Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2011, **9**, 7033

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PAPER

An efficient approach to pyrazolo[5,1-*a*]isoquinolin-2-amines *via* a silver(I)-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and nitrile†

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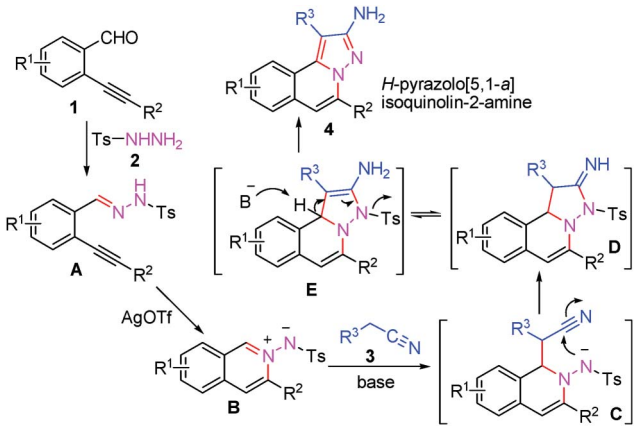
Received 8th June 2011, Accepted 27th June 2011
DOI: 10.1039/c1ob05917c

A three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and nitrile catalyzed by silver triflate under mild conditions is reported, which generates pyrazolo[5,1-*a*]isoquinolin-2-amines in good to excellent yields.

The development of novel and efficient methods using diversity-oriented synthesis approaches for the formation of small molecules with privileged scaffolds is an important part of chemical genetics,[1] and continues to be of major importance in synthetic organic chemistry.[2] Among the strategies, multi-component reactions represent an effective and straightforward methodology for the synthesis of cyclic and polycyclic structures, which has attracted much attention.[3] In our laboratory, it has been our aim to develop new cascade processes[4] for the generation of natural product-like compounds.[5] Recently, we have developed a facile route for the construction of diverse pyrazolo[5,1-*a*]isoquinolines starting from 2-alkynylbenzaldehyde or *N*′-(2-alkynylbenzylidene)hydrazide.[6] Subsequent biological assays discovered that some of these compounds exhibit promising biological activities for inhibition of CDC25B, TC-PTP, and PTP1B.[6d] Additionally, various biological effects[7] including antitumor activity[8] have been reported for isoquinoline-fused polycyclic compounds such as pyrimido[2,1-*a*]isoquinolines and imidazo[2,1-*a*]isoquinolines. In order to get more active hits from the corresponding biological evaluation, we need to introduce more diversities to the scaffold of pyrazolo[5,1-*a*]isoquinolines for the construction of functionalized pyrazolo[5,1-*a*]isoquinolines.

Therefore, pyrazolo[5,1-*a*]isoquinolin-2-amine was selected as the model compound for reaction development (Scheme 1). The introduction of an amino group in the scaffold would be beneficial for its further elaboration. In continuation of our recently developed methods for the silver-catalyzed reaction



Scheme 1 A possible mechanism for AgOTf-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and nitrile.

of *N*′-(2-alkynylbenzylidene)hydrazide,[6] we hypothesized that the conversion could be traced back to 2-alkynylbenzaldehyde, sulfonohydrazide, and nitrile. As illustrated in Scheme 1, 2-alkynylbenzaldehyde **1** condenses with sulfonohydrazide **2** to afford *N*′-(2-alkynylbenzylidene)hydrazide **A**. In the presence of a catalytic amount of silver triflate, isoquinolinium compound **B** could be produced *via* an intramolecular 6-*endo* cyclization. Subsequently, substituted acetonitrile **3** could become involved, to act as a nucleophile in the presence of a base to attack the isoquinolinium **B**. After generation of intermediate **C**, an intramolecular nucleophilic attack of nitrile could occur to furnish compound **D**, which could then undergo tautomerization and aromatization to produce the expected pyrazolo[5,1-*a*]isoquinolin-2-amine **4**.

