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Base-catalyzed three-component synthesis of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitriles

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Abstract

A base-catalyzed, one-pot and facile method for the synthesis of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitriles is reported. This procedure includes a novel three-component reaction of indolin-3-one with aromatic aldehydes and malononitrile in ethanol in the presence of ammonium acetate as the catalyst.

Keywords: ammonium acetate; multicomponent; pyrano[3,2-*b*]indole.

Introduction

Recently, different authors have reported the anticancer potential of indole (James et al., 2006; Singh et al., 2008; Kumar et al., 2010a; Kumar et al., 2010b; Ziedan et al., 2010) and a-pyrone derivatives (Marrison et al., 2002; Fairlamb et al., 2004; Zhang et al., 2007). On the basis of these studies it was speculated that combining the structural characteristics of both moieties could produce substantial enhancement in the anticancer activity of such compounds. Accordingly, due to their significant biological activities as well as their wide-ranging utility as synthetic intermediates for alkaloids, drug candidates and clinical pharmaceuticals (Miyamoto et al., 2006), a number of synthetic methods have been developed in pursuit of this structure. These include intramolecular hetero-Diels-Alder cycloaddition (Daviona et al., 2003) and cycloisomerization (Praveen et al., 2011).

Moreover, as there is increasing environmental consciousness in chemical research and industry, the challenge has been to create environmentally sustainable, clean procedures that avoid using metal ions as catalysts (Su et al., 2005; Sharma et al., 2008).

As part of a continuing effort in our laboratory toward the development of new multi-component condensation reactions (Damavandi, 2011), we became interested in the possibility of developing an efficient methodology for the preparation of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitrile derivatives through a three-component condensation reaction of indolin-3-one, aryl aldehydes, and malononitrile catalyzed by ammonium acetate. Herein, we report the details of the study (Scheme 1).

Results and discussion

In a preliminary experiment we found out that the three-component condensation of indolin-3-one, 4-chlorobenzaldehyde, and malononitrile in the presence of ammonium acetate (10 mol%) proceeded to efficiently afford 2-amino-4,5-dihydro-4-chlorophenylpyrano[3,2-*b*]indole-3-carbonitrile (compound **6** in Table 1). The catalyst has a significant effect on the model reaction of 4-chlorobenzaldehyde.

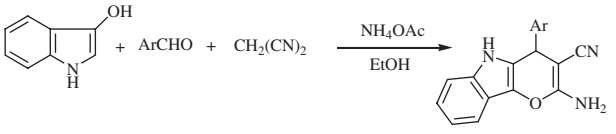
No reaction took place in the presence of proton acids and classical Lewis acids as catalysts, such as $AlCl_3$, $ZnCl_2$, TsOH, NH_2SO_3H, $Cu(OTf)_2$ and $Zn(OTf)_2$ (Table 1, entries 1–7).

Then we examined the reaction using bases as the catalysts under similar reaction conditions (Table 1, entries 8–13). Under the base catalysis of the three-component condensation reaction, the desired product **6** was obtained in moderate to excellent yields (57–90%). As shown in Table 1, ammonium acetate was found to be the most effective catalyst in terms of reaction time and yield.

Having optimized the catalyst, we then successfully synthesized a variety of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitrile derivatives. As shown in Scheme 1, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents react efficiently giving good to excellent yields of corresponding pyrano[3,2-*b*]indoles. The experimental procedure is convenient and rapid, and a variety of functional groups – such as methoxyl, nitro, hydroxyl and halides – are tolerated under these reaction conditions. Steric hindrance of the aldehydes influences the reaction only slightly and the corresponding pyrano[3,2-*b*]indoles **5**, **7**, **9** were obtained in good yields.

Conclusion

We have discovered an effective method for the synthesis of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitrile derivatives by a one-pot three-component reaction of indolin-3-one, aromatic aldehydes and malononitrile in ethanol using 10 mol% ammonium acetate as the catalyst. The noteworthy features of this procedure are cleanness of the reaction, an inexpensive catalyst, economical steps, high yields and operational simplicity.



