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Synthesis of novel benzo[*f*]chromene compounds catalyzed by ionic liquid

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Abstract

A facile method for the synthesis of benzo[*f*]chromene derivatives is reported. The procedure involves a novel three-component reaction of 1-naphthol or 2-naphthol, acetophenone derivatives and triethyl orthobenzoate in the presence of silica supported ionic liquid [pmim]$HSO_{4\ SiO_2}$ [silica supported 1-methyl-3-(triethoxysilylpropyl)imidazolium hydrogensulfate] as an efficient catalyst.

Keywords: benzo[*f*]chromene; ionic liquid; one-pot reaction.

Introduction

Currently, one of the major challenges of modern drug discovery is the design of highly efficient chemical reaction sequences providing a maximum of structural diversity using a minimum number of synthetic steps to assemble compounds with interesting properties (Dömling, 2002). 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, as well as the very large number of accessible compounds are among the described advantages of MCRs (Trost, 1995).

Recently, ionic liquids have become a powerful alternative to conventional molecular organic solvents due to their particular properties, such as undetectable vapor pressure and the ability to dissolve many organic and inorganic substances (Wasserscheid and Welton, 2007). In addition, the ionic liquids are readily recycled and tunable to specific chemical tasks. One type is Brønsted acidic task-specific ionic liquids. Among these ionic liquids possessing HSO_4 as a counteranion finds a broad application in organic synthesis, acting as both a solvent and a catalyst. Recently, immobilization processes involving acidic ionic liquids on solid supports have been designed (Du et al., 2006; Gupta et al., 2007; Wang et al., 2008). The heterogenization of catalysts and reagents can offer important advantages in handling, separation and reuse procedures. Immobilized acidic ionic liquids have been used as novel solid catalysts for a wide spectrum of reactions (Fischer et al., 1999; Qiao et al., 2006; Sugimura et al., 2007).

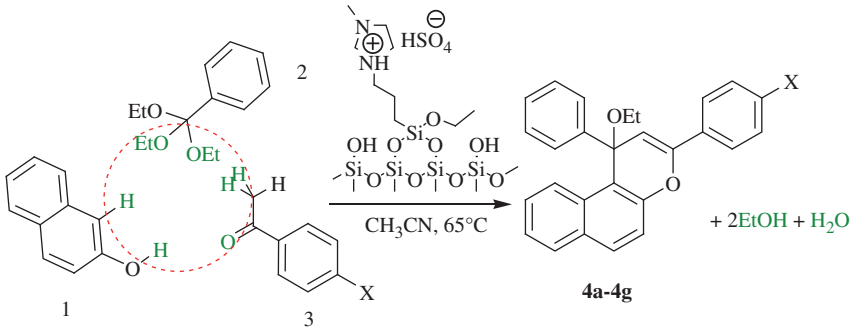
Chromenes and fused chromenes are biologically active compounds and they are used as cosmetics and pigments (Hafez et al., 1987; Ellis et al., 1997), spasmolytic, diuretic, anticoagulant, antianaphylactic (Triggle, 2003; Poupaert et al., 2005), antibacterial (Kidwai et al., 2005), anticancer agents (Mohr et al., 1975), and as potent apoptosis inducers (Gao et al., 2010).

Recently, many studies have been devoted to the synthesis of benzo[*f*]chromene compounds by developing and modification of synthetic methods. Claisen rearrangement of alkynyl aryl ethers from propargylic alcohols and naphthols under acid catalysis to synthesize 2*H*-1-benzopyran derivatives has been reported (Xu et al., 2009). In addition, several catalysts have been utilized for the synthesis of 2-amino-4*H*-chromenes such as cetyltrimethylammonium chloride (Ballini et al., 2000), cetyltrimethylammonium bromide under ultrasound irradiation (Jin et al., 2004), KF/Al_2O_3 (Wang et al., 2004), $TiCl_4$ (Sunil et al., 2006), triethylamine (Shestopalov et al., 2002), basic ionic liquids (Gong et al., 2008), iodine/K_2CO_3 (Ren and Cai, 2008), and DABCO (Balalaie et al., 2008). However, synthesis of 1-ethoxy-3-(4-aryl)-1-phenyl-1-*H*-benzo[*f*]chromene has never been reported up to now. In the course of our ongoing research for the efficient and convenient synthesis of a variety of heterocyclic compounds (Damavandi, 2011; Damavandi and Sandaroos, 2011a; Damavandi and Sandaroos, 2011b), we developed an efficient synthetic procedure for the synthesis of a series of benzo[*f*]chromenes by one-pot condensation of 2-naphthol or 1-naphthol, acetophenone derivatives and triethyl orthobenzoate catalyzed by silica supported ionic liquid of [pmim]$HSO_{4\ SiO_2}$ [silica supported 1-methyl-3-(triethoxysilylpropyl)imidazolium hydrogensulfate] (Scheme 1).

