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An eco-friendly synthesis of 2-aminochromenes and indolyl chromenes catalyzed by $InCl_3$ in aqueous media

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Abstract—A simple and convenient method for the synthesis of new 2-aminochromenes and indolyl chromenes via an indium trichloride catalyzed, three-component reaction in aqueous media is described.

Multicomponent reactions (MCRs) by virtue of their convergence, productivity, facile execution and generally high yields of products have attracted considerable attention from the point of view of combinatorial chemistry.[1] The first MCR was described by Strecker in 1850 for the synthesis of amino acids.[2] However, in the past decade there have been tremendous developments in three- and four-component reactions and great efforts have been and still are being made to find and develop new MCRs.[3] In this context, dihydropyridines (DHPs) show interesting features that make them attractive for use in MCRs.

The reduced form of the nicotinamide adenine dinucleotide coenzyme [NAD(P)H] plays a vital role in many bioreductions by transferring a hydride ion or an electron to substrates.[4] 1-Benzyl-1,4-dihydronicotinamide (BNAH), Hantzsch 1,4-dihydro pyridines (DHP), 10-methyl-9,10-dihydroacridine ($AcrH_2$) and many other 1,4-dihydropyridine derivatives have been used widely as models of NAD(P)H to mimic the reductions of various unsaturated compounds such as quinones,[5] ketones,[6] aldehydes,[7] imines[8] and alkenes.[9] Garden et al.[10] have reported the reduction of certain electron-withdrawing conjugated olefins using the Hantzsch 1,4-dihydropyridine ester. To our best knowledge, very little effort has been made towards the application of these NAD(P)H models in synthetic organic chemistry except for some chiral NAD(P)H models.[11] Hence, the use of NAD(P)H model compounds as a class of mild reducing agents in synthetic organic chemistry is of considerable interest.[1]

2-Aminochromenes are widely employed as pigments,[12] cosmetics, agrochemicals[13] and represent an important class of chemical entities being the main constituents of many natural products. Fused chromenes exhibit a wide spectrum of biological applications as antimicrobial, antiviral,[14] mutagenic, antiproliferative, sex pheromone, antitumour[15] and central nervous system agents. The most straightforward synthesis of this heterocyclic nucleus involves the MCR of araldehyde, malononitrile and an activated phenol in the presence of piperidine[16] using acetonitrile or ethanol as solvent. However, most of the reported methods require prolonged reaction times, reagents in stoichiometric amounts, and toxic solvents and generate moderate yields of the product. Due to the unique pharmacological properties of 2-aminochromenes, the development of synthetic methods enabling facile access to this heterocycle is desirable.

Lately, the utility of indium(III) Lewis acids[17] in organic synthesis has received a great deal of interest due to their relatively low toxicity, stability in air and water and recyclability. As part of our current studies on the design of new routes for the preparation of biologically active heterocyclic compounds and in the application of $InCl_3$[18] in organic synthesis, we herein disclose a simple and convenient method for the synthesis of 2-aminochromenes from the Hantzsch ester using a catalytic amount of $InCl_3$ in aqueous media at room temperature (Scheme 1).

Keywords: 2-Aminochromenes; Three-component reaction; Indium(III) chloride.
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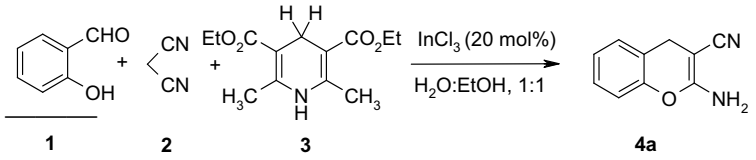
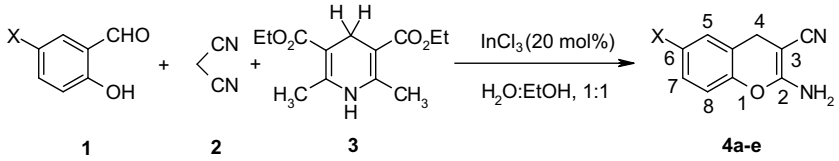


Scheme 1.

