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First example of multicomponent synthesis of 1-ethoxy-3-(4-aryl)-1-phenyl-1*H*-benzo[*f*] chromene derivatives

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Abstract

A new series of 1-ethoxy-3-(4-aryl)-1-phenyl-1*H*-benzo[*f*]chromenes have been synthesized efficiently. The procedure involves the multicomponent reaction of 2-naphthol, acetophenone derivatives, and triethyl orthobenzoate catalyzing by efficient bis(2-anilinotropone) Ti complex.

Keywords: Multicomponent reaction; Benzo[*f*]chromen; Catalyst

Natural products containing the chromene structure represent an important class of compounds [1,2]. Chromenes and fused chromenes are biologically active compounds since they are used as cosmetics and pigments [3,4], spasmolytic, diuretic, anticoagulant, antianaphylactic [5,6], antibacterial [7], anticancer agents [8], and as potent apoptosis inducers [9]. Accordingly, many studies have been devoted to the synthesis of the chromene ring systems. For instance, Claisen rearrangement of alkynyl aryl ethers from propargylic alcohols and naphthols under acid catalysis to synthesis 2*H*-1-benzopyran derivatives has been reported [10]. In addition, one-pot synthesis of 1,3-disubstituted-3*H*-benzo[*f*]chromenes has been reported by Yadav and coworkers [11]. Furthermore, several catalysts have been utilized for the synthesis of substituted 4*H*-chromenes such as cetyltrimethylammonium chloride [12], cetyltrimethylammonium bromide under ultrasound irradiation [13], KF/Al_2O_3 [14], $TiCl_4$ [15], triethylamine [16] and basic ionic liquids [17]. Moreover, recently we have reported synthesis of 1,3-diaryl-3*H*-benzo[*f*]chromenes using ferric hydrogensulfate [18]. However, synthesis of 1-ethoxy-3-(4-aryl)-1-phenyl-1*H*-benzo[*f*]chromene has never been reported up to now.

The usage of organometallic compounds will provide a broad exploration for new methods and techniques in organic synthesis. Our interests lie in organometallics [19] prompt us to make a utilization of such catalysts. In the course of our ongoing research for the efficient synthesis of a variety of heterocyclic compounds [20,21], we developed

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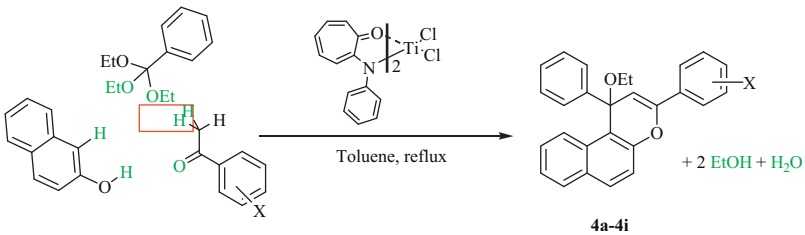


4a-4i

X= H (**4a**); *p*-Br (**4b**);*p*-Cl (**4c**); *p*-NO_2 (**4d**); *p*-Me (**4e**); *p*-OMe (**4f**); *p*-OH (**4g**); *p*-F (**4h**); *o*-OMe (**4i**)

Scheme 1. Synthesis of benzo[f]chromene derivatives **4a**–**4i**.

an efficient synthetic procedure for the synthesis of 1-ethoxy-3-(4-aryl)-1-phenyl-1*H*-benzo[*f*]chromenes from one-pot condensation of 2-naphthol, acetophenone derivatives and triethyl orthobenzoate catalyzing by bis(2-anilinotropone) Ti complex (Scheme 1).

1. Experimental

All chemicals were purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products. The products were characterized by their spectral data. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker 250-MHz spectrometer in chloroform as the solvent and TMS as internal standard. Elemental analysis was performed on a Thermo Finnigan EA1112 elemental analyzer. Bis(2-anilinotropone) Ti complex was prepared according to our previous report [19].

*1.1. General procedure for the synthesis of benzo[f]chromene derivatives **4a-4i***

A mixture of 2-naphthol (1 mmol), acetophenone derivatives (1 mmol), and triethyl orthobenzoate (1.1 mmol) and bis(2-anilinotropone) Ti complex (0.15 mmol) in toluene (8 mL) was stirred at reflux temperature for the appropriate time. The reaction was monitored by TLC and after completion of the reaction, the catalyst was simply recovered by filtration and washed by *n*-hexane. The residue was concentrated in vacuum and the crude product was recrystallized from EtOH:H_2O (3:1) to obtain the pure product.

