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Multicomponent reactions of pyridines, α-bromo carbonyl compounds and silylaryl triflates as aryne precursors: a facile one-pot synthesis of pyrido[2,1-*a*]isoindoles

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ABSTRACT

Multicomponent reactions (MCRs) involving pyridines, α-bromo ketones, and silylaryl triflates as aryne precursors were investigated. The reactions could also be extended to isoquinoline or α-bromo ethyl acetate. Substituted pyrido[2,1-*a*]isoindoles or isoindolo[2,1-*a*]isoquinolines could be obtained from this routine, which may have potential applications in antitumor drugs and fluorescent material fields.

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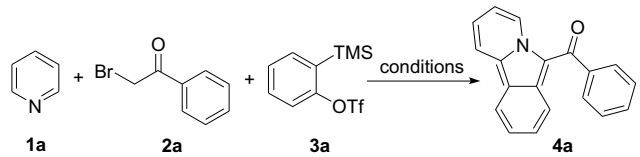
Pyrido[2,1-*a*]isoindole, as the analogue of antitumor batracilin,[1] the parent compound of many dyes,[2] and the structural unit of some highly fluorescent materials,[3] is of marked interest for its versatility. Although some accesses to this skeleton and its derivatives have progressed in decades,[4,5] some flaws have been in concomitance with them, namely as limitations in scopes,[4a,b] need of unhealthy radiation,[4c] demand for strict experimental conditions when transition metal catalysts were used,[4d] or the loss of yields in multi-steps routines.[5] So it is essential to develop more facile, atom economical, and reliable routes to prepare pyrido[2,1-*a*]isoindoles. In recent years, multicomponent reactions (MCRs) have been extensively studied due to their efficiency, atom economy and convenience in construction of multiple new bonds in one-pot processes, which played powerful roles in approach to complex structures and promoted the 'green chemistry'.[6]

Arynes are useful organic intermediates, and the relative reports mushroomed since the employment of (trimethylsilyl)phenyl triflates as aryne precursors due to the mild and tolerable conditions to generate arynes[7] and a variety of MCRs involving arynes have been developed in recent years.[8] It is well known that the cycloaddition of arynes could lead to formation of benzo rings which are not easy to synthesize by other methods.[9] Moreover, 1,3-dipolar cycloadditions are useful way to construct five-membered rings,[10] so the 1,3-dipolar cycloaddition of aryne could be a potential method to construct benzo five-membered rings.[9i–m] Based on the continuous interest on MCRs and aryne chemistry,[8f,11]

Table 1
Optimization of conditions for the one-pot synthesis of phenyl-pyrido[2,1-*a*]isoindol-6-yl-methanone **4a**[a]



Entry	Base	Solvent	Temperature (°C)	**1a/2a/3a**	Yield[b] (%)
1	NaH	CH_3CN	60	1:1:1.2	28
2	Et_3N	CH_3CN	60	1:1:1.2	41
3	K_3PO_4	CH_3CN	60	1:1:1.2	43
4	K_2CO_3	CH_3CN	60	1:1:1.2	39
5	Na_2CO_3	CH_3CN	60	1:1:1.2	50
6	Na_2CO_3	THF	60	1:1:1.2	Trace
7	Na_2CO_3	DME	60	1:1:1.2	54
8	Na_2CO_3	DME	rt	1:1:1.2	33
9	Na_2CO_3	DME	85	1:1:1.2	60
10	Na_2CO_3	DME	85	1:1:0.8	59[c]
11	Na_2CO_3	DME	85	1:1:1.5	55

[a] Reactions were carried out on a 0.3 mmol scale (based on α-bromo carbonyl compounds) and monitored by TLC (eluent/petroleum ether).
[b] Isolated yield based on **1a.**
[c] Isolated yield based on **3a**.