On the basis of this chemistry, our first attempt to effect the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **A1** and malononitrile **3a** was performed in the presence of 10 mol% of silver triflate (Scheme 2). Different bases and solvents were examined. Initially, a variety of bases such as K_3PO_4, Cs_2CO_3, K_2CO_3, Et_3N, DABCO, $^iPr_2NEt$ were added to the reaction in

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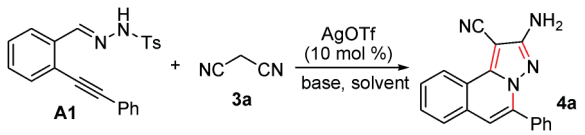
† Electronic supplementary information (ESI) available: Experimental procedure, characterization data, ^1H and ^{13}C NMR spectra of compounds **4**, and a CIF file of compound **4e**. CCDC reference number 826050. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05917c



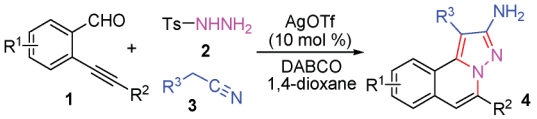
Scheme 2 Initial studies for the synthesis of pyrazolo[5,1-*a*]-isoquinolin-2-amine **4a**.

toluene. To our delight, the reaction worked most efficiently when DABCO was employed as the base, and the desired product **4a** was obtained in 67% yield. Subsequently, several solvents were screened. A similar result was observed when the reaction took place in THF (70% yield) or MeCN (71% yield). A higher yield was isolated when the reaction occurred in dichloroethane (85% yield). A further survey showed that the reaction performed in 1,4-dioxane afforded the corresponding product in 90% yield. With these results in hand, we re-explored the three-component reaction of 2-(2-phenylethynyl)benzaldehyde **1a**, sulfonohydrazide **2**, and malononitrile **3a** under the conditions mentioned above. Gratifyingly, pyrazolo[5,1-*a*]isoquinolin-2-amine **4a** was produced in 85% yield.

Next, investigations with various 2-alkynylbenzaldehydes **1** were conducted under the optimized conditions (10 mol% of AgOTf, DABCO, 1,4-dioxane). Table 1 shows the summary of results for the evaluation of the reactions. An excellent yield (96%) was obtained when 2-(2-phenylethynyl)benzaldehyde **1a**, sulfonohydrazide **2**, and ethyl 2-cyanoacetate **3b** were put in a single pot (entry 2). The substitution by a cyclopropyl group at the triple bond position of 2-alkynylbenzaldehydes **1b** showed a similar reactivity when sulfonohydrazide **2** and malononitrile **3a** were involved in the reaction (91% yield, entry 3). Reaction of 2-alkynylbenzaldehydes **1b**, sulfonohydrazide **2**, and ethyl 2-cyanoacetate **3b** decreased the yield of the desired product **4d** (65% yield, entry 4). Noticeably, 2-alkynylbenzaldehyde **1c** reacted with sulfonohydrazide **2** and malononitrile **3a** leading to the corresponding pyrazolo[5,1-*a*]isoquinolin-2-amine **4e** in an almost quantitative yield (entry 5). Additionally, the structure of compound **4e** was unambiguously identified by X-ray crystallography analysis (see the ESI†). A slightly lower yield was obtained when ethyl 2-cyanoacetate **3b** was used as a replacement in the reaction (90% yield, entry 6). Interestingly, 2-alkynylbenzaldehydes **1d** with a trimethylsilyl group attached to the triple bond was a good substrate in this transformation (entries 7 and 8), which was in contrast to the previous reports.[6] However, the product obtained was the desilylated one. Finally, reactions of a series of substituted 2-alkynylbenzaldehydes **1** with electron-donating groups or electron-withdrawing groups attached on the aromatic ring were explored under the standard conditions. All the reactions worked well to afford the desired pyrazolo[5,1-*a*]isoquinolin-2-amines in good to excellent yields (entries 9–18). For example, the conditions could be applicable to the reaction of fluoro-substituted 2-alkynylbenzaldehydes **1h**, sulfonohydrazide **2**, and ethyl 2-cyanoacetate **3b**, which gave rise to the expected product **4p** in 98% yield (entry 16).

