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"One-Pot" Multicomponent Approach to Indolizines and Pyrido[1,2-*a*]indoles

Huajian Zhu, Joachim Stöckigt, Yongping Yu, and Hongbin Zou*

Institute of Materia Medica, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, P. R. China

zouhb@zju.edu.cn

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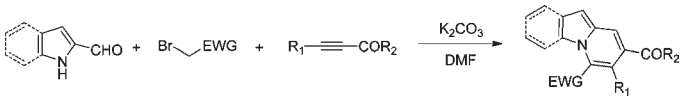
ABSTRACT



A new synthetic protocol for efficient and regiospecifc assembly of indolizines and pyrido[1,2-*a*]indoles by coupling of substituted methyl bromides and alkynes with corresponding pyrrole-2-carboxaldehyde and 1*H*-indole-2-carboxaldehyde has been developed. Additionally, a possible mechanism for the reaction is proposed.

During the past decade, the pharmacological potential of indolizines has been well recognized. Many indolizines have shown important biological activities, including anti-HIV,[1] anti-inflammatory,[2] 5-HT3 receptor antagonist,[3] H3 receptor antagonist,[4] as well as usage as molecular probes.[5] As a result, a variety of methods for their synthesis have emerged[6] and most synthetic strategies require starting from pyridinium *N*-methylides[6a−d] or pyridines with specific C2 functionalization.[6e−n] In recent published reports, the transition-metal-catalyzed intramolecular reaction of alkynylpyridines is the primary method of choice, but often, this approach suffers from limitations such as expensive metal catalyst or substrate complexity.[6e−k,7]

Herein, we report a facile, efficient, and regiospecific approach to provide indolizines with additional functional diversity using commercially available starting material. This "one-pot" three-component coupling reaction was also found to be suitable for the synthesis of pyrido[1,2-*a*]indoles which possess a wide array of important biological properties.[8] We also present two interesting examples

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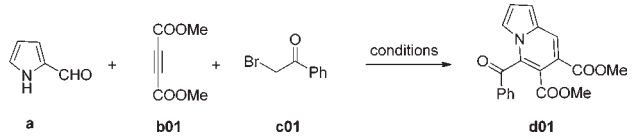
of tricyclic heterocycles synthesized using pyrrole-2-carboxaldehyde and special substrates.

Initially, the pyrrole-2-carboxaldehyde **a**, alkyne **b01**, and 2-bromo-1-phenylethanone **c01** were selected as a model system to optimize the reaction conditions. Different solvents were examined first, and the results indicated that solvent plays a major role in the cycloisomerization transformation (Table 1, entries 1−5).

Table 1. Optimization of Reaction Conditions[a]



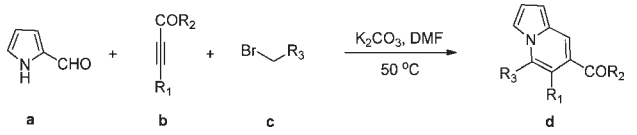
no.	base	solvent	temp (°C)	yield[b] (%)
1	K_2CO_3	MeCN	25	38
2	K_2CO_3	C_2H_5OH	25	trace
3	K_2CO_3	DCM	25	0
4	K_2CO_3	touene	25	0
5	K_2CO_3	DMF	25	75
6	Na_2CO_3	DMF	25	15
7	Et_3N	DMF	25	30
8	NaH	DMF	25	trace
9	K_2CO_3	DMF	40	91
10	**K_2CO_3**	**DMF**	**50**	**98**
11	K_2CO_3	DMF	65	89

[a] Reaction conditions: pyrrole-2-carboxaldehyde (0.2 mmol, 1.0 equiv), 2-bromo-1-phenylethanone (0.2 mmol, 1.0 equiv), alkyne (0.24 mmol, 1.2 equiv), base (0.4 mmol, 2.0 equiv), 1.5 mL of solvent, 12 h. [b] Determined by high-performance liquid chromatography based on the disappearance of the starting pyrrole-2-carboxaldehyde. The most successful entry is highlighted in bold.

Next, we tested the three-component coupling reaction in the presence of various bases. The base also plays a crucial role in the success of indolizine derivative **d01** synthesis (Table 1, entries 5−8), and K_2CO_3 was found to be the most favorable base for this transformation (entry 5, 75%). The reaction efficiency was also assessed with varying reaction temperatures. Significant improvement in the reaction yield was observed when the temperature was increased from 25 to 50 °C (75% to 95%, Table 1, entries 5 and 10). However, further increase of temperature resulted in a slight decrease in the yield (Table 1, entry 11).