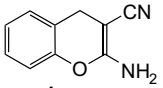
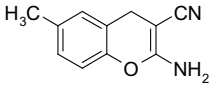
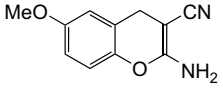
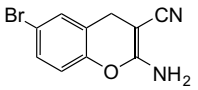
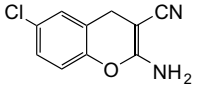


Scheme 2.

In order to study the scope and limitations of the three-component reaction, various Lewis acid catalysts, including $SnCl_2{\cdot}2H_2O$, NH_2SO_3H, CAN, $In(OTf)_3$ and $InCl_3$ and different solvent systems were investigated. The best overall yield (86%) was obtained with $InCl_3$ in water:ethanol (1:1). Optimum results were obtained using 20 mol % of $InCl_3$.

The reactions were carried out by first mixing salicylaldehyde **1**, malononitrile **2** and Hantzsch dihydropyridine ester[19] **3** in H_2O:ethanol (1:1). Then, a catalytic amount of $InCl_3$ (20 mol %) was added.[20] The reaction proceeded spontaneously at ambient temperature and was complete within 30 min (Scheme 2 and Table 1).

Table 1. Synthesis of 2-aminochromenes

Entry	X(**1**)	Product (**4**)	Time (min)	Yield[a] (%)
1	H	 **4a**	25	86
2	CH_3	 **4b**	35	84
3	OMe	 **4c**	40	82
4	Br	 **4d**	30	88
5	Cl	 **4e**	30	87

[a] Isolated yield.

The structures of compounds **4a**–**e** were confirmed by IR, ^1H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectrum of **4a**[21] displayed the molecular ion (M^+) peak at *m/z* 172. The ^1H NMR spectrum of **4a** exhibited a singlet at δ 3.41 for H-4 and a broad singlet at δ 6.77 (D_2O exchangeable) due to the $-NH_2$ protons. A distinguishing resonance at δ 24.1 for C-4 and δ 161.4 for C-2 were observed in the ^{13}C NMR spectrum.

We propose a plausible mechanism to account for the formation of **4** (Scheme 3).

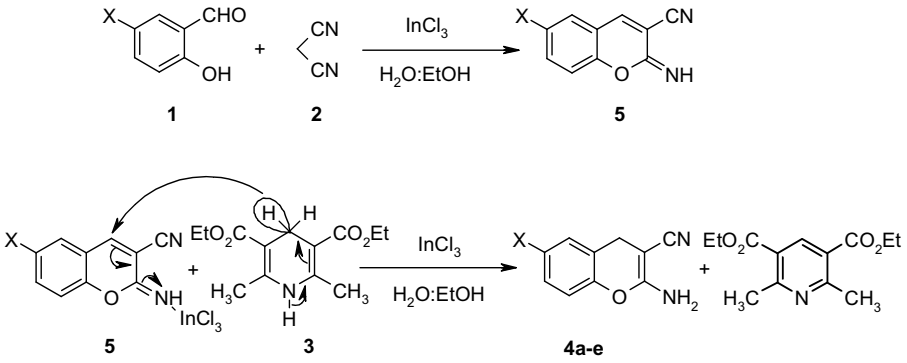
Encouraged by these results, we have examined this transformation using 2-hydroxynaphthalene-1-carboxaldehyde **6** and obtained the fused chromenes **7** in good yields (Scheme 4).[22]

The indole moiety[23] is probably the most common and important feature, of a variety of natural products and medicinal agents with significant biological activities including antimicrobial, antiviral and antitumour.[24] However, there have been no examples of indolyl chromenes reported. Thus, we investigated a three-component reaction involving salicylaldehyde and malononitrile with indole replacing the Hantzsch dihydropyridine ester in order to synthesize new indolyl chromenes **9a**–**g**. The presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably (Scheme 5).[25]

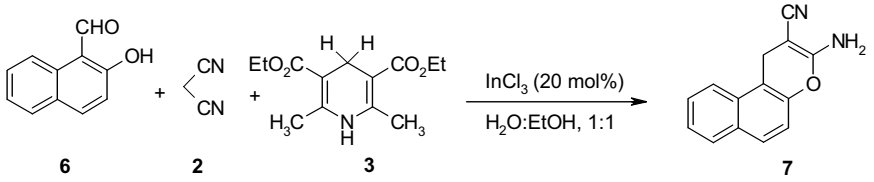
The structures of compounds **9a**–**g** were confirmed by spectroscopic and elemental data. The ^1H NMR of **9b**[26] displayed a singlet at δ 4.97 (H-4) and a broad singlet due to $-NH_2$ at δ 6.83 (D_2O exchangeable). Signals at δ 32.8 (C-4) and δ 160.6 (C-2) in the ^{13}C spectrum confirmed the formation of the product.