1-Ethoxy-1,3-diphenyl-1H-benzo[f]chromene (**4a**): After 7.5 h the yield was 87%; ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.60–7.40 (m, 6 H, ArH), 7.35–7.05 (m, 10 H, ArH), 5.72 (s, 1 H, CH), 3.62 (q, 2 H, J = 15.2 Hz, CH_2), 1.25 (t, 3 H, J = 15.2 Hz, CH_3). EIMS: m/z 378 (M^+). Anal. Calcd. for $C_{27}H_{22}O_2$: C, 85.69; H, 5.86%. Found: C, 85.38; H, 5.73%.

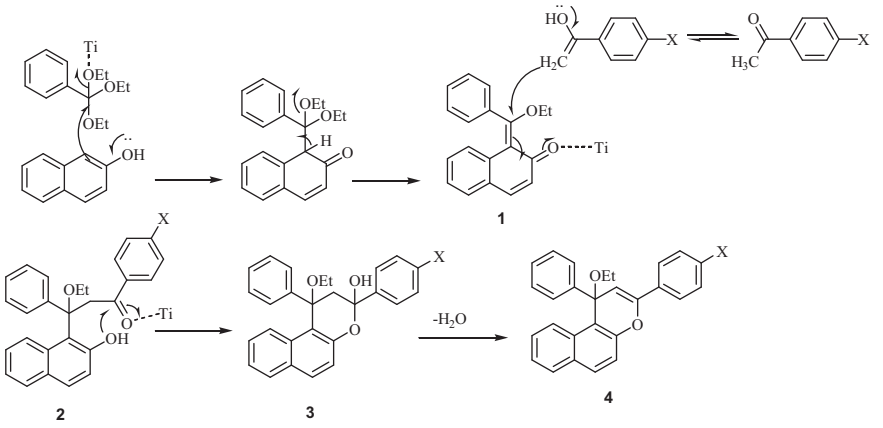
3-(4-Bromophenyl)-1-ethoxy-1-phenyl-1H-benzo[f]chromene (**4b**): After 8 h the yield was 86%; ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.65–7.45 (m, 5 H, ArH), 7.35–7.08 (m, 10 H, ArH), 5.65 (s, 1 H, CH), 3.57 (q, 2 H, J = 16.4 Hz, OCH_2), 1.22 (t, 3 H, J = 16.4 Hz, CH_3). EIMS: m/z 456 (M^+). Anal. Calcd. for $C_{27}H_{21}BrO_2$: C, 70.90; H, 4.63%. Found: C, 70.41; H, 4.52%.

3-(4-Chlorophenyl)-1-ethoxy-1-phenyl-1H-benzo[f]chromene (**4c**): After 8.5 h the yield was 90%; ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.60–7.42 (m, 4 H, ArH), 7.35–7.10 (m, 11 H, ArH), 5.63 (s, 1 H, CH), 3.55 (q, 2 H, J = 15.5 Hz, OCH_2), 1.18 (t, 3 H, J = 15.8 Hz, CH_3). EIMS: m/z 412 (M^+). Anal. Calcd. for $C_{27}H_{21}ClO_2$: C, 78.54; H, 5.13%. Found: C, 78.28; H, 5.03%.

1-Ethoxy-3-(4-nitrophenyl)-1-phenyl-1H-benzo[f]chromene (**4d**): After 8 h the yield was 80%; ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.95 (m, 2 H, ArH), 7.62–7.40 (m, 5 H, ArH), 7.35–7.25 (m, 3 H, ArH), 7.25–7.05 (m, 5 H, ArH), 5.90 (s, 1 H, CH), 3.63 (q, 2 H, J = 16.1 Hz, OCH_2), 1.16 (t, 3 H, J = 16.3 Hz, CH_3). EIMS: m/z 423 (M^+). Anal. Calcd. for $C_{27}H_{21}NO_4$: C, 76.58; H, 5.00; N, 3.31%. Found: C, 76.11; H, 5.08; N, 3.36%.

1-Ethoxy-1-phenyl-3-p-tolyl-1H-benzo[f]chromene (**4e**): After 7 h the yield was 87%; ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.60–7.40 (m, 3 H, ArH), 7.35–7.22 (m, 9 H, ArH), 7.20–7.05 (m, 3 H, ArH), 5.55 (s, 1 H, CH), 3.48 (q, 2 H, J = 14.3 Hz, OCH_2), 2.24 (s, 3 H, CH_3), 1.16 (t, 3 H, J = 14.5 Hz, CH_3). EIMS: m/z 392 (M^+). Anal. Calcd. for $C_{28}H_{24}O_2$: C, 85.68; H, 6.16%. Found: C, 85.38; H, 6.05%.

