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Switching of Regioselectivity in a Perfluorohexyl Iodide-Mediated Synthesis of Phenylimidazo[1,2-*a*]pyridines

Irwan Iskandar Roslan,[a] Gaik-Khuan Chuah,[a,*] Stephan Jaenicke [a,*]

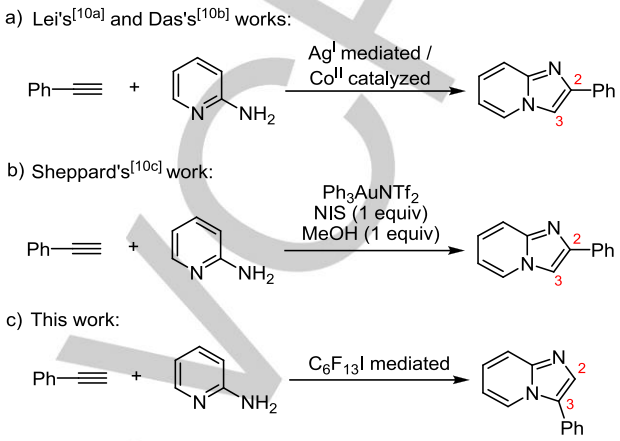
Abstract: An array of 3-phenylimidazo[1,2-a]pyridines has been synthesized via perfluorohexyl iodide-mediated coupling of 2-aminopyridines and phenylacetylenes. *In-situ* iodination of the terminal alkyne by perfluorohexyl iodide reverses the polarity by generating a transient electrophilic iodoalkyne, altering the regioselectivity of the phenyl group. The reaction then proceeds via a tandem electrophilic alkynylation and cyclization to form the fused ring product. The protocol affords the 3-phenyl isomer with full regioselectivity and is complementary to reported methodologies for the synthesis of the 2-phenyl isomer starting from the same substrates.

Introduction

The phenylimidazo[1,2-a]pyridine backbone can be found in many pharmaceuticals, natural products, bioactive compounds, biomolecules and agrochemicals.[1] For example, both the 2-phenyl and 3-phenyl regioisomers are found in drugs and bioactive compounds such as Zolpidem, Zolimidine, Miroprofen and TP-003.[2] The phenylimidazo[1,2-*a*]pyridine structural motif has also been used in the field of material sciences[3] and NHCs (N-heterocyclic carbene).[4] With extensive potential of applications, it is not surprising that phenylimidazo[1,2-*a*]pyridines are attractive targets to synthesize.

Current protocols for the synthesis of 2-phenylimidazo[1,2-*a*]pyridines include coupling of 2-aminopyridines with acetophenones,[5] nitroolefins,[6] propargylic alcohols,[7] aldehydes,[8] *α,β* unsaturated ketones[9] and phenylacetylenes.[10] Conversely, reported protocols for the synthesis of the 3-regioisomer typically couple 2-aminopyridines with haloalkynes,[11] phenylacetaldehydes,[12] phenyl-acetones and phenylacetophenones.[13] On seeing that the coupling partner employed for the synthesis of the two phenyimidazo[1,2-*a*]pyridine regioisomers are somewhat exclusive, we wanted to investigate if there are any substrates that could be used to synthesize both regioisomers, as this convenience would be highly desirable.

Lei[10a] and Das[10b] independently reported a protocol for the Ag^{I}-mediated and Co^{II}-catalyzed synthesis of 2-phenylimidazo[1,2-*a*]pyridine via coupling of phenylacetylene and 2-aminopyridines (Scheme 1a). Sheppard's group developed an alternative protocol to 2-phenylimidazo[1,2-*a*]pyridine via a Au^{I}-catalyzed coupling of the same substrate system (Scheme 1b). In their work, *N*-iodosuccinimide (NIS) was employed to generate an (iodoethynyl) benzene intermediate *in-situ* which then transformed to the *α*-iodoacetophenone intermediate via Au-catalyzed alkyne hydration before coupling to 2-aminopyridine to form the desired product. Inspired by Sheppard's work on *in-situ* iodination of phenylacetylenes, we hypothesized that if one employs a halogenating agent without the Au^{I} catalyst, the *α*-iodoacetophenone intermediate would not be formed. Instead, the *in-situ* halogenated phenylacetylene moiety would couple directly to 2-aminopyridine to form the 3-phenylimidazo[1,2-*a*]pyridine isomer (Scheme 1c). This is possible as the *in-situ* halogenation of the phenylacetylene nucleophile effects an "umpolung", bestowing an electrophilic character[14] of opposite reactivity upon the alkyne, thus achieving a switch in regioselectivity via electrophilic alkynylation



Scheme 1. Comparison between Lei's, Das's and Sheppard's protocols with our current work.

