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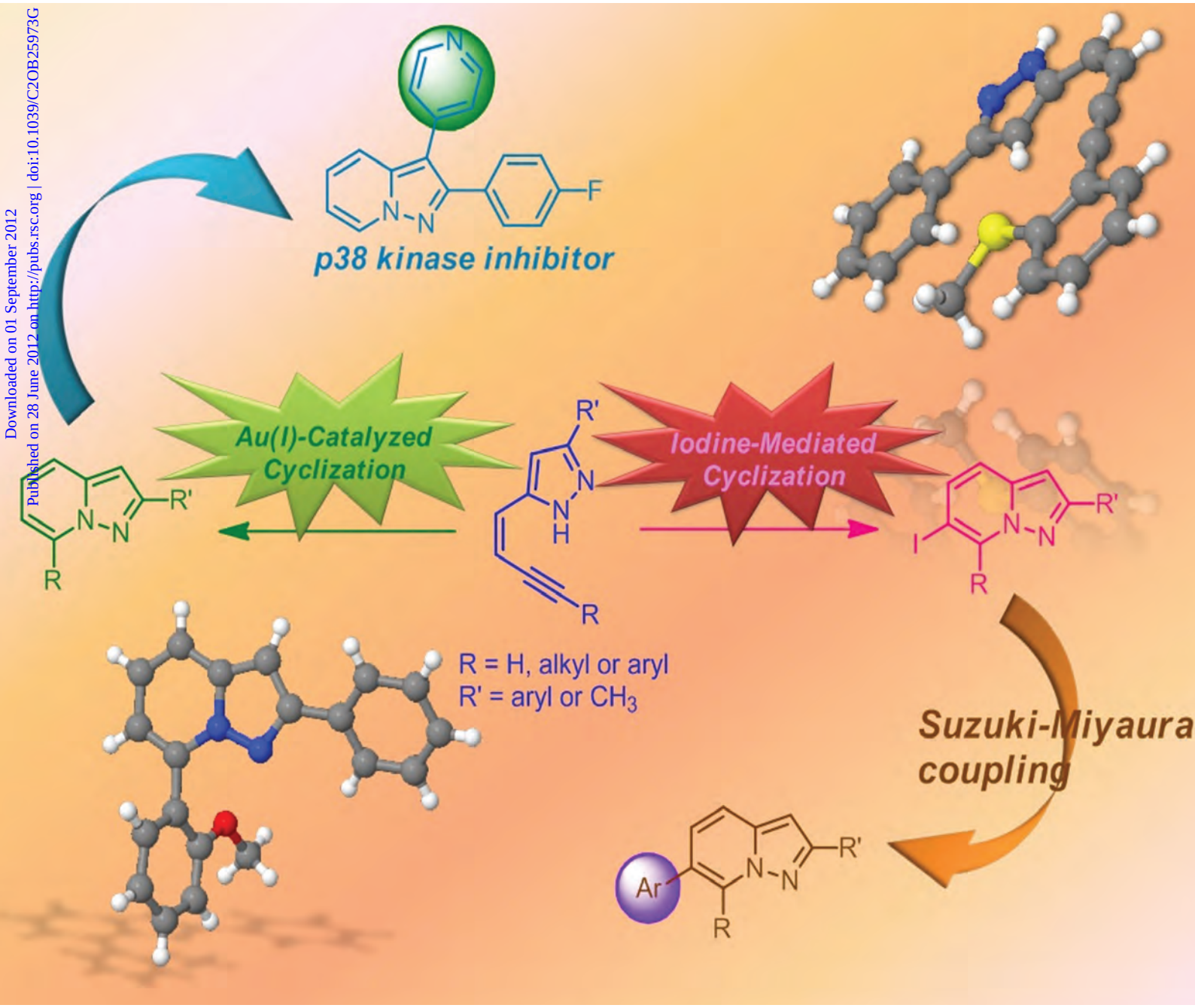

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PAPER

Au(I)-catalyzed and iodine-mediated cyclization of enynylpyrazoles to provide pyrazolo[1,5-*a*]pyridines†

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Pyrazolo[1,5-*a*]pyridines and 6-iodopyrazolo[1,5-*a*]pyridines were synthesized by gold-catalyzed and iodine-mediated cyclization of enynylpyrazoles in good to excellent yields, respectively. The iodinated adducts were further converted to 6-arylpyrazolo[1,5-*a*]pyridines *via* Suzuki–Miyaura coupling reaction and 6-cyanopyrazolo[1,5-*a*]pyridine by Ullmann condensation reaction. One of the cyclization adducts, 2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridine, was converted to a p38 kinase inhibitor, 2-(4-fluorophenyl)-3-(4-pyridinyl)pyrazolo[1,5-*a*]pyridine, in two steps.

Introduction

The pyrazolo[1,5-*a*]pyridine substructure exists widely in molecules of pharmaceutical interest. For instance, the 3-carboxylated pyrazolo[1,5-*a*]pyridines have been shown to be potent and selective $5HT_3$-antagonists,[1] the 2,3-disubstituted pyrazolo[1,5-*a*]-pyridines were evaluated as potent p38 kinase inhibitors and showed good anti-inflammatory activity,[2] a series of aminomethyl-substituted pyrazolo[1,5-*a*]pyridines were reported as high affinity D_4 receptor ligands,[3] 8,9-dihydrofuro[3,2-*c*]-pyrazolo[1,5-*a*]pyridines as melatonin receptor (MT_1/MT_2) ligands were discovered recently[4] and other substituted pyrazolo-[1,5-*a*]-pyridines were shown to exhibit anti-herpetic activity.[5]

Due to the broad spectrum of biological activities of pyrazolo-[1,5-*a*]pyridines, the development of an efficient method to construct these heterocycles has become an important issue. The general methods are the regioselective [3 + 2] cycloaddition of *N*-aminopyridines with alkenes[6] or alkynes,[7] the thermal cyclization of pyridinyl aziridines[2a,8] and the synthesis of pyrazolo[1,5-*a*]-quinolines *via* multicomponent reaction.[9] Recently, we reported a new synthetic method to provide pyrazolo[1,5-*a*]pyridines by the reaction of enediynones with hydrazine mediated by copper chloride.[10] However the drawbacks of this method are that a stoichiometric amount of copper chloride, high reaction temperature and long reaction time are required. In continuation of our study on the synthesis of pyrazolo[1,5-*a*]pyridines, a more efficient synthesis of pyrazolo[1,5-*a*]pyridines by the gold-catalyzed cyclization[11] of enynylpyrazoles and iodine-mediated cyclization[12] of enynylpyrazoles to provide iodinated pyrazolo[1,5-*a*]-pyridines is reported herein.

Results and discussion

The enediynones **1a–w** were prepared according to our previous report.[10] Treatment of **1a–w** with two equivalents of hydrazine in acetonitrile at 60 °C for 30 minutes gave enynylpyrazoles **2a–w** in 75–95% yields, respectively. (Table 1).

Our investigation on the cyclization of enynylpyrazoles to provide pyrazolo[1,5-*a*]pyridines was performed by screening of various transition metal catalysts, such as palladium, platinum, copper, silver, zinc and gold. The results are summarized in Table 2. The results shown palladium catalysts ($PdCl_2$ and $Pd(OAc)_2$ are not efficient at catalyzing this cyclization reaction (Table 2, entries 1 and 2). 10 mol% of CuCl was employed in this study and only a trace amount of **3d** was obtained. Using one equivalent of CuCl and stirring the reaction mixture for 48 hours, compound **3d** was obtained in 45% yield and 36% yield of starting material was recovered (Table 2, entry 3). 10 mol% of silver carbonate and zinc trifluoroacetate are able to promote this cyclization reaction to give the desired product in 70% and 80% yields, respectively (Table 2, entries 4 and 5). However, these reactions required refluxing temperature and long reaction time (three days). Platinum dichloride was also found to be an efficient catalyst in this reaction (Table 2, entry 6). Finally, gold catalysts were found to be the most powerful catalyst in this cyclization reaction. For instance, treatment of **2d** with 3 mol% of chloroauric acid ($HAuCl_4$) in THF at room temperature for 5 hours gave 2-phenyl-7-pentylpyrazolo[1,5-*a*]pyridine (**3d**) in 90% yield (Table 2, entry 7). Using the combination of 3 mol% of Ph_3PAuCl with 10 mol% of $AgSbF_6$ as the catalyst in THF gave **3d** in almost quantitative yield (Table 2, entry 8). Other

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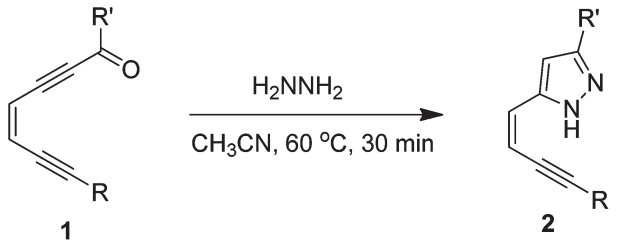
†Electronic supplementary information (ESI) available: Representative experimental procedure and spectroscopic data for all newly synthesized products. CCDC 883588 and 883589. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25973g

solvents, such as dichloromethane and 1,4-dioxane, gave the product **3d** in lower yields (Table 2, entries 9 and 10).

