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Hossein Eshghi[a], Mohammad Rahimizadeh[a] & Seyed Mohsen Mousavi[a]
[a] Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad 91775-1436, Iran
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$Fe(HSO_4)_3/SiO_2$: an efficient and heterogeneous catalyst for one-pot synthesis of 2-aryl-chromene-4-ones (flavanones)

Hossein Eshghi*, Mohammad Rahimizadeh and Seyed Mohsen Mousavi

Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad 91775-1436, Iran

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This paper is dedicated to Professor Hashem Sharghi on the occasion of his 65th birthday and his ongoing 35 years research and teaching in organic synthesis.

Silica ferric hydrogensulphate is an efficient heterogeneous catalyst for cyclisation of 2-hydroxychalcones to their corresponding flavanones (chromanone). This intramolecular oxa-Michael reaction was carried out in high yields in the presence of electron donating and electron withdrawing groups in the chalcone structure. Also, we found that aniline can act as an organic co-catalyst in direct synthesis of flavanones from 2-hydroxyacethophenone and aldehydes in the presence of $Fe(HSO_4)_3/SiO_2$. Flavanones were prepared in high yields in a new catalytic system with similar substituted effect in the indirect cyclisation method. The catalyst in all the above reactions is reusable without significant decreases in its activity after four times of recycling.

Keywords: $Fe(HSO_4)_3$; heterogeneous; flavanones; chalcones; oxa-Michael; organo-catalyst; silica ferric hydrogensulphate

1. Introduction

The flavanones are a group of natural products which are widely distributed in plants (Siddikov et al. 2008) and also available from synthetic sources. The major reported biological activities of these compounds include neuron protection (Vauzour et al. 2007), antitumour (Cabrera et al. 2007), anti-metastasis (Hsiao et al. 2007), antimicrobial (Ward et al. 1981), anti-oxidant (Jung et al. 2008), anti-inflammatory (Njamen et al. 2004) and antiviral activities (Paredes et al. 2003).

A commonly reported synthetic method for flavanones involve the Claisen–Schmidt reaction of *o*-hydroxyacetophenones with benzaldehydes to produce chalcone intermediates using different catalysts (Wang & Cheng 2006), and then cyclisation of chalcone with various bases (Chen et al. 2011), acids (Chaturvedi et al. 1992) and other catalysts (Climent et al. 1989).

Most of the existing procedures for the preparation of flavanone derivatives suffer from some drawbacks such as the use of corrosive reagents, limited synthetic scope, low yields, long reaction times, needs of large amount of catalyst, solvents and harsh reaction conditions. Therefore, the development of new methods that lead to a convenient procedure and better yield is still desirable.

The aim of this study was to investigate the efficiency of $Fe(HSO_4)_3/SiO_2$ as a catalyst in the synthesis of flavanones through cyclisation of 2-hydroxychalcones. Also, we wish to report the one-pot synthesis of flavanones via three-component Mannich reaction in the presence of silica ferric hydrogensulphate (SFHS) and aniline as an organic co-catalyst.

*Corresponding author. Email: heshghi@um.ac.ir

2. Results and discussion

The first application of SFHS in oxa-Michael reaction was demonstrated by intramolecular cyclisation of 2-hydroxychalcones (Scheme 1).

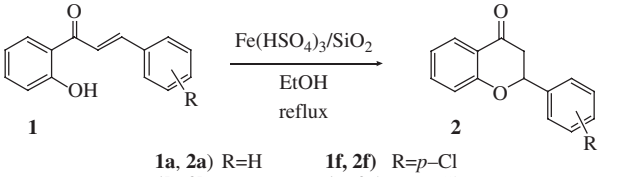
The effects of catalyst loading and solvent screening on the rate of cyclisation reactions are shown in Table S1. All reactions were carried out with 1 mmol of 2-hydroxychalcone (**1a**) in 2.5 mL solvent at reflux conditions or in solvent-free condition at room temperature. No reaction was observed without catalyst. The yield with unsupported ferric hydrogensulphate (FHS) was low. So the optimum conditions for the conversion of 2-hydroxylchalcones to the corresponding 2-aryl flavanones are 5 mol% $Fe(HSO_4)_3/SiO_2$ under reflux condition in EtOH.

Reusability of the catalyst in these reactions was also investigated. After each reaction, the catalyst was recovered by filtration and rinsed by CH_2Cl_2 and absolute EtOH. The recovered catalyst did not show a significant decrease in its activity at least after five new runs (Table S1, entries 14–18).