However, incorporating *in-situ* halogenation for tandem cyclization reactions that include an electrophilic alkynylation is challenging because the reaction conditions might not be compatible with the cyclization and side reactions may take place.[10b] Thus, it is not surprising that a one-step strategy for *in-situ* halogenation of a terminal alkyne has rarely been reported for the synthesis of heterocycles.[10b, 15] For the majority of these protocols, the final product still contains the halogen, which is not always desirable. Because of these complications, many groups employ the umpolung alkyne as substrate instead.[16]

We have previously worked on *in-situ* *α*-bromination of 1,3-dicarbonyls,[17] phenylacetones and phenylacetophenones[13] for the synthesis of imidazo[1,2-*a*]pyridines using $CBrCl_3$ as the Br source. We have also employed $CBrCl_3$ and perfluorohexyl iodide for the bromination and iodination of phenylacetylenes in the electrophilic alkynylation of 1,3-dicarbonyls to form furans.[18] Based on this, we tested the feasibility of *in-situ* halogenation of phenylacetylenes using $CBrCl_3$ or perfluorohexyl iodide for the cascade reactions to form the 3-phenylimidazo[1,2-*a*]pyridines. However, due to the less acidic nature of the terminal alkyne proton as compared to the *α*-protons in 1,3-dicarbonyls, slightly harsher reaction conditions may be required for this protocol.

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Herein, we report the successful synthesis of 3-phenylimidazo[1,2-*a*]pyridines via *in-situ* iodination of phenylacetylenes using perfluorohexyl iodide. This work complements the protocols reported by groups of Lei, Das and Sheppard for the synthesis of the 2-regioisomers. Starting with the same substrate system of phenylacetylene and 2-aminopyridine, it is now possible to obtain either the 2- or 3-regioisomer of phenylimidazo[1,2-*a*]pyridines. In addition, the *in-situ* halogenation of terminal alkynes to form 3-phenylimidazo[1,2-*a*]pyridines is superior to methodologies employing haloalkynes as substrates. Many of the haloalkynes are not commercially available and have to be presynthesized. Furthermore, conjugated unsaturated haloalkynes are lachrymatory compounds and many are highly toxic.[19] Hence, it is desirable to form the haloalkynes *in-situ* during reaction rather than to synthesize and store them as substrates.

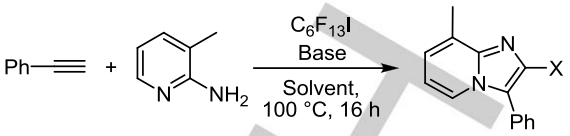
Results and Discussion

We began our optimization studies by employing 0.5 mmol of phenylacetylene **1a** with 1.0 mmol of 2-amino-3-methylpyridine **2a**, together with 1.0 mmol of $KHCO_3$ as base and 1.25 mmol of $CBrCl_3$ in 3 mL MeCN under refluxing conditions for 16 h (Table 1). Two main products were formed, including the desired 3-phenylimidazo[1,2-*a*]pyridine **3a** and the brominated derivative **4a**, which formed the major fraction (Table 1, entry 1). Interestingly, switching to perfluorohexyl iodide resulted in a strong preference for the formation of **3a** over its iodinated derivative **4b** (Table 1, entry 2). No 2-phenylimidazo[1,2-*a*]pyridine was formed. In comparison, a similar protocol involving the Cu^{II}-catalyzed coupling of phenylacetylene and 2-aminopyridine with molecular iodine as the halogen source formed 2-iodo-3-phenylimidazo[1,2-*a*]pyridine **4b** as the main product instead.[15a]

The exclusive regioselectivity to **3a** can be attributed to the detection of only (iodoethynyl)benzene as intermediate in the reaction mixture. This causes the umpolung reactivity of phenylacetylene. No *α*-iodinated acetophenone intermediate[10b] which gives rise to 2-regioisomer product was found. Various solvents were also screened for their suitability in this protocol (Table 1, entries 3 - 9). DMF was not suitable for this reaction, with low yields of **3a** and a large amount of (iodoethynyl)benzene (Table 1, entry 3). Nitromethane and 1,2-dichloroethane produced slightly better yields of **3a** but with a poor ratio of **3a**/**4b** compared to MeCN (Table 1, entries 2, 4 and 5). On the other hand, ethyl acetate gave a modest isolated yield of **3a** at 54 % (Table 1, entry 6). In dioxane or toluene, no reaction took place (Table 1, entries 7 and 8). Gratifyingly, a mixed solvent system of MeCN/toluene of ratio 5:1 (v/v) gave an improved yield of 71 % **3a** with only traces of **4b** formed (Table 1, entry 9).