With the optimized reaction conditions in hand, cyclization of other enynylpyrazoles **2a–c** and **2e–w** bearing different substituents on the alkyne terminus and pyrazole ring were also carried out and the results are summarized in Table 3. With the exception of compound **2f**, the reactions gave the pyrazolo[1,5-*a*]-pyridines all in good chemical yields. The low yield (46%) of 7-*t*-butylpyrazolo[1,5-*a*]pyridine **3f** obtained by cyclization of **2f** could be due to the steric hindrance caused by the *tert*-butyl group affecting the cyclization reaction. Compound **2e** bearing a less bulky substituent, an isobutyl group, at the alkyne terminus provides pyrazolo[1,5-*a*]pyridine **3e** in a slightly lower yield (86%) than compounds **2b–d** bearing a straight chain alkyl group. It was also found that the electron density on the aryl group at the alkyne terminus has little effect on this cyclization reaction. Cyclization of compounds **2g–p** under the optimized reaction conditions gave the desired products **3g–p** in excellent yields (92–98%). We also investigated the effect of the substituent on the aryl group at the 3-position of the pyrazole ring and found compounds bearing either an electron-donating group, such as **2q–t**, or an electron-withdrawing group, such as **2u** and **2v**, at the *para*-position of phenyl ring gave the pyrazolo[1,5-*a*]-pyridines **3q–v** all in good chemical yields (90–97%). Compound **2w** bearing methyl group at the 3-position of the pyrazolo ring was also converted to the pyrazolo[1,5-*a*]pyridine **3w** in good yield.

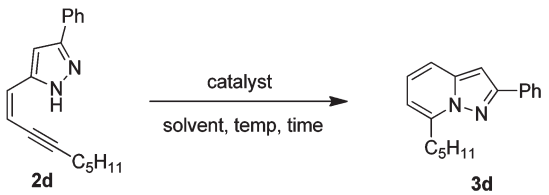
After successfully developing the gold-catalyzed cyclization of enynyl pyrazoles to provide pyrazolo[1,5-*a*]pyridines, we then turn our attention to the iodine-mediated cyclization reaction to prepare the iodinated pyrazolo[1,5-*a*]pyridines. Further functional group transformation would allow us to prepare various multi-substituted pyrazolo[1,5-*a*]pyridines. Thus, treatment of **2a** with two equivalents of iodine in CH_2Cl_2 at room temperature for four hours gave **4a** in 97% yield. Compounds **2b–o** and **2q–w** were also subjected to this cyclization reaction to give the iodinated products **4b–o** and **4q–w** in 60–99% yields (Table 4). The results indicated that this cyclization reaction proceeded very smoothly under the described reaction conditions. Compound **2f** bearing a *tert*-butyl group at the alkyne terminus also produced the cyclization product **4f** in good yield (72%). Compounds **4n–o** and **4t–v** bearing an electron-withdrawing group at the alkyne terminus or on the phenyl ring of the pyrazole ring

Table 1 Synthesis of enynylpyrazoles



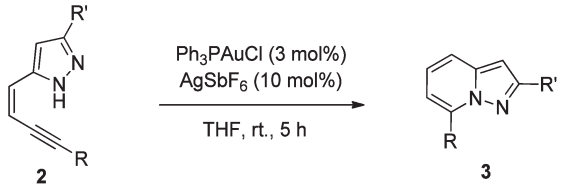
Entry	Enediynones	Products/yields (%)
1	**1a**, R = H; R′ = Ph	**2a**/93
2	**1b**, R = C_6H_{13}; R′ = Ph	**2b**/94
3	**1c**, R = C_4H_9; R′ = Ph	**2c**/93
4	**1d**, R = C_5H_{11}; R′ = Ph	**2d**/95
5	**1e**, R = *iso*-butyl; R′ = Ph	**2e**/92
6	**1f**, R = *tert*-butyl; R′ = Ph	**2f**/88
7	**1g**, R = Ph; R′ = Ph	**2g**/82
8	**1h**, R = *o*-$CH_3C_6H_4$; R′ = Ph	**2h**/86
9	**1i**, R = *m*-$CH_3C_6H_4$; R′ = Ph	**2i**/89
10	**1j**, R = *p*-$CH_3C_6H_4$; R′ = Ph	**2j**/84
11	**1k**, R = *o*-$CH_3OC_6H_4$; R′ = Ph	**2k**/83
12	**1l**, R = *m*-$CH_3OC_6H_4$; R′ = Ph	**2l**/86
13	**1m**, R = *p*-$OCH_3C_6H_4$; R′ = Ph	**2m**/86
14	**1n**, R = *p*-$NO_2C_6H_4$; R′ = Ph	**2n**/80
15	**1o**, R = *p*-CNC_6H_4; R′ = Ph	**2o**/80
16	**1p**, R = *o*-$SCH_3C_6H_4$; R′ = Ph	**2p**/80
17	**1q**, R = C_6H_{13}; R′ = *p*-$CH_3OC_6H_4$	**2q**/75
18	**1r**, R = Ph; R′ = *p*-$CH_3OC_6H_4$	**2r**/78
19	**1s**, R = *p*-$CH_3OC_6H_4$; R′ = *p*-$CH_3OC_6H_4$	**2s**/76
20	**1t**, R = *p*-CNC_6H_4; R′ = *p*-$CH_3OC_6H_4$	**2t**/78
21	**1u**, R = C_6H_{13}; R′ = *p*-$CF_3C_6H_4$	**2u**/76
22	**1v**, R = H; R′ = *p*-FC_6H_4	**2v**/87
23	**1w**, R = C_5H_{11}; R′ = CH_3	**2w**/90

Table 2 Optimization of reaction conditions



Entry	Catalysts	Equiv.	Solvent	Temp.	Time (h)	Yield (%)
1	$PdCl_2$	10 mol%	CH_3CN	Reflux	24	20
2	$Pd(OAc)_2$	10 mol%	THF	r.t.	24	11
3	CuCl	100 mol%	CH_3CN	r.t.	48	45
4	Ag_2CO_3	10 mol%	CH_3CN	Reflux	72	70
5	$Zn(C_2F_3O_2)_2{\cdot}xH_2O$	10 mol%	CH_3CN	Reflux	24	80
6	$PtCl_2$	10 mol%	CH_3CN	Reflux	24	77
7	$HAuCl_4$	3 mol%	THF	r.t.	5	90
8	$PPh_3AuCl/AgSbF_6$	3 mol%/10 mol%	THF	r.t.	5	99
9	$PPh_3AuCl/AgSbF_6$	3 mol%/10 mol%	CH_2Cl_2	r.t.	5	68
10	$PPh_3AuCl/AgSbF_6$	3 mol%/10 mol%	1,4-dioxane	r.t.	5	86

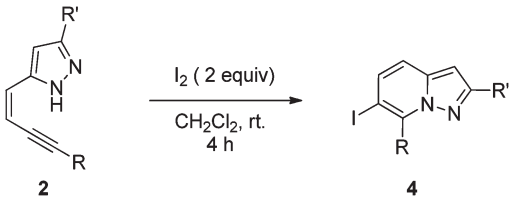
Table 3 Synthesis of pyrazolo[1,5-*a*]pyridines under optimized reaction conditions



