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Synthesis of pyrazolo[1,5-*a*]indoles via copper(I)-catalyzed intramolecular amination

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Abstract—A variety of pyrazolo[1,5-*a*]indole derivatives were synthesized via Cu(I)-catalyzed intramolecular amination reactions. This novel method provides a general and efficient synthesis to indoles fused with pyrazole rings in high yields.

The construction of substituted pyrazolo[1,5-*a*]indole skeleton has been our long-standing interest because it was reported for the first time by Katayama that pyrazolo[1,5-*a*]indole derivatives (e.g., derivative **A** Fig. 1) have fairly potent inhibitory activity against DNA topoisomerases I and II, and have strong cytotoxic activity against cancer cells.[1] Further study on the structure activity relationship (SAR) clarified that the size and polarity of the substituents were crucial for its activity.[2] The initial results prompted us to figure out a variety of pyrazolo[1,5-*a*]indole derivatives in the hopes of expanding the scope. Although, Alley[3] and Padwa[4] reported many years ago that 4-oxopyrazolo[1,5-*a*]indoline and 9,9a-dihydro-1*H*-pyrazolo[2,3-*a*]indole-2-carboxylate were synthesized during their experiments, further exploration on this subject had not been found. According to Katayama et al.,[5–7] several methods have been reported in preparing these kinds of compounds. A summarization of the literature shows that these methods can be basically generalized into two categories: (1) Pyrazole (C) and benzene (A) rings are connected to each other at the last synthetic step.[3,5,7] (2) Construction of the pyrazole ring is realized at the last step when either the carbonyl group is connected to the carbon atom[6] or the N-moiety is introduced to a carbonyl group.[7] Common to these existing methods is a nitrogen atom being connected to the benzene ring from the starting material. This process requires harsh reaction conditions and in most cases, gives poor yields. Thus, in order to make diverse substituents to be attached to ring A and ring C, we considered to search for an efficient way to form the skeleton B (Fig. 1) by connecting the N-moiety to the benzene ring directly. Herein, we report a novel, expedient and general synthetic method for preparation of pyrazolo[1,5-*a*]indole framework (Scheme 1).

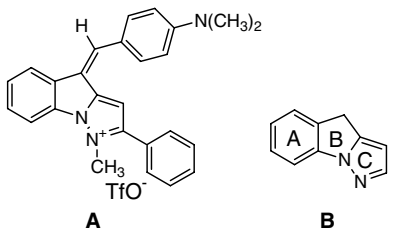

Figure 1. The structure of active compound and the basic skeleton.

As shown in Scheme 1, compound **3** could be synthesized by two main steps in which the intermediate pyrazoles were directly prepared from substituted 2-bromophenylacetic acid. The acid **1**, prepared by a modified literature procedure,[8] was converted to acid chloride, which immediately reacted with anion derived from ketones to form 1,3-diketones. By addition of hydrazine, 1,3-diketones were rapidly converted into pyrazoles.[9] The N-moiety was smoothly connected to the benzene ring through Cu(I)-catalyzed intramolecuar amination in a pressure tube at 110 °C for 20 h.

To our knowledge, copper catalysts have been shown to be efficient for the intermolecular amination of aryl halides with amides or pyrazoles.[10–14] Inspired by this,

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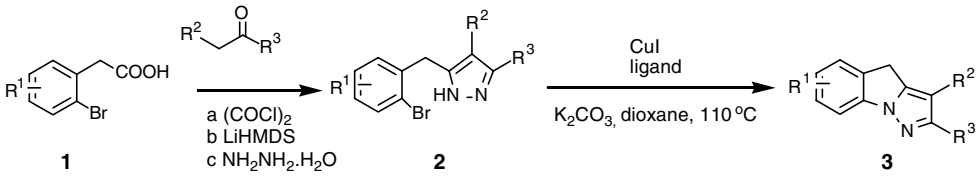


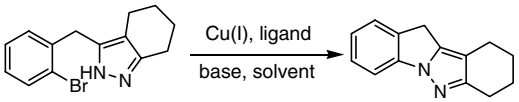
Scheme 1.