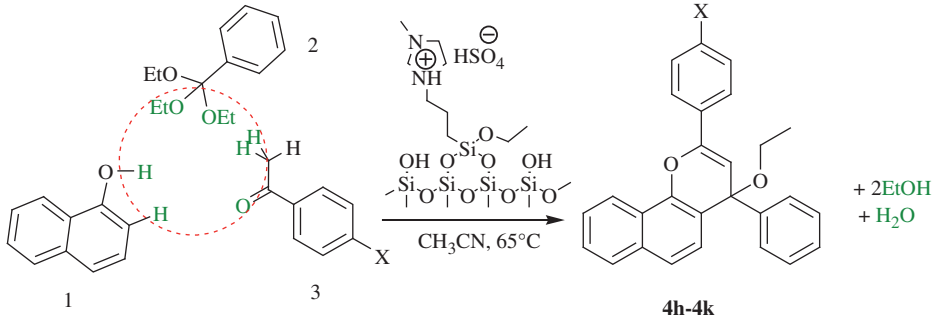
Results and discussion

Attempts have been made by many research groups to prepare supported catalysts in the area of transition metal catalyst mediated various organic reactions (De et al., 2002; Rechavi and Lemaire, 2002). In the present study, [pmim]$HSO_{4\ SiO_2}$ (Scheme 1) was prepared based on a published report (Chrobok et al., 2009).

Initial experiments were performed with 2-naphthol, acetophenone and triethyl orthobenzoate as the model substrates. When 2-naphthol (1 mmol) was treated with acetophenone (1 mmol) and triethyl orthobenzoate (1 mmol) in the



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



X=H-(**4h**); Cl-(**4i**); NO_2-(**4j**); Me-(**4k**)

Scheme 1 Synthesis of benzochromene derivatives **4a–4k**.

presence of a catalytic amount of [pmim]$HSO_{4\ SiO_2}$ (0.015 mmol) at 65°C in acetonitrile, the desired 1-ethoxy-1,3-diphenyl-1*H*-benzo[*f*]chromene (**4a**) was obtained in 85% yield (Scheme 1). To investigate the effect of solvent on the catalytic efficiency of [pmim]$HSO_{4\ SiO_2}$, various solvents were examined for the model reaction (Table 1). Protic solvents such as ethanol and methanol afforded poor results. Inversely, application of polar aprotic solvent such as acetonitrile significantly improved chemical yields and reaction times. Moreover, moderate yields were obtained using toluene and benzene as polar media for the model reaction.

We extended the model reaction using different derivatives of acetophenone. It was revealed that the electronic nature of substituted groups on acetophenone does not affect the reaction times as well as chemical yields. However, reaction efficiencies were slightly improved by changing the substituent groups from Br and Cl to the methoxy group. It can be suggested that the first step, nucleophilic attack of 2-naphthol to the triethyl orthobenzoate might be the rate determining step.

Furthermore, the use of 1-naphthol was also attempted in the reaction with acetophenone derivatives and triethyl orthobenzoate under optimized conditions. As shown in Scheme 1, the corresponding benzo[*f*]chromene derivatives **4h–j** were synthesized successfully in good yields.

Table 1 Effect of solvents on the catalytic efficiency of [pmim]$HSO_{4\ SiO_2}$.

