[1,2-a]pyridine (**6q**).* Following the general procedure with **5q** (106 mg, 0.3 mmol), the crude product was purified by flash chromatography on silica gel (1:9 ethyl acetate/petroleum ether) to provide 79 mg (55%) of **6q** as a brown solid. mp: 209−210 °C; NMR ^1H ($CDCl_3$, 400.13 MHz) δ 1.56 (s, 9H), 3.89 (s, 3H), 6.97 (d, J = 8.7 Hz, 2H), 7.11 (dd, J = 9.7, 1.9 Hz, 1H), 7.28 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 9.7 Hz, 1H), 8.48 (d, J = 1.3 Hz, 1H). NMR ^{13}C ($CDCl_3$, 100.9 MHz) δ 33.0(3C), 55.4, 56.4, 59.6, 113.5(2C), 118.5, 118.8, 121.4, 123.3, 127.0, 128.4, 132.9(2C), 141.0, 141.4, 144.5, 159.9. IR (neat): 679, 841, 1021, 1234, 1460, 1524, 1606, 2966. HRMS (ESI): (m/z) calcd for $C_{20}H_{20}ClIN_3O$ $[M + H]^+$ 480.0334; found, 480.0334.

*1-(tert-Butyl)-7-chloro-2-(4-fluorophenyl)-3-iodo-1H-pyrrolo-[3′,2′:4,5]imidazo[1,2-a]pyridine (**6r**).* Following the general procedure with **5r** (105 mg, 0.3 mmol), the crude product was purified by flash chromatography on silica gel (1:9 ethyl acetate/petroleum ether) to provide 98 mg (68%) of **6r** as a brown solid. mp: 185−186 °C. NMR ^1H ($CDCl_3$, 400.13 MHz) δ 1.56 (s, 9H), 7.06−7.18 (m, 3H), 7.35 (dd, J = 8.1, 5.5 Hz, 2H), 7.68 (d, J = 9.7 Hz, 1H), 8.49 (s,1H); NMR ^{13}C ($CDCl_3$, 101 MHz) δ 33.0(3C), 56.6, 59.7, 115.8 (d, J = 21.7 Hz, 2C), 118.6, 118.9, 121.4, 132.1 (d, J = 3.7 Hz), 127.1, 132.1,133.4 (d, J = 8.2 Hz, 2C), 139.7, 141.3, 144.6, 162.9 (d, J = 249.0 Hz, cq-F); NMR ^{19}F ($CDCl_3$, 376 MHz) δ −112.11. IR (neat): 784, 841, 1096, 1215, 1523, 1593, 2919. HRMS (ESI): (m/z) calcd for $C_{19}H_{17}ClIFN_3$ $[M + H]^+$ 468.0134; found, 468.0137.

*1-(tert-Butyl)-3-(4-methoxyphenyl)-2-phenyl-1H-pyrrolo-[3′,2′:4,5]imidazo[1,2-a]pyridine (**7**).* A mixture of **6d** (100 mg, 0.240 mmol), 4-methoxyphenylboronic acid (55 mg, 0.36 mmol), cesium carbonate (156 mg, 0.48 mmol), and $Pd(PPh_3)_4$ (27 mg, 0.024) in a mixture of dioxane/ethanol/eau (3 mL; 3/1/0.5, v/v/v) was heated under argon up to 100 °C. After 12 h, the reaction was quenched with water and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (3:7 ethyl acetate/petroleum ether) to provide 52 mg (55%) of 7 as a beige solid. mp: 162−163 °C; NMR ^1H ($CDCl_3$, 400.13 MHz) δ 1.59 (s, 9H), 3.74 (s, 3H), 6.74 (d, J = 8.6 Hz, 1H), 6.77 (dd, J = 12.9, 4.9 Hz, 2H), 7.05−7.15 (m, 1H), 7.25−7.30 (m, 1H), 7.37 (d, J = 5.8 Hz, 3H), 7.41−7.49 (m, 2H), 7.74 (d, J = 9.1 Hz, 1H), 8.50 (d, J = 7.0 Hz, 1H); NMR ^{13}C ($CDCl_3$, 100,9 MHz) δ 33.1 (3C), 55.3, 58.9, 110.2, 111.6, 113.7 (2C), 118.6, 121.5, 123.6, 127.1, 127.6, 128.2, 128.2 (2C), 129.6 (2C), 132.3 (2C), 135.9, 136.3, 138.8, 146.9, 157.3. IR (neat): 751, 832, 1028, 1240, 1296, 1240, 1506, 2987. HRMS (ESI): (m/z) calcd for $C_{26}H_{25}N_3O$ $[M + H]^+$ 396.2070, found: 396.2071.