we hypothesized that it might undergo intramolecular reactions if proper conditions were employed. This prompted us to test whether the intramolecular reaction could happen to produce the anticipated results. During the course of our investigation, we first explored the effects of solvents, ligands and bases on a typical reaction of 3-[2-bromophenylacetyl]-cyclohexen[1,2-*c*]pyrazole **2a** (Table 1). We were interested in the potential effects of ligands, so several ligands including TCHDA, PHAN and EDA were explored with CuI as the metal source, and PHAN/EDA offered the best result. When no ligands were utilized, the product was obtained in low yield. In the instance that no catalysts were introduced, no cyclized products were found. It was also found that when CuBr was used as a catalyst, it produced slightly lower yield. Our investigation of alternative bases showed that K_2CO_3 was the optimal protocol, and a stronger base, such as *t*-BuONa, offered a trace amount of products. In light of this, it is clear that using dioxane as a solvent, and CuI, PHAN or EDA and K_2CO_3 as the base, is the most optimal condition to synthesize pyrazolo[1,5-*a*]indoles.

With the optimal reaction protocol in hand, we then sought to study, and possibly expand, the scope of the intramolecular amination. PHAN was chosen as a ligand. A diversity-oriented synthesis of compounds including alkyl, aryl, and halogen substituted indolo-[1,5-*a*]pyrazoles was investigated and the result is listed in Table 2. As shown in the table, ring A, substituted with electrophilic functional groups, gave lower yields than the one substituted with nucleophilic functional groups (Table 2, entries **e**–**g**). The reaction yields did not obviously change when a variety of groups are substituted to ring C. The cyclization reaction proceeded well with almost all of these substrate and gave good satisfactory yields, except for some compounds with substituents in the ortho position of bromine atom (Table 2, entry **h**). Surprisingly, compounds **2i** and **2n**, which have a phenyl group fused to ring A, gave a trace amount of products under the given conditions and prolonged reaction time was helpful. Evidently, the increase in steric hindrance at the ortho position of ring A was influential to this intramolecular reaction while ligand PHAN was acting effectively. Then EDA was also used as a ligand and we found that it performed better than PHAN when steric hindrance at ortho position of bromine existed (Table 2, entry **h**). However, compounds **3i** and **3n** were obtained in low yields. During our investigation, we found that without the steric hindrance of ring A, the reaction using EDA as a ligand gave slightly lower yields than the one with PHAN in the case of **a**–**g**. Especially, when phenyl or methyl substituents were attached to 3-position of pyrazole ring, the reaction yields dropped dramatically.

In summary, we have developed a new method for the synthesis of pyrazolo[1,5-*a*]indoles **3** from pyrazole derivatives **2** via copper(I)-catalyzed intramolecular cyclization. This method provides a general, simplified, and easily operated route to pharmacologically attractive compounds and can afford products in good yields.

Table 1. Effects of solvents, ligands and bases on reaction of copper(I)-catalyzed intramolecular amination[a]