This mixed solvent system was subsequently employed to screen for a suitable base (Table 1, entries 10 - 14). No reaction occurred without a base, showing the importance of the base in the reaction (Table 1, entry 10). Two additional potassium salts were tested. KOAc was not suitable for the reaction while K_2CO_3 gave only a reduced yield of 50 % for **3a** (Table 1, entries 11 and 12). Other bicarbonate salts were also screened including $NaHCO_3$ and $CsHCO_3$ (Table 1, entries 13 and 14). Compared with $KHCO_3$, $CsHCO_3$ gave a significantly better yield of 85 % whereas $NaHCO_3$ gave poor results. Attempts to reduce the amount of perfluorohexyl iodide from 2 to 1.5 and 1.0 equiv caused a significant reduction in the yield of **3a** (Table 1, entries 15 and 16). Thus, the optimized conditions employed for further testing was 0.5 mmol of phenylacetylene **1a** with 2 equiv of 2-amino-3-methylpyridine **2a**, 1.0 mmol of $CsHCO_3$, 1.25 mmol of perfluorohexyl iodide in 3 mL mixed solvent system of MeCN/toluene 5:1 (v/v) under reflux for 16 h.

Table 1. Optimization parameters for synthesis of 3-phenylimidazo[1,2-*a*]pyridines.[a]

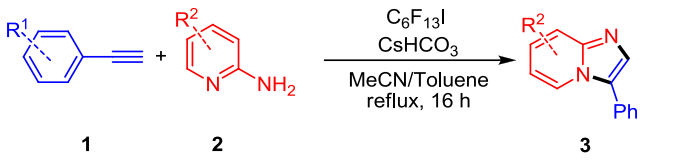


1a **2a** X = H, **3a**; X = Br, **4a**; X = I, **4b**

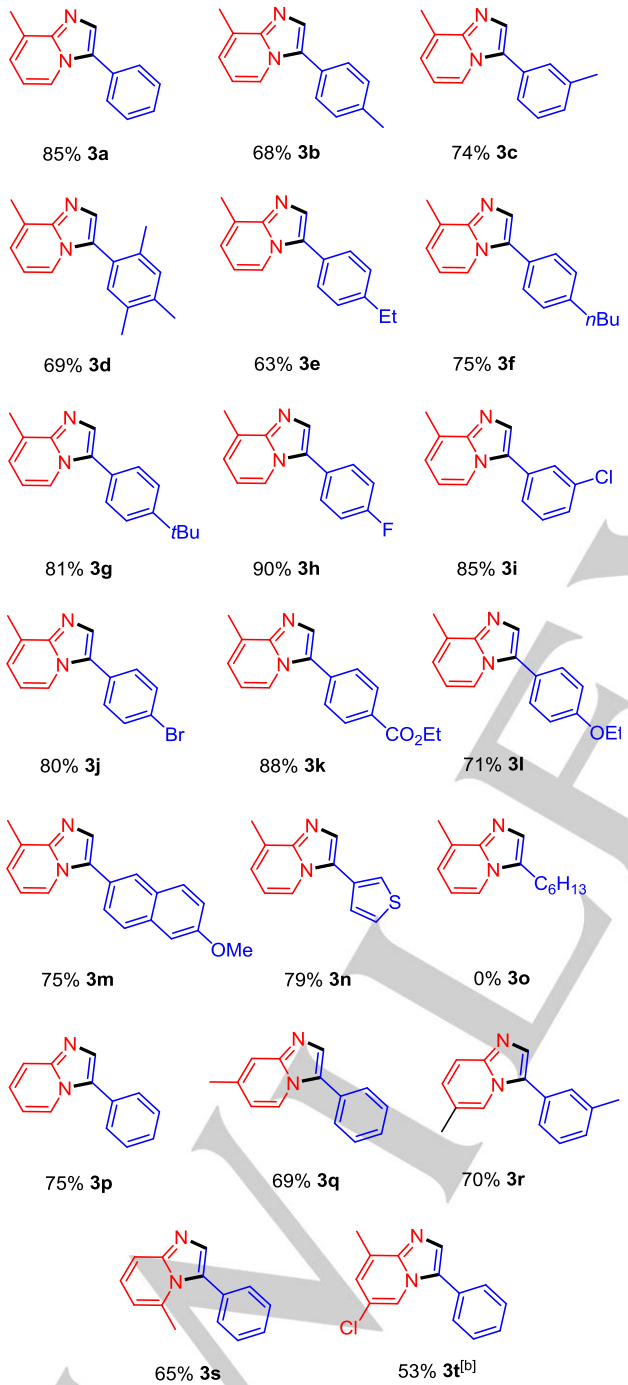
Entry	Solvent	Base	Yield of **3a**[b],[c] [%]	Yield of **4a/4b**[b] [%]
1[d],[e]	MeCN	$KHCO_3$	33	51
2[e]	MeCN	$KHCO_3$	70 (59)	7
3	DMF	$KHCO_3$	12	trace
4	NO_2Me	$KHCO_3$	38 (20)	16
5[e]	DCE	$KHCO_3$	38 (23)	10
6[e]	EtOAc	$KHCO_3$	63 (54)	5
7	dioxane	$KHCO_3$	0	0
8	toluene	$KHCO_3$	0	0
9[e]	MeCN/toluene	$KHCO_3$	79 (71)	trace
10[e]	MeCN/toluene	-	0	0
11[e]	MeCN/toluene	KOAc	0	0
12[e]	MeCN/toluene	K_2CO_3	70 (50)	12
13[e]	MeCN/toluene	$NaHCO_3$	45 (28)	trace
14[e]	MeCN/toluene	$CsHCO_3$	90 (85)	trace
15[e],[f]	MeCN/toluene	$CsHCO_3$	41 (22)	0
16[e],[g]	MeCN/toluene	$CsHCO_3$	10	0