*1-(tert-Butyl)-2-phenyl-3-(phenylethynyl)-1H-pyrrolo[3′,2′:4,5]-imidazo[1,2-a]pyridine (**8**).* In a sealed tube under inert atmosphere, to a solution of **6d** (100 mg, 0.240 mmol) in a mixture of DMF/Et_3N (2 mL; 1/1, v/v) were successively added phenyl acetylene (31 μL, 0.289 mmol), copper iodide (9 mg, 0.048 mmol), and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol). The reaction was stirred at 50 °C. After 6 h, the reaction was quenched with water and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (1:9 ethyl acetate/petroleum ether) to provide 70 mg (75%) of **8** as a beige solid. mp: 208−209 °C; NMR ^1H ($CDCl_3$, 400.13 MHz) δ 1.62 (s, 9H), 6.81 (td, J = 6.9, 1.4 Hz, 1H), 7. 09−7. Seventeen (m, 1H), 7.17−7.25 (m, 2H), 7.27−7.33 (m, 2H), 7.37−7.49 (m, 3H), 7.51−7.60 (m, 2H), 7.74 (d, J = 9.2 Hz, 1H), 8.48 (d, J = 7.0 Hz, 1H). NMR ^{13}C ($CDCl_3$, 100,9 MHz) δ: 32.9 (3C), 59.4, 83.5, 91.7, 95.7, 110.6, 118.7, 122.1, 123.5, 124.7, 127.1, 127.5, 127.8 (2C), 128.1 (2C), 128.1, 131.1 (2C), 131.2 (2C), 135.5, 138.3, 143.9, 146.9. IR (neat): 711, 734, 1090, 1187, 1303, 1598, 2202. HRMS (ESI): (m/z) calcd for $C_{27}H_{23}N_3$ $[M + H]^+$ 390.1965; found, 390.196.

*1-(tert-Butyl)-2-phenyl-1H-pyrrolo[3′,2′:4,5]imidazo[1,2-a]-pyridine (**9**).* In a sealed tube under inert atmosphere, a mixture of **6d** (100 mg, 0.240 mmol), cesium carbonate (156 mg, 0.48 mmol), and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol) in a mixture of dioxane/ethanol (3 mL, 2/1 v/v) was heated under microwave irradiation at 140 °C. After 30 min, the reaction was quenched with water and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (3:7 ethyl acetate/petroleum ether) to provide 59 mg (85%) of **9** as a beige solid. mp: 222−223 °C; NMR ^1H ($CDCl_3$, 400.13 MHz) δ 1.60(s, 9H), 6.29(s, 1H), 6.77 (t, J = 6.9 Hz, 1H), 7.09 (dd, J = 9.0, 6.8 Hz, 1H), 7.32−7.39 (m, 3H), 7.46 (dd, J = 7.7, 1.6 Hz, 2H), 7.65 (d, J = 9.2 Hz, 1H), 8.48 (d, J = 7.1 Hz, 1H); NMR ^{13}C ($CDCl_3$, 101 MHz) δ 33.1 (3C), 58.5, 100.8, 110.1, 118.4, 121.4, 123.4, 127.6 (2C), 127.9, 128.9, 130.1 (2C), 137.7, 138.5, 141.5, 146.7. IR (neat): 610, 703, 808, 1099, 1250.13, 1334, 1508, 2982.. HRMS (ESI): (m/z) calcd for $C_{19}H_{20}N_3$ $[M + H]^+$ 290.1652; found, 290.1653.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00555.

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Notes

The authors declare no competing financial interest.

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