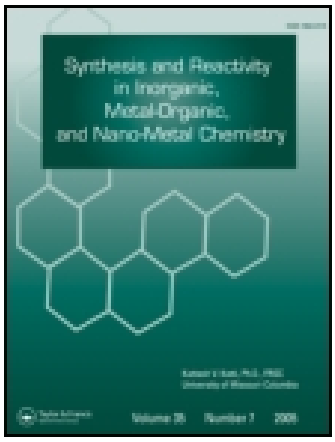

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Heterogeneous Titanium Catalyst for the Synthesis of Novel 2-(4-aryl)-4-ethoxy-4-phenyl-4H-benzo[h] chromene Derivatives

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Heterogeneous Titanium Catalyst for the Synthesis of Novel 2-(4-aryl)-4-ethoxy-4-phenyl-4*H*-benzo[*h*] chromene Derivatives

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A new series of 2-(4-aryl)-4-ethoxy-4-phenyl-4*H*-benzo[*h*]chromene derivatives have been synthesized. The procedure involves the multicomponent reaction of 1-naphthol, acetophenone derivatives, and triethyl orthobenzoate catalyzing by efficient bis[7-tert-butyl-2-anilinotropone] Ti complex.

Keywords benzo[*h*]chromene, catalyst, multicomponent

INTRODUCTION

Nowadays, one of the major challenges of modern drug discovery is the design of highly efficient chemical reaction sequences providing the maximum structural diversity using a minimum number of synthetic steps to assemble compounds with interesting properties.[1] Recently multicomponent reactions (MCRs) have emerged as a highly valuable synthetic tool in the realm of modern drug discovery. The atom economical and convergent character, the simplicity of a one-pot procedure, the possible structural variations, the accessible complexity of the molecules, and the very large number of accessible compounds are among the described advantages of MCRs.[2]

Natural products containing the chromene structure represent an important class of compounds. Chromenes and fused chromenes are biologically active compounds because they are used as cosmetics and pigments;[3] spasmolytic, diuretic, anticoagulant, antianaphylactic,[4,5] antibacterial,[6] and anticancer agents;[7] and as potent apoptosis inducers.[8]

Due to these important biological activities, their synthesis is very important to organic chemists and 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.[9] In addition, one-pot synthesis of 1,3-disubstituted-3*H*-benzo[*f*]chromenes has been reported by Yadav et al.[10] Furthermore, several catalysts have been utilized for the synthesis of substituted 4*H*-chromenes such as cetyltrimethylammonium chloride,[11] cetyltrimethylammonium bromide under ultrasound irradiation,[12] KF/Al_2O_3,[13] $TiCl_4$,[14] triethylamine,[15] basic ionic liquids,[16] iodine/K_2CO_3,[17] and DABCO.[18] However, synthesis of 2-(4-aryl)-4-ethoxy-4-phenyl-4*H*-benzo[*h*]chromene has never been communicated up to now.

The usage of organometallic compounds will provide a broad exploration for new methods and techniques in organic synthesis. Our interests 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,[20–22] we developed an efficient synthetic procedure for the synthesis of benzo[*h*]chromenes from one-pot condensation of 1-naphthol, acetophenone derivatives, and triethyl orthobenzoate catalyzing by bis[7-tert-butyl-2-anilinotropone] Ti complex. Herein, we wish to report the details of this study.

EXPERIMENTAL

General

All Chemicals were purchased from Merck, Fluka, and Sigma-Aldrich. 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[7-tert-butyl-2-anilinotropone] Ti complex was prepared according to our previous report.[19]

General Procedure for the Synthesis of Benzo[f]chromene Derivatives 4a–4i

A mixture of 1-naphthol (1 mmol), acetophenone derivatives (1 mmol), and triethyl orthobenzoate (1.1 mmol) and bis[7-tert-butyl-2-anilinotropone] Ti complex (0.15 mmol) in toluene (7 mmol) was stirred at reflux temperature for the appropriate

