Ultrasonics Sonochemistry 31 (2016) 626–630

Contents lists available at ScienceDirect

Ultrasonics Sonochemistry

journal homepage: www.elsevier.com/locate/ultson

Short communication

Ultrasonic-assisted synthesis of flavones by oxidative cyclization of 2′-hydroxychalcones using iodine monochloride

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ARTICLE INFO

Article history:
Received 8 January 2016
Received in revised form 10 February 2016
Accepted 10 February 2016
Available online 11 February 2016

Keywords:
2′-Hydroxychalcones
Flavones
Iodine monochloride
Ultrasonic irradiation
Oxidative cyclization

ABSTRACT

This paper presents an efficient methodology for the synthesis of flavones *via* the oxidative cyclization of 2′-hydroxychalcones in the presence of iodine monochloride with DMSO under ultrasound irradiation. Ultrasonic irradiation enhances the cyclization reaction and leads to reduced reaction time at lower reaction temperatures while generating flavones with high yields.

1. Introduction

Flavones or 2-phenylchromones are abundant in numerous naturally occurring products and constitute an important group of oxygen heterocycles that are widely distributed in the plant kingdom as secondary metabolites [1].

Recently, much attention has been paid to the synthesis of flavones because of their various biological activities, such as anti-inflammatory [2], antiestrogenic [3], antioxidant, anticancer, anti-HIV, anti-hypertensive [4], anti-antimicrobial [5], cardiovascular [6], anti-diabetic [7], anti-allergic [8] and chemo preventative activities [9].

A variety of flavone synthesis methods have been developed. Traditionally flavones have been prepared by Baker–Venkataraman rearrangement [10–12], Allan–Robinson [13], *via* an intermolecular Wittig [14] and Auwers synthesis [15]. Similarly, oxidation of flavanones to flavones is well known in the literature [16,17].

Alternatively, oxidative cyclization of 2′-hydroxychalcones constitutes an important route for the synthesis of flavones, and a number of oxidizing agents such as I_2-DMSO [18], oxalic acid [19], $InBr_3$, and $InCl_3$ [20], $FeCl_3$ [21], I_2-Al_2O_3 [22], Na_2TeO_3 [23], CuI [24], NH_4I [25], DDQ [26] etc. have been reported in the literature for this conversion.

Some synthesis methods are not very satisfactory due to drawbacks such as low yields, high reaction temperature, long reaction time and formation of mixture of product containing flavones, flavanones and aurones have been reported in some cases. Therefore, the development of a new method for efficient synthesis of flavones is strongly desirable.

Iodine monochloride is a versatile reagent for the synthesis of a large number of organic compounds being employed, for example, as a source of electrophilic iodine in the synthesis of mono- or tri-iodinated fluorine aromatic compounds [27]. It can be used as an oxidant to afford 1,3-dioxolan-2-ylium ions from 1,3-dioxolanes [28]. Other examples of synthetic applications of this reagent also include electrophilic cyclizations to obtain various heterocyclic compounds such as 4-iodoisocoumarins [29], 3-iodochromones [30] and 3-substituted-2-chalcogenbenzo[*b*] furans [31].

Ultrasound has increasingly been used in organic synthesis. It is reported that the ultrasound irradiation can lead to the apparent improvement of the reaction efficiency with increased yields and reduced reaction time Ultrasound has increasingly been used in organic synthesis. Studies have shown that ultrasound irradiation can lead to improved reaction efficiency *via* increased yields and reduced reaction time [32]. It is also observed that reactions under ultrasound irradiation are commonly easier to work-up than those in conventional stirring methods [33]. Additionally, in many cases, reactions under ultrasound irradiation represent environmentally friendly processes, using small amounts of solvents and consuming less energy [34]. What's more, ultrasonic irradiation provides minimal side reactions [35]. To the best of our knowledge, there is no report in the literature on the preparation of flavones from 2′-hydroxychalcones using ultrasound irradiation.

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http://dx.doi.org/10.1016/j.ultsonch.2016.02.018
1350-4177/

We purpose in this work an improved synthesis of flavones using an equimolar amount of iodine monochloride with DMSO under ultrasound irradiation. This method allows for high yields in a short time and at low reaction temperatures.

