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Enantioselective Synthesis of 2-Amino-4-(Nitromethyl)-4*H*-Chromene-3-Carbonitriles from 2-Iminochromenes

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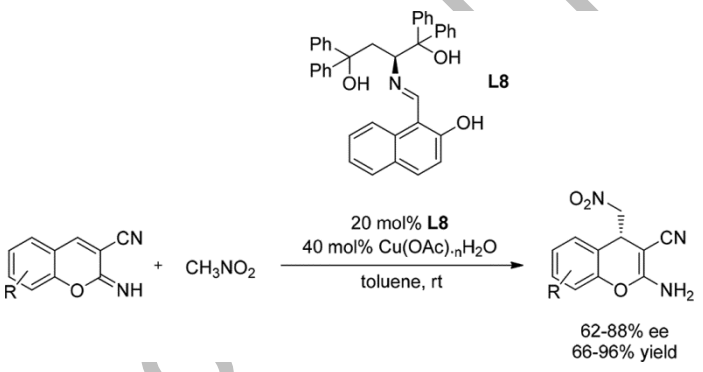
Abstract

A series of medicinally important 2-amino-4-(nitromethyl)-4*H*-chromene-3-carbonitriles were synthesized using enantioselective conjugate addition of nitromethane to 2-iminochromenes. The reactions were performed using **L8**-Cu (II) catalytic system and moderate to good enantioselectivities (62-88%) and yields (66-96%) were obtained.



KEYWORDS: 2-iminochromene, amino alcohol catalyst, nitromethane, enantioselective conjugate addition

INTRODUCTION

Chromene derivatives are an important class of heterocyclic compounds, widely distributed in natural products. Among a variety of chromene derivatives, 2-amino-4*H*-chromenes are particularly important since they are recognized as 'privileged medicinal scaffolds'[1,2]. In recent years, functionalized 2-amino-4*H*-chromenes have demonstrated a wide range of biological properties, such as antimicrobial and antifungal[3], antioxidant[4], antitumor and anticancer[5], anti-HIV[6], antiproliferation[7], and antiinflammatory[8]. For example, ethyl 2-amino-6-bromo-4-(1-cyano-2-ethoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate (HA 14-1) and related compounds are early Bcl-2 antagonists and have been shown to synergize with various anticancer therapies of diverse mechanisms of action. 2-Amino-3-cyano-4*H*-chromene bearing a 3-bromo-4,5-dimethoxyphenyl at the 4-position (MX58151) represents a promising class of proapoptotic small-molecule agents with multiple action modes against the breast cancer cell lines (Scheme 1).[9]

There are a number of methods reported for the synthesis of racemic 2-amino-3-nitrile-chromenes[10]. Given the fact that enantiomers often indicate distinct biological activity, the efficient access to optically pure 2-amino-3-nitrile-chromenes would be extremely desirable to further study the correlation between the chirality and their propensities for biological activities to acquire more potent and appropriate pharmaceutical candidates. Although there are a few papers on the asymmetric conjugate additions of nitroalkanes to unsaturated systems[11], examples on the enantioselective assembly of 2-amino-4-(nitromethyl)-4*H*-chromene-3-carbonitrile structures are still rather scarce and general approach for their synthesis is via a cascade Michael-cyclization sequence of 2-(E)-2-

nitrovinylphenols and malononitrile.[12] Recently, Wang et al. reported the enantioselective conjugate addition of nitroalkanes to 2-iminochromenes catalyzed by hydrogen bonding catalysts such as quinine-thiourea derivatives.[13] However, there is still a limited number of chiral catalysts which are active in the conjugate addition reactions to 2-iminochromenes. Herein, we report an alternative catalytic method for the enantioselective synthesis of 2-amino-4-(nitromethyl)-4*H*-chromene-3-carbonitriles using a simple amino alcohol derived ligand **L8** and Cu (II) ions.

RESULTS AND DISCUSSION

2-iminochromenes (**1a-f**) were synthesized and characterized by previously reported methods[14]. Our initial investigation commenced with screening catalytic activities of a variety of (L)-amino acids, **L1-6**, L-aspartic acid derived amino alcohol **L7** and its Schiff base derivative **L8**, which were reported by our group and applied successfully in the asymmetric Henry reactions of aromatic aldehydes[15]. None of the catalysts worked well as an organocatalyst with regard to the enantioselectivity and we obtained the products as a racemic mixture. Then we performed the reactions using **L**-Cu(II) catalytic system. The screening results of **L1-8** in a model asymmetric conjugate addition reaction between nitromethane (1.5 equiv) and **1a** (1 equiv) using **L** (20 mol %) and copper (II) acetate (20 mol %) in ethanol at room temperature, are summarized in Table 1.

