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Novel multicomponent synthesis of pyrido[2,3-*b*]indoles

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Abstract

A series of pyrido[2,3-*b*]indole derivatives was synthesized *via* a novel multicomponent reaction catalyzed by ferric hydrogen sulfate.

Keywords: ferric hydrogen sulfate; multicomponent; pyrido[2,3-*b*]indole.

Introduction

Multi-component reactions play an important role in modern synthetic organic chemistry, as they generally occur in a single pot and exhibit a high atom-economy and selectivity (Trost, 1995; Dömling, 2002; Toure and Hall, 2009). They also deliver fewer by-products compared to the classical stepwise synthetic routes (Nicolaou et al., 2006; Wang et al., 2007). Synthesis of pyridoindole (α-carboline) derivatives has attracted considerable interest due to the recent discoveries of several naturally occurring compounds containing this skeleton (Veale et al., 1995; Menta et al., 2001). Among these compounds, pyrido[2,3-*b*]indoles have received immense attention because of their various pharmacological and biological activities, such as their anticancer activity against colon and lung cancers, central nervous system activity in mammals and use as a biological control agent for receptor research on bio-enzyme inhibitors (inhibition of human leukocyte elastase) (Nielsch et al., 1999; Beccalli et al., 2001; Ritzeler et al., 2001). A literature survey has revealed that a number of pyridoindoles have been synthesized using a wide range of reagents and methods (Meyer and Guyot, 1996; Molina et al., 1997, 1998; Barun et al., 1999; Ryabova et al., 2001, 2009; Hostyn et al., 2011). Nevertheless, there are no reports for a one-pot multi-component strategy utilizing substituted (triethoxymethyl)arene, 1-methyl-1*H*-indol-2-ol and cyanoacetamide to synthesize pyrido[2,3-*b*]indoles. In connection with our recent interest aimed at the development of efficient protocols for the preparation of biologically active heterocycles (Damavandi, 2011), we now report efficient synthesis of 2,9-dihydro-2-oxo-4-aryl-1*H*-pyrido[2,3-*b*]indole-3-carbonitrile derivatives through one-pot cyclocondensation of substituted (triethoxymethyl)arene, 1-methyl-1*H*-indol-2-ol and cyanoacetamide catalyzed by ferric hydrogen sulfate, $Fe(HSO_4)_3$.

Results and discussion

Treatment of (triethoxymethyl)benzene, cyanoacetamide and 1-methyl-1*H*-indol-2-ol in acetonitrile in the presence of 10 mol% $Fe(HSO_4)_3$ under reflux conditions furnished 2,9-dihydro-9-methyl-2-oxo-4-phenyl-1*H*-pyrido[2,3-*b*]indole-3-carbonitrile in high yield (Scheme 1). Encouraged by this success, the methodology was extended to the synthesis of a variety of 2,9-dihydro-2-oxo-4-aryl-1*H*-pyrido[2,3-*b*]indole-3-carbonitriles. More specifically, various derivatives of (triethoxymethyl)benzene were subjected to the reaction with cyanoacetamide and 1-methyl-1*H*-indol-2-ol to furnish the corresponding pyrido[2,3-*b*]indoles. The representative examples are shown in Scheme 2. The use of (triethoxymethyl)benzene derivatives substituted with either electron-withdrawing or electron-donating groups afforded the expected products in good to high yields.

A mechanism for this reaction is proposed in Scheme 3. The first step may involve a cross coupling between 1-methyl-1*H*-indol-2-ol and (triethoxymethyl)benzene that results in the formation of α,β-unsaturated compound **X**. Nucleophilic attack of cyanoacetamide on the β-position of the intermediate product **X**, which may be activated by the catalyst, generates the intermediate product **Y**. Intramolecular condensation reaction of **Y** leads to the final product.

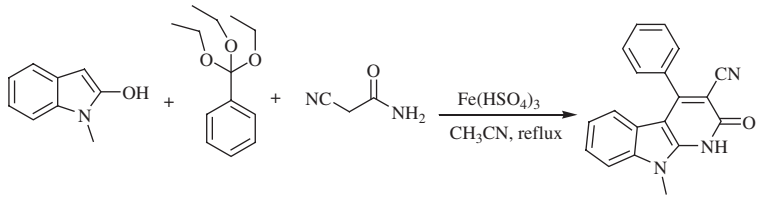
Conclusion

A novel protocol for the one-pot synthesis of 2,9-dihydro-2-oxo-4-aryl-1*H*-pyrido[2,3-*b*]indole-3-carbonitrile derivatives utilizing easily accessible 1-methyl-1*H*-indol-2-ol, substituted (triethoxymethyl)arene and cyanoacetamide in the presence of an inexpensive catalyst is described.

