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A one-pot, four-component synthesis of α-carboline derivatives

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ABSTRACT

A one-pot method for the efficient and simple synthesis of novel 1*H*-indolo[2,3-*b*]pyrazolo[4,3-*e*]pyridines via a four-component condensation reaction of indolin-2-one, 3-oxo-3-phenylpropanenitrile, and various hydrazines and aldehydes in the ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim]Br) is reported.

Pyrido[2,3-*b*]indoles (α-carbolines) display a number of interesting biological properties.[1] For example, natural products containing this unit such as grossularine-1 and grossularine-2, marine alkaloids isolated from *Dendrodoa grossularia* in 1989 (Fig. 1), have attracted considerable interest due to their antiproliferative activity.[2] Similarly, mescengricin, isolated from *Streptomyces griseoflavus*, was found to protect neuronal cells by suppressing the excitotoxicity induced by L-glutamate (Fig. 1).[3] Moreover, several synthetic α-carboline derivatives are anxiolytic or neuroprotectant agents.[4] Also, several synthetic α-carbolines have been found to exhibit antiviral and antitumor activity,[5–7] and many have been patented.[8]

Much effort has been devoted to the synthesis of α-carbolines. Surprisingly, direct functionalization of the α-carboline skeleton has been studied only briefly.[9] In most cases, the substitution is incorporated prior to formation of the α-carboline ring system resulting in lengthy synthetic routes, or in limitations in the availability of substituted starting materials.[10,11] These approaches are based on substituted indole,[12,11,13] an arylalkyne,[14] or arylalkene,[15] oxoindole,[4a,16] azaindole,[17] or pyridine[18,19] starting materials.

The multicomponent reaction (MCR) strategy offers significant advantages over conventional linear-type synthesis due to its flexible, convergent, and atom-efficient nature.[20] In recent years, the combinatorial synthesis of small-molecule heterocyclic libraries has emerged as a valuable tool in the search for novel lead structures.[21] The success of combinatorial chemistry in drug discovery benefits from advances in heterocyclic MCR methodology and, according to current synthetic requirements, environmentally benign multi-component procedures are particularly welcome.

As part of our continuing efforts on the development of new routes for the synthesis of biologically active heterocyclic compounds,[22] herein we report an efficient synthesis of new α-carboline derivatives via a simple procedure under green conditions.

To achieve suitable conditions for the above transformation, we investigated the reaction of indolin-2-one (**1**), 3-oxo-3-phenylpropanenitrile (**2**), phenylhydrazine (**3a**) and benzaldehyde (**4a**) under various conditions (Scheme 1). We found that the best result was obtained in the presence of *p*-toluenesulfonic acid (*p*-TSA) at 140 °C in [bmim]Br (Table 1, entry 1). The result was good in terms of yield and product purity; without *p*-TSA, only a trace of product was obtained even after 12 h (Table 1, entry 2).

After optimizing the reaction conditions, the scope of this method, particularly in regard to library construction, was evaluated using hydrazines **3a–c**, and aromatic aldehydes **4a–k**. The corresponding 1*H*-indolo[2,3-*b*]pyrazolo[4,3-*e*]pyridines **5a–q** were obtained in moderate to excellent yields (Table 2). To the best of our knowledge, this procedure represents the first example of an efficient, four-component method for the synthesis of 1*H*-indolo[2,3-*b*]pyrazolo[4,3-*e*]pyridines.

The nature of these compounds as 1:1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, a molecular ion peak at the appropriate *m/z* value. Compounds **5a–q** are stable solids whose structures were established by IR, ^{1}H, and ^{13}C NMR spectroscopy and by elemental analysis.

When this reaction was carried out with an aliphatic aldehyde such as butanal or pentanal, the TLC and ^{1}H NMR spectra of the crude reaction mixture showed the presence of a combination of

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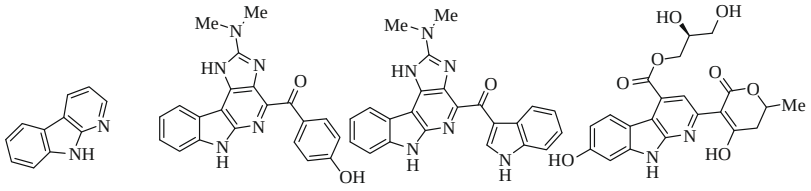
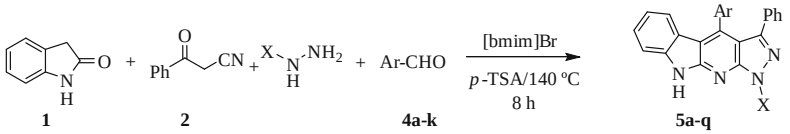
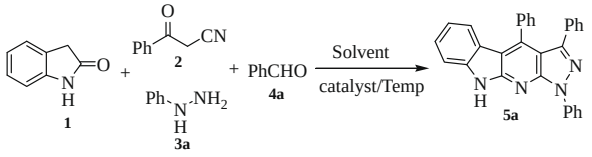


Figure 1. α-Carboline and examples of α-carboline-containing natural products.



Scheme 1.