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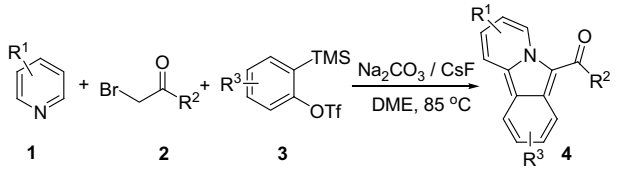
Table 2
The MCRs utilizing various pyridines, α-bromo carbonyl compounds, and different aryne precursors[a]



1a: R^1 = H; **1b**: R^1 = 4-CH_3; **1c**: R^1 = 3-CH_3;
1d: 2-C_2H_5-3-CH_3-Pyridine;
2a: R^2 = C_6H_5; **2b**: R^2 = *p*-Cl-C_6H_4; **2c**: R^2 = CH_3; **2d**: R^2 = OC_2H_5;
3a: R^3 = H; **3b**: 4-CH_3-5-CH_3-Triflate; **3c**: R^3 = 4-CH_3

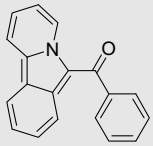
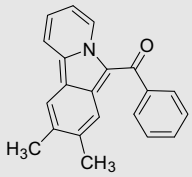
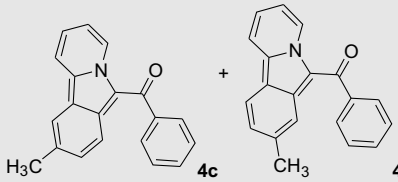
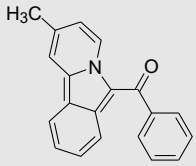
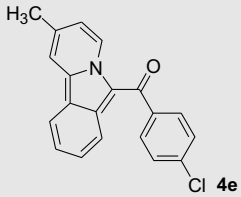
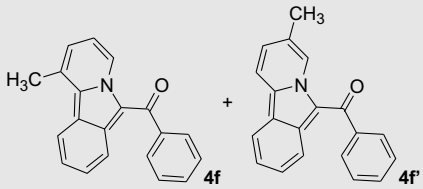
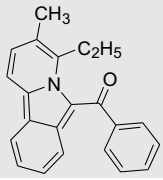
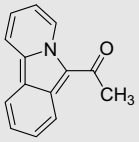
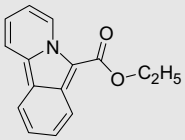
Entry	1	2	3	Product	Yield (%)[b]
1	**1a**	**2a**	**3a**	 **4a**	60
2	**1a**	**2a**	**3b**	 **4b**	49
3	**1a**	**2a**	**3c**	 **4c** + **4c'**	52 (1:1)[c]
4	**1b**	**2a**	**3a**	 **4d**	51
5	**1b**	**2b**	**3a**	 **4e**	58
6	**1c**	**2a**	**3a**	 **4f** + **4f'**	59 (1:1)[d]
7	**1d**	**2a**	**3a**	 **4g**	43

Table 2 (*continued*)

Entry	1	2	3	Product	Yield (%)[b]
8	**1a**	**2c**	**3a**	 **4h**	40
9	**1a**	**2d**	**3a**	 **4i**	37

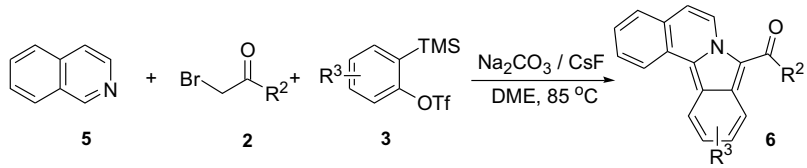
[a] Reactions were carried out on a 0.3 mmol scale and monitored by TLC.
[b] Isolated yield based on **1a.**
[c] The total yield of inseparable mixture of 8-methyl and 9-methyl products at a ratio of 1:1; the ratio of the mixture was identified by ^{1}H NMR.
[d] The total yield of inseparable mixture of 1-methyl and 3-methyl products at a ratio of 1:1; the ratio of the mixture was identified by ^{1}H NMR.

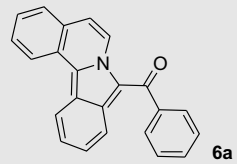
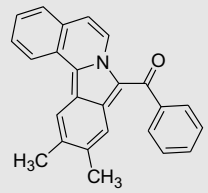
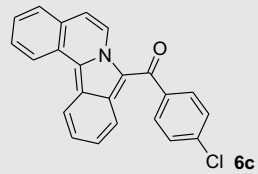
we would like to report a facile one-pot synthesis of pyrido[2,1-*a*]-isoindoles via 1,3-dipolar cycloaddition of arynes utilizing pyridines, α-bromo carbonyl compounds, and silylaryl triflates as three components.