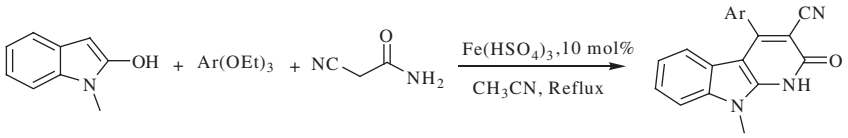
Experimental section

General

Chemicals were either prepared in our laboratories or purchased from Merck, Fluka and Aldrich Chemicals. All yields refer to isolated products. Infrared (IR) spectra were recorded in KBr disks on a Shimadzu-IR 470 spectrophotometer. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded in DMSO-d_6 at 400 MHz on a Bruker 400-MHz spectrometer. ^{13}C NMR spectra were recorded at 62.5 MHz. Flash column chromatography was performed with



Scheme 1 Synthesis of 2,9-dihydro-9-methyl-4-phenyl-2-oxo-1*H*-pyrido[2,3-*b*]indole-3-carbonitrile.



1-8

Ar=4-$CH_3OC_6H_4$ - (**1**) (82%); C_6H_5 - (**2**) (80%); 4-$CH_3C_6H_4$ (**3**) (78%); 4-BrC_6H_4 (**4**) (73%);

2-BrC_6H_4 - (**5**) (70%); 4-ClC_6H_4 (**6**) (72%); 2-ClC_6H_4 - (**7**) (67%); 4-$NO_2C_6H_4$ - (**8**) (65%).

Scheme 2 One-pot synthesis of pyrido[2,3-*b*]indole derivatives **1–8**.

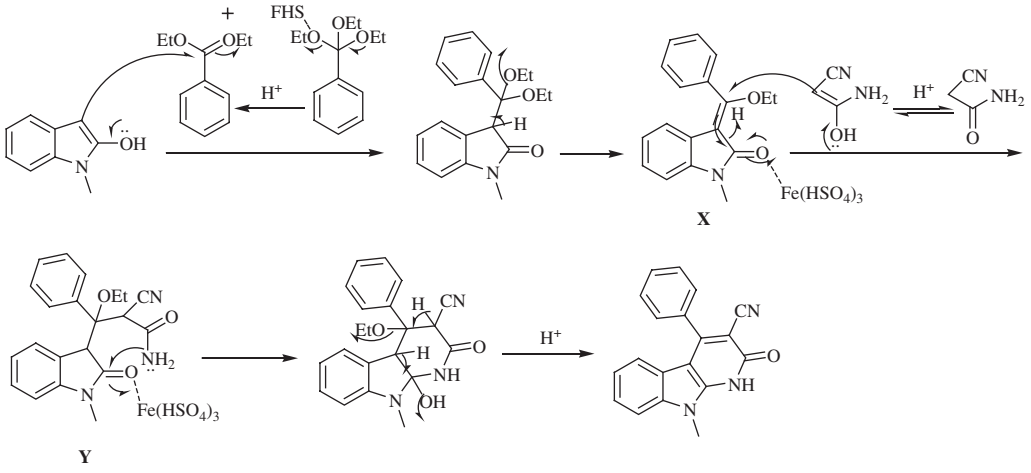
300- and 400-mesh silica gel and thin layer chromatography (TLC) was performed on pre-coated silica gel plates (60F-254). Elemental analyses were performed on Thermo Finnigan EA1112 elemental analyzer.

General procedure for the synthesis of pyrido[2,3-*b*]-indole compounds 1–8

A mixture of (triethoxymethyl)arene (1 mmol), 1-methyl-1*H*-indol-2-ol (1 mmol) and cyanoacetamide (1.1 mmol) was stirred under reflux with ferric hydrogen sulfate (0.1 mmol) in acetonitrile (6 ml) for a period of time. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was recovered by filtration. The solvent was removed from the filtrate by distillation and the residue of the crude product was purified by column chromatography eluting with *n*-hexane/ethyl acetate (5:1).