In summary, we have described a novel and efficient route to pyrazolo[5,1-*a*]isoquinolin-2-amines by a three-component cascade cyclization strategy. This AgOTf-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and nitrile proceeds smoothly with the formation of one carbon–carbon and

Table 1 Synthesis of pyrazolo[5,1-*a*]isoquinolin-2-amines *via* AgOTf-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and nitrile



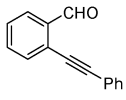
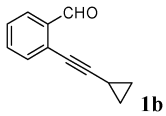
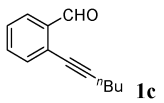
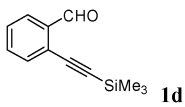
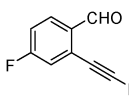
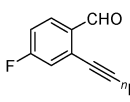
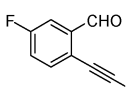
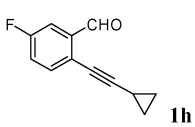
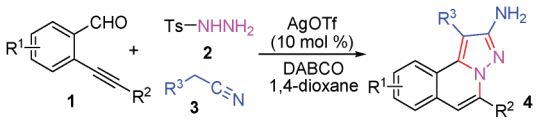
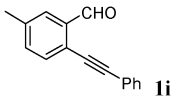
Entry	2-Alkynylbenzaldehyde	Nitrile	Product	Yield (%)[a]
1	 **1a**	**3a**	**4a**	85
2	**1a**	**3b**	**4b**	96
3	 **1b**	**3a**	**4c**	91
4	**1b**	**3b**	**4d**	65
5	 **1c**	**3a**	**4e**	99
6	**1c**	**3b**	**4f**	90
7	 **1d**	**3a**	**4g**	99[b]
8	**1d**	**3b**	**4h**	93[b]
9	 **1e**	**3a**	**4i**	84
10	**1e**	**3b**	**4j**	90
11	 **1f**	**3a**	**4k**	96
12	**1f**	**3b**	**4l**	88
13	 **1g**	**3a**	**4m**	66
14	**1g**	**3b**	**4n**	98
15	 **1h**	**3a**	**4o**	87
16	**1h**	**3b**	**4p**	98

Table 1 (*Contd.*)



Entry	2-Alkynylbenzaldehyde	Nitrile	Product	Yield (%)[a]
17	 **1i**	 **3a**	**4q**	96
18	**1i**	 **3b**	**4r**	68

[a] Isolated yield based on 2-alkynylbenzaldehyde **1**. [b] Desilylated compound was obtained (R^2 = H).

three carbon–nitrogen bonds. Diverse pyrazolo[5,1-*a*]isoquinolin-2-amines are generated in good to excellent yields under mild conditions starting from easily available materials. Library construction and subsequent biological evaluation are in progress in our laboratory.

Experimental section

General experimental procedure for the synthesis of pyrazolo[5,1-*a*]isoquinolin-2-amines *via* an AgOTf-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and nitrile: A mixture of 2-alkynylbenzaldehyde **1** (0.3 mmol, 1.0 equiv), AgOTf (7.7 mg, 10 mol%), and sulfonohydrazide **2** (0.3 mmol, 1.0 equiv) in 1,4-dioxane (1.0 mL) was stirred at 70 °C vigorously for 1 h. Then nitrile **3** (0.6 mmol, 2.0 equiv) and DABCO (0.6 mmol, 2.0 equiv) were added. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (5.0 mL) and diluted with ethyl acetate (5.0 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to provide the desired product **4**.

