Reactivity of 3-Iodoimidazo[1,2-*a*]pyridines Using a Suzuki-Type Cross-Coupling Reaction

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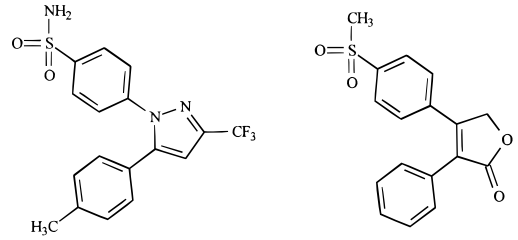
The influence of base and solvent in Suzuki cross-coupling reaction on various 2-substituted-3-iodoimidazo[1,2-*a*]pyridines was reported. The reactivity was largely influenced by nature of the substituent. Optimized yields and shortened times of reaction were obtained using strong bases in DME.

Introduction

Recently a new series of diaryl heterocycles including rofecoxib and celecoxib have been developed as selective cyclooxygenase-2 inhibitors for the treatment of acute and chronic inflammatory diseases (Scheme 1).[1] Selective inhibition of this enzyme might avoid the side effects of currently available nonsteroidal antiinflammatory drugs while retaining their therapeutic efficacy. Recent clinical trials have confirmed the superior gastrointestinal safety profile of both compounds when compared to naproxen,[2] diclofenac,[3] or ibuprofen.[4]

In continuation of our studies on the reactivity of nitrogen bridgehead heterocycles,[5] we were then interested in the preparation and the pharmacological evaluation of 2,3-diarylimidazo[1,2-*a*]pyridines. To develop a convenient synthetic pathway in good agreement with rapid pharmacomodulation, we were interested in studying the Suzuki-type cross-coupling reaction. To the best of our knowledge, the application of this reaction to these series was only reported by R. E. Tenbrink on 6-bromo derivatives,[6] while 3-arylation was described by Y. Kawai and A. Badger using the Stille coupling reaction.[7] In this work, we turned our interest to studying the reactivity of the imidazo[1,2-*a*]pyridine ring system toward boronic acid. In this way, the incidence of various parameters was investigated: nature of the 2-substituent, nature of the boronic acid, and conditions of the reaction (bases and solvents).

Scheme 1



Celecoxib Rofecoxib

It is well established that imidazo[1,2-*a*]pyridines undergo electrophilic attack at the 3-position.[8] Thus bromination was achieved using NBS in CCl_4,[9] NBS in $CHCl_3$,[10] bromine in NaOH,[10] or bromine in acetic acid.[11] The iodination reaction was in contrast poorly studied. Iodination of 2-phenylimidazo[1,2-*a*]pyridine and (3-nitrofuran-2-yl)imidazo[1,2-*a*]pyridine was reported using iodine in ethanol[12] or iodine in pyridine,[13] respectively. More recently, 2,6-dichloroimidazo[1,2-*a*]pyridine was iodinated using NIS in $CHCl_3$[14] or in acetonitrile.[15]

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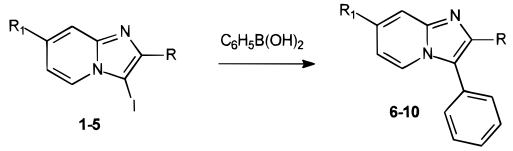
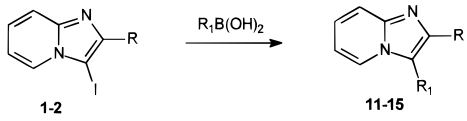
Table 1[a]



compd	R	R_1	method	time (h)	yield (%)
1, **6**	$CO_2C_2H_5$	H	A	48	73
			C	0.5	91
2, **7**	C_6H_5	H	A	48	44
			B	20	71
			C	4	75
			D	0.5	71
3, **8**	pFC_6H_4	H	A	48	47
4, **9**	$C(CH_3)_3$	CH_3	A	48	39
			B	48	28
			C	7	66
			D	0.5	77
5, **10**	H	H	A	48	48
			D	0.5	69

[a] Couplings were carried out at 75 °C in the presence of 5% $Pd(PPh_3)_4$ and 2 equiv of Na_2CO_3 in toluene (method A) or 2 equiv of NaOH in toluene (method B) or 2 equiv of Na_2CO_3 in DME (method C) or 2 equiv of NaOH in DME (method D).