2,9-Dihydro-4-(4-methoxyphenyl)-9-methyl-2-oxo-1*H*-pyrido[2,3-*b*]indole-3-carbonitrile (1) After 4 h the yield was 82%; IR: ν_{max} 3255, 3110, 2955, 2830, 2235, 1645, 1555, 1440, 1133 cm^{-1}; ^1H NMR: δ 10.85 (1H, s, NHCO), 7.60–7.35 (2H, m, ArH), 7.28 (2H, d, *J*=7.1 Hz, ArH), 7.12 (2H, d, *J*=7.4 Hz, ArH), 6.95 (2H, d, *J*=7.1 Hz, ArH), 3.80 (s, OCH_3), 3.65 (3H, s, indole); ^{13}C NMR: δ 165.8, 155.1, 150.4, 135.8, 128.2, 126.3, 124.6, 124.4, 124.2, 122.1, 121.4, 119.6, 115.3, 111.9, 112.6, 99.8, 55.8, 35.2. Anal. calcd for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.56; H, 4.55; N, 12.73.

2,9-Dihydro-9-methyl-2-oxo-4-phenyl-1*H*-pyrido[2,3-*b*]indole-3-carbonitrile (2) After 5 h the yield was 80%; IR: ν_{max} 3250, 3120, 2965, 2833, 2230, 1642, 1551, 1431 cm^{-1}; ^1H NMR: δ 11.02 (1H, s, NHCO), 7.55 (1H, d, *J*=6.3 Hz, ArH), 7.43 (1H, d, *J*=6.3 Hz, ArH), 7.33–7.15 (7H, m, ArH), 3.62 (3H, s, indole); ^{13}C NMR: δ 169.3, 155.2, 138.5, 129.2, 125.5, 124.2, 123.7, 122.47, 120.4, 118.5, 118.0,



Scheme 3 Proposed mechanism for the synthesis of pyrido[2,3-*b*]indoles catalyzed by $Fe(HSO_4)_3$.

117.5, 116.1, 114.6, 110.8, 96.2, 34.5. Anal. calcd for $C_{19}H_{13}N_3O$: C, 76.24; H, 4.38; N, 14.04. Found: C, 75.90; H, 4.34; N, 14.42.

2,9-Dihydro-9-methyl-2-oxo-4-*p*-tolyl-1*H*-pyrido[2,3-*b*]indole-3-carbonitrile (3) After 5 h the yield was 78%; IR: ν_{max} 3254, 3119, 2976, 2835, 2218, 1647, 1551, 1422 cm^{-1}; ^1H NMR: δ 10.80 (1H, s, NHCO), 7.46 (1H, d, *J*=7.1 Hz, ArH), 7.57 (1H, d, *J*=7.1 Hz, ArH), 7.30–7.12 (6H, m, ArH), 3.52 (s, CH_3, indole), 2.12 (s, CH_3); ^{13}C NMR: δ 161.9, 156.1, 139.6, 135.5, 129.3, 128.7, 127.1, 125.9, 125.3, 124.0, 121.8, 120.1, 117.8, 115.1, 112.9, 95.2, 34.6, 24.9. Anal. calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.49; H, 4.78; N, 13.38.

4-(4-Bromophenyl)-2,5-dihydro-2-oxo-1*H*-pyrido[3,2-*b*]indole-3-carbonitrile (4) After 6 h the yield was 73%; IR: ν_{max} 3246, 3125, 2983, 2826, 2217, 1656, 1509, 1452 cm^{-1}; ^1H NMR: δ 10.90 (1H, s, NHCO), 7.57 (1H, d, *J*=6.2 Hz, ArH), 7.40–7.30 (3H, m, ArH), 7.15 (2H, d, *J*=6.4 Hz, ArH), 7.80 (2H, d, *J*=6.4 Hz, ArH), 3.55 (s, CH_3, indole); ^{13}C NMR: δ 168.5, 160.7, 139.2, 132.3, 129.5, 128.3, 127.9, 124.8, 124.1, 122.6, 121.8, 121.6, 117.3, 116.5, 111.3, 96.6, 32.7. Anal. calcd for $C_{19}H_{12}BrN_3O$: C, 60.34; H, 3.20; N, 11.11. Found: C, 60.21; H, 3.14; N, 11.05.