Entry	Solvent	Time (h)	Isolated yield (%)
1	CH_3CN	6	85
2	EtOH	8	64
3	MeOH	8	60
4	DMSO	6	80
5	Toluene	8	72

Reaction conditions: 1.0 equiv. of 2-naphthol, 1.0 equiv. of acetophenone, 1.0 equiv. of triethyl orthobenzoate, 15 mol% of [pmim]$HSO_{4\ SiO_2}$, 4 mL of solvent and at 65°C.

Conclusion

We report an effective methodology for the synthesis of a series of novel substituted benzo[*f*]chromenes by the one-pot three component reaction of 2-naphthol or 1-naphthol, acetophenone and triethyl orthobenzoate utilizing silica supported ionic liquid of [pmim]$HSO_{4\ SiO_2}$.

Experimental

General

All chemicals and ionic liquids were purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products. ^{1}H NMR spectra were recorded on a Bruker 250-MHz spectrometer in DMSO-d_6 as the solvent and TMS as internal standard.

Elemental analysis was performed on a Thermo Finnigan EA1112 elemental analyzer. The catalyst [pmim]$HSO_{4\ SiO_2}$ (extent of labeling 0.25 mmol/g loading) was prepared as reported previously (Chrobok et al., 2009).

General procedure for the synthesis of benzo[*f*]-chromene derivatives 4a–g

A mixture of 2-naphthol (1 mmol), an acetophenone (1 mmol), triethyl orthobenzoate (1.1 mmol) and ionic liquid catalyst (0.15 mmol) in CH_3CN (4 mmol) was stirred at 65°C for the period of time indicated below. The reaction was monitored by TLC and, after completion of the reaction, the catalyst was recovered by filtration and washed with dichloromethane. The residue was concentrated under reduced pressure and the crude product was crystallized from ethanol/H_2O (3:1).

General procedure for the synthesis of benzo[*f*]-chromene derivatives 4h–k

The procedure described above was conducted in the presence of 1-naphthol under otherwise identical conditions. Products **4h–k** were crystallized from ethanol/water (3:1).

1-Ethoxy-1,3-diphenyl-1*H*-benzo[f]chromene (4a) After 6 h the yield was 85%; mp 211–213°C; ^{1}H NMR: δ 7.60–7.40 (6 H, m), 7.35–7.05 (10 H, m), 5.72 (1 H, s), 3.62 (2 H, q, *J*=7 Hz), 1.25 (3 H, t, *J*=7 Hz); EI-MS: *m/z* 378 (M^+). Anal. Calcd for $C_{27}H_{22}O_2$: C, 85.69; H, 5.86%. Found: C, 84.18; H, 5.73%.

3-(4-Bromophenyl)-1-ethoxy-1-phenyl-1*H*-benzo[*f*]chromene (4b) After 7 h the yield was 85%; mp 217–219°C; ^{1}H NMR: δ 7.65–7.45 (5 H, m, ArH), 7.35–7.08 (10 H, m, ArH), 5.65 (1 H, s, CH), 3.57 (2 H, q, *J*=7 Hz), 1.22 (3 H, t, *J*=7 Hz); EIMS: *m/z* 456 (M^+). Anal. Calcd for $C_{27}H_{21}BrO_2$: C, 70.90; H, 4.63%. Found: C, 68.73; H, 4.52%.

3-(4-Chlorophenyl)-1-ethoxy-1-phenyl-1*H*-benzo[*f*]chromene (4c) After 7 h the yield was 88%; mp 233–235°C; ^{1}H NMR: δ 7.60–7.42 (4 H, m), 7.35–7.10 (11 H, m), 5.63 (1 H, s), 3.55 (2 H, q, *J*=7 Hz), 1.18 (3 H, t, *J*=7 Hz); 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%.

1-Ethoxy-3-(4-nitrophenyl)-1-phenyl-1*H*-benzo[*f*]chromene (4d) After 8 h the yield was 80%; mp 245–246°C; ^{1}H NMR: δ 7.95 (2 H, m), 7.62–7.40 (5 H, m), 7.35–7.25 (3 H, m), 7.25–7.05 (5 H, m), 5.90 (1 H, s), 3.63 (2 H, q, *J*=7 Hz), 1.16 (3 H, t, *J*=7 Hz); 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, 75.07; H, 5.08; N, 3.36%.

