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PAPER

In(III)-Catalyzed tandem reaction of chromone-derived Morita–Baylis–Hillman alcohols with amines

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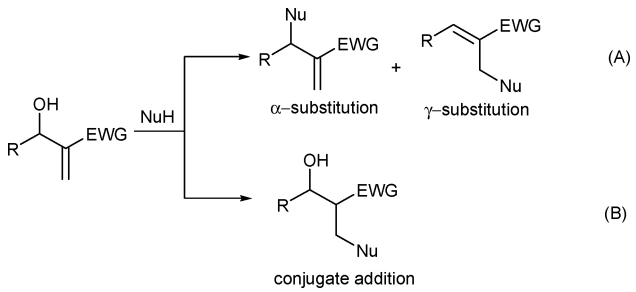
The reaction of chromone-derived cyclic Morita–Baylis–Hillman alcohols with amines catalyzed by $In(OTf)_3$ in a one pot process was developed for the convenient and efficient synthesis of 2-substituted-3-aminomethylenechromans. The tandem allylic amination/chromen ring-opening/Michael cyclization reactions were involved in this protocol.

Introduction

Morita–Baylis–Hillman (MBH) adducts, which possess both allylic hydroxyl and Michael acceptor units in the identical molecule, have been illustrated as valuable synthons and starting materials for the synthesis of various biologically active molecules.[1–2] Recently MBH adduct as an electrophilic substrate has achieved fruitful results in the allylic substitution reactions with various nucleophiles, including C-nucleophiles, such as arenes and heteronucleophiles, such as the compounds bearing –OH, –SH and –NH groups.[3] Among them, the carbon–nitrogen bond formation by *N*-nucleophilic substitution plays an important role for the diversity of synthetic compounds with biological activities.[1–3] Generally, the MBH acetate was employed in the nucleophilic substitutions with amines, because hydroxyl group was usually considered as an inefficient leaving group. However, the advantages of directly using allyl alcohol as an allylic reagent were noteworthy: no further functionalization was required for the activation of hydroxyl group and water was the sole by-product after the reaction.[4] Although many synthetic methods could be employed in performing the allylic amination of MBH acetates, the *N*-nucleophilic substitution of MBH alcohols was seldom reported.[5] The reaction of MBH adducts with amines could proceed through two ways: either conjugate addition (Scheme 1, path B),[5a–e] or allylic amination accompanied with dehydration affording α- and γ-products (Scheme 1, path A).[5f–h]



Scheme 1 The reaction of MBH alcohols with *N*-nucleophile.

Benzopyranyl structural moiety is a common heterocyclic framework that can be found in numerous natural compounds and pharmaceutical molecules.[6] 3-Aminomethylchromons and their derivatives 3-aminomethylenechromans (Fig. 1) have shown important biological activities,[7] such as nonsteroidal aromatase inhibitors, antimicrobial effects, and are also interesting as scaffolds in the synthesis of versatile benzopyranyl heterocycle libraries in drug discovery.[8] As the Morita–Baylis–Hillman reaction is becoming an environmentally benign and important C–C bond formation reaction, the application of the allylic amination of chromone-derivatised MBH adducts could be efficient methods to construct diverse 3-aminomethylchromone derivatives.

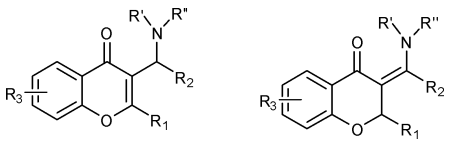


Fig. 1 3-Aminomethylchromon derivatives.

Although chromone-derived MBH adducts, which exhibited a cyclic structural unit of MBH adduct, have been used in the synthesis of many heterocycles such as quinoline derivatives and azopinoindoles,[9] the allylic amination of such substrates has been seldom reported. As an expansion of our research on the nucleophilic substitution of cyclic MBH adduct, we describe herein the preliminary results of the reaction between chromone-derived MBH alcohols and amines in a one pot process, in which an unexpected tandem allylamination/ring-opening/Michael cyclization reactions was observed to provide 3-aminomethylenechromans in high yields.