2-Amino-5-phenylpyrazolo[5,1-*a*]isoquinoline-1-carbonitrile (**4a**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.32 (s, 2H), 7.29 (s, 1H), 7.47–7.53 (m, 3H), 7.65–7.70 (m, 2H), 7.77–7.79 (m, 2H), 7.91–7.93 (m, 1H), 8.46–8.48 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 69.7, 112.6, 115.9, 120.7, 122.1, 127.7, 127.9, 128.1, 129.2, 129.4, 129.5, 130.1, 133.0, 137.2, 140.4, 159.2; HRMS calcd for $C_{18}H_{12}N_4$ (M^+ + H): 285.1140, found: 285.1147.

2-Amino-5-cyclopropylpyrazolo[5,1-*a*]isoquinoline-1-carbonitrile (**4b**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.90–0.91 (m, 2H), 1.07–1.09 (m, 2H), 2.45–2.50 (m, 1H), 6.34 (s, 2H), 6.93 (s, 1H), 7.59–7.61 (m, 2H), 7.77–7.78 (m, 1H), 8.39–8.40 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 7.4, 11.1, 69.4, 106.5, 116.0, 119.8, 122.0, 127.0, 127.1, 129.2, 130.2, 139.7, 140.2, 159.3; HRMS calcd for $C_{15}H_{12}N_4$ (M^+ + Na): 271.0960, found: 271.0977.

2-Amino-5-butylpyrazolo[5,1-*a*]isoquinoline-1-carbonitrile (**4c**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.89 (t, J = 7.2 Hz, 3H), 1.33–1.38 (m, 2H), 1.67–1.71 (m, 2H), 2.91–2.94 (m, 2H), 6.31 (s, 2H), 7.03 (s, 1H), 7.61–7.62 (m, 2H), 7.79–7.80 (m, 1H), 8.38–8.40 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.7, 21.9, 28.3, 30.1, 69.2, 109.7, 116.0, 120.1, 122.0, 127.0, 127.1, 129.3, 130.0, 138.5, 139.7, 159.2; HRMS calcd for $C_{16}H_{16}N_4$ (M^+ + H): 265.1453, found: 265.1464.

2-Aminopyrazolo[5,1-*a*]isoquinoline-1-carbonitrile (**4d**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.29 (s, 2H), 7.24 (d, J = 6.4 Hz, 1H), 7.65–7.73 (m, 2H), 7.89–7.91 (m, 1H), 8.26 (d, J = 6.4 Hz, 1H), 8.40 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 69.0, 112.2, 115.9, 121.2, 122.2, 126.1, 127.7, 128.1, 129.4, 129.8, 139.3, 159.7; HRMS calcd for $C_{12}H_8N_4$ (M^+ + Na): 231.0647, found: 231.0660.

2-Amino-8-fluoro-5-phenylpyrazolo[5,1-*a*]isoquinoline-1-carbonitrile (**4e**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.34 (s, 2H), 7.28 (s, 1H), 7.50–7.59 (m, 4H), 7.71–7.76 (m, 3H), 8.46 (dd, J = 8.4, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 69.7, 111.9, 112.1 (d, $^2J_{CF}$ = 22 Hz), 115.8, 116.9 (d, $^2J_{CF}$ = 24 Hz), 117.7, 125.1 (d, $^3J_{CF}$ = 10 Hz), 128.1, 129.4, 132.2 (d, $^3J_{CF}$ = 10 Hz), 132.7, 138.1, 140.2, 159.1, 161.9 (d, $^1J_{CF}$ = 246 Hz); HRMS calcd for $C_{18}H_{11}FN_4$ (M^+ + Na): 325.0865, found: 325.0861.