2. Experimental

2.1. Chemicals and apparatus

All solvents and reagents were purchased from Fluka and Sigma–Aldrich and used without further purification. 2′-hydroxy substituted chalcones were prepared by base-catalyzed condensation between 2′-hydroxyacetophenone and the appropriate benzaldehyde using a literature procedure [36]. Wijs' Reagent (0.1 mol/l, 0.2 N) was purchased from Panreac. The ultrasonication was performed in a Bioblock 750 W ultrasound cleaner with a low frequency of 20 kHz (amplitude of 30%). The melting points of the isolated products were measured on a Reichert-Heizbank apparatus. ^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$ on a Bruker Avance III HD (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer using TMS as internal standard.

2.2. General procedure for the synthesis of flavones

For a typical synthesis, 2′-hydroxychalcones (0.5 mmol) was dissolved in Wijs' reagent (5 mL). The acetic acid was removed in vacuo. Then, the resulting solid and DMSO (5 mL) were charged in a 10 mL glass reactor. The reaction mixture was heated in an oil bath at 50 ± 2 °C. The ultrasound probe was immersed directly in the reactor. The ultrasonic generator (Bioblock Scientific 750 W) emits the sound vibration into the reaction mixture. Sonification was achieved at low frequencies of 20 kHz (amplitude of 30%). The reaction time was fixed at 30 min. When the reaction time was over, the mixture was allowed to cool, poured into 10 mL water and extracted with chloroform (3 × 20 mL). The organic layer was washed with sodium thiosulphate (3 × 10 mL) until neutrality and dried with $MgSO_4$ anhydrous. After filtration, the solvent was removed under reduced pressure to furnish the crude product. The yields of the reactions were calculated from the mass of the isolated pure product.

It is noteworthy that flavones were obtained in excellent yields without the use of any column chromatography. The reactions were clean and isolated compounds provided an NMR pure (>97% purity) product.

2.3. Spectroscopic analysis

In general, no further purification method was required. All the products were previously reported and characterized by the melting point, IR, ^{1}H NMR, ^{13}C NMR.

The spectral data of the isolated compounds, taken as representative examples, are listed below.

2.3.1. 2-Phenyl-4H-chromen-4-one

IR [ν, cm^{-1}] 3088 (C=C–H, Ar–H), 1645 (C=O), 1568 (C=C, Ar), 1128 (COC). ^{1}H NMR [δ, ppm] 8.17 (dd, 1H, J_{H-H} = 1.2 Hz; J_{H-H} = 8 - Hz), 7.85–7.83 (m, 2H), 7.63 (t, 1H, J_{H-H} = 8 Hz), 7.50–7.44 (m, 4H), 7.35 (t, 1H, J_{H-H} = 8 Hz), 6.76 (s, 1H); ^{13}C NMR [δ, ppm] 178.5, 164.4, 156.3, 134.3, 132.1, 131.3, 129.1 (2C), 126.5 (2C), 125.7, 125.6, 123.1, 118.1, 106.8.

2.3.2. 2-(4-chlorophenyl)-4H-chromen-4-one

IR [ν, cm^{-1}] 3086 (C=C–H, Ar–H), 1647 (C=O), 1601, 1568 (C=C, Ar), 1132 (COC). ^{1}H NMR [δ, ppm] 8.23 (dd, 1H, J_{H-H} = 1.6 Hz; J_{H-H} = 8 Hz), 7.88 (d, 2H, J_{H-H} = 8.4 Hz), 7.75–7.71 (m, 1H), 7.58 (d, 1H, J_{H-H} = 8 Hz), 7.50 (d, 2H, J_{H-H} = 8.4 Hz), 7.44 (t,1H, J_{H-H} = 8 Hz), 6.87 (s, 1H); ^{13}C NMR [δ, ppm] 178.1, 162.1, 156.1, 137.8, 133.8, 130.2, 129.3 (2C), 127.5 (2C), 125.7, 125.3, 123.8, 118.0, 107.6.