1-Ethoxy-3-(4-methoxyphenyl)-1-phenyl-1H-benzo[f]chromene (**4f**): After 9 h the yield was 90%; ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.63–7.35 (m, 3 H, ArH), 7.30–7.15 (m, 8 H, ArH), 7.10–7.02 (m, 4 H, ArH), 5.77



Scheme 2.

(s, 1 H, CH), 3.72 (s, 3 H, OCH_3), 3.44 (q, 2 H, J = 15.8 Hz, OCH_2), 1.14 (t, 3 H, J = 15.6 Hz, CH_3). EIMS: m/z 408 (M^+). Anal. Calcd. for $C_{28}H_{24}O_3$: C, 82.33; H, 5.92%. Found: C, 82.21; H, 5.83%.

4-(1-Ethoxy-1-phenyl-1H-benzo[f]chromen-3-yl)phenol (**4g**): After 7 h the yield was 88%; ^{1}H NMR (250 MHz, DMSO-d_6): δ 9.45 (s, 1 H, OH), 7.60–7.45 (m, 2 H, ArH), 7.35–7.20 (m, 10 H, ArH), 7.15–7.05 (m, 3 H, ArH), 5.65 (s, 1 H, CH), 3.52 (q, 2 H, J = 15 Hz, OCH_2), 1.10 (t, 3 H, J = 15.3 Hz, CH_3). EIMS: m/z 394 (M^+). Anal. Calcd. for $C_{27}H_{22}O_3$: C, 82.21; H, 5.62%. Found: C, 81.98; H, 5.54%.

1-Ethoxy-3-(4-fluorophenyl)-1-phenyl-1H-benzo[f]chromene (**4h**): After 6 h the yield was 87%; ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.60–7.50 (m, 4 H, ArH), 7.35–7.15 (m, 11 H, ArH), 5.57 (s, 1 H, CH), 3.40 (q, 2 H, J = 13.7 Hz, OCH_2), 1.07 (t, 3 H, J = 13.7 Hz, CH_3). EIMS: m/z 396 (M^+). Anal. Calcd. for $C_{27}H_{21}FO_2$: C, 81.80; H, 5.34%. Found: C, 81.63; H, 5.27%.

1-Ethoxy-3-(2-methoxyphenyl)-1-phenyl-1H-benzo[f]chromene (**4i**): After 6 h the yield was 85%; ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.55–7.45 (m, 4 H, ArH), 7.40–7.25 (m, 8 H, ArH), 7.25–7.05 (m, 3 H, Ar), 5.60 (s, 1 H, CH), 3.72 (s, 3 H, OMe), 3.41 (q, 2 H, J = 14.1 Hz, OCH_2), 1.07 (t, 3 H, J = 14.1 Hz, CH_3). EIMS: m/z 408 (M^+). Anal. Calcd. for $C_{28}H_{24}O_3$: C, 82.33; H, 5.92%. Found: C, 82.22; H, 5.86%.

2. Results and discussion

Initial experiment was performed by the one-pot reaction of 2-naphthol, acetophenone and triethyl orthobenzoate as the model reaction. When 2-naphthol (1 mmol) was treated with acetophenone (1 mmol) and triethyl orthobenzoate (1 mmol) in the presence of a catalytic amount of bis(2-anilinotropone) Ti complex (0.015 mmol) at reflux condition in toluene, the desired 1-ethoxy-1,3-diphenyl-1*H*-benzo[*f*]chromene (**4a**) was obtained in 87% yield. No corresponding benzo[*f*]chromene was isolated in the absence of the catalyst highlighting the role of the catalyst to promote the reaction. Encouraged by this success, we then extended the model reaction using different derivatives of acetophenone. It was revealed that the electronic nature of substituted groups on acetophenone does not significantly affect the reaction times as well as chemical yields.

The reasonable mechanism for the synthesis of 1-ethoxy-3-(4-aryl)-1-phenyl-1*H*-benzo[*f*]chromenes is illustrated in Scheme 2. Naphthol C-alkylation *via* a Knoevenagel addition between 2-naphthol and triethyl orthobenzoate results in α,β-unsaturated compound (**1**), possessing ethoxy substituent on its β position. Nucleophilic attack of enolized acetophenone on β-position of the intermediate **1**, gives the intermediate **2**. Intramolecular cyclization of **2** gives **3** which undergoes dehydration to furnish product **4**.

3. Conclusion

In summary, we have demonstrated an efficient, novel and clean synthesis of a new series of benzo[*f*] chromene derivatives. 1-Ethoxy-3-(4-aryl)-1-phenyl-1*H*-benzo[*f*]chromenes were synthesized efficiently through

multi-component cyclocondensations of 2-naphthol, acetophenone derivatives, and triethyl orthobenzoate catalyzed by bis(2-anilinotropone) Ti complex.

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