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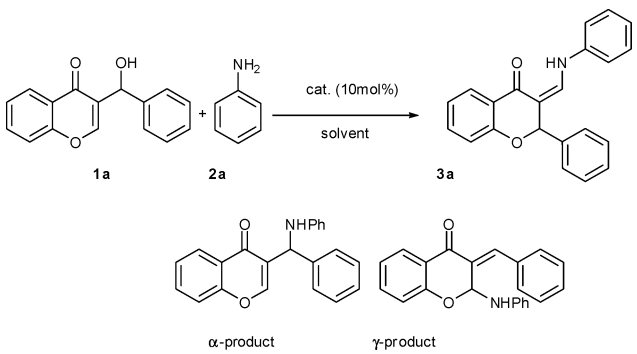
Table 1 Catalytic reaction of **1a** with **2a**[a]

Entry	Catalyst	Solvent	T/°C	Yield of **3a** (%)
1	$In(OTf)_3$	THF	Reflux	28
2	$In(OTf)_3$	Toluene	Reflux	>99
3	$In(OTf)_3$	MeCN	Reflux	41
4	$In(OTf)_3$	DCM	Reflux	Trace
5	$Sc(OTf)_3$	Toluene	Reflux	65
6	$FeCl_3$	Toluene	Reflux	69
7	AgOTf	Toluene	Reflux	90
8	$InBr_3$	Toluene	Reflux	16
9	—[b]	Toluene	Reflux	0
10	$In(OTf)_3$	Toluene	r.t.	0
11	$In(OTf)_3$	Water	Reflux	61

[a] **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (0.02 mmol), solvent (2 mL), 72 h. [b] Without catalyst.

Results and discussion

An initial investigation was performed by employing 3-(hydroxy(phenyl)methyl)-chromone **1a** and aniline **2a** as substrates in the presence of the catalyst $In(OTf)_3$ (10 mol%) in refluxing THF. To our surprise, unlike the reactions of the Morita–Baylis–Hillman alcohols derived from cycloenone with amines,[5f] this protocol gave neither α- nor γ-products eventually, but 2-phenyl-3-aminomethylene-chroman **3a** in 28% yield (Scheme 2). The experimental results for screening solvent and catalyst are summarized in Table 1. A quantitative yield of **3a** can be achieved when toluene was used instead of THF (Table 1, entry 2). Several other Lewis acids were screened. In all cases the product **3a** was obtained, but in decreased yields. (Table 1, entries 5–8). No reaction occurred either at room temperature or without catalyst, and the starting materials were recovered (Table 1, entries 9 and 10). Water was also used as a solvent but the yield was decreased to 61% (Table 1, entry 11).

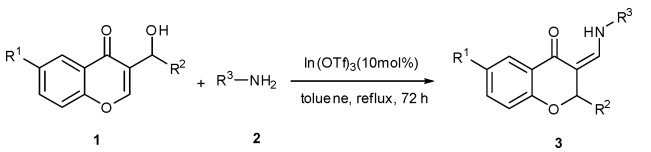


Scheme 2 Reaction of **1a** with **2a** catalyzed by Lewis acid.

As shown in Table 2, the substrate scope of this tandem reaction is quite broad. An array of anilines (**2b–2f**) with both electron-withdrawing and electron-donating substituents were employed in the reactions with MBH alcohol **1a** under the catalysis of $In(OTf)_3$. Good to excellent yields (78–99%) were obtained (entries 2–6). Besides, several aliphatic amines with either acyclic (**2g–2i**) or cyclic (**2j**) substituent were suitable to this reaction, affording the corresponding products (**3g–3j**) in moderate yields (entries 7–10).

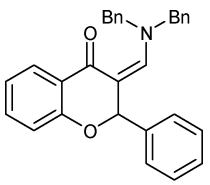
Subsequently, we examined the chromone-derived MBH alcohols bearing different functional groups. Importantly, not only MBH alcohols (**1b–1d**) derived from aromatic aldehydes can undergo the tandem reaction smoothly to provide corresponding products, 2-aryl-3-aminomethylenechromanes (**3k–3m**), in very good yields (Table 2, entries 11–13), the ones **1e–1g** derived from aliphatic aldehydes were also suitable to the tandem reaction, albeit in slightly decreased yields (Table 2, entries 14–16). Furthermore, the MBH alcohols **1e** and **1g** can also react with benzylamine (**2g**) to give desired products (**3q–3r**) in moderate yields (Table 2, entries 17–18). When secondary amine, dibenzylamine (**2k**) was used in the reaction with **1a** under the same conditions, the tandem reaction product **3s** was also obtained in 78% yield (entry 19).