1-12

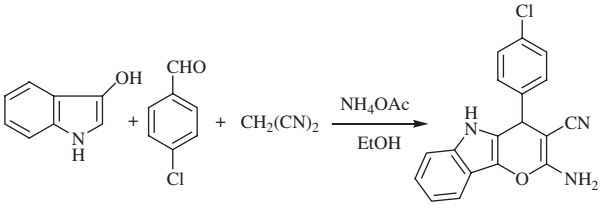
Ar=4-$CH_3OC_6H_4$ - (**1**); C_6H_5 - (**2**); 4-$CH_3C_6H_4$ - (**3**); 4-BrC_6H_4 - (**4**); 2-BrC_6H_4 - (**5**); 4-ClC_6H_4 - (**6**); 2-ClC_6H_4 - (**7**); 4-$NO_2C_6H_4$ - (**8**); 2-$NO_2OC_6H_4$ - (**9**); 4-FC_6H_4 - (**10**); 2-furanyl - (**11**); 1-naphthyl - (**12**)

Scheme 1 Synthesis of pyrano[3,2-*b*]indole derivatives **1–12**.

Experimental

Chemicals were either prepared in our laboratories or purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products. The infrared (IR) spectra were recorded using KBr disks on a Shimadzu-IR 470 spectrophotometer. The ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 250-MHz spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard. Flash column chromatography was performed using 300- and 400-mesh silica gel and analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel plates (60F-254). Elemental analyses were performed on Thermo Finnigan EA1112 elemental analyzer.

Table 1 One-pot synthesis of 5-amino-7-(4-chlorophenyl)-1,7-dihydropyrano[3,2-*b*]pyrrole-6-carbonitrile (**6**) in the presence of various catalysts.



Entry	Catalyst (10 mol%)	Yield (%)
1	$AlCl_3$	0
2	$FeCl_3$	0
3	$ZnCl_2$	0
4	$Cu(OTf)_2$	0
5	$Zn(OTf)_2$	0
5	TsOH	0
6	*p*-TSA	0
7	NH_2SO_3H	0
8	Pyridine	57
9	Imidazole	63
10	Et_3N	82
11	Piperidine	77
12	DBU	57
13	NH_4OAc	90

Reaction conditions: indolin-3-one (1 mmol), *p*-chlorobenzaldehyde (1 mmol), malononitrile (1 mmol), EtOH (8 ml), reflux for 3 h. DBU, diaza(1,3)bicyclo[5.4.0]undecane.

General procedure for the synthesis of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitrile derivatives

A mixture of indolin-3-one (1 mmol), aldehyde (1 mmol), malononitrile (1 mmol) and ammonium acetate (0.15 mmol) in EtOH (8 ml) was stirred and heated under reflux. After completion of the reaction, as indicated by TLC analysis, the mixture was cooled to room temperature, treated with cold water (10 ml), and stirred for an additional 5 min. The precipitated solid was filtered off and crystallized from EtOH–H_2O (3:1). Further purification was carried out by silica gel column chromatography eluting with n-hexane/ethyl acetate (9:1) to afford pure products. The compounds are characterized as follows.

2-Amino-4,5-dihydro-4-(4-methoxyphenyl)pyrano[3,2-*b*]indole-3-carbonitrile (1) After 3.0 h the yield was 78%; IR: ν 1,665 (NH_2), 2,218 (CN), 3,224 and 3,259 cm^{-1} (NH_2); ^{1}H NMR: δ_H 3.63 (s, 3H, OCH_3), 5.41 (s, 1H, CH), 6.89 (bs, 2H, NH_2), 6.82–6.99 (m, 2 H); 7.04–7.13 (m, 4 H); 7.56 (d,1 H, *J*=8.0); 7.87 (d, 1 H, *J*=7.8), 10.14 (bs, 1H, NH). Analysis calculated for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.75; H, 4.67; N, 13.11.

2-Amino-4,5-dihydro-4-phenylpyrano[3,2-*b*]indole-3-carbonitrile (2) After 2.5 h the yield was 88%; IR: ν 1,659 (NH_2); 2,214 (CN); 3,222 and 3,244 cm^{-1} (NH_2); ^{1}H NMR: δ_H 5.18 (s, 1H, CH), 6.69 (bs, 2H, NH_2), 7.00–7.18 (m, 2H), 7.28–7.56 (m, 5H), 7.72 (d, 1 H, *J*=8.1); 8.11 (d, 1 H, *J*=7.0), 11.05 (bs, 1H, NH). Analysis calculated for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63. Found: C, 74.98; H, 4.49; N, 14.60.