The initial examination using pyridine **1a**, α-bromo phenyl ethanone **2a**, and aryne precursor **3a** at a ratio of 1:1:1.2 was conducted in dried CH_3CN. After refluxing overnight, 1.5 equiv of NaH and 4.0 equiv of CsF were added and the mixture was stirred under 60 °C. When the reaction terminated (monitored by TLC), the expected product phenyl-pyrido[2,1-*a*]isoindol-6-yl-methanone **4a** was affored in a yield of 28% (Table 1, entry 1). We then focused on optimizing the reaction conditions. Different bases were initially tested. The use of organic base Et_3N could enhance the yield to 41% (Table 1, entry 2). Some weak inorganic bases were also applied to the optimization (e.g., a clear reaction induced by K_3PO_4 with a yield of 43%) (Table 1, entries 3–5), and Na_2CO_3 was chosen as the proper base for the higher yield (Table 1, entry 5). Then, several solvents ordinarily used in reactions of aryne were checked. In THF, we only got trace amount of **4a** probably due to the poor solubility of CsF in THF (Table 1, entry 6). An improved yield was observed in DME (Table 1, entry 7). Our further study demonstrated that the relatively remarkable factor was the temperature when cycloaddition happened. The yield rose to 60% at 85 °C, but decreased dramatically to 33% at rt (Table 1, entries 8 and 9). Next, different ratios of starting materials were compared, and the ratio 1:1:1.2 (**1a**:**2a**:**3a**) was proven to be the favored one (Table 1, entries 9–11). Therefore, the optimized reaction condition was that 1.0 equiv of pyridines, 1.0 equiv of α-bromo carbonyl compounds, and 1.2 equiv of aryne precursors were refluxed in DME overnight, then the reaction proceeded at 85 °C after addition of 1.5 equiv of Na_2CO_3 and 4.0 equiv of CsF.[15,16]

With the optimized conditions in hand, the scope of the reaction was investigated, and the typical results are summarized in Table 2. The corresponding pyrido[2,1-*a*]isoindoles were obtained smoothly in yields from 54% to 60% using symmetrically substituted pyridines, α-bromo aryl ethanones and symmetrical arynes (Table 2. entries 1, 2, 4, and 5). When the unsymmetrically substituted pyridine **1c** was employed, 1:1 mixture of 1-methyl and 3-methyl substituted products was obtained in a total yield of 59% (Table 2, entry 6), and we gained only one compound without other isomers from unsymmetrical **1d** due to the ethyl group attaching to the nitrogen-neighbored carbon atom of pyridine from one side (Table 2, entry 7). If the unsymmetrical 4-methyl triflate **3c** participated in the reaction, the ratio of the 1:1 inseparable mix-

Table 3
Further scope expansion of the MCR: the new approach to isoindolo[2,1-*a*]isoquinolines[a]



Entry	2	3	Product	Yield[b] (%)
1	**2a**	**3a**	 **6a**	42
2	**2a**	**3b**	 **6b**	49
3	**2b**	**3a**	 **6c**	48

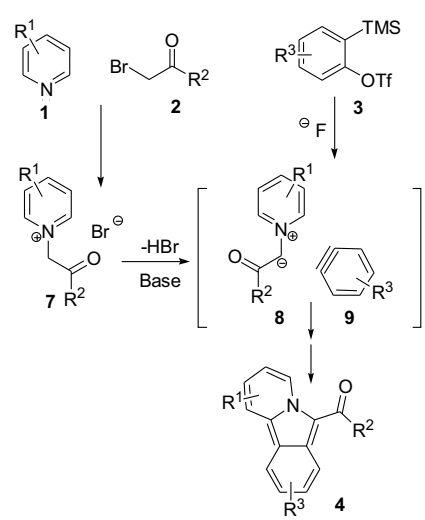
[a] Reactions were carried out on a 0.3 mmol scale and monitored by TLC.
[b] Isolated yield based on **5**.