The best ligand **L8** was selected for further optimization of the reaction conditions and optimizations mainly focused on the effects of solvents. The results are given in Table 2

All solvents provided moderate to excellent conversions however enantioselectivities were slightly lower in alcohols then the other organic solvents (entry 1-5). Best yields and enantioselectivities were obtained in acetonitrile (entry 7) and toluene (entry 10). In a final optimization reaction we used 40 mol% $Cu(OAc)_2nH_2O$ (**L8**:Cu(II) ratio was 1:2) in toluene and obtained 88% ee and 91% yield (entry 11).

With the optimized reaction conditions in hand, we assessed the scope of the asymmetric conjugate addition of nitromethane to various 2-iminochromenes (**2a-f**). All the reactions proceeded with moderate to good stereochemical control (88% ee max) and good yields (96% max) (Table 3). Most of the reactions were completed within 48 h, although longer reaction times were required for the conjugate addition to **2c** and **2d**. The opposite enantiomer was obtained excessively in the reaction of **2e** with nitromethane.

The mechanism and the asymmetric induction of this transformation can be rationalized as in Scheme 2.

The initial step of this conjugate addition reaction is the formation of intermediate **3** in the presence of **L8** – Cu (II) catalytic system. We propose that the multiple hydrogen bonds and coordination to copper atom lower the HOMO−LUMO energy gap of nitroalkane and **1a** resulting in the formation of the addition product. Enantioselectivities obtained in this reaction depends on the chiral and steric environment of intermediate **3**. The result of 1,4-addition is the formation of **4** and in the final step of the reaction, **4** undergoes a proton shift to generate the desired addition product **2a**.

EXPERIMENTAL

General

All reagents were obtained from commercial sources and were used without further purification. Silica gel F_{254} (Merck 5554) precoated plates were used for thin layer chromatography. ^{1}HNMR and ^{13}CNMR spectra were carried out using a 400 MHz Bruker NMR spectrometer at ambient temperature. Melting points were recorded with an electro thermal digital melting points apparatus. Kromasil column was used for chiral HPLC analysis. 2-iminochromenes (**1a-f**) were synthesized by previously reported methods and characterized by reported spectroscopic data and melting points[13].

General Procedure For The Conjugate Addition Of Nitromethane To 2-Iminochromenes

The corresponding 2-iminochromene (**1a-f**) (0.30 mmol) was added to the mixture of **L** (0.06 mmol), $Cu(OAc)_2nH_2O$ (0.12 mmol) and nitromethane (0.90 mmol) in appropriate solvent (5 mL). The resulting suspension was stirred at room temperature until the addition was completed. The solvent was removed under vacuum and the product was extracted with dichloromethane:water. The organic phase was dried with Na_2SO_4 and filtered, and the dichloromethane fraction was evaporated under vacuum. The crude product was purified with column chromatography (1:3 ethyl acetate:hexane) to give the addition product. The racemic samples for HPLC analysis were prepared using DBU catalyzed conjugate addition of nitromethane to 2-iminochromenes in methanol.

2a-f were characterized using previously reported spectroscopic data[12,13] except for **2d**. **2d** was fully characterized as it was not previously reported.

(S)-2-Amino-6-Hydroxy-4-(Nitromethyl)-4H-Chromene-3-Carbonitrile (2d)

White crystal; 66% yield; mp 165 °C (decomp.); ^{1}HNMR (400 MHz, DMSO-d_6): δ(ppm) 9.45 (s, 1H), 7.01 (s, 2H), 6.87-6.84 (d, J= 8.8 Hz, 1H), 6.71-6.68 (dd, J= 2.8, 8.8 Hz, 1H), 6.65 (d, J= 2.8 Hz, 1H), 4.74-4.69 (dd, J= 5.2, 12.4 Hz, 1H), 4.63-4.58 (dd, J= 5.6, 12.4 Hz, 1H), 4.22-4.19 (t, J=5.2 Hz, 1H). ^{13}CNMR (400 MHz, DMSO-d_6): δ(ppm) 162.4, 153.9, 142.1, 120.0, 119.9, 116.8, 115.8, 113.5, 80.7, 49.5, 34.9. IR (KBr): 3450, 3333, 2190, 1652, 1615, 1580, 1539, 1498, 1427, 1220 cm^{-1}. Anal. Calcd. for: $C_{11}H_9N_3O_4$ (%): C, 53.44; H, 3.67; N, 17.00, Found: C, 53.42.; H, 3.68; N, 16.99.

CONCLUSION

In summary, we have successfully applied **L8**-Cu(II) catalytic system in the enantioselective conjugate addition of nitromethane to electrophilic 2-iminochromenes with good yields (66-96%) and ee (62-88 %) values. This is the first Cu (II) catalyzed method for the asymmetric synthesis of 2-amino-4-(nitromethyl)-4*H*-chromene-3-carbonitriles. The method is operationally simple and tolerates substantial variation in the two reacting partners. On the other hand, L-(+)-aspartic acid-derived Schiff base ligand is an advantageous catalyst as it can be prepared from cheap and easily accessible starting materials in an easy 3-step procedure.