Table 2[a]



compd	R	R_1	method	time (h)	yield (%)
11	$CO_2C_2H_5$	2-thienyl	A	72	18
			C	0.5	64
12	$CO_2C_2H_5$	3-thienyl	A	72	0
			C	0.5	56
13	$CO_2C_2H_5$	methyl	A	48	0
			C	48	0
14	C_6H_5	2-thienyl	D	48	≈30[b]
			E	3	70
			F	3	53
15	C_6H_5	methyl	D	6	85
			E	48	5
			F	48	0

[a] Couplings were carried out at 75 °C in the presence of 5% $Pd(PPh_3)_4$ and 2 equiv of Na_2CO_3 in toluene (method A) or 2 equiv of Na_2CO_3 in DME (method C) or 2 equiv of NaOH in DME (method D) or 2 equiv of $Ba(OH)_2$ in DME (method E) or at reflux in the presence of 2 equiv of $Ba(OH)_2$ in THF (method F) [b] Evaluated by TLC.

Results and Discussion

In a first approach, the iodination was attempted in pyridine[13] but purification was rather difficult and led to a poor yield, thus we turned our interest to the procedure using NIS in acetonitrile.[15] Under these conditions the diversely substituted imidazo[1,2-*a*]pyridines afforded the expected iodinated compounds as a precipitate in the reaction mixture. Only the ethyl imidazo[1,2-*a*]pyridine-2-carboxylate appears to be poorly reactive toward NIS.

First, the coupling reaction of benzeneboronic acid was applied to 3-iodoimidazo[1,2-*a*]pyridine diversely substituted in the 2-position. The reaction was carried out in a heterogeneous mixture of toluene and aqueous sodium carbonate solution, in the presence of catalytic amount of tetrakis(triphenylphosphine)palladium(0) at 75 °C for 2 days (method A). The use of higher temperatures in order to improve the yield and shorten the reaction time led to significant degradation of the heterocycle. From the results reported in Table 1, we noted a marked effect upon the nature of the substituent on the rate of coupling. The presence of an ester group on the 2-position appeared to favor the iodo substitution compared to 2-phenyl and 2-*tert*-butyl groups or hydrogen. These results could be explained by the electronic-withdrawing effect of the carbonyl group.

To optimize the reaction conditions, we decided to investigate the reactivity of 3-iodoimidazo[1,2-*a*]pyridine using various bases and solvents. We have observed that whatever the base, the reaction time was greatly shortened and the yield markedly improved by replacement of toluene by 1,2-dimethoxyethane. Thus, the coupling was completed cleanly from **1** in 30 min using sodium carbonate in DME (method C), leading to compound **6** (91% yield of isolated product after column chromatography). Under the same conditions, a few hours were still needed for an efficient coupling starting from **2** and **4** (4 and 7 h, respectively) in accordance with the reactivity order deduced from Table 1. These reaction times were markedly shortened by modifying the nature of the base (NaOH, method D) leading to **7**, **9**, and **10** in 30 min in around 70% yields.

We then decided to exemplify the coupling reaction with different boronic acids (Table 2). In our case, thien-2-yl, thien-3-yl, and methylboronic acids appeared to be less reactive than benzeneboronic acid since no reaction occurred with method A conditions after a few days of heating. Thienylboronic acids could be coupled to the ester compound **1** using method C (Na_2CO_3/DME) but provided lower yields (about 60%) than with benzeneboronic acid. As far as the 2-phenyl compound **2** is concerned, method D (NaOH/DME) was unable to give the expected coupling product with thien-2-ylboronic acid in good yield. From this observation, the reaction was then performed using $Ba(OH)_2$ in THF (method F) according to the literature,[16] giving 53% yield after 3 h of heating. To determine the importance of the solvent, we investigated the coupling reaction using $Ba(OH)_2$ in DME in 70% yield.

Reaction of **1** with methylboronic acid was unsuccessful through method C due to the long reaction time leading to saponification of the ester function. Methyl coupling was performed only starting from phenyl compound **2** using method D (NaOH, DME) after 6 h of heating in good yield (85%). Attempt to shorten the reaction time using $Ba(OH)_2$ in DME or THF led to almost no reaction.