Entry	Enynylpyrazoles	Products/yields (%)
1	**2a**, R = H; R′ = Ph	**3a**/98
2	**2b**, R = C_6H_{13}; R′ = Ph	**3b**/99
3	**2c**, R = C_4H_9; R′ = Ph	**3c**/99
4	**2d**, R = C_5H_{11}; R′ = Ph	**3d**/99 (75)[a]
5	**2e**, R = *iso*-butyl; R′ = Ph	**3e**/86 (75)
6	**2f**, R = *tert*-butyl; R′ = Ph	**3f**/46[b] (13)
7	**2g**, R = Ph; R′ = Ph	**3g**/97 (69)
8	**2h**, R = *o*-$CH_3C_6H_4$; R′ = Ph	**3h**/98 (61)
9	**2i**, R = *m*-$CH_3C_6H_4$; R′ = Ph	**3i**/94 (46)
10	**2j**, R = *p*-$CH_3C_6H_4$; R′ = Ph	**3j**/96 (63)
11	**2k**, R = *o*-$CH_3OC_6H_4$; R′ = Ph	**3k**/95 (73)
12	**2l**, R = *m*-$CH_3OC_6H_4$; R′ = Ph	**3l**/94 (45)
13	**2m**, R = *p*-$CH_3OC_6H_4$; R′ = Ph	**3m**/98 (73)
14	**2n**, R = *p*-$NO_2C_6H_4$; R′ = Ph	**3n**/94 (45)
15	**2o**, R = *p*-CNC_6H_4; R′ = Ph	**3o**/92
16	**2p**, R = *o*-$CH_3SC_6H_4$; R′ = Ph	**3p**/92
17	**2q**, R = C_6H_{13}; R′ = *p*-$CH_3OC_6H_4$	**3q**/91 (74)
18	**2r**, R = Ph; R′ = *p*-$CH_3OC_6H_4$	**3r**/96 (67)
19	**2s**, R = *p*-$CH_3OC_6H_4$; R′ = *p*-$CH_3OC_6H_4$	**3s**/90 (71)
20	**2t**, R = *p*-CNC_6H_4; R′ = *p*-$CH_3OC_6H_4$	**3t**/97 (44)
21	**2u**, R = C_6H_{13}; R′ = *p*-$CF_3C_6H_4$	**3u**/95 (42)
22	**2v**, R = H; R′ = *p*-FC_6H_4	**3v**/90
23	**2w**, R = C_5H_{11}, R′ = CH_3	**3w**/92

[a] Values in parentheses are the yields obtained by one-pot reaction reported previously.[10] [b] 40% of starting material was recovered.

Table 4 Synthesis of 6-iodopyrazolo[1,5-*a*]pyridines by iodine-mediated cyclization

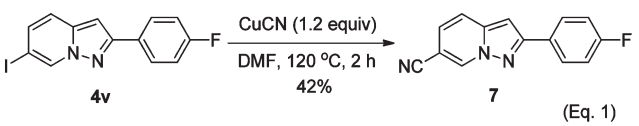


Entry	Enynylpyrazoles	Products/yields (%)
1	**2a**, R = H; R′ = Ph	**4a**/97
2	**2b**, R = C_6H_{13}; R′ = Ph	**4b**/98
3	**2c**, R = C_4H_9; R′ = Ph	**4c**/99
4	**2d**, R = C_5H_{11}; R′ = Ph	**4d**/99
5	**2e**, R = *iso*-butyl; R′ = Ph	**4e**/86
6	**2f**, R = *tert*-butyl; R′ = Ph	**4f**/72
7	**2g**, R = Ph; R′ = Ph	**4g**/99
8	**2h**, R = *o*-$CH_3C_6H_4$; R′ = Ph	**4h**/92
9	**2i**, R = *m*-$CH_3C_6H_4$; R′ = Ph	**4i**/90
10	**2j**, R = *p*-$CH_3C_6H_4$; R′ = Ph	**4j**/99
11	**2k**, R = *o*-$OCH_3C_6H_4$; R′ = Ph	**4k**/94
12	**2l**, R = *m*-$OCH_3C_6H_4$; R′ = Ph	**4l**/95
13	**2m**, R = *p*-$OCH_3C_6H_4$; R′ = Ph	**4m**/98
14	**2n**, R = *p*-$NO_2C_6H_4$; R′ = Ph	**4n**/68
15	**2o**, R = *p*-CNC_6H_4; R′ = Ph	**4o**/60
16	**2q**, R = C_6H_{13}; R′ = *p*-$CH_3OC_6H_4$	**4q**/88
17	**2r**, R = Ph; R′ = *p*-$CH_3OC_6H_4$	**4r**/85
18	**2s**, R = *p*-$OCH_3C_6H_4$; R′ = *p*-$CH_3OC_6H_4$	**4s**/78
19	**2t**, R = *p*-CNC_6H_4; R′ = *p*-$CH_3OC_6H_4$	**4t**/68
20	**2u**, R = C_6H_{13}; R′ = *p*-$CF_3C_6H_4$	**4u**/64
21	**2v**, R = H; R′ = *p*-FC_6H_4	**4v**/82
22	**2w**, R = C_5H_{11}; R′ = CH_3	**4w**/90

gave the products in slightly lower yields. The lower yields of product formation could be due to the lower electron density of the triple bond that will affect the coordination of the iodonium ion to the triple bond to mediate the cyclization reaction. The electron-withdrawing groups on the phenyl ring would also reduce the electron density and nucleophilicity of the pyrazole ring affecting the cyclization reaction.

The proposed mechanisms for the formation of pyrazolo[1,5-*a*]-pyridines **3** and iodinated products **4** are shown in Scheme 1. First of all, the gold catalyst could coordinate to the triple bond to form a complex **I-1** that could then undergo 6-*endo*-dig hydroamination to give intermediate **I-2**.[13] After removal of a proton from **I-2**, the gold compound **I-3** would undergo protonation to give the product **3** and regenerate the gold catalyst to continue the reaction cycle. On the other hand, iodine could coordinate the triple bond to form **II-1**, then iodonium amination could generate the intermediate **II-2**. Removal of the proton by iodide would give the product **4**.

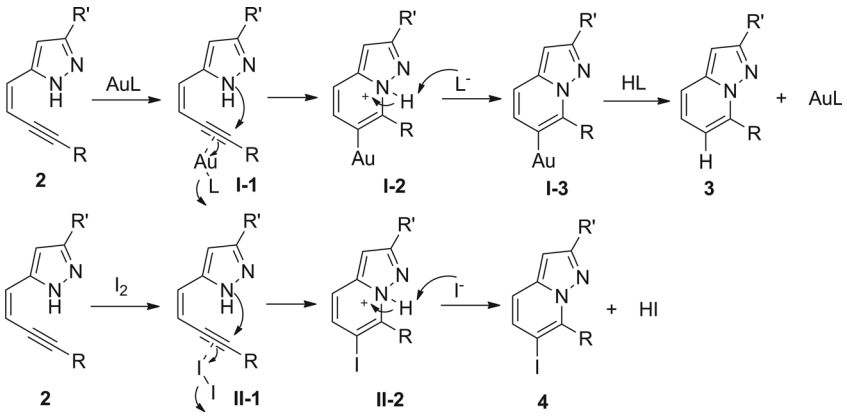
To demonstrate the synthetic utility of the iodinated pyrazolo-[1,5-*a*]pyridines, some of these products were converted to 6-aryl substituted pyrazolo[1,5-*a*]pyridines by Suzuki–Miyaura cross-coupling reactions[14] of **4** with arylboronic acids **5** using $Pd(OAc)_2$ as the catalyst. The results are summarized in Table 5. All the reactions proceed very smoothly to give a high yield of the 6-arylated pyrazolo[1,5-*a*]pyridines except the electron poor boronic acids (Table 5, entries 5, 6 and 7). An iodinated pyrazolo[1,5-*a*]pyridine **4v** was also coupled with copper cyanide[15] to give the cyano substituted adduct **7** in 42% yield (eqn (1))