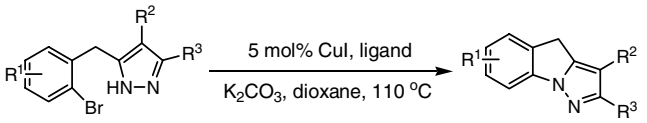


2a **3a**

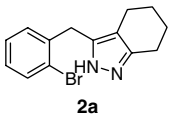
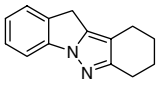
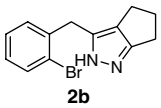
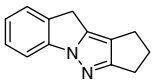
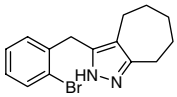
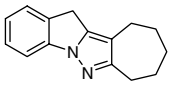
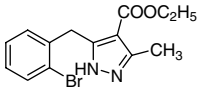
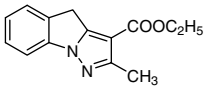
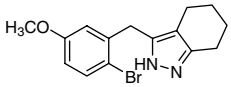
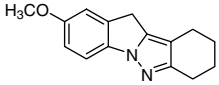
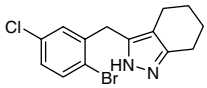
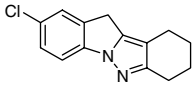
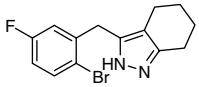
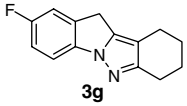
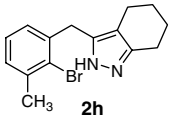
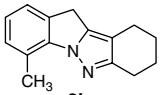
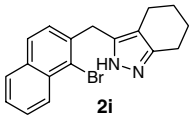
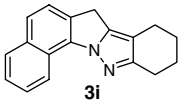
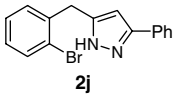
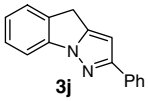
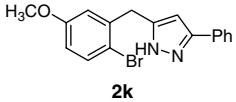
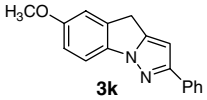
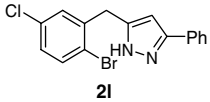
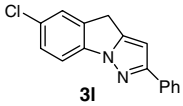
Entry	Solvent	Cu(I)	Ligand	Base (mol %)	Yield[b] (%)
1	Dioxane	CuI		K_2CO_3 (250)	21
2	Dioxane		PHAN	K_2CO_3 (250)	0
3	Dioxane	CuBr	PHAN	K_2CO_3 (250)	85
4	Toluene	CuI	PHAN	K_2CO_3 (250)	48
5	Dioxane	CuI	PHAN	Cs_2CO_3 (140)	80
6	Dioxane	CuI	PHAN	*t*-BuONa (250)	Trace
7	Dioxane	CuI	PHAN[d]	K_2CO_3 (250)	91
8	Dioxane	CuI	TCHDA[c]	K_2CO_3 (250)	64
9	Dioxane	CuI	EDA[e]	K_2CO_3 (250)	90

[a] Reaction conditions: **2a** (1 mmol), Cu(I) (0.05 mmol), ligand (0.1 mmol), base (2.5 mmol) and solvent (3 mL) in a pressure tube, 110 °C, 20 h.
[b] Isolated yields after silica gel chromatography.
[c] TCHDA: *trans*-1,2-cyclohexanediamine.
[d] PHAN: 1,10-phenanthroline.
[e] EDA: ethylenediamine, 0.3 mmol.

Table 2. Synthesis of a variety of pyrazolo[1,5-*a*]indoles via copper(I)-catalyzed intramolecular amination[a]



2 **3**

Entry	**2**[16]	**3**[17]	Yield[b] (%)
1[18]	 **2a**	 **3a**	91[c]/90[d]
2	 **2b**	 **3b**	89/87
3	 **2c**	 **3c**	78/74
4[15,18]	 **2d**	 **3d**	82/69
5	 **2e**	 **3e**	92/86
6	 **2f**	 **3f**	81/76
7	 **2g**	 **3g**	77/70
8	 **2h**	 **3h**	61[e]/88
9	 **2i**	 **3i**	Trace/44
10	 **2j**	 **3j**	98/45
11[18]	 **2k**	 **3k**	96/46
12	 **2l**	 **3l**	83/42

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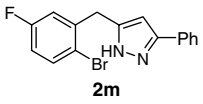
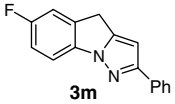
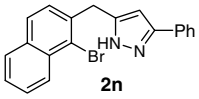
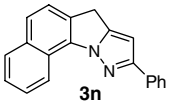
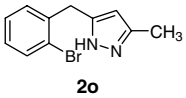
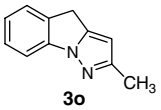
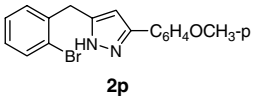
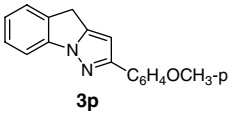
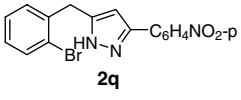
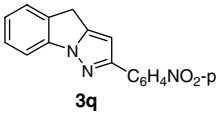
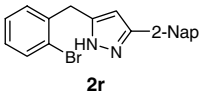
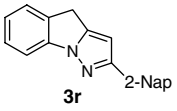
13	 **2m**	 **3m**	95/50
14	 **2n**	 **3n**	Trace/45
15	 **2o**	 **3o**	89/37
16	 **2p**	 **3p**	86/51
17	 **2q**	 **3q**	97/63
18	 **2r**	 **3r**	64/54

[a] Reaction conditions: A mixture of **2** (1 mmol), Cu(I) (0.05 mmol), ligand, K_2CO_3 (2.5 mmol) and 1,4-dioxane (3 mL) was reacted in a pressure tube at 110 °C for 20 h.
[b] Yields are isolated yields after chromatography.
[c] 10 mol % PHAN was used as ligand.
[d] 30 mol % EDA was used as ligand.
[e] Time was prolonged to 40 h.