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (2.0 equiv), base (2 equiv), halogenating agent (2.5 equiv) in 3 mL of solvent at 100 °C for 16 h. [b]Yield (from GC) with respect to **1a**. [c]Isolated yields in parenthesis. [d]Reaction conducted using $CBrCl_3$ as the halogenating agent instead of $C_6F_{13}I$. [e]Reaction was conducted under reflux with [f]1.5 equiv of $C_6F_{13}I$ or [g]1.0 equiv used.

Table 2. Scope of reaction.[a]



1 2 3



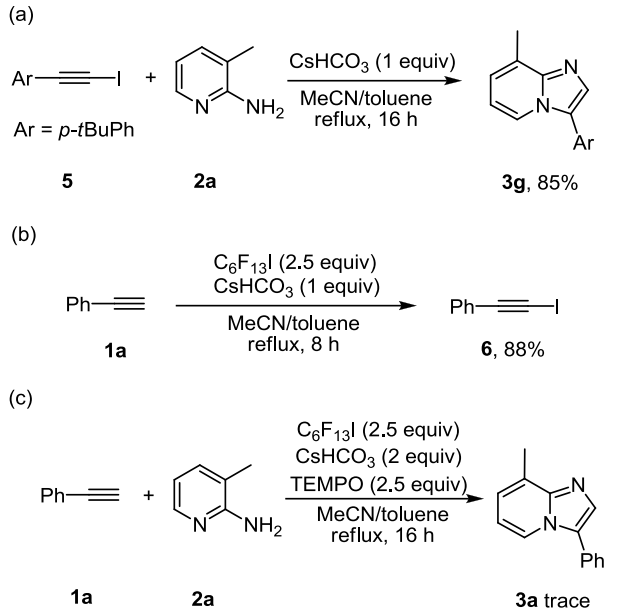
[a]Reaction conditions: **1** (0.5 mmol), **2** (2.0 equiv), $CsHCO_3$ (2 equiv), $C_6F_{13}I$ (2.5 equiv) in 3 mL MeCN/toluene 5:a (v/v) under reflux for 16 h. Isolated yields reported. [b]Reaction time of 24 h.