Conclusion

After studying many different methods using varying bases and solvents, the results led us to define the best conditions of Suzuki reaction on 3-iodoimidazo[1,2-*a*]-pyridine depending on the nature of boronic acid and 2-substituent. The base sensitivity of ester function prevented us from using bases stronger than Na_2CO_3 or too long reaction time under Suzuki conditions. However, the good reactivity of 2-ester compound **1** allowed the

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coupling reaction with phenyl and thienylboronic acids to be carried out very efficiently in a short reaction time using 2 equiv of Na_2CO_3 in DME (56−91% yields). In the case of 2-phenyl and 2-alkyl analogues **2**−**4** the lower reactivity but the higher stability led us to use NaOH or $Ba(OH)_2$ in DME with 70−85% yields. Methylboronic acid appeared to be uncompatible with utilization of $Ba(OH)_2$. Further confirmation of this reactivity was obtained by studying methods A and D on the parent heterocycle **5** (Table 1).

In conclusion, the Suzuki cross-coupling procedure reported here represents a new general and convenient synthetic approach in good agreement with rapid pharmacomodulation of 3-arylimidazo[1,2-*a*]pyridines. The extension of this method on other bridgehead nitrogen heterocycles is in progress.

Experimental Section

General. Commercial reagents were used as received without additional purification. Previously reported imidazo[1,2-*a*]pyridines were obtained using the described procedure: Ethyl imidazo[1,2-*a*]pyridine-2-carboxylate,[17] 2-phenylimidazo[1,2-*a*]pyridine,[18] 2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine,[9] 2-*tert*-butyl-7-methylimidazo[1,2-*a*]pyridine,[19] imidazo[1,2-*a*]pyridine.[20] NMR spectra were run at 200 MHz (^{1}H) and 50 MHz (^{13}C) in $CDCl_3$. Possible inversion of two values in the ^{13}C NMR spectra is expressed by an asterisk. Melting points are uncorrected.

Preparation of Iodo Compounds. General Procedure for Reaction with Iodine. To a solution of ethyl imidazo[1,2-*a*]pyridine-2-carboxylate (15.8 mmol) in pyridine (10 mL) was added iodine (6 g, 23.6 mmol). The reaction mixture was heated at 50 °C for 5 h and then poured into water (20 mL). The aqueous solution was extracted with dichloromethane. The combined organic extracts were washed with water (3 × 20 mL) and dried over calcium chloride, and the solvent was removed under reduced pressure. The residual material was purified by column chromatography (neutral alumina, dichloromethane as eluant).

Ethyl 3-iodoimidazo[1,2-*a*]pyridine-2-carboxylate (1): 46% yield; mp 144 °C (brown powder); ^{1}H NMR δ: 8.31 (dt, 1H, J = 7 Hz, J = 1.1 Hz, H-5), 7.72 (dt, 1H, J = 9.2 Hz, J = 1.1 Hz, H-8), 7.38 (ddd, 1H, J = 7 Hz, H-7), 7.05 (td, 1H, H-6), 4.54 (q, 2H, J = 7.1 Hz, CH_2), 1.51 (t, 3H, CH_3); ^{13}C NMR δ: 163.1 (CO), 148.2 (C-8a), 138.5 (C-2), 127.5 (C-5,C-7), 119.6 (C-8), 115.1 (C-6), 68.5 (C-3), 61.9 (CH_2), 14.8 (CH_3).

General Procedure for Reaction with NIS. To a solution of imidazo[1,2-*a*]pyridine (4 mmol) in dry acetonitrile (5 mL) was added *N*-iodosuccinimide (0.95 g, 4 mmol). The reaction mixture was stirred at room temperature for 30 min, and the resulting white solid was filtered off, dried, and used without further purification.

3-Iodo-2-phenylimidazo[1,2-*a*]pyridine (2): 83% yield; mp 168 °C (lit.[12] mp 166 °C); ^{13}C NMR δ: 148.3 (C-2, C-8a), 133.5 (Ph-1), 129.3 (2C, Ph-2,6), 128.9 (C-7), 128.8 (2C, Ph-3,5), 127.1 (Ph-4), 126.5 (C-5), 118.0 (C-8), 113.4 (C-6), 60.4 (C-3).

3-Iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine (3): 89% yield; mp 185 °C; ^{1}H NMR δ: 8.22 (d, 1H, J = 6.8 Hz, H-5), 8.08 (dd, 2H, J = 5.4 Hz, J = 8.9 Hz, Ph-2,6), 7.63 (d, 1H, J = 9 Hz, H-8), 7.28 (ddd, 1H, J = 6.8 Hz, J = 1.2 Hz, H-7), 7.20 (t, 2H, J = 8.9 Hz, Ph-3,5), 6.94 (td, 1H, H-6); ^{13}C NMR δ: 163.3 (^1J = 247.6 Hz, Ph-4), 148.5 (C-8a*), 147.7 (C-2*), 130.7 (^3J = 8 Hz, Ph-2,6), 130.1 (Ph-1), 126.9 (C-7), 126.1 (C-5), 118.0 (C-8), 115.7 (^2J = 21.6 Hz, Ph-3,5), 113.7 (C-6), 59.7 (C-3).