(Eq. 1)

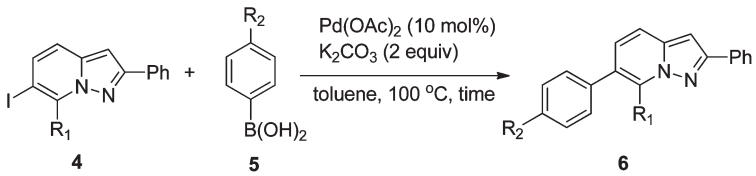
(1)

On the other hand, compound **3v** was converted to a p38 kinase inhibitor **9** in two steps (Scheme 2). Treatment of **3v** with one equivalent of *N*-bromosuccinimide in DMF at room temperature for 90 minutes gave **8** in 85% yield. Compound **8** was then coupled with 4-pyridinylboronic acid (**5f**) using $Pd(PPh_3)_2Cl_2$ and Na_2CO_3 as the base according to the literature procedure,[2] but the final product **9** was obtained in only 12% yield. A significant amount (52%) of starting material **8** was recovered. To optimize the reaction conditions, the catalyst was replaced by $Pd(OAc)_2$ and the base was changed to K_2CO_3. Stirring the reaction mixture of **8** and **5f** in DMF at 120 °C for 8 hours, the final product **9** was then obtained in 32% yield and the amount of the recovered starting material **8** was reduced to 36% yield.



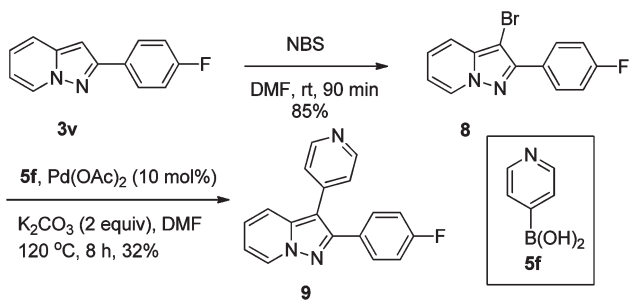
Scheme 1 Proposed mechanisms for the formation of pyrazolo[1,5-*a*]pyridines **3** and iodinated products **4**.

Table 5 Suzuki–Miyaura coupling reactions of **4** with aryl boronic acids



Entry	Compounds	Arylboronic acids	Time (h)	Products/yields (%)
1	**4b**, $R_1 = C_6H_{13}$	**5a**, R_2 = H	5	**6a**/90
2	**4b**, $R_1 = C_6H_{13}$	**5b**, R_2 = OMe	8	**6b**/87
3	**4i**, $R_1 = m\text{-}CH_3C_6H_4$	**5a**, R_2 = H	8	**6c**/85
4	**4i**, $R_1 = m\text{-}CH_3C_6H_4$	**5b**, R_2 = OMe	8	**6d**/70
5	**4i**, $R_1 = m\text{-}CH_3C_6H_4$	**5c**, $R_2 = NO_2$	24	**6e**/20[a]
6	**4i**, $R_1 = m\text{-}CH_3C_6H_4$	**5d**, R_2 = F	24	**6f**/32[a]
7	**4i**, $R_1 = m\text{-}CH_3C_6H_4$	**5e**, R_2 = Cl	24	**6g**/43[a]
8	**4k**, $R_1 = o\text{-}CH_3OC_6H_4$	**5a**, R_2 = H	8	**6h**/95
9	**4k**, $R_1 = o\text{-}CH_3OC_6H_4$	**5b**, R_2 = OMe	8	**6i**/73

[a] Entries 5, 6 and 7 also obtained compound **3i** in 15, 13 and 12% yields, respectively.



Scheme 2 Synthesis of p38 kinase inhibitor.

Conclusions

We have developed an efficient synthetic method to convert enynylpyrazoles to pyrazolo[1,5-*a*]pyridines and 6-iodopyrazolo[1,5-*a*]pyridines by gold-catalyzed cyclization and iodine-mediated cyclization reactions, respectively. The 6-iodopyrazolo-[1,5-*a*]pyridines were further converted to 6-arylpyrazolo[1,5-*a*]-pyridines by Suzuki–Miyaura cross-coupling reaction. We have also demonstrated synthetic utility by preparing a p38 kinase inhibitor. Since pyrazolo[1,5-*a*]pyridines are important heterocycles in both pharmaceutical science and material chemistry, we believe the synthetic methods described here would have a strong impact on these areas.

Experimental section

General considerations

Solvents were purified and dried by standard procedures. Flash column chromatography was performed using 230–400 mesh silica according to standard techniques. Melting points: Barnstead melting point apparatus. MS were run on SHIMADZU QP2010 by EI (70 ev). ^{1}H NMR spectra were measured on 500 MHz spectrometers. Natural abundance ^{13}C NMR spectra were measured using pulse Fourier transform, on a 500 MHz NMR spectrometer operating at 125 MHz. Chemical shifts are given in parts per million (ppm) and coupling constant J in hertz (Hz) for both nuclei, with the solvent (usually $CDCl_3$) peak as an internal standard. The reference peak for ^{1}H is δ 7.26 of $CDCl_3$, and for ^{13}C it is the central peak at δ 77.0.

General procedure for the synthesis of enynylpyrazoles 2

Hydrazine monohydrate (0.3 mmol) was added to a solution of enediynones (**1**) (0.15 mmol) in CH_3CN (5 ml). The reaction mixture was stirred at 60 °C for 30 minutes. After cooling to room temperature, the solution was filtered through $MgSO_4$ and celite on cotton plug and washed with ethyl acetate. After removal of solvent, the residue was purified by column chromatography (silica gel) to give the products (**2a–w**). Characterization data of **2** can be found in the ESI.†

General procedure for the synthesis of pyrazolo[1,5-*a*]pyridines 3

Chloro(triphenylphosphine)gold(I) (0.0045 mmol) and silver hexafluoroantimonate(V) (0.015 mmol) were added to a solution of enynylpyrazoles (**2**) (0.15 mmol) in THF at room temperature for 5 hours. The reaction mixture was directly passed through celite and washed with ethyl acetate. After removal of solvent, the residue was purified by column chromatography (silica gel) to give the products (**3a–w**). Data of most compounds **3** were found in the paper was reported.[10]

2-Phenylpyrazolo[1,5-*a*]pyridine (3a). Characterization data was consistent with that reported in the literature:[6c] white solid; m.p.: 110–112 °C; R_f = 0.56 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.49 (d, J = 7.0 Hz, 1H), 7.98 (d, J = 7.5 Hz, 2H), 7.51 (d, J = 9.0 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.80 (s, 1H), 6.73 (td, J = 7.0, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.5, 141.5, 133.1, 128.7(2C), 128.4, 128.3, 126.4(2C), 123.4, 117.8, 111.6, 93.6 ppm; MS (EI) 194 (M^+, 100), 193 (M^+, 94); HRMS (EI) calcd for $C_{13}H_{10}N_2$ 194.0844, found 194.0843.

4-(2-Phenylpyrazolo[1,5-*a*]pyridin-7-yl)benzonitrile (3o). Yellow solid; m.p.: 184–186 °C; R_f = 0.46 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.20 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 7.2 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.59 (dd, J = 8.8, 1.2 Hz, 1H), 7.45–7.33 (m, 4H), 7.20 (dd, J = 9.2, 7.2 Hz, 1H), 6.93 (s, 1H), 6.87 (dd, J = 7.2, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 153.1, 142.7, 138.1, 138.0, 132.0(2C), 129.0(2C), 128.6(2C), 128.5, 126.5(2C), 123.3, 118.6, 118.2, 113.2, 112.7, 94.4; MS (EI) 295 (M^+, 100), 294 ($M^+ - H^+$, 67); HRMS (EI) calcd for $C_{20}H_{13}N_3$ 295.1109, found 295.1110.