Next, a wide array of arylacetylenes was tested for their compatibility under the optimized reaction condition (Table 2). Good yields were obtained when a methyl group was at the *ortho, meta* or *para* position (Table 2, **3b** - **3d**). Longer alkyl substituents at the *para* position were also well tolerated, including ethyl, *n*-butyl and *tert*-butyl (Table 2, **3e** - **3g**). Fluoro, chloro, and bromo-substituted phenylacetylene also proceeded with good to excellent yields (Table 2, **3h** - **3j**). An ester and ethoxy moiety at the *para* position did not interfere with the reaction and yields of 88 % and 71 %, respectively were obtained (Table 2, **3k** and **3l**). Gratifyingly, other aromatic derivatives of phenylacetylene, including naphthalene and thiophene, coupled efficiently with 2-amino-3-methylpyridine **2a** as well, to form **3m** and **3n** with yields of 75 % and 79 %, respectively. Unfortunately, 1-octyne was unreactive under the reaction conditions (Table 2, **3o**). This is not surprising as the halogenation of terminal alkynes with $CBrCl_3$ and perfluorohexyl iodide has only been reported for arylacetylenes.[20]

Derivatives of 2-aminopyridine were also screened under the optimized conditions. 75 % of **3p** was formed when 2-aminopyridine was employed. Methyl groups at the C-4 and C-5 position were well tolerated under the reaction conditions (Table 2, **3q** and **3r**). It is interesting to see that with a methyl substituent at the C-6 position, **3s** was formed with a yield of 65 % yield. For the synthesis of 3-phenylimidazo[1,2-*a*]pyridines, there has been many reports in the literature where the 6-methyl substituted 2-aminopyridines reacted sluggishly or were unreactive to their respective substrates.[13, 16b, 21] In addition, 2-amino-5-chloro-3-picoline proceeded with a modest yield of **3t** at 53 % albeit at a longer reaction time of 24 h.

Studies were conducted to better understand the mechanism of the reaction. Firstly, as the (iodoethynyl)benzene has been observed in some of the reaction mixtures during optimization studies, we wanted to prove that iodination of the terminal alkyne indeed occurs prior to coupling with the 2-aminopyridine moiety. A reaction was done under the optimized conditions using the iodoalkyne **5**, 2 equiv of 2-amino-3-methylpyridine **2a** and 1 equiv of $CsHCO_3$ without any addition of the halogenating agent, perfluorohexyl iodide (Scheme 2a). 85 % of **3g** was obtained after 16 h which confirms that the reaction proceeds via the iodoalkyne intermediate.

Next, we wanted to see if $CsHCO_3$ or 2-aminopyridine is responsible for deprotonation of phenylacetylene **1a** prior to iodination. 0.5 mmol of **1a** was added to 3 mL MeCN/toluene 5:1 (v/v) solvent mixture system with 1 equiv of $CsHCO_3$ and 2.5 equiv of perfluorohexyl iodide (Scheme 2b). 88 % of (iodoethynyl)benzene **6** was obtained after 8 h, showing that $CsHCO_3$ is involved in the deprotonation step. This is supported by the lack of reaction in the absence of $CsHCO_3$ (Table 1, entry 10). To check if the reaction proceeds via a radical pathway, 2.5 equiv of 2,2,6,6-tetramethylpiperidin-1-yl oxyl (TEMPO) as radical scavenger was added to the reaction mixture (Scheme 2c). After 16 h, only trace amounts of the desired product **3a** was formed, providing strong support that the reaction pathway is radical in nature. This is similar to the findings of Sasson's group for *in-situ* halogenation of 1,3-dicarbonyls and terminal arylaetylenes using perfluorohexyl iodide.[20a, 20b]



Scheme 2. Mechanistic studies to determine the (a) reaction intermediate (b) role of $CsHCO_3$ in the initial iodination step and (c) radical nature of reaction.

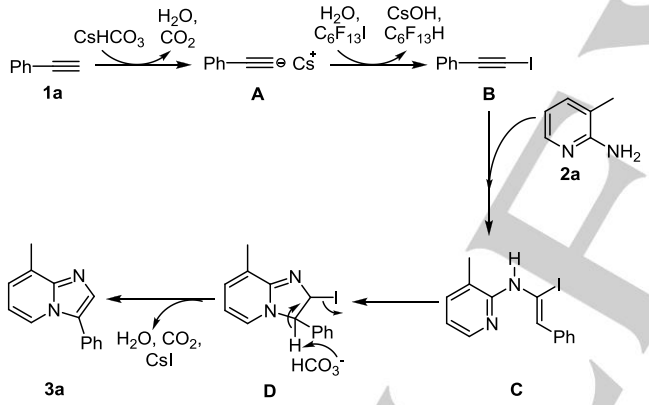


Figure 1. Plausible reaction mechanism

Based on the results of the optimization experiments and mechanistic studies, the formation of **3a** is postulated to occur as shown in Figure 1. The reaction begins with deprotonation of phenylacetylene **1a** to form the ionic salt **A**. The C-I bond in perfluorohexyl iodide is homolytically cleaved to give C_6F_{13}• and I• radicals.[20a, 20b] Iodination of **A** by I• forms the iodoalkyne intermediate **B**. This umpolung intermediate then undergoes an electrophilic alkynylation reaction with 2-amino-3-methylpyridine **2a** to form **C**. Cycloisomerization of **C** yields intermediate **D** with an acidic proton. This proton will be deprotonated by another molecule of $CsHCO_3$ to give the desired product **3a**, releasing H_2O, CO_2 and CsI salt.