Similarly, the protocol was extended to synthesize indole with fused chromenes **10** in good yield by reaction of 2-hydroxynaphthalene-1-carboxaldehyde and malononitrile with indole (Scheme 6).[27]

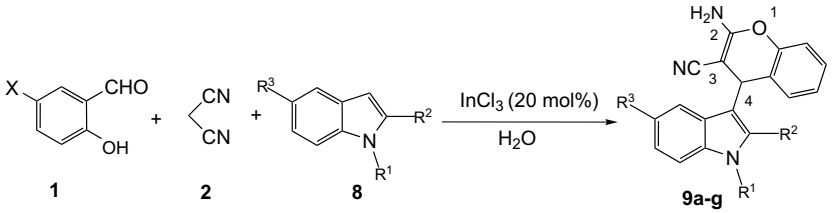
In conclusion, we have developed a simple and clean method for the synthesis of novel 2-aminochromenes



Scheme 3.

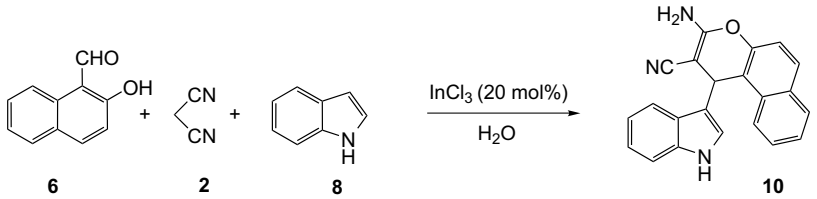


Scheme 4.



	X	R^1	R^2	R^3	Time (hr)	Yield (%)
9a	H	H	H	H	1.2	84
9b	H	CH_3	H	H	1.0	86
9c	H	H	CH_3	H	1.0	87
9d	H	H	H	OCH_3	1.1	87
9e	H	H	H	Br	2.0	80
9f	H	H	H	Cl	2.0	81
9g	Br	CH_3	H	H	1.2	84

Scheme 5.



Scheme 6.

and indolyl chromenes catalyzed by indium(III) chloride in aqueous media at room temperature. Advantages of this method are its generality, short reaction times and easy work-up. Biological evaluation of these derivatives is underway.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.102.