7-(2-(Methylthio)phenyl)-2-phenylpyrazolo[1,5-*a*]pyridine (3p). Yellow solid; m.p.: 144–146 °C; R_f = 0.54 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 (d, J = 6.8 Hz, 2H), 7.57 (dd, J = 8.8, 1.2 Hz, 1H), 7.50–7.27 (m, 7 Hz), 7.17 (dd, J = 8.8, 1.2 Hz, 1H), 6.89 (s, 1H), 6.75 (dd, J = 6.8, 1.2 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 142.0, 139.2, 139.1, 133.9, 133.5, 130.5, 129.6, 128.4(2C), 128.0, 127.7, 126.6(2C), 125.3, 122.9, 117.2, 113.3, 93.9, 17.2; MS (EI) 316 (M^+, 68), 269 (100); HRMS (EI) calcd for $C_{20}H_{16}SN_2$ 316.1034, found 316.1033.

2-(4-Fluorophenyl)pyrazolo[1,5-*a*]pyridine (3v). Characterization data was consistent with that reported in the literature:[6c] yellow solid; m.p.: 144–146 °C; R_f = 0.44 (*n*-hexane–ethyl acetate = 5 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.46 (dd, J = 7.0, 1.0 Hz, 1H), 7.94 (m, 2H), 7.50 (d, J = 8.5 Hz, 1H), 7.16–7.09 (m, 3H), 6.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.9 (d, J = 246.1 Hz), 152.6, 141.6, 129.4 (d, J = 3.3 Hz), 128.4, 128.1 (d, J = 8.2 Hz), 123.5, 117.8; MS (EI) 212 (M^+, 100), 211 ($M^+ - H^+$, 100); HRMS (EI) calcd for $C_{13}H_9FN_2$ 212.0750, found 212.0752.

2-Methyl-7-pentylpyrazolo[1,5-*a*]pyridine (3w). Colorless liquid; R_f = 0.48 (*n*-hexane–ethyl acetate = 20 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31 (d, J = 8.5 Hz, 1H), 7.01 (dd, J = 9.0, 7.0 Hz, 1H), 6.51 (d, J = 7.0 Hz, 1H), 6.29 (s, 1H), 3.12 (t, J = 7.5 Hz, 2H), 2.52 (s, 3H), 1.85 (m, J = 7.5 Hz, 2H), 1.45–1.41 (m, 4H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.8, 141.6, 141.5, 123.0, 114.5, 108.4, 96.1, 31.5, 30.7, 25.7, 22.5, 14.1, 13.9; MS (EI) 202 (M^+, 35), 173 (20), 159 (23), 146 (100); HRMS (EI) calcd for $C_{13}H_{18}N_2$ 202.1470, found 202.1470.

General procedure for the synthesis of 6-iodo-pyrazolo[1,5-*a*]-pyridines 4

Iodine (0.3 mmol) was added to a solution of enynylpyrazoles (**2**) (0.15 mmol) in CH_2Cl_2 at room temperature for 4 hours. The reaction mixture was then quenched with saturated $Na_2S_2O_{3(aq)}$ (10.0 mL) and water (10.0 mL). The resulting solution was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration and removal of solvent, the residue was purified by column chromatography (silica gel) to give the products (**4a–w**).

6-Iodo-2-phenylpyrazolo[1,5-*a*]pyridine (4a). Brown liquid; R_f = 0.58 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73 (d, J = 7.0 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 6.77 (s, 1H), 6.39 (d, J = 11.5 Hz, 1H), 5.98 (dd, J = 11.5, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.2, 142.9, 131.8, 131.2, 128.8(2C), 128.3, 125.7(2C), 121.3, 104.6, 93.0, 82.9; MS (EI) 320 (M^+, 23), 254 (15), 194 (100); HRMS (EI) calcd for $C_{13}H_9N_2I$ 319.9810, found 319.9810.

7-Hexyl-6-iodo-2-phenylpyrazolo[1,5-*a*]pyridine (4b). Beige solid; m.p.: 52–54 °C; R_f = 0.68 *n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.00 (d, J = 7.0 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.36 (d, J = 9.5 Hz, 1H), 7.14 (d, J = 9.5 Hz, 1H), 6.79 (s, 1H), 3.48 (t, J = 8.0 Hz, 2H), 1.82 (m, J = 7.0 Hz, 2H), 1.57–1.36 (m, 6H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.6, 143.5, 141.2, 133.1, 132.7, 128.6(2C), 128.3, 126.5(2C), 116.1, 94.4, 78.1, 34.9, 31.4, 29.2, 25.6, 22.5, 14.0; MS (EI) 404 (M^+, 44), 334 (100), 207(16); HRMS (EI) calcd for $C_{19}H_{21}N_2I$ 404.0749, found 404.0747.

7-Butyl-6-iodo-2-phenylpyrazolo[1,5-*a*]pyridine (4c). Beige solid; m.p.: 48–50 °C; R_f = 0.71 *n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 (d, J = 7.5 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.36 (d, J = 9.5 Hz, 1H), 7.14 (d, J = 9.0 Hz, 1H), 6.80 (s, 1H), 3.50 (t, J = 8.0 Hz, 2H), 1.81 (q, J = 7.0 Hz, 2H), 1.57 (m, J = 7.5 Hz, 2H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$,

125 MHz): δ 152.6, 143.5, 141.2, 133.1, 132.7, 128.6(2C), 128.3, 126.5(2C), 116.1, 94.4, 78.2, 34.6, 27.9, 22.7, 13.9; MS (EI) 376 (M^+, 100), 334 (100), 207(30); HRMS (EI) calcd for $C_{17}H_{17}N_2I$ 376.0436, found 376.0434.

6-Iodo-7-pentyl-2-phenylpyrazolo[1,5-*a*]pyridine (4d). Beige solid; m.p.: 50–52 °C; R_f = 0.70 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.00 (d, J = 7.5 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 8.37 (t, J = 8.0 Hz, 2H), 7.15 (d, J = 9.0 Hz, 1H), 6.8 (s, 1H), 3.48 (t, J = 8.0 Hz, 2H), 1.84 (m, J = 7.5 Hz, 2H), 1.53 (m, J = 7.0 Hz, 2H), 1.45 (m, J = 6.0 Hz, 2H), 0.97 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.7, 143.6, 141.2, 133.2, 132.8, 128.7, 128.4, 126.5, 116.2, 94.4, 78.2, 34.9, 31.7, 25.4, 22.3, 14.0; MS (EI) 390 (M^+, 23), 334 (100), 207(8); HRMS (EI) calcd for $C_{18}H_{19}N_2I$ 390.0593, found 390.0595.

6-Iodo-7-isobutyl-2-phenylpyrazolo[1,5-*a*]pyridine (4e). Brown liquid; R_f = 0.66 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.00 (d, J = 7.5 Hz, 2H), 7.45 (t, J = 7.0 Hz, 2H), 7.39–7.35 (m, 2H), 7.15 (d, J = 9.5 Hz, 1H), 6.79 (s, 1H), 3.41 (d, J = 7.0 Hz, 2H), 2.61 (m, J = 6.5 Hz, 1H), 1.08 (d, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.4, 142.7, 141.2, 133.1, 132.9, 128.6(2C), 128.3, 126.4(2C), 116.2, 94.3, 79.5, 42.9, 26.9, 22.6(2C); MS (EI) 376 (M^+, 34), 334 (100), 207(14); HRMS (EI) calcd for $C_{17}H_{17}N_2I$ 376.0436, found 376.0438.

7-*tert*-Butyl-6-iodo-2-phenylpyrazolo[1,5-*a*]pyridine (4f). Brown liquid; R_f = 0.61 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.00 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 9.0 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 9.0 Hz, 1H), 6.76 (s, 1H), 1.93 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.3, 146.4, 142.3, 139.0, 133.2, 128.6(2C), 128.2, 126.3(2C), 116.5, 93.4, 71.5, 39.5, 31.0(3C); MS (EI) 376 (M^+, 43), 334 (100); HRMS (EI) calcd for $C_{17}H_{17}N_2I$ 376.0437, found 376.0439.