Table 2 In(III)-Catalyzed reaction of MBH alcohols (**1**) with amines (**2**)[a]



Entry	MBH Alcohol (R^1,R^2)	Amine (R_3)	Yield of **3** (%)
1	**1a**, R^1=H, R^2=Ph	**2a**, Ph	**3a**, 99
2	**1a**	**2b**, 4-ClC_6H_4	**3b**, 99
3	**1a**	**2c**, 4-BrC_6H_4	**3c**, 99
4	**1a**	**2d**, 4-F-C_6H_4	**3d**, 78
5	**1a**	**2e**, 4-$MeOC_6H_4$	**3e**, 92
6	**1a**	**2f**, 4-Me-C_6H_4	**3f**, 82
7	**1a**	**2g**, Bn	**3g**, 68
8	**1a**	**2h**, n-C_8H_{17}	**3h**, 75
9	**1a**	**2i**, n-$C_{12}H_{25}$	**3i**, 66
10	**1a**	**2j**, Cy	**3j**, 60
11	**1b**, R^1=H,R^2 = 2-BrC_6H_4	**2a**	**3k**, 82
12	**1c**, R^1=H,R^2 = 4-ClC_6H_4	**2a**	**3l**, 83
13	**1d**, R^1=Me, R^2=Ph	**2a**	**3m**, 99
14	**1e**, R^1=H,R^2 = n-C_3H_7	**2a**	**3n**, 55
15	**1f**, R^1=H,R^2=Cy	**2a**	**3o**, 85
16	**1g**, R^1=H,R^2=$C_6H_5(CH_2)_2$	**2a**	**3p**, 65
17	**1e**	**2g**	**3q**, 68
18	**1g**	**2g**	**3r**, 58
19	**1a**	**2k**, Bn_2NH	**3s**, 78

[a] MBH alcohol **1** (0.2 mmol), amine **2** (0.3 mmol), $In(OTf)_3$ (0.02 mmol).



3s

The molecular structure of the tandem reaction product **3** was further confirmed by X-ray crystallographic analysis of **3k** (Fig. 2).[10] The distance between NH and carbonyl is 2.014 Å, which falls into the range of hydrogen bonding interaction.

Based on the results of X-ray analysis, *cis*-configuration of the newly formed double bond could be determined.

The plausible mechanism of the tandem reaction of MBH alcohol with amine was proposed, and shown in Scheme 3. The MBH alcohol derived from chromone was activated by $In(OTf)_3$. The *N*-nucleophile attacked γ-position of MBH alcohol to carry out allylic amination reaction accompanied with dehydration, generating an intermediate **A**. Subsequently, intermediate **A**. underwent chromone ring-opening[9b–c] to form an active Michael acceptor **B** which was followed by intramolecular oxa-Michael cyclization to yield 2-substituted-3-aminomethylenechroman **3**.

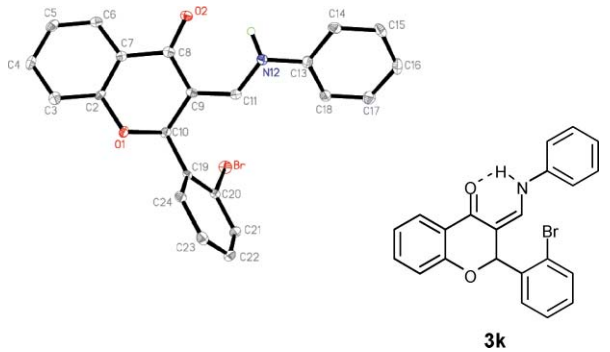
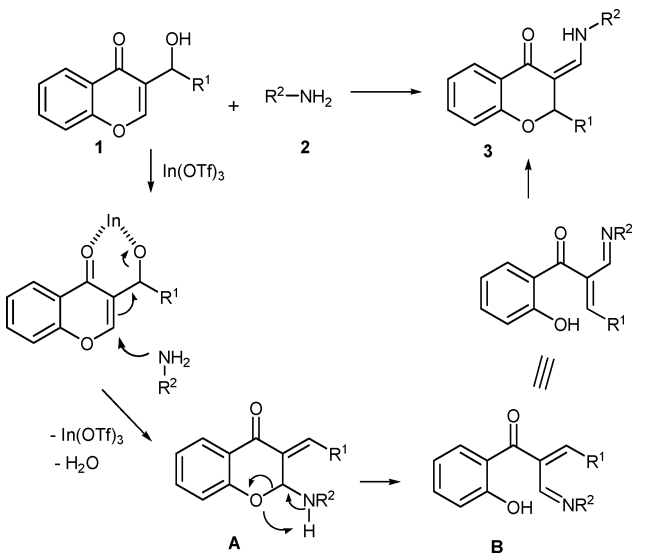
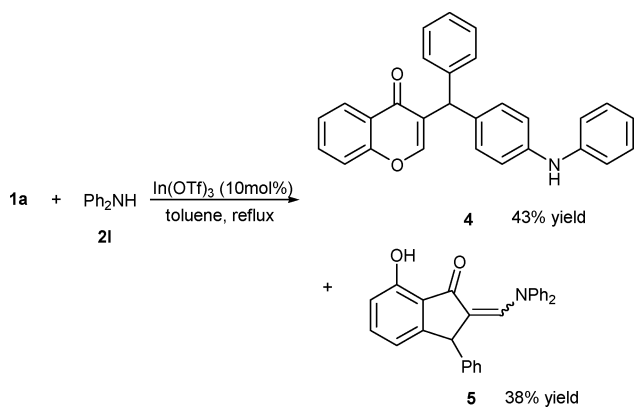


Fig. 2 ORTEP drawing of **3k** with thermal ellipsoids at 30% probability levels.