In order to show the generality of the intramolecular oxa-Michael reactions, various substituted chalcones were subjected to cyclisation using SFHS as catalyst. The results of these reactions are shown in Table S2. Both electron-donating and electron-withdrawing substituted chalcones undergo cyclisation, but the latters were more reactive. The results of Table S2 demonstrate that the reaction is chemoselective and further oxidation of flavonone to flavone was not observed. Other functional group like hydroxyl was not oxidised under these conditions. Generally, *ortho*-substituted chalcones are cyclised slower than *meta*- or *para*-isomer because of large steric effect. All the isolated products were well characterised by their IR, ^{1}H NMR spectral analysis. The ^{1}H NMR (100 MHz, $CDCl_3$) spectra of compounds **2a**–**2i** showed a doublet of doublet in 5.1–5.9 and a multiplet in 2.7–3.3 region as characteristic bands of flavanones (Supplementary data).

In a possible mechanism for these conversions, the chalcone is activated by coordination with catalyst followed by hydroxyl attack to electrophilic carbon atom and regeneration of the catalyst.

On the other hand, in continuation to our previous investigations on the three-component Mannich reaction of aldehyde, amine and enolisable ketone to prepare the β-aminocarbonyl compounds (Eshghi et al. 2011, 2013), we found that there is no report in using 2-hydroxy acetophenone as enolisable ketone component in these reactions. So we decided to carry out the Mannich reaction of benzaldehyde, aniline and 2-hydroxyacetophenone in the presence of SFHS as catalyst in ethanol under reflux condition. Surprisingly, only flavanone **2a** was obtained instead of β-aminocarbonyl compound. So, we try to optimise the reaction condition for this novel one-pot flavanones synthesis (Table S3). As can be seen, the aniline acts as an organic co-catalyst in this reaction and the reaction does not proceed in the absence of catalyst or co-catalyst.



1a, **2a**) R=H **1f, 2f)** R=*p*–Cl
1b, **2b**) R=*p*–Me **1g, 2g)** R=*o*–Cl
1c, **2c**) R=*p*–i–Pr **1h, 2h)** R=*p*–NO_2
1d, **2d**) R=*p*–OMe **1i, 2i)** R=*m*–OH
1e, **2e**) R=*m*–OMe

Scheme 1. Intramolecular oxa-Michael reaction catalyzed with SFSH.

$Fe(HSO_4)_3/SiO_2$ was recovered by simple filtration and aniline was removed by acid treatment of organic phase. Reusability of the catalyst in this reaction was also examined. After five times recycling of catalyst, no significant decrease in reaction yields or rate was observed.

After the reaction condition was optimised, the reaction was performed with different substituted benzaldehydes (Scheme 2), and the obtained results are shown in Table S4. Electron-withdrawing group increases the rate of reaction, while the electron-donating group decreases the rate. The steric effect of bulky groups in *ortho*-position are also decreases the rate of reaction.

While writing this manuscript, we noticed a similar protocol has been reported by Kavala et al. (2012) but stoichiometric rather than catalytic amount of aniline was used. They also screened the effect of different amines and concluded that aniline was the most suitable amine for this conversion. A possible mechanism for this transformation is suggested in Scheme S3. The initially formed imine and 2-hydroxyacetophenone are both activated by coordination with SFHS catalyst. The enol forms of 2-hydroxyacetophenone attacks the electrophilic carbon of coordinated imine, to form the intermediate (**I**). Coordination of this intermediate with SFHS gave intermediate (**II**) which may easily be cyclised with either S_N1 or S_N2 mechanism, or eliminated to chalcone and then cyclised to product. TLC monitoring of the reaction mixture did not show any chalcone formation and substitution effects ruled out the S_N1 mechanism (Table S4, entry 8). So S_N2-type intramolecular cyclisation or nucleophilic participation borderline mechanisms are more probable for this reaction. Aniline and SFHS regenerate and initiate a new catalytic cycle.