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19. Several Hantzsch dihydropyridine derivatives were synthesized and applied in this reaction. Other 4,4-dihydro derivatives afforded the products, but the yields were slightly lower than with **3**. 4-Substituted (alkyl or aryl) Hantzsch dihydropyridines did not react under the conditions.
20. *General procedure for the synthesis of 2-amino-4H-chromene-3-carbonitrile*: To a stirred mixture of appropriate salicylaldehyde (1 mmol), malononitrile (1 mmol) and Hantzsch dihydropyridine ester (1 mmol) in water:ethanol (1:1) (10 mL), a catalytic amount of indium(III) chloride (20 mol %) was added and the mixture was stirred at room temperature for the appropriate time (Table 1). After complete conversion as indicated by TLC, the product was extracted with ethyl acetate (2×15 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate–hexane, 2:8) to afford pure product (**4a**–**e**).
21. *2-Amino-4H-chromene-3-carbonitrile* **4a** *(Table 1, entry 1)*: white solid; mp: 125 °C. ν_{max} (KBr): 3447, 3335, 2190, 1661, 1412, 1267, 1229, 753 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 3.41 (s, 2H), 6.77 (br s, 2H, NH_2), 6.91 (d, 1H, $J = 7.65$ Hz), 7.05 (t, 1H, $J = 6.15$ Hz), 7.14 (d, 1H, $J = 7.65$ Hz), 7.17 (t, 1H, $J = 7.6$ Hz). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 24.1, 49.4, 116.4, 120.1, 121.6, 124.9, 128.4, 129.3, 149.8, 161.4. MS (*m*/*z*): 172 (M^+). Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.70; H, 4.64; N, 16.23.
22. *3-Amino-1H-benzo[f]chromene-2-carbonitrile* **7**: light yellow solid; mp: 196 °C. ν_{max} (KBr): 3444, 3314, 2190, 1674, 1588, 1409, 1236, 808, 739 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 3.74 (s, 2H), 6.84 (br s, 2H, NH_2), 7.14 (d, 1H, $J = 9.15$ Hz), 7.46 (t, 1H, $J = 6.9$ Hz), 7.56 (t, 1H, $J = 6.85$ Hz), 7.79 (t, 2H, $J = 8.4$ Hz), 7.89 (d, 1H, $J = 8.4$ Hz).^{13}C NMR (DMSO-d_6, 125 MHz): δ 22.2, 49.8, 112.4, 117.2, 121.8, 123.5, 125.6, 127.8, 128.8, 129.2, 130.7, 131.3, 146.8, 160.8. MS (*m*/*z*): 222 (M^+). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.62; H, 4.49; N, 12.52.
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25. **General procedure for the synthesis of indolyl chromenes**: To a stirred mixture of salicylaldehyde (1 mmol), malononitrile (1 mmol) and indole (1 mmol) in water (10 mL), a catalytic amount of indium(III) chloride (20 mol %) was added and the mixture was stirred at room temperature for the appropriate time (Scheme 5). After complete conversion as indicated by TLC, the product was extracted with ethyl acetate (2×15 mL). The combined extracts was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate–hexane, 3:7) to afford pure product (**9a**–**g**).

26. *2-Amino-4-(1-methyl-1H-indol-3yl)-4H-chromene-3-carbonitrile* **9b** (Scheme 5): yellow solid; mp: 202 °C. ν_{max} (KBr): 3452, 3340, 2192, 1654, 1403, 1226, 743 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 3.69 (s, 3H), 4.97 (s, 1H), 6.83 (br s, 2H, NH_2), 6.88 (t, 1H, $J = 7.65$ Hz), 6.94 (t, 1H, $J = 7.65$ Hz), 7.02 (t, 1H, $J = 9.2$ Hz), 7.08 (d, 2H, $J = 7.65$ Hz), 7.14 (t, 1H, $J = 8.4$ Hz), 7.23 (s, 1H), 7.27 (d, 1H, $J = 8.4$ Hz), 7.33 (d, 1H, $J = 7.65$ Hz). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 32.7, 32.8, 56.7, 110.5, 116.3, 118.7, 119.2, 121.4, 121.7, 124.2, 124.9, 126.1, 127.8, 128.4, 129.8, 137.7, 148.9, 160.6. MS (m/z): 301 (M^+). Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.68; H, 4.95; N, 13.89.

27. *3-Amino-1-(1H-indol-3yl)-1H-benzo[f]chromene-2-carbonitrile* **10**: white solid; mp: 216 °C. ν_{max} (KBr): 3435, 3331, 2185, 1661, 1483, 1230, 759 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 5.54 (s, 1H), 6.78 (t, 1H, $J = 7.65$ Hz), 6.93 (t, 1H, $J = 7.6$ Hz), 7.18 (d, 1H, $J = 7.65$ Hz), 7.25 (d, 1H, $J = 8.4$ Hz), 7.30 (t, 2H, $J = 9.15$ Hz), 7.35 (t, 2H, $J = 6.85$ Hz), 7.82 (t, 2H, $J = 7.6$ Hz), 8.07 (d, 1H, $J = 8.4$ Hz), 10.87 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 31.0, 58.3, 112.2, 116.2, 117.2, 118.7, 119.0, 121.4, 123.6, 124.2, 125.3, 125.7, 127.3, 128.9, 129.6, 131.1, 131.3, 137.2, 147.0, 160.3. MS (m/z): 337 (M^+). Anal. Calcd for $C_{22}H_{15}N_3O$: C, 78.32; H, 4.48; N, 12.45. Found: C, 78.27; H, 4.42; N, 12.38.