With the optimized conditions in hand, the scope and limitations of the coupling reaction were next examined by employing various substituted methyl bromides and alkynes (Table 2). The alkynes presented in Table 2 all have at least one electron-withdrawing group. We also examinded alkynes such as allylene, cyclopropylacetylene, phenylacetylene, and ethynyltrimethylsilane, and no reaction was observed. This demonstrates the importance of an electron-withdrawing group on the alkyne for the reaction. Notably, the alkynes bearing two electron-withdrawing groups gave the desired products with better isolated yields than those with only one electron-withdrawing group (Table 2, entries 1−4, 8−27). An additional observation

Table 2. Scope of Coupling Reaction[a]



no.	R_1	R_2	R_3	product **d**	yield[b] (%)
1	COOMe	MeO	C_6H_5CO	**d01**	72
2	COOEt	EtO	C_6H_5CO	**d02**	85
3	H	MeO	C_6H_5CO	**d03**	63
4	H	C_6H_5	C_6H_5CO	**d04**	65
5[c]	Me	MeO	C_6H_5CO	**d05**	61
6[c]	Me	MeO	4-Br-C_6H_5CO	**d06**	59
7[c]	C_6H_5	EtO	4-Br-C_6H_4CO	**d07**	53
8	COOMe	MeO	4-Br-C_6H_4CO	**d08**	78
9	COOEt	EtO	4-Br-C_6H_4CO	**d09**	89
10	H	MeO	4-Br-C_6H_4CO	**d10**	62
11	COOMe	MeO	4-Me-C_6H_4CO	**d11**	88
12	COOMe	MeO	4-Cl-C_6H_4CO	**d12**	80
13	COOMe	MeO	4-MeO-C_6H_4CO	**d13**	86
14	COOMe	MeO	C_3H_5CO	**d14**	78
15	COOMe	MeO	COOEt	**d15**	60
16[c]	COOMe	MeO	CN	**d16**	64
17	COOEt	EtO	4-Me-C_6H_4CO	**d17**	97
18	COOEt	EtO	4-Cl-C_6H_4CO	**d18**	87
19	COOEt	EtO	4-MeO-C_6H_4CO	**d19**	98
20	COOEt	EtO	C_3H_5CO	**d20**	82
21	COOEt	EtO	COOEt	**d21**	63
22[c]	COOEt	EtO	CN	**d22**	68
23	H	MeO	4-Me-C_6H_4CO	**d23**	85
24	H	MeO	4-Cl-C_6H_4CO	**d24**	76
25	H	MeO	4-MeO-C_6H_4CO	**d25**	82
26	H	MeO	C_3H_5CO	**d26**	75
27	H	MeO	C_3H_7CO	**d27**	51
28[c]	Me	MeO	4-MeO-C_6H_4CO	**d28**	66
29[c]	Me	MeO	C_3H_5CO	**d29**	52
30[c]	Me	MeO	CN	**d30**	42
31[c]	C_6H_5	EtO	C_3H_5CO	**d31**	53

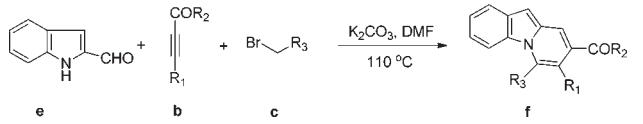
[a] Reaction were performed in anhydrous DMF at 50 °C in the presence of base. [b] Isolated yield. [c] The reaction was performed at 90 °C.

was that no reaction took place under the studied reaction conditions if one terminal of alkyne contained a methyl or phenyl group (Table 2, entries 5−7 and 28−31). In these cases, the desired products **d05**−**07** and **d28**−**31** were obtained in moderate yields when we raise the reaction temperature to 90 °C. Unexpectedly, only one single regioisomer with the R_1 group adjacent to the R_3 group was observed (entries 3−7, 10, and 23−31) when asymmetric alkynes were utilized for the synthesis of corresponding indolizines. The structures were confirmed by HRMS and NMR spectra data.