ture of 8-methyl and 9-methyl products implied the aryne reaction mechanism[12] (Table 2, entry 3). Besides the α-bromo aryl ethanones, the α-bromo alkyl ethanone **2c** was conducted into the MCRs and a slightly lower yield of corresponding product **4h** was obtained (Table 2, entry 8). Using α-bromo ethyl acetate **2d** instead of α-bromo ketones, we successfully got the aimed product **4i** in a yield of 37% (Table 2, entry 9). As can be seen from Table 2, by utilizing various substituted pyridines, α-bromo carbonyl compounds, and different aryne precursors, multiple substituted groups were introduced to parent structure of pyrido[2,1-*a*]isoindole, and moderate yields were obtained.

For further scope expansion of this MCR, other nitrogen-bearing heterocyclic compounds were employed to take the place of pyridines. Isoquinoline was found to have good acceptance and the corresponding products isoindolo[2,1-*a*]isoquinolines, as the analogues of antitumor drugs, were afforded in moderate yields[13] (Table 3).

On the basis of relative reports,[14] a plausible mechanism of the MCR is shown in Scheme 1. The pyridine **1** and the α-bromo carbonyl compound **2** produce the pyridium salt **7**,[14a] then the base captures an activated proton from α carbon of carbonyl group of **7** and generates azomethine ylide **8**. Next, the 1, 3-dipolar cycloaddition reaction between **8** and aryne intermediate **9** induced by fluoride occurs. We might envision that the resulting cycloaddition product is unstable and easily oxidized by the air in the absence of any other oxidants to obtain the stable aromatized product **4** (Scheme 1).[14b,c]

In conclusion, we have disclosed a facile synthesis of pyrido[2,1-*a*]isoindoles based upon MCRs of pyridines, α-bromo ketones, and silylaryl triflates as aryne precursors, which could be extended to employ isoquinoline or α-bromo ethyl acetate as substrates. The products of the MCRs would be potentially useful due to the wide occurrence of their analogues in drugs and materials. The details of mechanism and synthetic applications of this methodology are being further studied in our laboratory.



Scheme 1. The plausible mechanism of formation of pyrido[2,1-*a*]isoindoles.

Acknowledgments

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Supplementary data

The relevant spectroscopic data of all the new compounds mentioned in the Letter. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.118.

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15. *Preparation of phenyl(pyrido[2,1-a]isoindol-6-yl)methanone* **4a**. *Typical experimental procedure:* Pyridine (**1a**, 0.3 mmol), 2-bromo-1-phenylethanone (**2a**, 0.3 mmol) and (trimethylsilyl)phenyl triflate (**3a**, 0.36 mmol) were mixed in 3 mL of dried DME and the solution was stirred at reflux overnight, then Na_2CO_3 (0.45 mmol) and CsF (1.2 mmol) were added rapidly. The reaction was carried out at 85 °C and monitored by TLC (7:1 P.E./EtOAc eluent). After total conversion of the triflate (about 0.8 h later), the reaction mixture was filtrated through a short pad of silica gel to remove indiscerptible materials, and then evaporated under vacuum to get rid of the solvent, and the residue was purified by chromatography (15:1 P.E./EtOAc eluent) to give **4a** (about 49 mg) in 60% yield.
16. *Selected data for* **4a**: Yellow solid, mp: 101–105 °C. IR (neat): 3055, 1633, 1582, 1560, 1475, 1450, 1430, 1319, 1295, 1247, 1230, 1210, 1120, 943, 756, 728, 702, 655 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 10.61 (d, J = 6.9 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 6.8 Hz, 2H), 7.57–7.48 (m, 4H), 7.34 (t, J = 6.9 Hz, 1H), 7.26–7.19 (m, 2H), 6.83 (d, J = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 114.1, 117.2, 118.5, 119.2, 119.7, 120.0, 121.4, 125.5, 128.1, 128.3, 128.6, 129.4, 130.2, 132.6, 135.0, 142.4, 183.1. MS (EI, 70 eV): m/z (%) = 272 (37) $[M^+ + 1]$, 271 (100) $[M^+]$, 270 (100) $[M^+ - 1]$. HRMS (EI^+): calcd for $[C_{19}H_{13}NO]^+$: m/z 271.0997. Found 271.1004.