Table 1
Optimization of the reaction conditions[a]



Entry	Conditions	Time (h)	Yield (%)
1	[bmim]Br/140 °C/*p*-TSA	8	85
2	[bmim]Br/140 °C	12	Trace
3	[bmim]Br/120 °C/*p*-TSA	12	75
4	[bmim]Br/140 °C/Et_3N	24	Trace
5	[bmim]BF_4/120 °C/*p*-TSA	24	37
6	EtOH (reflux)/*p*-TSA	15	Trace
7	CH_3CN (reflux)/*p*-TSA	15	Trace
8	DMF/120 °C/*p*-TSA	15	Trace
9	HOAc (reflux)/*p*-TSA	15	Trace
10	Solvent-free/120 °C/*p*-TSA	15	35

[a] Indolin-2-one (1 mmol), benzaldehyde (1 mmol), 3-oxo-3-phenyl propanenitrile (1 mmol), phenylhydrazine (1 mmol), catalyst (0.1 g).

Table 2
Synthesis of indolopyrazolopyridines **5**

Product	Ar	X	Yield[a] (%)
5a	C_6H_5	Ph	85
5b	4-O_2N–C_6H_4	Ph	92
5c	3-O_2N–C_6H_4	Ph	88
5d	2-O_2N–C_6H_4	Ph	88
5e	4-Br–C_6H_4	Ph	81
5f	3-Br–C_6H_4	Ph	80
5g	4-Cl–C_6H_4	Ph	75
5h	3-Cl–C_6H_4	Ph	76
5i	4-F–C_6H_4	Ph	81
5j	4-Me–C_6H_4	Ph	72
5k	4-HO–C_6H_4	Ph	80
5l	C_6H_5	4-O_2N–C_6H_4	68
5m	4-O_2N–C_6H_4	4-O_2N–C_6H_4	71
5n	3-O_2N–C_6H_4	4-O_2N–C_6H_4	70
5o	4-Cl–C_6H_4	4-O_2N–C_6H_4	68
5p	4-O_2N–C_6H_4	H	63
5q	3-O_2N–C_6H_4	H	61

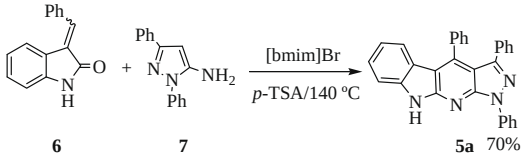
[a] Yield of isolated product.

starting materials and numerous by-products, the yield of the expected product being very poor.

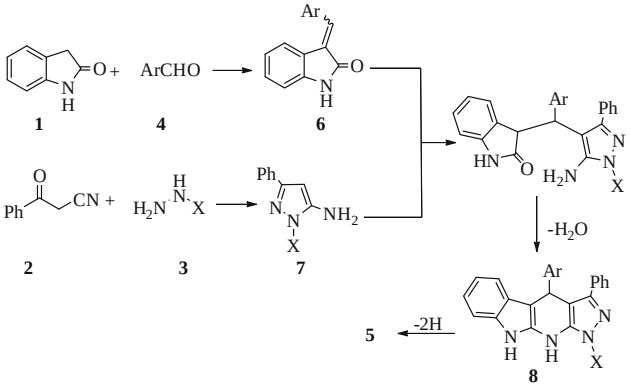
From a mechanistic view point, it is notable that when indolin-2-one (**1**), 3-oxo-3-phenylpropanenitrile (**2**), phenylhydrazine (**3a**), and benzaldehyde (**4a**) were reacted for 2 h, intermediates were formed which could be isolated. Reaction of these intermediates in the presence of *p*-TSA under the same reaction conditions afforded product **5a** in 70% yield (Scheme 2).

According to these results, the formation of products **5** can be rationalized by initial formation of arylideneindolin-2-one **6** via condensation of **1** and **4**. Subsequent Michael-type addition of **7** (formed in situ by reaction of hydrazine **3** with nitrile **2**), to the intermediate **6** followed by cyclization afforded **8**. The final product **5** was then formed by oxidation of intermediate **8** (Scheme 3).

In summary, we have developed a facile, one-pot, four-component procedure for the preparation of 1*H*-indolo[2,3-*b*]pyrazolo[4,3-*e*]pyridines of potential synthetic and biological interest. Prominent among the advantages of this new method are novelty, good yields, and easy work-up.



Scheme 2.



Scheme 3.

Typical procedure for the preparation of 1,3,4-triphenyl-1H-indolo[2,3-b]pyrazolo[4,3-e]pyridine (**5a**): A mixture of indolin-2-one (1 mmol), benzaldehyde (1 mmol), 3-oxo-3-phenylpropanenitrile (1 mmol), phenylhydrazine (1 mmol), *p*-TSA (0.3 mmol), and [bmim]Br (0.30 g) was heated at 140 °C for 8 h (TLC). After cooling, the reaction mixture was washed with water (15 mL) and the residue crystallized from EtOH to afford pure **5a** as a cream powder (85%); mp 249 °C (dec). IR (KBr): 3214, 3147, 1596 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 6.92–8.43 (19H, m, H-Ar), 12.19 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 110.0, 111.5, 112.3, 120.0, 121.1, 121.2, 121.9, 126.0, 127.0, 127.6, 128.6, 128.9, 129.3, 129.3, 129.4, 129.5, 133.1, 135.6, 139.9, 140.3, 140.7, 146.9, 153.4. MS (EI, 70 eV) *m/z*: 436 (M^+). Anal. Calcd for $C_{30}H_{20}N_4$: C, 82.55; H, 4.62; N, 12.84. Found: C, 82.39; H, 4.58; N, 12.78.

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Supplementary data

Supplementary data (experimental procedures and spectral data of the products) associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.077.

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