2-*tert*-Butyl-3-iodo-7-methylimidazo[1,2-*a*]pyridine (4): 68% yield; mp 120 °C; ^{1}H NMR δ: 8.08 (d, 1H, J = 7 Hz, H-5), 7.35 (d, 1H, J = 1.6 Hz, H-8), 6.70 (d, 1H, H-6), 2.40 (s, 3H, CH_3), 1.57 (s, 9H, CH_3); ^{13}C NMR δ: 156.5 (C-2), 147.0 (C-8a), 135.9 (C-7), 125.3 (C-5), 116.2 (C-8), 115.6 (C-6), 55.6 (C-3), 33.6 (tBu), 30.6 (3C, tBu), 21.5 (CH_3).

3-Iodoimidazo[1,2-*a*]pyridine (5): 87% yield; mp 167 °C; ^{1}H NMR δ: 8.14 (dt, 1H, J = 6.8 Hz, J = 1.1 Hz, H-5), 7.70 (s, 1H, H-2), 7.66 (dt, 1H, J = 9.1 Hz, J = 1.1 Hz, H-8), 7.28 (ddd, 1H, J = 6.8 Hz, H-7), 6.97 (td, 1H, H-6); ^{13}C NMR δ: 147.7 (C-8a), 140.2 (C-2), 126.6 (C-7), 126.0 (C-5), 118.1 (C-8), 114.0 (C-6), 61.5 (C-3).

General Procedure for the Suzuki Reaction. Method A: To a mixture of 3-iodoimidazo[1,2-*a*]pyridine derivative (1 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in toluene (8 mL) was added the corresponding aryl or alkyl boronic acid (1.1 mmol) followed by the addition of sodium carbonate (212 mg, 2 mmol) in water (4 mL). The reaction mixture was heated at 75 °C with vigorous stirring under nitrogen atmosphere, and the rate of the reaction was followed by TLC. After 24 h of stirring, a second portion boronic acid (1.1 mmol) was added. After the starting aryl halide was consumed, the reaction mixture was poured into water and then extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with water (20 mL), dried over calcium chloride, and concentrated to dryness under vacuo. The crude products were purified by column chromatography (silica gel eluting with dichloromethane).

Method B: To a mixture of 3-iodoimidazo[1,2-*a*]pyridine derivative (1 mmol) and $Pd(PPh_3)_4$ (58 mg, 0,05 mmol) in toluene (8 mL) was added phenylboronic acid (134 mg, 1.1 mmol) followed by the addition of sodium hydroxide (80 mg, 2 mmol) in water (4 mL). The reaction mixture was heated at 75 °C with vigorous stirring under nitrogen atmosphere. After the starting aryl halide was consumed, the reaction mixture was worked up as described in method A.

Method C: The reaction was carried out as described in method B using the corresponding aryl or alkylboronic acid, but the solvent was changed to dimethoxyethane and the base to sodium carbonate.

Method D: The same conditions as described in method B were applied using the corresponding aryl or alkylboronic acid, but the solvent was changed to dimethoxyethane.

Method E: The reaction conditions described in method B were applied using the corresponding aryl or alkylboronic acid, but the solvent was changed to dimethoxyethane and the base to barium hydroxide.

Method F: The reaction was carried out as described in method B using 2-thienyl or 2-methylboronic acid, but the base was changed to barium hydroxide and the solvent to tetrahydrofuran.

Ethyl 3-phenylimidazo[1,2-*a*]pyridine-2-carboxylate (6): colorless crystals; 91% yield (method C); mp 96 °C (lit.[21] mp 88−90 °C); ^{13}C NMR δ: 163.8 (CO), 144.7 (C-8a), 133.4 (C-2), 131.0 (3C, Ph-1,2,6), 129.8 (Ph-4), 129.2 (2C, Ph-3,5), 128.5 (C-3), 126.6 (C-7), 124.4 (C-5), 119.4 (C-8), 114.1 (C-6), 61.3 (CH_2), 14.7 (CH_3).