Applications of this method to the synthesis of potential biological active compounds are being undertaken and will be reported in due course.

Acknowledgements

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15. *Preparation of* **2d**: Ethyl acetoacetate (1.30 g, 10 mmol) dissolved in dry THF (5 mL) was placed in an addition funnel which was mounted on a three-necked flask containing 60% sodium hydride (0.42 g, 10.5 mmol) suspended in dry THF (10 mL). The flask was cooled to 0 °C in an ice-bath before the ethyl acetoacetate was added to it in drops. The solution of ethyl acetoacetate anion was added to the acid chloride solution by a syringe immediately after the addition was completed. The resulting mixture was stirred overnight at room temperature. Water (10 mL) was added and the resulting mixture was stirred for 15 min. Then the aqueous layer was extracted with ether (10 mL) twice. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4.

After filtration and evaporation of solvents, EtOH (50 mL) was added to the crude oil, and then 10 mL of AcOH and hydrazine monohydrate were added. The mixture was stirred for 10 min and the procedure of the reaction was exothermic reaction. Then the product was extracted with ethyl acetate and the extracts were washed with saturated sodium bicarbonate. **2d** was obtained after silica gel chromatography.

16. *General procedure for synthesis of* **2**: Ketone (10 mmol) was dissolved in 25 mL dry toluene, and then the solution was cooled to 0 °C under nitrogen. LiHMDS (10.5 mL, 1.0 M in THF, 10.5 mmol) was added quickly via syringe with stirring. As soon as the anion was formed in one minute, the acid chloride (5 mmol) in 5 mL of dry toluene was added rapidly via syringe and the reaction mixture was allowed to stir at room temperature for 5 min, and then 10 mL of AcOH was added with stirring. EtOH (50 mL) and THF (25 mL) were added to form a homogeneous mixture, then hydrazine monohydrate (10 mL, 10.3 g, 205.8 mmol) was added. The mixture was stirred for 10 min. The resulting solution was extracted with 100 mL of EtOAc, the organic fraction was then washed with saturated sodium bicarbonate and brine, dried over Na_2SO_4 (anhydrous) and evaporated under reduced pressure. The resulting residue was isolated by chromatography (Silica Gel H 120 g, solvents: petroleum ether/ethyl acetate) to afford white solid **2**.
17. *General procedure for synthesis of* **3**: CuI (10 mg, 0.05 mmol), 1,10-phenanthroline (18 mg, 0.1 mmol) and K_2CO_3 (345 mg, 2.5 mmol) were added to a solution of compound **2** (1.0 mmol) dissolved in anhydrous 1,4-dioxane (3 mL) in a pressure tube under the protection of Argon. The reaction mixture was stirred at 110 °C for 20 h and filtered through a pad of celite. After the removal of solvent under reduced pressure, the residue was purified by chromatography (Silica Gel H 10 g, solvents: petroleum ether/ethyl acetate) to give **3** as a solid.
18. All new compounds have been characterized by ^{1}H NMR, ^{13}C NMR and HRMS. Data for selected compounds: 3-[2-Bromobenzyl]-cyclohexen[1,2-*c*]pyrazole **2a**: 78% yield, mp 84–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) ppm 1.89–1.55 (m, 4H), 2.28 (s, 2H), 2.59 (d, $J = 5.6$ Hz, 2H), 4.02 (s, 2H), 7.13–6.97 (m, 2H), 7.23–7.13 (m, 1H), 7.61–7.45 (m, 1H), 10.92–10.17 (br, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) ppm 20.5, 22.6, 23.3, 23.7, 33.0, 114.1, 124.9, 127.9, 128.4, 130.9, 133.1, 138.8, 143.3, 144.0. HRMS: $C_{14}H_{15}N_2{}^{81}Br$ calcd, 292.0398; found, 292.0381, $C_{14}H_{15}N_2{}^{79}Br$ calcd, 290.0419; found, 290.0421.