2-Amino-5-butyl-8-fluoropyrazolo[5,1-*a*]isoquinoline-1-carbonitrile (**4f**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.92 (t, J = 7.2 Hz, 3H), 1.34–1.43 (m, 2H), 1.69–1.72 (m, 2H), 2.92–2.96 (m, 2H), 6.35 (s, 2H), 7.07 (s, 1H), 7.51–7.55 (m, 1H), 7.65 (d, J = 9.6 Hz, 1H), 8.39–8.42 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.7, 21.9, 28.2, 30.1, 69.2, 109.0, 111.4 (d, $^2J_{CF}$ = 22 Hz), 115.8, 116.1 (d, $^2J_{CF}$ = 24 Hz), 117.0, 124.9 (d, $^3J_{CF}$ = 10 Hz), 132.2 (d, $^3J_{CF}$ = 10 Hz), 139.5, 139.6, 159.1, 161.9 (d, $^1J_{CF}$ = 246 Hz); HRMS calcd for $C_{16}H_{15}FN_4$ (M^+ + Na): 305.1178, found: 305.1189.

2-Amino-9-fluoro-5-phenylpyrazolo[5,1-*a*]isoquinoline-1-carbonitrile (**4g**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.34 (s, 2H), 7.30 (s, 1H), 7.49–7.55 (m, 4H), 7.75–7.76 (m, 2H), 7.98–8.00 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 69.9, 106.6 (d, $^2J_{CF}$ = 24 Hz), 112.2, 115.6, 118.5 (d, $^2J_{CF}$ = 24 Hz), 121.5 (d, $^3J_{CF}$ = 10 Hz), 127.0, 128.1, 129.2, 129.4, 130.8 (d, $^3J_{CF}$ = 9 Hz), 132.8, 136.6, 139.5, 159.1, 160.6 (d, $^1J_{CF}$ = 245 Hz); HRMS calcd for $C_{18}H_{11}FN_4$ (M^+ + H): 303.1046, found: 303.1057.

2-Amino-5-cyclopropyl-9-fluoropyrazolo[5,1-*a*]isoquinoline-1-carbonitrile (**4h**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.90–0.91 (m, 2H), 1.08–1.10 (m, 2H), 2.45–2.50 (m, 1H), 6.42 (s, 2H), 7.02 (s, 1H), 7.53–7.57 (m, 1H), 7.88–7.91 (m, 1H), 7.98 (d, J = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 7.4, 11.1, 69.5, 106.3, 106.5(d, $^2J_{CF}$ = 24 Hz), 115.8, 118.4(d, $^2J_{CF}$ = 24 Hz), 120.6 (d, $^3J_{CF}$ = 10 Hz), 127.3, 130.2 (d, $^3J_{CF}$ = 9 Hz), 138.9, 139.8, 159.3, 160.1 (d, $^1J_{CF}$ = 243 Hz); HRMS calcd for $C_{15}H_{11}FN_4$ (M^+ + Na): 289.0865, found: 289.0879.

2-Amino-9-methyl-5-phenylpyrazolo[5,1-*a*]isoquinoline-1-carbonitrile (**4i**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.47 (s, 3H), 6.26 (s, 2H), 7.20 (s, 1H), 7.44–7.49 (m, 4H), 7.75–7.76 (m, 3H), 8.18 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.5, 69.4, 112.5, 116.0, 120.7, 121.2, 127.5, 127.9, 128.1, 129.1, 129.4, 131.0, 133.0, 136.3, 137.4, 139.9, 159.0; HRMS calcd for $C_{19}H_{14}N_4$ (M^+ + H): 299.1297, found: 299.1321.

Ethyl 2-amino-5-phenylpyrazolo[5,1-*a*]isoquinoline-1-carboxylate (**4j**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (t, J = 7.2 Hz, 3H), 4.44–4.50 (m, 2H), 5.16 (s, 2H), 7.07 (s, 1H), 7.48–7.51 (m, 3H), 7.56–7.59 (m, 2H), 7.69–7.71 (m, 1H), 7.77–7.79 (m, 2H), 9.67–9.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 60.6, 93.4, 114.3, 123.2, 127.1, 127.2, 127.7, 128.5, 129.2, 129.6, 129.9, 131.5, 134.1, 137.8, 140.5, 158.5, 164.9;

HRMS calcd for $C_{20}H_{17}N_3O_2$ (M^+ + H): 332.1399, found: 332.1396.