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Full experimental detail, ^{1}H and ^{13}C NMR spectra of all known compounds and **2d**, HPLC chromatograms, optical rotations. This material can be found via the "Supplementary Content" section of this article's webpage.

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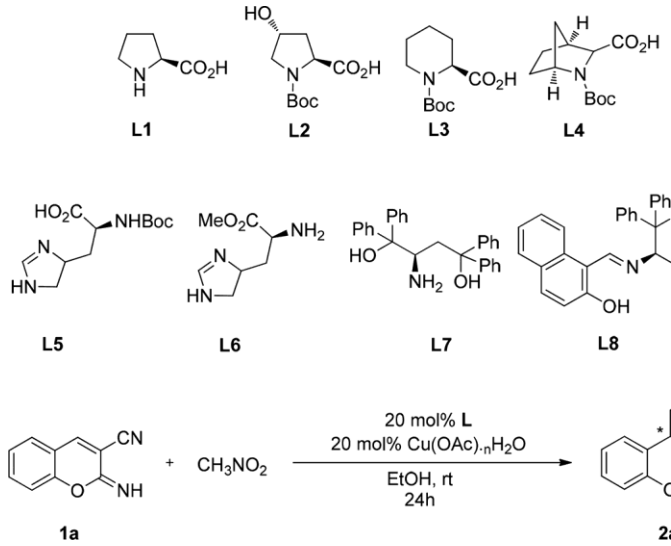
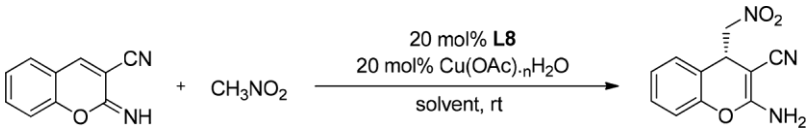
Table 1. Screening of **L1**-**8** – Cu(II) in the asymmetric conjugate addition of nitromethane to 2-iminochromene (**1a**) as model reaction



Catalyst	Yield[a] (%)	ee[b] (%)
L1	76	6
L2	77	-
L3	56	-
L4	72	-
L5	76	-
L6	81	10
L7	88	10
L8	93	12

[a]Isolated yield. [b]Determined by HPLC.

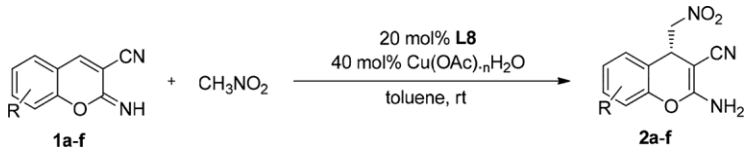
Table 2. Optimization of the reaction conditions

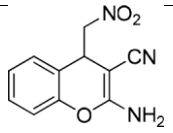
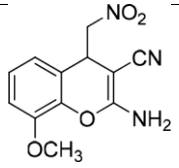
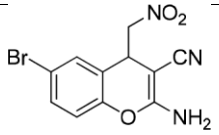
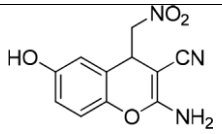
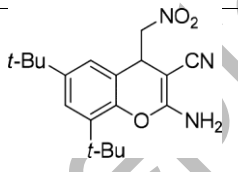
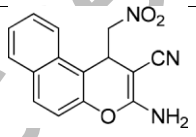


No	Solvent	Time (h)	Yield[a] (%)	ee[b] (%)
1	Methanol	24	94	-
2	Methanol:Water	18	92	-
3	Ethanol	24	93	12
4	2-Propanol	24	91	22
5	*t*-Butanol	24	93	59
6	Ethylacetate	48	72	70
7	Acetonitrile	48	84	72
8	Dichloromethane	72	66	64
9	THF	48	69	70
10	Toluene	48	90	74
11 [c]	Toluene	48	91	88

[a]Isolated yield. [b]Determined by HPLC. The absolute configuration was assigned by comparison of the specific rotation value with the reported data in Ref. 11c,d. [c] 40 mol% $Cu(OAc)_2.nH_2O$ was used.

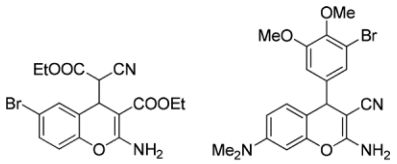
Table 3. Scope of the asymmetric conjugate addition to electrophilic 2-iminochromenes



No	Product	Time (h)	Yield[a] (%)	ee[b] (%)
2a		48	91	88
2b		48	96	62
2c		72	80	85
2d		96	66	-[c]
2e		48	81	84
2f		48	87	80

[a]Isolated yield. [b]Determined by HPLC. The absolute configuration was assigned by comparison of the specific rotation value with the reported data in Ref. 11c,d. [c]We were not able to determine ee% with Kromasil column for 2d.

Scheme 1. Biologically active 2-amino-4*H*-chromenes.



HA 14-1 MX58151

Scheme 2. Proposed reaction mechanism