1-Ethoxy-1-phenyl-3-p-tolyl-1*H*-benzo[*f*]chromene (4e) After 6 h the yield was 88%; mp 218–220°C; ^{1}H NMR: δ 7.60–7.40 (3 H, m), 7.35–7.22 (9 H, m), 7.20–7.05 (3 H, m), 5.55 (1 H, s), 3.48 (2 H, q, *J*=7 Hz), 2.24 (3 H), 1.16 (3 H, t, *J*=7 Hz); EIMS: *m/z* 392 (M^+). Anal. Calcd for $C_{28}H_{24}O_2$: C, 85.68; H, 6.16%. Found: C, 84.33; H, 6.05%.

1-Ethoxy-3-(4-methoxyphenyl)-1-phenyl-1*H*-benzo[*f*]-chromene (4f) After 5 h the yield was 90%; mp 216–218°C; ^{1}H NMR: δ 7.63–7.35 (3 H, m), 7.30–7.15 (8 H, m), 7.10–7.02 (4 H, m), 5.77 (1 H, s), 3.72 (3 H, s), 3.44 (2 H, q, *J*=7 Hz), 1.14 (3 H, t, *J*=7 Hz); EIMS: *m/z* 408 (M^+). Anal. Calcd for $C_{28}H_{24}O_3$: C, 82.33; H, 5.92%. Found: C, 81.46; H, 5.83%.

4-(1-Ethoxy-1-phenyl-1*H*-benzo[*f*]chromen-3-yl)phenol (4g) After 5 h the yield was 84%; mp 253–255°C; ^{1}H NMR: δ 9.45 (1 H, s), 7.60–7.45 (2 H, m), 7.35–7.20 (10 H, m), 7.15–7.05 (3 H, m), 5.65 (1 H, s), 3.52 (2 H, q, *J*=7 Hz), 1.10 (3 H, t, *J*=7 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, 81.43; H, 5.54%.

1-Ethoxy-1,3-diphenyl-1*H*-benzo[*f*]chromene (4h) After 7 h the yield was 87%; mp 208–210°C; ^{1}H NMR: δ 7.90 (1H, d, *J*=8 Hz), 7.74–7.40 (4 H, m), 7.35–7.05 (11 H, m), 5.65 (1 H, s), 3.55 (2 H, q, *J*=7 Hz,), 1.21 (3 H, t, *J*=7 Hz); 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%.

3-(4-Chlorophenyl)-1-ethoxy-1-phenyl-1*H*-benzo[*f*]chromene (4i) After 4 h the yield was 91%; mp 214–215°C; ^{1}H NMR: δ 7.85 (1 H, d, *J*=7 Hz), 7.70–7.45 (6 H, m), 7.35–7.14 (8 H, m), 5.57 (1 H, s), 3.52 (2 H, q, *J*=7 Hz), 1.20 (3 H, t, *J*=7 Hz); 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%.

1-Ethoxy-3-(4-nitrophenyl)-1-phenyl-1*H*-benzo[*f*]chromene (4j) After 5 h the yield was 92%; mp 221–223°C; ^{1}H NMR: δ 7.95 (2 H, m), 7.65–7.35 (5 H, m), 7.35–7.10 (8 H, m), 5.70 (1 H, s), 3.60 (2 H, q, *J*=7 Hz), 1.18 (3 H, t, *J*=7 Hz); 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%.

1-Ethoxy-1-phenyl-3-p-tolyl-1*H*-benzo[*f*]chromene (4k) After 5 h the yield was 88%; mp 217–219°C; ^{1}H NMR: δ 7.85–7.40 (3 H, m), 7.35–7.20 (7 H, m), 7.15–7.05 (5 H, m), 5.63 (1 H, s), 3.48 (2 H, q, *J*=7 Hz), 2.24 (3 H, s), 1.19 (3 H, t, *J*=7 Hz); EIMS: *m/z* 392 (M^+). Anal. Calcd for $C_{28}H_{24}O_2$: C, 85.68; H, 6.16%. Found: C, 85.17; H, 6.26%.

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