2-Amino-4,5-dihydro-4-p-tolylpyrano[3,2-*b*]indole-3-carbonitrile (3) After 3.0 h the yield was 86%; IR: ν 1,661 (NH_2), 2,224 (CN), 3,213 and 3,259 cm^{-1} (NH_2): ^{1}H NMR: δ_H 2.33 (s, 3H, CH_3), 5.33 (s, 1H, CH), 6.75 (bs, 2H, NH_2), 6.99–7.04 (m, 2 H), 7.20–7.36 (m, 4 H), 7.63 (d, 1 H, *J*=7.9), 7.90 (d, 1 H, *J*=7.1), 10.42 (bs, 1H, NH). Analysis calculated for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 74.68; H, 5.00; N, 13.79.

2-Amino-4-(4-bromophenyl)-4,5-dihydropyrano[3,2-*b*]indole-3-carbonitrile (4) After 2.0 h the yield was 90%; IR: ν 1,670 (NH_2), 2,226 (CN), 3,240 and 3,361 cm^{-1}(NH_2); ^{1}H NMR: δ_H 5.50 (s, 1H, CH), 6.70 (bs, 2 H, NH_2), 7.07–7.16 (m, 2 H); 7.30–7.44 (m, 4 H); 7.68 (d, 1 H, *J*=7.6); 8.01 (d, 1 H, *J*=7.0), 11.02 (bs, 1H, NH). Analysis calculated for $C_{18}H_{12}BrN_3O$: C, 59.03; H, 3.30; N, 11.47. Found: C, 58.76; H, 3.27; N, 11.40.

2-Amino-4-(2-bromophenyl)-4,5-dihydropyrano[3,2-*b*]indole-3-carbonitrile (5) After 3.0 h the yield was 82%; IR: ν 1,664 (NH_2), 2,217 (CN), 3,225 and 3,252 cm^{-1} (NH_2); ^{1}H NMR: δ_H 5.43 (s, 1H, CH), 6.81 (s, 2H, NH_2), 6.93 (d, 1 H, *J*=7.2); 7.18–7.55 (m, 6 H); 7.92 (d, 1 H, *J*=6.2), 9.70 (bs, 1H, NH). Analysis calculated for $C_{18}H_{12}BrN_3O$: C, 59.03; H, 3.30; N, 11.47. Found: C, 58.76; H, 3.26; N, 11.19.

2-Amino-4-(4-chlorophenyl)-4,5-dihydropyrano[3,2-*b*]indole-3-carbonitrile (6) After 2.0 h the yield was 90%; IR: ν 1,667 (NH_2), 2,219 (CN), 3,202 and 3,244 cm^{-1} (NH_2); ^{1}H NMR: δ_H 5.49 (s, 1H, CH), 6.68 (s, 2H, NH_2), 7.21–7.42 (m, 2 H); 7.46–7.59 (m, 4 H); 7.63 (d, 1 H, *J*=6.7); 8.01 (d, 1 H, *J*=7.0), 10.54 (bs, 1H, NH). Analysis calculated for $C_{18}H_{12}ClN_3O$: C, 70.81; H, 3.96; N, 13.76. Found: C, 70.55; H, 3.90; N, 13.71.

2-Amino-4-(2-chlorophenyl)-4,5-dihydropyrano[3,2-*b*]indole-3-carbonitrile (7) After 2.5 h the yield was 87%; IR: ν 1,664 (NH_2), 2,211 (CN), 3,222 and 3,241 cm^{-1} (NH_2); ^1H NMR: δ_H 5.63 (s, 1H, CH), 6.59 (bs, 2H, NH_2), 6.81 (s, 1 H); 7.02–7.21 (m, 2 H); 7.29–7.38 (m, 4 H); 7.46 (d, 1 H, *J*=6.7), 10.39 (bs, 1H, NH). Analysis calculated for $C_{18}H_{12}ClN_3O$: C, 70.81; H, 3.96; N, 13.76. Found: C, 70.64; H, 3.89; N, 13.52.