7,8,9,10-Tetrahydro-11*H*-indolo[1,2-*b*]indazole **3a**: 91% yield, mp 104–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) ppm 1.95–1.64 (m, 4H), 2.56 (t, $J = 5.50, 5.50$ Hz, 2H), 2.81 (t, $J = 6.03, 6.03$ Hz, 2H), 3.68 (s, 2H), 7.09 (t, $J = 7.43, 7.43$ Hz, 1H), 7.42–7.28 (m, 2H), 7.53 (d, $J = 7.73$ Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) ppm 21.0, 23.7, 23.8, 24.6, 27.8, 110.1, 111.1, 123.8, 126.2, 128.3, 133.5, 141.1, 141.4, 165.6. HRMS: $C_{14}H_{14}N_2$ calcd, 210.1157; found, 210.1151.

Ethyl 3-[2-bromobenzyl]-5-methyl-pyrazole-4-formate **2d**: 68% yield, mp 104–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) ppm 1.21 (t, $J = 7.11, 7.11$ Hz, 3H), 2.40 (s, 3H), 4.21 (q, $J = 7.10, 7.10, 7.10$ Hz, 2H), 4.30 (s, 2H), 6.97 (d, $J = 7.29$ Hz, 1H), 7.03 (t, $J = 6.93, 6.93$ Hz, 1H) 7.13 (t, $J = 6.97, 6.97$ Hz, 1H), 7.52 (d, $J = 7.87$ Hz, 1H), 11.80–10.14 (br, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) ppm 13.2, 14.6, 34.4, 60.2, 109.6, 125.0, 128.0, 128.5, 130.6, 133.1, 138.5, 148.4, 150.3, 164.6. HRMS: $C_{14}H_{15}N_2O_2{}^{81}Br$ calcd, 324.0296; found, 324.0344, $C_{14}H_{15}N_2O_2{}^{79}Br$ calcd, 322.0317; found, 322.0320.

Ethyl 2-methyl-indolo[1,2-*a*]pyrazole-3-formate **3d**: 82% yield, mp 93–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) ppm 1.40 (t, $J = 6.88, 6.88$ Hz, 3H), 2.61 (s, 3H), 4.01 (s, 2H), 4.33 (q, $J = 6.80$ Hz, 6.8 Hz, 6.8 Hz, 2H), 7.31–7.15 (m, 1H), 7.52–7.35 (m, 2H), 7.61 (d, $J = 7.83$ Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) ppm 14.8, 14.9, 30.5, 60.4, 111.1, 125.3, 126.4, 128.6, 133.4, 136.0, 140.4, 149.8, 156.1, 164.1. HRMS: $C_{14}H_{14}N_2O_2$ calcd, 242.10055; found, 242.1050.

3-[2-Bromo-5-methoxybenzyl]-5-phenyl-pyrazole **2k**: 73% yield, mp 100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) ppm 3.67 (s, 3H), 4.04 (s, 2H), 6.35 (s, 1H), 6.64 (d, $J = 8.01$ Hz, 1H), 6.76 (s, 1H), 7.37–7.18 (m, 3H), 7.41 (d, $J = 8.52$ Hz, 1H), 7.64 (d, $J = 6.21$ Hz, 2H), 10.86–9.43 (br, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) ppm 34.2, 55.8, 102.6, 114.4, 115.2, 116.7, 126.0(×2), 128.4, 129.1(×2), 131.9, 133.8, 139.7, 146.9, 148.9, 159.4. HRMS: $C_{17}H_{15}N_2O^{81}Br$ calcd, 344.0347; found, 344.0364, $C_{17}H_{15}N_2O^{79}Br$ calcd, 342.0368; found, 342.0384.

6-Methoxy-2-phenyl-pyrazolo[1,5-*a*]indole **3k**: 96% yield, mp 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) ppm 3.81 (s, 3H), 3.82 (s, 2H), 6.54 (s, 1H), 6.90 (dd, $J = 8.51, 2.16$ Hz, 1H), 6.99 (s, 1H), 7.35–7.25 (m, 1H), 7.46–7.35 (m, 2H), 7.57 (d, $J = 8.53$ Hz, 1H), 7.87 (d, $J = 7.91$ Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) ppm 29.0, 56.2, 98.5, 111.1, 112.9, 113.1, 126.1(×2), 128.1, 129.1(×2), 134.4, 134.9, 135.4, 145.6, 155.9, 157.6. HRMS: $C_{17}H_{14}N_2O$ calcd, 262.1106; found, 262.1111.