2,3-Diphenylimidazo[1,2-*a*]pyridine (7): colorless crystals; 71% yield (method D); mp 150 °C (lit.[22] mp 151.5−153 °C); ^{13}C NMR δ: 145.2 (C-8a), 142.9 (C-2), 134.6 (Ph-1), 131.2 (2C, Ph′-2,6), 130.3 (Ph′-1), 130.0 (2C, Ph′-3,5), 129.3 (Ph′-4), 128.7 (2C, Ph-2,6*), 128.5 (2C, Ph-3,5*),127.9 (Ph-4), 125.1 (C-7), 123.7 (C-5), 121.5 (C-3), 118.0 (C-8), 112.7 (C-6).

2-(4-Fluorophenyl)-3-phenylimidazo[1,2-*a*]pyridine (8): colorless crystals; 47% yield (method A); mp 104 °C; ^{1}H NMR δ: 7.97 (dt, 1H, J = 7 Hz, J = 1 Hz, H-5), 7.77−7.63 (m, 3H, H-8, Ph-2,6), 7.57−7.43 (m, 5H, Ph′), 7.22 (ddd, 1H, J = 9.2 Hz, J = 7 Hz, H-7), 7.03 (t, 2H, J = 8.9 Hz, Ph-3,5), 6.75 (td,

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1H, H-6); ^{13}C NMR δ: 162.8 (^{1}J = 247 Hz, Ph-4), 145.2 (C-8a), 141.9 (C-2), 131.1 (2C, Ph′-2,6), 130.8 (Ph-1*), 130.7 (Ph′-1*), 130.2 (^{3}J = 9 Hz, 2C, Ph-2,6), 130.1 (2C, Ph′-3,5), 129.4 (Ph′-4), 125.1 (C-7), 123.7 (C-5), 121.3 (C-3), 117.9 (C-8), 115.6 (^{2}J = 21.6 Hz, 2C, Ph-3,5), 112.8 (C-6). Anal. Calcd for $C_{19}H_{13}FN_2$: C, 79.15; H, 4.54; N, 9.72. Found: C, 79.36; H, 4.38; N, 9.84.

7-Methyl-3-phenyl-2-*tert*-butylimidazo[1,2-*a*]pyridine (9): colorless oil wich solidified upon standing; 77% (method D); ^{1}H NMR δ: 7.50−7.57 (m, 3H, Ph-2,6, H-5), 7.38−7.41 (m, 4H, Ph-3,4,5, H-8), 6.48 (d, 1H, J = 7.2 Hz, J = 1.5 Hz, H-6), 2.40 (s, 3H, CH_3), 1.34 (s, 9H, CH_3); ^{13}C NMR δ: 152.3 (C-2), 144.0 (C-8a), 134.9 (C-7), 132.5 (2C, Ph-2,6), 132.3 (Ph-1), 129.3 (2C, Ph-3,5), 129.2 (Ph-4), 123.0 (C-5), 119.5 (C-3), 115.7 (C-8), 114.4 (C-6), 33.9 (tBu), 31.7 (3C, tBu), 21.6 (CH_3). Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.91; H, 7.65; N, 10.60.

3-Phenylimidazo[1,2-*a*]pyridine (10): colorless oil (lit.[23] mp 97−98 °C); 69% yield (method D); ^{1}H NMR δ: 8.38 (dt, 1H, J = 6.8 Hz, J = 1.2 Hz, H-5), 7.74 (s, 1H, H-2), 7.72 (br d, 1H, J = 9.2 Hz, H-8), 7.65−7.45 (m, 5H, Ph), 7.24 (ddd, 1H, J = 6.8 Hz, H-7), 6.84 (td, 1H, J = 1.2 Hz, H-6), ^{13}C NMR δ: 146.6 (C-8a), 133.0 (C-2), 129.8 (Ph-1), 129.6 (2C, Ph-2,6), 128.8 (Ph-4), 128.5 (2C, Ph-3,5), 126.2 (C-3), 124.6 (C-7), 123.8 (C-5), 118.7 (C-8), 112.9 (C-6).