Scheme 3 Proposed mechanism of the reaction of chromone-derived MBH alcohol with amine.

It was interesting to note that if the reaction of MBH alcohol **1a** with diphenylamine **2l** was carried out under the catalysis of $In(OTf)_3$, the α-regioselective product of Friedel–Crafts alkylation (**4**) was formed in 43% yield, as well as unexpected indenone **5** was obtained in 38% yield *via* cascade allylic amination/chromen ring-opening/C-nucleophilic Friedel–Crafts cyclization (Scheme 4).



Scheme 4 Reaction of **1a** with diphenylamine **2l**.

Conclusions

In summary, we developed the reaction of chromone-derived Morita–Baylis–Hillman alcohols with amines under $In(OTf)_3$ catalysis for the synthesis of 2-substituted-3-aminomethylene-chromans. This protocol combined allylic amination, ring-opening, Michael cyclization reactions in a one pot process. A tentative mechanism for the tandem reactions was proposed. Investigation of the tandem reactions and their application in the synthesis of biologically active compounds is ongoing.

Experimental

General Methods

The ^1H and ^{13}C NMR spectra were recorded on Bruker-AV 300 spectrometer and chemical shift reported in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard. IR spectra were recorded on a Bruker tensor 27 infrared spectrometer. HRMS spectra were recorded on GCT-Mass Micromass spectrometer. Melting points were measured on Beijing-Tiker X-4 apparatus without correction. All reactions were carried out in oven dried flasks. Common reagents were purchased from commercial sources and were used without further purification. The Morita–Baylis–Hillman alcohols were prepared according to literature methods.[11] All reactions were performed under nitrogen atmosphere.

Typical experimental procedures for the reaction of MBH alcohol with amine

To a stirred solution of 3-(hydroxy(phenyl)methyl)-chromone (**1a**, 51 mg, 0.2 mmol) in toluene (2 mL) at room temperature was added aniline (**2a**, 35 μL, 0.3 mmol) and $In(OTf)_3$ (11 mg, 0.02 mmol) sequentially and the reaction mixture was heated to reflux for 72 h. Upon completion of the reaction as judged by TLC, the reaction was quenched with water and extracted with DCM twice. The combined extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/8) to afford the product **3a**.

(*Z*)-2-Phenyl-3-((phenylamino)methylene)chroman-4-one (3a). Compound **3a** was isolated as a yellow solid (65 mg, yield >99%). **m.p.** 101–104 °C. **IR νmax (film, cm^{-1})**: 3053, 2960, 2919, 2858, 1649, 1601, 1466, 1277, 1218, 1150, 1100, 1022, 801, 753, 695, 499. **^{1}H NMR (300 MHz, $CDCl_3$)**: 11.91 (d,1H, J = 12.0 Hz), 7.95 (dd, 1H, J = 1.6 Hz, 7.8 Hz), 7.52–7.35 (m, 6H), 7.28–7.23 (m, 2H), 7.08–6.84 (m, 6H), 6.06 (s, 1H); **^{13}C NMR (75 MHz, $CDCl_3$)**: 182.2, 158.1, 141.2, 139., 138.0, 133.5, 128.7,127.7, 126.8, 125.6, 122.7, 122.6, 120.7, 116.8, 115.2, 104.6, 80.3. **HRMS (EI)**: m/z calcd for $C_{22}H_{17}NO_2$: 327.1259 (M^+), found 327.1262.

Acknowledgements

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10 CCDC 784290 contains the supplementary crystallographic data for **3k**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/datarequest/cif, and are in the ESI. Crystal, data for compound **3k**: $C_{22}H_{16}BrNO_2$, M = 406.27, Monoclinic, a = 15.7458(9) Å, α = 90°, b = 5.1545(2) Å, β = 92.048(2)°, c = 20.8004(10) Å, γ = 90°, V = 1687.12(14) Å ^{3}, T = 173(2) K, space group = $P2_1/c$, Z = 4, Number of Reflections = 6168, Independent reflections = 3846, [R(int) = 0.0554], Final R indices [$I > 2\delta(I)$] R_1 = 0.0850, wR_2 = 0.1138, R indices (all data) R_1 = 0.1359, wR_2 = 0.1247.

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