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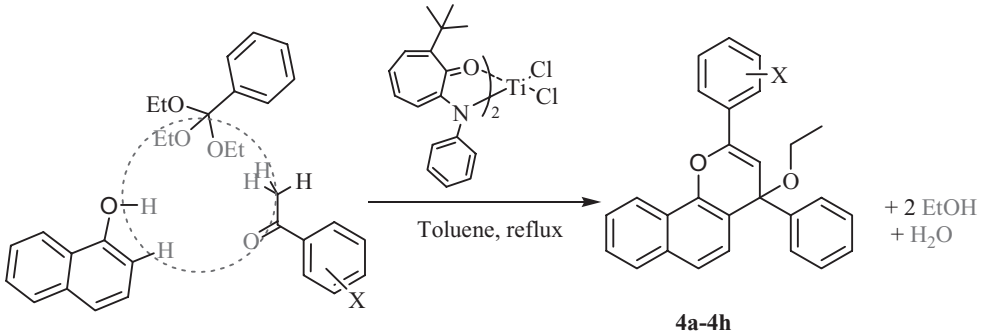
time. The reaction was monitored by TLC and after completion of the reaction, the catalyst was simply recovered by filtration and washed by *n*-hexane. The residue was concentrated *in vacuo* and the crude product was recrystallized from ethanol:H_2O (3:1) to obtain the pure product.

For 1-ethoxy-1,3-diphenyl-1H-benzo[*f*]chromene (**4a**), after 6 h the yield was 85%. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.90 (1H, d, J = 7.7 Hz, ArH), 7.74–7.40 (4 H, m, ArH), 7.35–7.05 (11 H, m, ArH), 5.65 (1 H, s, CH), 3.55 (2 H, q, J = 15 Hz, CH_2), 1.21 (3 H, t, 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, 84.02; H, 5.76.

For 3-(4-chlorophenyl)-1-ethoxy-1-phenyl-1H-benzo[*f*]chromene (**4c**), after 5 h the yield was 90%. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.85 (1H, d, J = 6.8 Hz), 7.70–7.45 (6 H, m, ArH), 7.35–7.14 (8 H, m, ArH), 5.57 (1 H, s, CH), 3.52 (2 H, q, J = 14.1 Hz, OCH_2), 1.20 (3 H, t, J = 14.1 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, 77.24; H, 5.03.

For 1-ethoxy-3-(4-nitrophenyl)-1-phenyl-1H-benzo[*f*]chromene (**4d**), after 6 h the yield was 90%. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.95 (2 H, m, ArH), 7.65–7.35 (5 H, m, ArH), 7.35–7.10 (8 H, m, ArH), 5.70 (1 H, s, CH), 3.60 (2 H, q, J = 14.7 Hz, OCH_2), 1.18 (3 H, t, J = 14.7 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, 74.83; H, 5.06; N, 3.22.

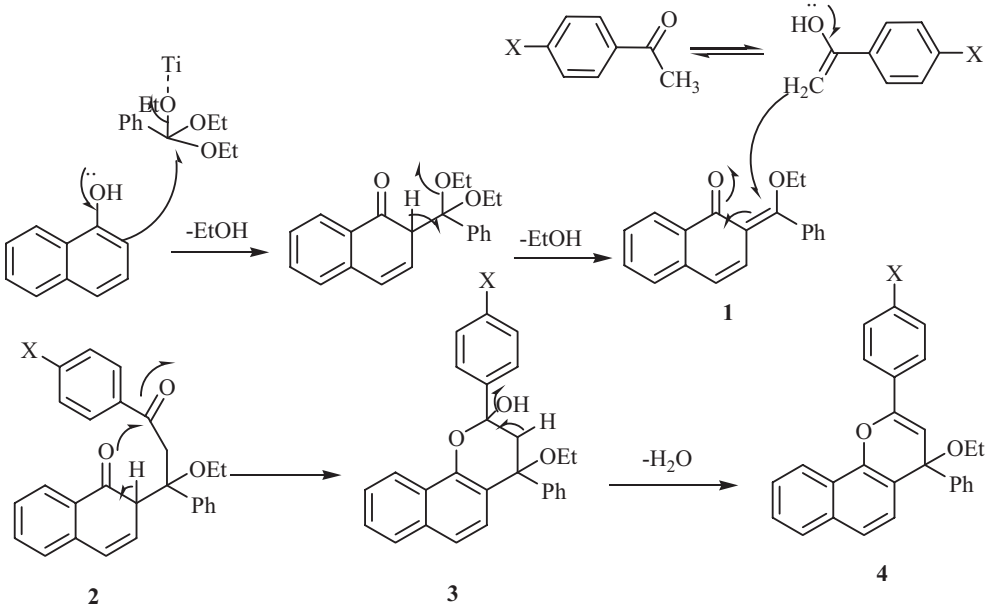
For 1-ethoxy-1-phenyl-3-p-tolyl-1H-benzo[*f*]chromene (**4e**), after 6 h the yield was 85%. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.85–7.40 (3 H, m, ArH), 7.35–7.20 (7 H, m, ArH), 7.15–7.05 (5 H, m, ArH), 5.63 (1 H, s, CH), 3.48 (2 H, q, J = 15.1 Hz, OCH_2), 2.24 (3 H, s, CH_3), 1.19 (3 H, t, J = 15.4 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, 84.17; H, 6.26.