Ethyl 3-(thien-2-yl)imidazo[1,2-*a*]pyridine-2-carboxylate (11): brown powder; 64% yield (method C); mp 84 °C; ^{1}H NMR δ: 8.10 (dt, 1H, J = 7 Hz, J = 1.1 Hz, H-5), 7.74 (dt, 1H, J = 9.2 Hz, J = 1.2 Hz, H-8), 7.62 (dd, 1H, J = 5.1 Hz, J = 1.3 Hz, H-5′), 7.33 (dd, 1H, J = 3.5 Hz, J = 1.3 Hz, H-3′), 7.31 (ddd, 1H, J = 7 Hz, H-7), 7.25 (dd, 1H, J = 5.1 Hz, J = 3.5 Hz, H-4′), 6.88 (t, 1H, J = 7 Hz, H-6), 4.40 (q, 2H, J = 7.1 Hz, CH_2), 1.36 (t, 3H, J = 7.1 Hz, CH_3); ^{13}C NMR δ: 163.4 (CO), 145.2 (C-8a), 135.2 (C-2), 131.0 (C-3′), 129.2 (C-5′), 128.0 (C-2′), 127.8 (C-4′), 126.9 (C-7), 124.8 (C-5), 122.3 (C-3), 119.4 (C-8), 114.3 (C-6), 61.5 (CH_2), 14.7 (CH_3). Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.91; H, 4.47; N, 10.38.

Ethyl 3-(thien-3-yl)imidazo[1,2-*a*]pyridine-2-carboxylate (12): brown powder; 56% yield (method C); mp 134 °C; ^{1}H NMR δ: 8.09 (dt, 1H, J = 7 Hz, J = 1.2 Hz, H-5), 7.74 (dt, 1H, J = 9.2 Hz, J = 1.2 Hz, H-8), 7.66 (dd, 1H, J = 3.0 Hz, J = 1.2 Hz, H-2′), 7.55 (dd, 1H, J = 5 Hz, H-4′), 7.34 (dd, 1H, H-5′), 7.29 (ddd, 1H, J = 7 Hz, H-7), 6.87 (td, 1H, H-6), 4.40 (q, 2H, J = 7.2 Hz, CH_2), 1.39 (t, 3H, CH_3); ^{13}C NMR δ: 163.8 (CO), 144.8 (C-8a), 133.8 (C-2), 129.34 (C-5′), 128.0 (C-3′), 127.5 (C-2′), 126.5 (C-7), 126.4 (C-4′), 125.0 (C-3), 124.7 (C-5), 119.5 (C-8), 114.1 (C-6), 61.4 (CH_2), 14.7 (CH_3). Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.62; H, 4.51; N, 10.23.

2-Phenyl-3-(thien-2-yl)imidazo[1,2-*a*]pyridine (14): colorless crystals; 70% yield (method E); mp 164 °C; ^{1}H NMR δ: 8.03 (dt, 1H, J = 6.8 Hz, J = 1.2 Hz, H-5), 7.79 (m, 2H, Ph-2,6), 7.72 (dt, 1H, J = 9 Hz, J = 1.2 Hz, H-8), 7.64 (dt, 1H, J = 4.6 Hz, J = 1.6 Hz, H-5′), 7.40−7.24 (m, 6H, Ph-3,4,5, H3′, H4′, H-7), 6.83 (td, 1H, J = 6.8 Hz, H-6); ^{13}C NMR δ: 145.8 (C-8a), 144.9 (C-2), 134.2 (Ph-1), 130.7 (C-3′), 130.4 (|C-1′|), 129.3 (C-5′), 128.7 (2C, Ph-2,6*), 128.5 (C-4′), 128.4 (2C, Ph-3,5*), 128.1 (Ph-4), 126.5 (C-3), 125.6 (C-7), 124.3 (C-5), 117.9 (C-8), 113.8 (C-6). Anal. Calcd for $C_{17}H_{12}N_2S$: C, 73.89; H, 4.38; N, 10.14. Found: C, 74.04; H, 4.40; N, 10.14.

3-Methyl-2-phenylimidazo[1,2-*a*]pyridine (15): yellow powder; 85% yield (method D); mp 157 °C (lit.[9] mp 158−160 °C); ^{1}H NMR δ: 7.94 (dt, 1H, J = 6.8 Hz, J = 1.2 Hz, H-5), 7.84 (m, 2H, Ph-2,6), 7.68 (dt, 1H, J = 9 Hz, H-8), 7.35−7.56 (m, 3H, Ph-3,4,5), 7.21 (ddd, 1H, J = 9 Hz, J = 6.8 Hz, H-7), 6.89 (t, 1H, J = 6.8 Hz, H-6), 2.68 (s, 3H, CH_3); ^{13}C NMR δ: 144.8 (C-8a), 142.9 (C-2), 135.3 (Ph-1), 128.9 (2C, Ph-2,6*), 128.8 (2C, Ph-3,5*), 127.8 (Ph-4), 123.9 (C-7), 123.3 (C-5), 117.9 (C-8), 116.30 (C-3), 112.4 (C-6).

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