Ethyl 2-amino-5-cyclopropylpyrazolo[5,1-*a*]isoquinoline-1-carboxylate (**4k**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86–0.90 (m, 2H), 1.14–1.19 (m, 2H), 1.48 (t, J = 7.2 Hz, 3H), 2.56–2.63 (m, 1H), 4.44–4.50 (m, 2H), 5.29 (s, 2H), 6.17 (s, 1H), 7.50–7.62 (m, 3H), 9.62–9.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.3, 11.5, 14.5, 60.2, 92.9, 108.0, 122.1, 126.0, 126.2, 127.2, 128.6, 131.2, 139.9, 158.3, 164.6; HRMS calcd for $C_{17}H_{17}N_3O_2$ (M^+ + H): 296.1399, found: 296.1397.

Ethyl 2-amino-5-butylpyrazolo[5,1-*a*]isoquinoline-1-carboxylate (**4l**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J = 7.2 Hz, 3H), 1.48 (t, J = 7.2 Hz, 3H), 1.43–1.53 (m, 2H), 1.78–1.85 (m, 2H), 3.03–3.07 (m, 2H), 4.44–4.49 (m, 2H), 5.22 (s, 2H), 6.89 (s, 1H), 7.50–7.57 (m, 2H), 7.63–7.65 (m, 1H), 9.62–9.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 14.9, 22.8, 29.2, 31.2, 60.5, 93.1, 111.2, 122.7, 126.3, 126.6, 127.6, 128.9, 131.5, 139.0, 140.0, 158.5, 165.0; HRMS calcd for $C_{18}H_{21}N_3O_2$ (M^+ + H): 312.1712, found: 312.1721.

Ethyl 2-aminopyrazolo[5,1-*a*]isoquinoline-1-carboxylate (**4m**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (t, J = 7.2 Hz, 3H), 4.44–4.49 (m, 2H), 5.23 (s, 2H), 7.05 (d, J = 7.2 Hz, 1H), 7.56–7.61 (m, 2H), 7.67–7.70 (m, 1H), 8.01 (d, J = 7.2 Hz, 1H), 9.65–9.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 60.7, 93.2, 113.5, 123.9, 125.9, 127.3, 127.5, 128.0, 129.2, 131.3, 139.6, 159.2, 164.8; HRMS calcd for $C_{14}H_{13}N_3O_2$ (M^+ + H): 256.1086, found: 256.1101.

Ethyl 2-amino-8-fluoro-5-phenylpyrazolo[5,1-*a*]isoquinoline-1-carboxylate (**4n**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.37 (t, J = 6.8 Hz, 3H), 4.35–4.40 (m, 2H), 6.05 (s, 2H), 7.33 (s, 1H), 7.45–7.55 (m, 4H), 7.70–7.76 (m, 3H), 9.68–9.72 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.3, 59.9, 92.0, 111.4 (d, $^2J_{CF}$ = 20 Hz), 112.7, 115.5 (d, $^2J_{CF}$ = 24 Hz), 118.9, 128.1, 129.2, 129.5, 129.8 (d, $^3J_{CF}$ = 9 Hz), 133.0 (d, $^3J_{CF}$ = 10 Hz), 133.4, 137.9, 138.9, 158.3, 161.6 (d, $^1J_{CF}$ = 246 Hz), 163.9; HRMS calcd for $C_{20}H_{16}FN_3O_2$ (M^+ + H): 350.1305, found: 350.1321.