2.3.3. 2-(4-methoxyphenyl)-4H-chromen-4-one

IR [ν, cm^{-1}] 3051 (C=C–H, Ar–H), 1640 (C=O), 1602, 1572 (C=C, Ar), 1132 (COC). ^{1}H NMR [δ, ppm] 8.22 (dd, 1H, J_{H-H} = 1.2 Hz; J_{H-H} = 8 Hz), 7.88 (d, 2H, J_{H-H} = 8.8 Hz), 7.72–7.67 (m, 1H), 7.55 (d, 1H, J_{H-H} = 8 Hz), 7.41 (m, 1H), 7.01 (d,2H, J_{H-H} = 8.8 Hz), 6.82 (s, 1H), 3.88 (s, 3H); ^{13}C NMR [δ, ppm] 178.2, 165.4, 163.2, 156.2, 134.5, 128.7 (2C), 125.8, 125.6, 123.1, 122.3, 118.0, 114.7, 114.6, 104.7, 55.6.

2.3.4. 2-(3,4-dimethoxyphenyl)-4H-chromen-4-one

IR [ν, cm^{-1}] 3065 (C=C–H, Ar–H), 1696 (C=O), 1606 (C=C, Ar), 1143 (COC). ^{1}H NMR [δ, ppm] 8.23 (dd, 1H, J_{H-H} = 1.6 Hz; J_{H-H} = 8 - Hz), 7.72 (m, 1H), 7.59 (d, 2H, J_{H-H} = 8.8 Hz), 7.44 (m, 1H), 7.40 (d, 1H, J_{H-H} = 2 Hz), 6.99 (d,1H, J_{H-H} = 8.8 Hz), 6.90 (s, 1H), 3.99 (s, 3H), 3.97 (s, 3H); ^{13}C NMR [δ, ppm] 178.3, 163.3, 156.1, 152.0, 149.2, 133.5, 125.6, 125.0, 124.2, 123.8, 119.9, 117.9, 111.1, 108.7, 106.4, 56.0 (2C).

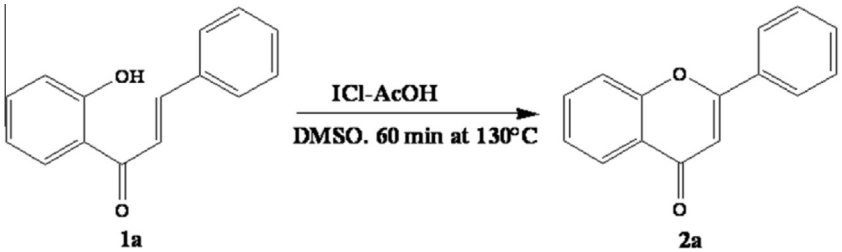
2.3.5. 2-(3,4,5-trimethoxyphenyl)-4H-chromen-4-one

IR [ν, cm^{-1}] 3063 (C=C–H, Ar–H), 1694 (C=O), 1574 (C=C, Ar), 1152 (COC). ^{1}H NMR [δ, ppm] 8.23 (dd, 1H, J_{H-H} = 1.2 Hz; J_{H-H} = 8 Hz), 7.73 (m, 1H), 7.61 (d, 1H, J_{H-H} = 8.4 Hz), 7.44 (t, 1H, J_{H-H} = 7.6 Hz), 7.15 (s, 2H), 6.88 (s,1H), 6.90 (s, 1H), 3.97 (s, 6H), 3.94 (s, 3H); ^{13}C NMR [δ, ppm] 178.4, 163.5, 156.2, 153.5, 141.2, 133.9, 126.8, 125.7, 125.4, 123.6, 118.1 (2C), 107.2, 103.7 (2C), 61.1, 56.3 (2C).

Table 1
Optimization of the DMSO amount.

Entry	Amount of DMSO (mL)	Yield[a,b] (%)
1	0	N.R
2	1	16
3	2	29
4	3	49
5	5	96
6	10	97

[a] Reaction condition: 2′-hydroxychalcone (0.5 mmol), ICl (0.5 mmol), acetic acid (5 mL), refluxed in open air for 60 min at 130 °C.
[b] Isolated yield of flavone.



Scheme 1. Oxidative cyclization of 2′-hydroxychalcone to flavone.