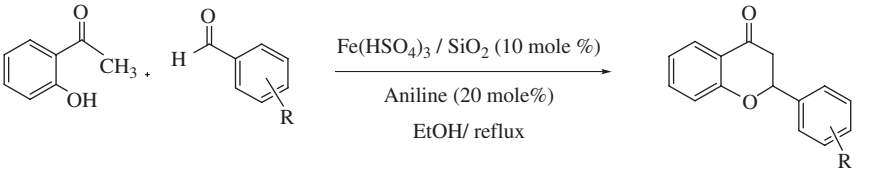
3. Experimental

3.1. *General*

Chemicals were either prepared in our laboratories or purchased from Merck (Germany), Fluka (Switzerland) and Aldrich (USA) Chemical Companies. All yields refer to the isolated products. Melting points are recorded on an Electro thermal type 9100 melting point apparatus. IR spectra were recorded on a Thermo Nicolet AVATAR-370-FT-IR spectrophotometer (USA). The ^1H NMR spectra were recorded on a Bruker AC 100 spectrometer (Germany) at 100 MHz. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constant *J* is given in Hertz. Elemental analyses were obtained on a Thermo Finnigan Flash EA micro-analyser. Silica-supported FHS was prepared as we have previously reported (Eshghi et al. 2012, 2013). Chalcone **1** was prepared according to the reported procedure (Lin et al. 2002).

3.2. *General procedure for the synthesis of flavanones 2a–2i*

$Fe(HSO_4)_3/SiO_2$ (5 mol%) was added to a stirred solution of 2-hydroxychalcones (**1**) (1.0 mmol) in ethanol (2.5 mL). The reaction mixture was heated with stirring at reflux conditions for the appropriate time. After completion of the reaction as monitored by TLC, the mixture was cooled, filtered and the solvent was evaporated in vacuum. Products **2a–2i** were purified by silica gel



Scheme 2. Direct synthesis of flavanones catalyzed with SFSH in the presence of aniline as an organo catalyst.

column chromatography using hexane–diethyl acetate (9:1 to 4:1) as eluent. The separated catalyst was rinsed with CH_2Cl_2 and absolute ethanol, dried and re-used.

3.3. *General procedure for the one-pot synthesis of flavanones 2a–2i in the presence of Fe $(HSO_4)_3/SiO_2$/aniline catalytic system*

A mixture of $Fe(HSO_4)_3/SiO_2$ (10 mol%) and aniline (20 mol%) was added to a stirred solution of 2-hydroxyacetophenone (1.0 mmol) and aldehydes (1.0 mmol) in ethanol (3 mL). The reaction mixture was heated with stirring at reflux conditions for the appropriate time. After completion of the reaction as indicated by TLC, the mixture was cooled, filtered and the organic phase was evaporated in vacuum. Crude products dissolved in CH_2Cl_2 (10 mL), washed with 5% hydrochloric acid (10 mL) and water (10 mL), dried over $MgSO_4$ and solvent was evaporated in vacuum.

Products **2a–2i** were purified by silica gel column chromatography using hexane–diethyl acetate (9:1 to 4:1) as eluent. The separated catalyst was rinsed with CH_2Cl_2 and absolute ethanol, dried and re-used.

3.4. *Spectral data of the prepared compounds*

3.4.1. *2-Phenyl-4-chromanone (**2a**)*

Yield 95%; m.p. 75–76°C, lit. (Kumar et al. 2009) m.p. 75–76°C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 7.95 (dd, 1H, $J_1 = 7.7$, $J_2 = 1.5$ Hz), 6.9–7.8 (m, 8H), 5.5 (dd,1H, $J_1 = 12.3$, $J_2 = 4.6$ Hz), 2.7–3.3 (m, 2H). IR (KBr, cm^{-1}) ν: 3063, 3035, 1690 (C═O), 1637, 1605.

3.4.2. *2-(4-Methylphenyl)-4-chromanone (**2b**)*

Yield 93%; m.p. 80–82°C, lit. (Kavala et al. 2012) m.p. 81–83°C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 8.0 (dd, 1H, $J_1 = 7.7$, $J_2 = 1.5$ Hz), 7.0–7.67 (m, 7H), 5.5 (dd,1H, $J_1 = 12.3$, $J_2 = 3.0$ Hz), 2.7–3.3 (m, 2H), 2.4 (s, 3H). IR (KBr, cm^{-1}) ν: 3063, 2960, 1694 (C═O), 1606, 1576.

3.4.3. *2-(4-Isopropylphenyl)-4-chromanone (**2c**)*

Yield 83%; m.p. 77°C, lit. (Hoshino & Takeno 1986) m.p. 76–77°C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 7.9–8.1 (m, 2H), 7.20–7.67 (m, 3H), 7.0–7.2(m, 3H), 5.5 (dd, 1H, $J_1 = 12.3$, $J_2 = 3.0$ Hz), 4.2–4.6 (m, 1H), 2.76–3.3 (m, 2H), 1.38 (m, 6H). IR (KBr, cm^{-1}) ν: 3345, 3055, 2921, 1690 (C═O), 1602, 1576.