6-Iodo-2,7-diphenylpyrazolo[1,5-*a*]pyridine (4g). Brown liquid; R_f = 0.54 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.83 (d, J = 7.5 Hz, 2H), 7.59–7.51 (m, 6H), 7.36 (t, J = 7.5 Hz, 2H), 7.30 (t, J = 7.5 Hz, 2H), 6.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.1, 141.9, 141.5, 135.9, 133.0, 132.7, 130.1(2C), 129.4, 128.5(2C), 128.4(2C), 128.3, 126.5(2C), 117.6, 94.6, 79.4; MS (EI) 396 (M^+,100), 395 ($M^+ - H^+$, 73); HRMS (EI) calcd for $C_{19}H_{13}N_2I$ 396.0124, found 396.0122.

6-Iodo-2-phenyl-7-*o*-tolylpyrazolo[1,5-*a*]pyridine (4h). Brown solid; m.p.: 118–120 °C; R_f = 0.54 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.82 (d, J = 9.5 Hz, 2H), 7.52 (d, J = 10.5 Hz, 1H), 7.48–7.28 (m, 8H), 6.87 (s, 1H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.4, 142.2, 141.2, 137.0, 136.2, 132.8, 132.4, 130.1, 129.8, 128.4 (2C), 128.3, 126.5(2C), 126.0, 117.6, 94.6, 80.0, 19.0; MS (EI) 410 (M^+,100), 409 ($M^+ - H^+$, 88); HRMS (EI) calcd for $C_{20}H_{15}N_2I$ 410.0280, found 410.0281.

6-Iodo-2-phenyl-7-*m*-tolylpyrazolo[1,5-*a*]pyridine (4i). Brown solid; m.p.: 78–80 °C; R_f = 0.52 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.84 (d, J = 7.0 Hz, 2H), 7.52 (d, J = 9.0 Hz, 1H), 7.48–7.27 (m, 8H), 6.86 (s, 1H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.1, 142.1, 141.5, 138.0, 135.8, 133.0, 132.8, 130.6, 130.1, 128.5(2C), 128.4, 128.3, 127.1, 126.5(2C), 117.5, 94.6, 79.5, 21.5; MS (EI) 410 (M^+,100), 409 ($M^+ - H^+$, 67), 283 (14); HRMS (EI) calcd for $C_{20}H_{15}N_2I$ 410.0280, found 410.0279.

6-Iodo-2-phenyl-7-*p*-tolylpyrazolo[1,5-*a*]pyridine (4j). Brown solid; m.p.: 138–140 °C; R_f = 0.53 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.84 (d, J = 7.5 Hz, 2H), 7.52 (d, J = 9.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.38–7.28 (m, 7H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.1, 142.0, 141.5, 139.3, 133.0, 132.9, 132.8, 130.0(2C), 129.1(2C), 128.4(2C), 128.3, 126.5(2C), 117.5, 94.6, 79.5, 21.6; MS (EI) 410 (M^+, 100), 409 ($M^+ - H^+$, 99); HRMS (EI) calcd for $C_{20}H_{15}N_2I$ 410.0280, found 410.0281.

6-Iodo-7-(2-methoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyridine (4k). Yellow solid; m.p.: 182–184 °C; R_f = 0.51 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.82 (d, J = 7.0 Hz, 2H), 7.54 (t, J = 8.0 Hz, 1H), 7.50 (d, J = 9.0 Hz, 1H), 7.36–7.27 (m, 4H), 7.15 (dd, J = 7.5, 1.0 Hz, 1H), 7.0 (d, J = 8.5 Hz, 1H), 6.85 (s, 1H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.2, 152.9, 141.2, 140.1, 133.1, 132.4, 131.3, 131.0, 128.4(2C), 128.2, 126.5(2C), 125.5, 120.7, 117.5, 111.7, 94.4, 80.6, 55.9; MS (EI) 426 (M^+, 36), 395 (100); HRMS (EI) calcd for $C_{20}H_{15}ON_2I$ 426.0229, found 426.0229.

6-Iodo-7-(3-methoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyridine (4l). Yellow solid; m.p.: 136–138 °C; R_f = 0.47 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.85 (d, J = 7.0 Hz, 2H), 7.52 (d, J = 9.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 8.0 Hz, 2H), 7.32–7.28 (m, 2H), 7.13 (dt, J = 7.5, 1.0 Hz, 1H), 7.10–7.08 (m, 2H), 6.87 (s, 1H), 3.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.4, 153.1, 141.7, 141.5, 137.0, 132.9, 132.8, 129.5, 128.5(2C), 128.3, 126.5(2C), 122.4, 117.6, 115.5, 115.3, 94.6, 79.3, 55.3; MS (EI) 426 (M^+, 36), 425 ($M^+ - H^+$, 67); HRMS (EI) calcd for $C_{20}H_{15}ON_2I$ 426.0229, found 426.0229.

6-Iodo-7-(4-methoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyridine (4m). Yellow solid; m.p.: 188–200 °C; R_f = 0.48 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.84 (d, J = 7.0 Hz, 2H), 7.52–7.49 (m, 3H), 7.36 (t, J = 8.0 Hz, 2H), 7.32–7.25 (m, 2H), 7.09 (d, J = 8.5 Hz, 2H), 6.86 (s, 1H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.2, 153.0, 141.8, 141.5, 131.1, 132.9, 131.7(2C), 128.5(2C), 128.3, 128.1, 126.5(2C), 117.4, 113.7(2C), 94.6, 79.8, 55.2; MS (EI) 426 (M^+,100), 425 ($M^+ - H^+$, 61); HRMS (EI) calcd for $C_{20}H_{15}ON_2I$ 426.0229, found 426.0228.

6-Iodo-7-(4-nitrophenyl)-2-phenylpyrazolo[1,5-*a*]pyridine (4n). Brown solid; m.p.: 196–198 °C, R_f = 0.44 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.43 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 7.0 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 9.0 Hz, 1H), 7.38–7.31 (m, 4H), 6.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.5, 148.3, 141.9, 141.4, 139.4, 132.9, 132.3, 131.7(2C), 128.7, 128.6(2C), 126.5(2C), 123.8(2C), 118.6, 95.1, 78.9; MS (EI) 441 (M^+,100), 440 ($M^+ - H^+$, 32); HRMS (EI) calcd for $C_{19}H_{12}O_2N_3I$ 440.9974, found 440.997.

4-(6-Iodo-2-phenylpyrazolo[1,5-*a*]pyridin-7-yl)benzonitrile (4o). Yellow solid; m.p.: 182–184 °C; R_f = 0.46 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 7.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 9.5 Hz, 1H), 7.39–7.31 (m, 4H), 6.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.4, 141.4, 140.1, 139.7, 132.9, 132.4, 132.3(2C), 131.3(2C), 128.7, 128.6(2C), 126.5(2C), 118.6, 118.5, 113.3, 95.0, 78.9; MS (EI) 421 (M^+,100), 420 ($M^+ - H^+$, 52); HRMS (EI) calcd for $C_{20}H_{12}N_3I$ 421.0076, found 421.0076.

7-Hexyl-6-iodo-2-(4-methoxyphenyl)pyrazolo[1,5-*a*]pyridine (4q). Brown liquid; R_f = 0.58 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 9.5 Hz, 1H), 6.99 (d, J = 9.0 Hz, 2H), 6.71 (s, 1H), 3.87 (s, 3H), 3.46 (t, J = 8.0 Hz, 2H), 1.81 (q, J = 7.5 Hz, 2H), 1.54 (q, J = 7.0 Hz, 2H), 1.40 (m, 4H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 159.9, 152.5, 143.4, 141.2, 132.7, 127.7(2C), 125.8, 115.9, 114.1(2C), 93.7, 77.8, 55.3, 34.8, 31.4, 29.2, 25.6, 22.5, 14.1; MS (EI) 434 (M^+, 31), 364 (100); HRMS (EI) calcd for $C_{20}H_{23}ON_2I$ 434.0855, found 434.0854.

6-Iodo-2-(4-methoxyphenyl)-7-phenylpyrazolo[1,5-*a*]pyridine (4r). Yellow solid; m.p.: 180–182 °C, R_f = 0.52 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.75 (d, J = 9.0 Hz, 2H), 7.58–7.49 (m, 6H), 7.26 (d, J = 9.5 Hz, 1H), 6.89 (d, J = 9 Hz, 2H), 6.78 (s, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz):159.8, 153.0, 141.8, 141.5, 136.0, 132.9, 130.1(2C), 129.3, 128.3(2C), 127.8(2C), 125.5, 117.4, 113.9(2C), 94.0, 79.0, 55.2; MS (EI) 426 (M^+, 100), 425 ($M^+ - H^+$, 46); HRMS (EI) calcd for $C_{20}H_{15}ON_2I$ 426.0229, found 426.0227.