4a-4h

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

SCH. 1. Synthesis of benzo[*h*]chromene derivatives **4a–4h**.



SCH. 2. Proposed mechanism for the synthesis of benzo [*h*]chromene derivatives catalyzed by bis[7-tert-butyl-2-anilinotropone] Ti complex.

For 4-(4-ethoxy-4-phenyl-4*H*-benzo[*h*]chromen-2-yl)phenol (**4g**), after 5 h the yield was 84%. ^{1}H NMR (250 MHz, DMSO-d_6): $\delta = 9.84$ (1 H, s, OH), 8.02 (1H, d, $J = 7.8$ Hz, ArH), 7.60–7.40 (7 H, m, ArH), 7.37–7.10 (6 H, m, ArH), 5.47 (1 H, s, CH), 3.35 (2 H, q, $J = 13.1$ Hz, OCH_2), 1.10 (3 H, t, $J = 13.1$ 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, 79.55; H, 5.25.

RESULTS AND DISCUSSION

Initial experiment was performed by the one-pot reaction of 1-naphthol, acetophenone, and triethyl orthobenzoate as the model reaction. When 1-naphthol (1 mmol) was treated with acetophenone (1 mmol) and triethyl orthobenzoate (1 mmol) in the presence of a catalytic amount of bis[7-tert-butyl-2-anilinotropone] Ti complex (0.015 mmol) at reflux condition in toluene, the desired 4-ethoxy-2,4-diphenyl-4*H*-benzo[*h*]chromene (**4a**) was obtained in 85% yield. No corresponding benzo[*h*]chromene was isolated in the absence of the catalyst highlighting the role of the catalyst to push the reaction forward.

Encouraged by this success, we then extended the model reaction using different derivatives of acetophenone (Scheme 1). It was revealed that the electronic nature of substituted groups on acetophenone does not affect the reaction times as well as chemical yields (Scheme 2). Furthermore, other available titanium salts such as $TiCl_4$ and $Ti(OAc)_4$ were examined for the one-pot condensation, but no corresponding products were isolated. It can be concluded that the presence of two electronegative chelates in the organometallic catalyst provide more electrophilic Lewis acid which catalyzes the reaction efficiently.

The reasonable mechanism for the synthesis of 2-(4-aryl)-4-ethoxy-4-phenyl-4*H*-benzo[*h*]chromene derivatives is shown in Scheme 2. Naphthol C-alkylation via a Knoevenagel addition between 1-naphthol and triethyl orthobenzoate results in an 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 **2**. Intramolecular cyclization of **2** gives **3**, which undergoes dehydration to obtain product **4**.

CONCLUSION

In summary, we have demonstrated an efficient synthesis of a new series of benzo[*h*]chromene derivatives. 2-(4-aryl)-4-ethoxy-4-phenyl-4*H*-benzo[*h*]chromenes were synthesized efficiently through multicomponent cyclocondensations of 1-naphthol, acetophenone derivatives, and triethyl orthobenzoate catalyzed by bis[7-tert-butyl-2-anilinotropone] Ti complex.

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