3.4.4. *2-(4-Methoxyphenyl)-4-chromanone (**2d**)*

Yield 92%; m.p. 75–77°C, lit. (Chimenti et al. 2010) m.p. 75–77°C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 7.95 (d, 1H, $J = 8.3$ Hz), 7.3–7.76 (m, 2H), 6.9–7.2 (m, 5H), 5.5 (dd, 1H $J_1 = 12.9$, $J_2 = 3.7$ Hz), 3.9 (s, 3H), 2.74–3.6 (m, 2H). IR (KBr, cm^{-1}) ν: 3088, 3026, 2961, 2937, 2834, 1693 (C═O), 1641, 1603.

3.4.5. *2-(3-Methoxyphenyl)-4-chromanone (**2e**)*

Yield 80%; m.p. 78–80°C, lit. (Jiang et al. 2011) m.p. 79–80°C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 7.95 (dd, 1H, $J_1 = 8.6$, $J_2 = 2.5$ Hz), 7.25–7.63 (m, 2H), 6.88–7.2 (m, 5H), 5.5 (dd, 1H, $J_1 = 12.3$, $J_2 = 4.6$ Hz), 3.85 (s, 3H), 2.77–3.1 (m, 2H, CH_2). IR (KBr, cm^{-1}) ν: 3060, 3015, 2921, 2831, 1685 (C═O), 1608, 1489.

3.4.6. *2-(4-Chlorophenyl)-4-chromanone (**2f**)*

Yield 93%; m.p. 92–94°C, lit. (Kavala et al. 2012) m.p. 93–95°C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 8.0 (dd, 1H, $J_1 = 9.2$, $J_2 = 1.5$ Hz), 7.85 (m, 1H), 7.2–7.7 (m, 4H), 6.9–7.2 (m, 2H), 5.5 (dd, 1H, $J_1 = 12.3$, $J_2 = 3.0$ Hz), 2.8–3.2 (m, 2H). IR (KBr, cm^{-1}) ν: 3064, 2925, 2847, 1707 (C═O), 1606, 1490.

3.4.7. *2-(2-Chlorophenyl)-4-chromanone (**2g**)*

Yield 85%; m.p. 95–97°C, lit. (Jiang et al. 2011) m.p. 96–97°C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 8.0 (dd, 1H, $J_1 = 9.2$, $J_2 = 1.5$ Hz), 6.97–7.9 (m, 7H), 5.9 (dd, 1H, $J_1 = 12.3$, $J_2 = 4.6$ Hz), 2.7–3.0 (m, 2H). IR (KBr, cm^{-1}) ν: 3068, 2921, 1691 (C═O), 1646, 1607.

3.4.8. *2-(4-Nitrophenyl)-4-chromanone (**2h**)*

Yield 91%; m.p. 156–157°C, lit. (Kavala et al. 2012) m.p. 156–157°C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 7.95 (dd, 1H, $J_1 = 7.7$, $J_2 = 1.5$ Hz), 6.8–7.7 (m, 7H), 5.5 (dd, 1H, $J_1 = 12.3$, $J_2 = 4.6$ Hz), 2.8–3.2 (m, 2H). IR (KBr, cm^{-1}) ν: 3019, 2921, 2847, 1720 (C═O), 1519, 1348 (NO_2).

3.4.9. *2-(3-Hydroxyphenyl)-4-chromanone (**2i**)*

Yield 90%; m.p. 143–144°C, lit. (Furlong & Nudelman 1985) m.p. 141–144°C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 6.86–8.04 (m, 8H), 5.5 (dd, 1H, $J_1 = 11.4$, $J_2 = 4.6$ Hz), 5.12 (s, 1H, OH), 2.75–3.25 (m, 2H). IR (KBr, cm^{-1}) ν: 3370, 3047, 3023, 2921, 1637 (C═O), 1613, 1580.

4. Conclusions

In conclusion, this study demonstrates the application of silica-supported FHS as a catalyst for the oxa-Michael cyclisation of 2-hydroxychalcones to the corresponding flavanone derivatives. Also, this efficient catalyst can catalysed the one-pot direct flavanone synthesis from 2-hydroxyacetophenone and aldehydes in the presence of aniline as organic co-catalyst. Therefore, the novelty of this method is the simplicity of the procedure, the mildness of the reaction conditions, high yields, the ease of catalyst separation and its reusability.

Supplementary material

Supplementary material relating to this article is available online, alongside Tables S1–S4, Schemes S1–S3 and spectral data.

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