Conclusions

In summary, we have demonstrated a perfluorohexyl iodide-mediated coupling of commercially available phenylacetylenes and 2-aminopyridines to form 3-phenylimidazo[1,2-*a*]pyridines through a series of cascade reactions that includes an initial iodination of terminal alkyne moiety followed by electrophilic alkynylation and cycloisomerization. The perfluorohexyl iodide effectively iodinates the terminal alkyne, changing its reactivity. This enables switching of the regioselectivity so that the 3-regioisomer product is formed exclusively instead of the 2-regioisomer. This protocol extends the scope of the phenylacetylene/2-aminopyridine substrate system, selectively forming either the 2- or the 3-regioisomer of phenylimidazo[1,2-*a*]pyridine. Furthermore, the facile *in-situ* halogenation of terminal alkynes under the reaction conditions offers a safer and more convenient access to this class of heterocyclic compounds

Experimental Section

Typical Procedure for the Formation of Imidazo[1,2-*a*]pyridines

A 25-mL round-bottomed flask was charged with phenylacetylene 1a (54.9 µL, 0.5 mmol), 2-amino-3-methylpyridine 2a (101 µL, 1.0 mmol), $CsHCO_3$ (194 mg, 1.0 mmol) and $C_6F_{13}I$ (270 µL, 1.25 mmol) in 3 mL of MeCN/toluene 5:1 (v/v) solvent mixture. The reaction mixture was stirred under reflux for 16 h. The mixture was then diluted with H_2O and extracted with EtOAc (15 mL×5). The combined organic layer was washed with brine and dried with anhydrous Na_2SO_4. After filtration, the solvent was removed by rotary evaporation and the residue was purified by column chromatography using hexane and ethyl acetate (v/v=2/1) as eluent to afford 3a with 85 % yield.

8-Methyl-3-phenylimidazo[1,2-*a*]pyridine (3a):

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 6.9 Hz, 1H), 7.66 (s, 1H), 7.56-7,42 (m, 4H), 7.37 (t, J = 7.1 Hz, 1H), 6.96 (d, J = 6.9 Hz, 1H), 6.68 (t, J = 6.9 Hz, 1H), 2.63 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 146.4, 131.7, 129.5, 129.0, 128.2, 128.0, 127.8, 126.0, 123.0, 121.1, 112.4, 16.9. HRMS (ESI) calcd for $C_{14}H_{13}N_2$ $[M+H]^+$: 209.1073; found 209.1072..

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Keywords: alkynes • cyclization • regioselectivity • C-H activation • synthetic methods

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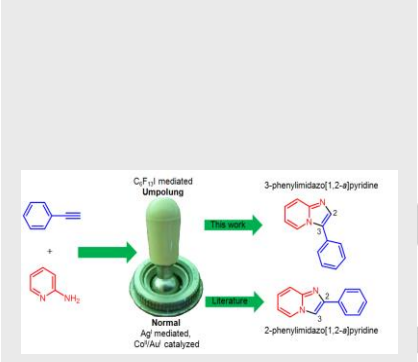
Entry for the Table of Contents

Layout 1:

COMMUNICATION

A protocol for the synthesis of 3-phenylimidazo[1,2-*a*]pyridines via perfluorohexyl iodide-mediated coupling of 2-aminopyridines and phenylacetylenes is reported, proceeding via *in-situ* iodination of the terminal alkyne. The iodination reverses the polarity by generating a transient electrophilic iodoalkyne, altering the regioselectivity of the phenyl group.



In-situ Bromination*

Irwan Iskandar Roslan, Gaik-Khuan Chuah and Stephan Jaenicke**

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Switching of regioselectivity in a perfluorohexyl iodide-mediated synthesis of phenylimidazo[1,2-*a*]pyridines

*one or two words that highlight the emphasis of the paper or the field of the study