Ethyl 2-amino-5-butyl-8-fluoropyrazolo[5,1-*a*]isoquinoline-1-carboxylate (**4o**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J = 7.2 Hz, 3H), 1.47 (t, J = 7.2 Hz, 3H), 1.43–1.52 (m, 2H), 1.75–1.83 (m, 2H), 3.01–3.04 (m, 2H), 4.43–4.48 (m, 2H), 5.21 (s, 2H), 6.80 (s, 1H), 7.21–7.25 (m, 2H), 9.70–9.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.8, 22.8, 29.1, 31.1, 60.6, 93.0, 110.4, 110.7 (d, $^2J_{CF}$ = 22 Hz), 115.1 (d, $^2J_{CF}$ = 23 Hz), 119.4, 130.6 (d, $^3J_{CF}$ = 9 Hz), 133.5 (d, $^3J_{CF}$ = 9 Hz), 139.9, 140.0, 158.4, 162.6 (d, $^1J_{CF}$ = 248 Hz), 164.8; HRMS calcd for $C_{18}H_{20}FN_3O_2$ (M^+ + H): 330.1618, found: 330.1592.

Ethyl 2-amino-9-fluoro-5-phenylpyrazolo[5,1-*a*]isoquinoline-1-carboxylate (**4p**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.38 (t, J = 6.8 Hz, 3H), 4.35–4.41 (m, 2H), 6.09 (s, 2H), 7.39 (s, 1H), 7.48–7.58 (m, 4H), 7.75–7.77 (m, 2H), 7.98 (t, J = 6.8 Hz, 1H), 9.45–9.48 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.2, 60.0, 92.1, 111.3 (d, $^2J_{CF}$ = 25 Hz), 113.0, 118.9 (d, $^2J_{CF}$ = 24 Hz), 119.0, 123.1, 127.7, 128.1, 129.0, 129.6, 130.0, 133.5, 136.4, 158.3, 160.2 (d, $^1J_{CF}$ = 232 Hz), 163.9; HRMS calcd for $C_{20}H_{16}FN_3O_2$ (M^+ + H): 350.1305, found: 350.1305.

Ethyl 2-amino-5-cyclopropyl-9-fluoropyrazolo[5,1-*a*]isoquinoline-1-carboxylate (**4q**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–0.85 (m, 2H), 1.03–1.05 (m, 2H), 1.35 (t, J = 6.8 Hz, 3H), 2.45–2.50 (m, 1H), 4.32–4.34 (m, 2H), 6.09 (s, 2H), 6.94 (s, 1H), 7.38–7.42 (m, 1H), 7.72–7.75 (m, 1H), 9.30–9.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.3, 11.3, 14.2, 59.9, 91.9, 107.0, 111.1 (d, $^2J_{CF}$ = 26 Hz), 117.4 (d, $^2J_{CF}$ = 24 Hz), 122.1 (d, $^3J_{CF}$ = 11 Hz), 127.7, 129.1 (d, $^3J_{CF}$ = 9 Hz), 137.8, 139.2, 158.4, 159.6 (d, $^1J_{CF}$ = 240 Hz), 163.9; HRMS calcd for $C_{17}H_{16}FN_3O_2$ (M^+ + Na): 336.1124, found: 336.1143.

Ethyl 2-amino-9-methyl-5-phenylpyrazolo[5,1-*a*]isoquinoline-1-carboxylate (**4r**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (t, J = 7.2 Hz, 3H), 2.58 (s, 3H), 4.46–4.51 (m, 2H), 5.18 (s, 2H), 7.05 (s, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.46–7.52 (m, 3H), 7.61 (d, J = 8.0 Hz, 1H), 7.77–7.79 (m, 2H), 9.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 22.0, 60.2, 92.7, 113.9, 122.9, 126.7, 126.8, 128.1, 129.0, 129.1, 129.5, 130.5, 133.9, 136.7, 139.7, 147.0, 158.3, 164.6; HRMS calcd for $C_{21}H_{19}N_3O_2$ (M^+ + H): 346.1556, found: 346.1558.

Acknowledgements

Financial support from the National Natural Science Foundation of China (No. 21032007) is gratefully acknowledged.

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