6-Iodo-2,7-bis(4-methoxyphenyl)pyrazolo[1,5-*a*]pyridine (4s). Beige solid; m.p.: 192–194 °C, R_f = 0.55 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (d, J = 9.0 Hz, 2H), 7.50 (d, J = 9.0 Hz, 2H), 7.24 (d, J = 9.5 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 6.77 (s, 1H), 3.92 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 160.1, 159.8, 152.9, 141.7, 141.6, 133.0, 131.7(2C), 128.2, 127.8(2C), 125.6 117.2, 113.9(2C), 113.6(2C), 94.0, 79.3, 55.2; MS (EI) 456 (M^+, 44), 85(56), 71 (75); HRMS (EI) calcd for $C_{21}H_{17}O_2N_2I$ 456.0335, found 456.0336.

4-(6-Iodo-2-(4-methoxyphenyl)pyrazolo[1,5-*a*]pyridin-7-yl)-benzonitrile (4t). Yellow solid; m.p.: 188–190 °C; R_f = 0.46 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 9.5 Hz, 1H), 7.32 (d, J = 9.5 Hz, 1H), 6.90 (d, J = 8.5 Hz, 2H), 6.81 (s, 1H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.1, 153.3, 141.4, 140.2, 139.6, 132.8, 132.3(2C), 131.3(2C), 127.8(2C), 125.1, 118.5, 118.3, 114.0, 94.3, 78.4, 55.2; MS (EI) 451 (M^+, 100), 450 ($M^+ - H^+$, 67); HRMS (EI) calcd for $C_{21}H_{14}ON_3I$ 451.0182, found 451.0181.

7-Hexyl-6-iodo-2-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-*a*]-pyridine (4u). Brown liquid; R_f = 0.50 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.10 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 9.0 Hz, 1H), 7.17 (d, J = 9.0 Hz, 1H), 6.84 (s, 1H), 3.48 (t, J = 8.0 Hz, 2H), 1.81 (m, J = 7.5 Hz, 2H), 1.54 (m, J = 8.0 Hz, 2H), 1.45–1.36 (m, 4H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 151.1, 143.6, 141.3, 136.6, 133.1, 130.2 (q, J_{C-F} = 31.8 Hz), 126.6(2C), 125.6 (q, J_{C-F} = 4.1 Hz, 2C), 116.3, 94.9, 78.9, 34.8, 29.2, 25.6, 22.5, 14.1; MS (EI) 472 (M^+, 94), 402 (100), 275 (44); HRMS (EI) calcd for $C_{20}H_{20}N_2F_3I$ 472.0623, found 472.0625.

2-(4-Fluorophenyl)-6-iodopyrazolo[1,5-*a*]pyridine (4v). Yellow liquid; R_f = 0.33 (*n*-hexane–ethyl acetate = 3 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 (dd, J = 8.5, 5.5 Hz, 2H), 7.21 (d, J = 2.0 Hz, 1H), 7.09 (t, J = 8.5 Hz, 2H), 6.71 (s, 1H), 6.34 (d, J = 12.0 Hz, 1H), 5.96 (dd, J = 12.0, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.7 (d, J = 246.5 Hz), 149.1, 142.1, 132.1, 127.8 (d, J = 2.7 Hz), 127.6 (d, J = 8.3 Hz), 120.6, 115.8 (d, J = 21.3 Hz), 104.5, 92.8, 83.1; MS (EI) 337 (M^+, 100), 336 ($M^+ - H^+$, 95); HRMS (EI) calcd for $C_{13}H_8N_2FI$ 337.9716, found 337.9714.

6-Iodo-2-methyl-7-pentylpyrazolo[1,5-*a*]pyridine (4w). Yellow liquid; R_f = 0.52 (*n*-hexane–ethyl acetate = 20 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30 (d, J = 9.0 Hz, 1H), 7.03 (d, J = 9.0 Hz, 1H), 6.27 (s, 1H), 3.38 (t, J = 7.5 Hz, 1H), 2.48 (s, 3H), 1.75 (m, J = 7.5 Hz, 2H), 2.48 (s, 3H), 1.75 (m, J = 7.5 Hz, 2H), 1.51–1.37 (m, 4H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 151.2, 143.0, 140.7, 132.4, 115.4, 97.0, 77.3, 34.8, 31.6, 25.6, 22.4, 14.0; MS (EI) 328 (M^+, 12), 272 (100); HRMS (EI) calcd for $C_{13}H_{17}IN_2$ 328.0436, found 328.0436.

7-Hexyl-2,6-diphenylpyrazolo[1,5-*a*]pyridine (6a). Green liquid; R_f = 0.52 (*n*-hexane–ethyl acetate = 10 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.06 (d, J = 8.0 Hz, 2H), 7.49–7.36 (m, 9H), 7.06 (d, J = 9.0 Hz, 1H), 6.85 (s, 1H), 3.19 (t, J = 8.0 Hz), 1.89 (m, 7.0 Hz, 2H), 1.31–0.127 (m, 6H), 0.89 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 152.7, 141.1, 139.9, 139.4, 133.8, 129.6 (2C), 128.6 (2C), 128.3 (2C), 128.1, 127.2, 126.4 (2C), 124.7, 114.5, 93.4, 31.2, 29.2, 28.5, 26.6, 22.4, 14.0; MS (EI) 354 (M^+, 30), 284 (100), 283 (59); HRMS (EI) calcd for $C_{25}H_{26}N_2$ 354.2096, found 354.2097.

7-Hexyl-6-(4-methoxyphenyl)-2-phenylpyrazolo[1,5-*a*]pyridine (6b). Brown liquid; R_f = 0.66 (*n*-hexane–ethyl acetate = 30 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.05 (d, J = 7.0 Hz, 2H), 7.48–7.29 (m, 6H), 7.04 (d, J = 9.0 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H), 6.83 (s, 1H), 3.88 (s, 3H), 3.18 (t, J = 7.5 Hz, 2H), 1.87 (m, J = 7.5 Hz, 2H), 1.40–1.25 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.8, 152.6, 141.0, 139.9, 133.8, 131.8, 130.6, 128.6, 128.0, 126.7, 126.4, 124.3, 114.4, 113.7, 93.3, 55.3, 31.2, 29.2, 28.5, 26.6, 22.5, 14.0; MS (EI) 384 (M^+, 27), 314 (72), 214 (77), 202 (68); HRMS (EI) calcd for $C_{26}H_{28}N_2O$ 384.2202, found 384.2200.

2,6-Diphenyl-7-(*m*-tolyl)pyrazolo[1,5-*a*]pyridine (6c). White solid; m.p.: 166–168 °C; R_f = 0.60 (*n*-hexane–ethyl acetate = 30 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (d, J = 7.5 Hz, 2H), 7.61 (d, J = 9.0 Hz, 1H), 7.36–7.09 (m, 13H), 6.89 (s, 1H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.3, 141.1, 138.7, 138.3, 138.0, 133.5, 132.7, 131.0, 129.7, 129.5, 128.7, 128.4, 128.1, 127.9, 126.7, 126.5, 126.4, 125.6, 125.5, 116.5,

93.6, 19.6; MS (EI) 360 (M^+, 68), 345 (100); HRMS (EI) calcd for $C_{26}H_{20}N_2$ 360.1626, found 360.1628.

6-(4-Methoxyphenyl)-2-phenyl-7-(*m*-tolyl)pyrazolo[1,5-*a*]-pyridine (6d). White solid; m.p.: 206–208 °C; R_f = 0.55 (*n*-hexane–ethyl acetate = 30 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (d, J = 7.0 Hz, 2H), 7.60 (d, J = 9.0 Hz, 1H), 7.38–7.25 (m, 5H), 7.14 (d, J = 4.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 6.89 (s, 1H), 6.74 (d, J = 9.0 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.3, 153.2, 141.0, 137.6, 133.5, 132.8, 131.0, 130.5, 129.7, 128.6, 128.4, 128.0, 126.6, 125.5, 125.2, 116.4, 113.4, 93.5, 53.1, 19.6; MS (EI) 390 (M^+, 82), 375 (81), 345 (100); HRMS (EI) calcd for $C_{27}H_{22}N_2O$ 390.1732, found 390.1729.