4-(2-Bromophenyl)-2,5-dihydro-2-oxo-1*H*-pyrido[3,2-*b*]indole-3-carbonitrile (5) After 6 h the yield was 70%; IR: ν_{max} 3255, 3134, 2991, 2806, 2228, 1650, 1544, 1487 cm^{-1}; ^1H NMR: δ 10.57 (1H, s, NHCO), 7.60 (1H, d, *J*=7.0 Hz, ArH), 7.45–7.37 (2H, m, ArH), 7.22–7.14 (5H, m, ArH), 3.63 (s, CH_3, indole); ^{13}C NMR: δ 163.3, 155.2, 139.7, 135.5, 132.1, 129.8, 125.9, 125.2, 124.6, 123.3, 121.9, 121.0, 118.8, 118.6, 118.1, 115.7, 94.1, 31.6. Anal. calcd for $C_{19}H_{12}BrN_3O$: C, 60.34; H, 3.20; N, 11.11. Found: C, 60.27; H, 3.13; N, 11.07.

4-(4-Chlorophenyl)-2,9-dihydro-9-methyl-2-oxo-1*H*-pyrido[2,3-*b*]indole-3-carbonitrile (6) After 5.5 h the yield was 72%; IR: ν_{max} 3263, 3115, 2980, 2802, 2212, 1652, 1535, 1470 cm^{-1}; ^1H NMR: δ 11.02 (1H, s, NHCO), 7.55 (1H, d, *J*=7.5 Hz, ArH), 7.46 (1H, d, *J*=7.7 Hz, ArH), 7.25–7.18 (4H, m, ArH), 7.04 (2H, d, *J*=7.7 Hz, ArH), 3.55 (s, CH_3, indole); ^{13}C NMR: δ 166.4, 161.1, 138.9, 135.3, 129.7, 127.4, 124.93, 124.7, 123.6, 122.1, 121.5, 120.5, 118.8, 116.7, 111.1, 93.6, 33.1. Anal. calcd for $C_{19}H_{12}ClN_3O$: C, 68.37; H, 3.62; N, 12.59. Found: C, 67.91; H, 3.53; N, 12.51.

4-(2-Chlorophenyl)-2,9-dihydro-9-methyl-2-oxo-1*H*-pyrido[2,3-*b*]indole-3-carbonitrile (7) After 7 h the yield was 67%; IR: ν_{max} 3250, 3142, 2997, 2812, 2211, 1667, 1553, 1465 cm^{-1}; ^1H NMR: δ 10.92 (1H, s, NHCO), 7.50 (1H, d, *J*=6.5 Hz, ArH), 7.43 (1H, d, *J*=6.5 Hz, ArH), 7.30–7.24 (2H, m, ArH), 7.20–7.05 (4H, m, ArH), 3.60 (s, CH_3, indole); ^{13}C NMR: δ 169.5, 158.4, 139.7, 134.4, 131.1, 128.9, 125.5, 124.2, 122.9, 122.1, 120.8, 120.1, 118.9, 118.7, 116.9, 116.3, 98.5, 34.5. Anal. calcd for $C_{19}H_{12}ClN_3O$: C, 68.37; H, 3.62; N, 12.59. Found: C, 67.84; H, 3.55; N, 12.49.

2,9-Dihydro-9-methyl-4-(4-nitrophenyl)-2-oxo-1*H*-pyrido[2,3-*b*]indole-3-carbonitrile (8) After 8 h the yield was 65%; IR: ν_{max} 3255, 3175, 2995, 2810, 2217, 1637, 1552, 1516, 1481, 1345 cm^{-1}; ^1H NMR: δ 10.85 (1H, s, NHCO), 8.09 (2H, d, *J*=7.2 Hz, ArH), 7.65–7.50 (3H, m, ArH), 7.40 (1H, d, *J*=7.7 Hz, ArH), 7.10 (2H, d, *J*=7.7 Hz, ArH), 3.62 (s, CH_3, indole); ^{13}C NMR: δ 167.7, 159.2, 154.1, 148.3, 144.4, 129.9, 127.4, 125.9, 125.2, 123.3, 122.1, 121.7, 120.4, 119.5, 115.6, 114.1, 95.5, 34.6. Anal. calcd for $C_{19}H_{12}N_4O_3$: C, 66.28; H, 3.51; N, 16.27. Found: C, 66.01; H, 3.42; N, 16.16.

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