As presented in Table 2, the generality of this process was expanded by the utilization of a variety of substituted methyl bromides. The methyl bromides with a substituted phenyl acyl group produced better reaction efficiencies than those with substituents of ester, alkyl acyl, and cycloalkyl acyl (Table 2, entries 11−27), while the substituent of the poor electron-withdrawing cyano group

required a higher reaction temperature (Table 2, entries 16, 22, and 30). Additionally, the electronic property of the substituent on the aryl ring also has some influence on the efficiency of cycloisomerization (entries 11−13, 17−19). For instance, in entries 17−22, the isolated yields vary from 63% to 98% in which **c19** with a electron-rich aryl ring quantitively transformed to **d19** (98%, entry 19) while **c21** with an ester substituent cyclized to **d21** in a moderate yield (63%, entry 21).

Table 3. Synthesis of Pyrido[1,2-*a*]indoles[a]

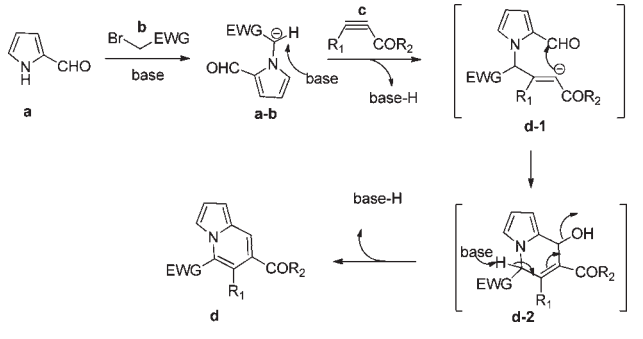


no.	R_1	R_2	R_3	product **f**	yield[b] (%)
1	COOMe	OMe	C_6H_5CO	**f01**	46
2	COOMe	OMe	4-Br-C_6H_4CO	**f02**	41
3	COOMe	OMe	4-MeO-C_6H_4CO	**f03**	58
4	COOMe	OMe	C_3H_5CO	**f04**	40
5	COOEt	OEt	C_6H_5CO	**f05**	49
6	H	OMe	C_6H_5CO	**f06**	45

[a] Reactions were performed in anhydrous DMF at 110 °C in the presence of base. [b] Isolated yield.

In order to gain further insight about this process, 1*H*-indole-2-carboxyaldehyde **e** was also utilized in this transformation providing access to the pyrido[1,2-*a*]indole scaffold (**f**, Table 3). Initial attempts with the same conditions as indolizines syntheses resulted in no observation of pyrido[1,2-*a*]indoles being formed. Consistent with our initial observations for the synthesis of the indolizines (Table 2, entry 5−7 and 28−31), the cycloisomerization transformations were achieved at a higher temperature to afford the corresponding pyrido[1,2-a]indoles (Table 3). This might be ascribed to the decrease in electron density of nitrogen in the indole ring as compared to pyrrole-2-carboxaldehyde.

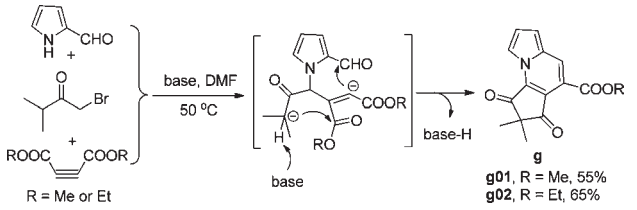
Scheme 1. Possible Mechanism for the Synthesis of Indolizines



On the basis of the results presented above, we proposed the following possible mechanism for this reaction, as shown in Scheme 1. In the presence of base, nucleophilic attack of the nitrogen in pyrrole-2- carboxaldehyde to the substituted methyl bromide lead to *N*-substituted pyrrole-2-carboxaldehyde **a-b**, followed by a further nucleophilic attack of **a-b**, to the alkyne **c**. Subsequently, the newly formed active intermediate **d-1** undergoes an intramolecular cycloisomerization to afford the desired product **d**.

Interestingly, when 1-bromo-3-methylbutan-2-one and alkynes with two ester groups were chosen as substrates, new tricyclic heterocycles (**g**) were formed in moderate yields (Scheme 2). The possible mechanism is shown in Scheme 2 which proceeds through a spontaneous intramolecular cyclization similar to the one proposed in Scheme 1.

Scheme 2. Synthesis of Tricyclic Heterocycles from Pyrrole-2-carboxaldehyde



In summary, we have developed a new synthetic protocol for efficient and regiospecific assembly of indolizines and pyrido[1,2-*a*]indoles from commercially available starting materials. We also demonstrated two interesting and special cases for tricyclic heterocycle synthesis from pyrrole-2-carboxaldehyde.

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Supporting Information Available. Experimental procedures and compound characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.