6-(4-Nitrophenyl)-2-phenyl-7-(*m*-tolyl)pyrazolo[1,5-*a*]pyridine (6e). Yellow solid; m.p.: 238–240 °C; R_f = 0.38 (*n*-hexane–ethyl acetate = 5 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.37 (d, J = 9.0 Hz, 1H), 8.06 (d, J = 7.5 Hz, 2H), 7.79 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 9.5 Hz, 1H), 7.39–7.25 (m, 6H), 7.13 (t, J = 7.5 H, 1H), 6.95 (, 1H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 154.1, 141.3, 138.7, 138.3, 133.1, 131.8, 130.8, 130.2, 130.1, 129.4, 128.5, 128.4, 128.3, 126.5, 125.9, 125.2, 124.3, 123.2, 117.1, 94.2, 19.6; MS (EI) 405 (M^+, 100), 404 ($M^+ - H^+$, 87); HRMS (EI) calcd for $C_{26}H_{19}N_3O_2$ 405.1477, found 405.1478.

6-(4-Fluorophenyl)-2-phenyl-7-(*m*-tolyl)pyrazolo[1,5-*a*]pyridine (6f). Beige solid; m.p.: 208–210 °C; R_f = 0.56 (*n*-hexane–ethyl acetate = 30 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (d, J = 7.0 Hz, 2H), 7.62 (d, J = 9.0 Hz, 1H), 7.37 (t, J = 7.5 Hz, 2H), 7.32–7.23 (m, 4H), 7.15–7.07 (m, 4H), 6.90–6.87 (m, 3H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.6 (d, J = 245.1 Hz), 153.5, 141.1, 138.2, 138.0, 134.7 (d, J = 3.6 Hz), 133.4, 132.5, 131.0 (d, J = 7.4 Hz), 130.9, 129.8, 128.8, 128.4, 128.1, 126.5 (d, J = 75.6 Hz), 125.6, 124.5, 116.6, 115.0 (d, J = 21.0 Hz), 93.7, 19.6; MS (EI) 378 (M^+, 100), 379 (M + 1, 30); HRMS (EI) calcd for $C_{26}H_{19}N_2F$ 378.1532, found 378.1534.

6-(4-Chlorophenyl)-2-phenyl-7-(*m*-tolyl)pyrazolo[1,5-*a*]pyridine (6g). Beige solid; m.p.: 182–184 °C; R_f = 0.62 (*n*-hexane–ethyl acetate = 30 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.91 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 9.0 Hz, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.33–7.19 (m, 8H), 7.09 (d, J = 8.5 Hz, 2H), 6.90 (s, 1H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.2, 141.5, 138.1, 137.6, 137.5, 133.3, 132.6, 132.0, 131.8, 131.2, 129.5, 128.9, 128.4, 128.1, 127.8, 126.5, 124.0, 116.5, 93.8, 21.4; MS (EI) 394 (M^+, 100), 396 (M + 2, 52); HRMS (EI) calcd for $C_{26}H_{19}N_2Cl$ 394.1237, found 394.1235.

7-(2-Methoxyphenyl)-2,6-diphenylpyrazolo[1,5-*a*]pyridine (6h). White solid; m.p.: 172–174 °C; R_f = 0.58 (*n*-hexane–ethyl acetate = 30 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89 (d, J = 7.5 Hz, 2H), 7.60 (d, J = 9.0 Hz, 1H), 7.38–7.17 (m, 11H), 6.95–6.91 (m, 2H), 6.88 (s, 1H), 3.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.1, 152.8, 141.2, 139.2, 133.7, 132.1, 130.3, 129.4, 128.4, 127.9, 127.7, 126.6, 126.4, 126.2, 126.0, 122.4, 120.4, 116.4, 111.3, 93.4, 55.6; 376 (M^+, 97), 359 (67), 345 (100), HRMS (EI) calcd for $C_{18}H_{20}N_2O$ 376.1576, found 376.1579.

7-(2-Methoxyphenyl)-6-(4-methoxyphenyl)-2-phenylpyrazolo-[1,5-*a*]pyridine (6i). White solid; m.p.: 212–214 °C; R_f = 0.60 (*n*-hexane–ethyl acetate = 30 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88 (d, J = 7.0 Hz, 2H), 7.57 (d, J = 9.0 Hz, 1H), 7.39–7.20 (m, 6H), 7.12 (d, J = 8.5 Hz, 2H), 6.95 (m, 2H), 6.86 (s, 1H), 6.75 (d, J = 8.5 Hz, 2H), 3.76 (s, 3H), 3.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.3, 158.2, 152.7, 141.0, 135.2, 133.8, 132.0, 131.5, 130.4, 130.1, 128.4, 127.9, 126.5, 122.6, 120.5, 116.3, 113.2, 111.4, 93.4, 55.7, 55.1; MS (EI) 406 (M^+, 12), 375 (21), 284 (11), 149 (21); HRMS (EI) calcd for $C_{27}H_{22}N_2O_2$ 406.1681, found 406.1679.

2-(4-Fluorophenyl)pyrazolo[1,5-*a*]pyridine-6-carbonitrile (7). Characterization data was consistent with that reported in the literature[2a]: brown solid; m.p.: 128–130 °C; R_f = 0.32 (*n*-hexane–ethyl acetate = 2 : 1 as eluent);^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.73 (s, 1H), 7.91 (dd, J = 9.0, 5.5 Hz, 2H), 7.31–7.27 (m, 2H), 7.14 (t, J = 8.5 Hz, 2H), 6.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.1 (d, J = 246.5 Hz), 152.8, 140.2, 135.5, 131.4, 128.8 (d, J = 3.1 Hz), 128.2 (d, J = 32.5 Hz), 118.5, 115.8 (d, J = 21.5 Hz), 94.2, 73.8, 29.6; MS (EI) 237 (M^+, 100), 236 ($M^+ - H^+$, 99); HRMS (EI) calcd for $C_{14}H_8N_3F$ 237.0702, found 237.0704.

3-Bromo-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridine (8). Characterization data was consistent with that reported in the literature[2a]: tan solid; R_f = 0.45 (*n*-hexane–ethyl acetate = 5 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.43 (d, J = 7.0 Hz, 1H), 8.04 (dd, J = 8.5, 5.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 1H), 7.23–7.16 (m, 3H), 6.83 (t, J = 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.1 (d, J = 247.4 Hz), 149.4, 139.9, 130.2 (d, J = 8.3 Hz), 128.6, 128.0 (d, J = 3.1 Hz), 124.4, 116.9, 115.5 (d, J = 21.5 Hz), 112.7, 81.9; MS (EI) 292 (M + 2, 100), 290 (M^+, 100), 211 (83); HRMS (EI) calcd for $C_{12}H_8BrFN_2$ 289.9855, found 289.9854.

2-(4-Fluorophenyl)-3-(pyridin-4-yl)pyrazolo[1,5-*a*]pyridine (9). White solid; m.p.: 136–138 °C; R_f = 0.48 (*n*-hexane–ethyl acetate = 5 : 1 as eluent); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.57 (brs, 2H), 8.50 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 7.53 (m, 2H), 7.26–7.19 (m, 3H), 7.05 (t, J = 8.5 Hz, 2H), 6.85 (dt, J = 7.0, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.9 (d, J = 247.5 Hz), 150.8, 150.1, 141.1, 139.4, 130.7 (d, J = 8.3 Hz), 128.6, 128.4 (d, J = 3.1 Hz), 125.0, 124.0, 116.5, 115.6 (d, J = 21.5 Hz), 112.8, 107.1; MS (EI) 290 (M + 1, 30), 289 (M^+, 100); (HRMS (EI) calcd for $C_{18}H_{12}N_3F$ 289.1015, found 289.1014.

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