2-Amino-4,5-dihydro-4-(4-nitrophenyl)pyrano[3,2-*b*]indole-3-carbonitrile (8) After 3.0 h the yield was 91%; IR: ν 1,661 (NH_2), 2,211 (CN), 3,224 and 3,256 cm^{-1} (NH_2); ^1H NMR: δ_H 5.49 (s, 1H, CH), 6.60 (bs, 2H, NH_2), 6.85 (s, 1 H); 7.02–7.20 (m, 3 H); 7.43–7.51 (m, 3 H); 7.66 (d, 1 H, *J*=8.01), 10.22 (bs, 1H, NH). Analysis calculated for $C_{18}H_{12}N_4O_3$: C, 65.06; H, 3.64; N, 16.86. Found: C, 64.78; H, 3.60; N, 16.79.

2-Amino-4,5-dihydro-4-(2-nitrophenyl)pyrano[3,2-*b*]indole-3-carbonitrile (9) After 2.0 h the yield was 82%; IR: ν 1,669 (NH_2), 2,225 (CN), 3,218 and 3,231 cm^{-1} (NH_2); ^1H NMR: δ_H 5.72 (s, 1H, CH), 6.71 (s, 2H, NH_2), 7.22 (d, 1 H, *J*=7.76); 7.26–7.42 (m, 3 H); 7.46–7.59 (m, 2 H); 7.76 (d, 1 H, *J*=7.6); 7.99 (d, 1 H, *J*=6.9), 10.11 (bs, 1H, NH). Analysis calculated for $C_{18}H_{12}N_4O_3$: C, 65.06; H, 3.64; N, 16.86. Found: C, 64.86; H, 3.53; N, 16.75.

2-Amino-4-(4-fluorophenyl)-4,5-dihydropyrano[3,2-*b*]indole-3-carbonitrile (10) After 2.0 h the yield was 88%; IR: ν 1,661 (NH_2), 2,200 (CN), 3,224 and 3,262 cm^{-1} (NH_2); ^1H NMR: δ_H 5.11 (s, 1H, CH), 6.75 (bs, 2H, NH_2), 7.12–7.29 (m, 4 H); 7.38–7.52 (m, 2 H); 7.63 (d, 1 H, *J*=7.1); 8.20 (d, 1 H, *J*=8.01), 10.24 (bs, 1H, NH). Analysis calculated for $C_{18}H_{12}FN_3O$: C, 70.81; H, 3.96; N, 13.76. Found: C, 70.56; H, 3.91; N, 13.68.

2-Amino-4-(furan-2-yl)-4,5-dihydropyrano[3,2-*b*]indole-3-carbonitrile (11) After 4.0 h the yield was 77%; IR: ν 1,663 (NH_2), 2,221 (CN), 3,230 and 3,251 cm^{-1} (NH_2); ^1H NMR: δ_H 5.33 (s, 1H, CH), 6.72 (bs, 2 H, NH_2), 7.01 (m, 1 H); 7.11–7.20 (m, 2 H); 7.27–7.53 (m, 2 H); 7.64 (d, 1 H, *J*=6.1); 8.06 (d, 1 H, *J*=7.0), 10.44 (bs, 1H, NH). Analysis calculated for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00; N, 15.15. Found: C, 68.89; H, 3.94; N, 15.04.

2-Amino-4,5-dihydro-4-(naphthalen-1-yl)pyrano[3,2-*b*]indole-3-carbonitrile (12) After 4.0 h the yield was 75%; IR: ν 1,656 (NH_2), 2,218 (CN), 3,221 and 3,261 cm^{-1} (NH_2); ^1H NMR: δ_H 5.43 (s, 1H, CH), 6.65 (bs, 2H, NH_2), 6.87–7.17 (m, 3 H); 7.28–7.40 (m, 6 H); 7.59 (d, 1 H, *J*=8.6); 7.84 (d, 1 H, *J*=7.8), 9.85 (bs, 1H, NH). Analysis calculated for $C_{22}H_{15}N_3O$: C, 78.32; H, 4.48; N, 12.46. Found: C, 78.11; H, 4.39; N, 12.41.

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