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Cyclization of 2′-hydroxychalcones to flavones using ammonium iodide as an iodine source – an eco-friendly approach

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Abstract: Ammonium iodide on exposure to air decomposes to ammonia and iodine. The *in situ* generated iodine was used for the cyclization of 2′-hydroxychalcones to the corresponding flavones under solvent-free conditions in good to excellent yields. This method could serve as an attractive alternative to the existing methods for synthesis of flavones and the use of toxic molecular iodine is avoided.

Keywords: flavones; 2′-hydroxychalcone; ammonium iodide; solvent-free; *in situ* iodine.

INTRODUCTION

There are a number of environmental implications for the use of large volumes of organic solvents since they are utilized in larger quantities than the solutes they carry and are transferred into the environment through evaporation and leakage. Due to the increasing concern for the harmful effects of organic solvents on the environment and human body, organic reactions that are conducted without conventional organic solvents have aroused the attention of organic chemists. Many organic reactions have been reported to proceed efficiently under solvent-free conditions and some showed enhanced selectivity.[1]

Therefore, the synthetic endeavors of more and more chemists are devoted toward nature-friendly syntheses[2a] and to reduce the drastic prerequisites of reactions. Thus, a paradigm shift from using solvents toward solvent-free reactions not only simplifies organic syntheses but also improves process conditions for large-scale syntheses. Therefore, it is now often claimed that “the best solvent is no solvent”.[2b]

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Flavonoids are a group of low molecular weight compounds mainly occurring in the plant kingdom and flavones constitute a major class among the flavonoids. This class of molecules has been extensively investigated and 4000 chemically unique flavonoids have been isolated from plants.[3] They continue to attract a great deal of attention as they possess biological activities, such as antioxidant effects,[4] antiviral,[5] and leishmanicidal activity,[6] ovipositor stimulant of phytoalexins,[7] anti-HIV,[8] vasodilator,[9] bactericidal,[10] DNA cleavage,[11] anti-inflammatory,[12] antimutagenic,[13] anti-allergic[14] and anticancer.[15–18] Especially, flavones (2-phenylchromones) exhibit a wide variety of activities.[19]

The main known synthetic methods for obtaining flavones are oxidative cyclization of 2′-hydroxychalcones,[20] the cyclodehydration of 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione[21] and *via* an intermolecular Wittig reaction.[22] Reagents that have been used for the oxidation of 2′-hydroxychalcones and flavanones to obtain flavones are SeO_2–pentan-1-ol,[20] Pd–C/vacuum,[22] I_2–DMSO,[23] SeO_2–DMSO,[24] 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)–dioxane,[25] $NaIO_4$––DMSO,[26] nickel peroxide–dioxane,[27] H_2O_2–NaOH,[28] Dowex H^+–2-propanol,[23a,29] SeO_2–dioxane,[30] SeO_2–3-methyl-1-butanol (isoamyl alcohol),[31] Br_2––NaOH,[32] $Tl(NO_3)_3{\cdot}3H_2O$[33] and I_2–triethylene glycol.[34]

Most of these methods are of limited use as they suffer from low yields and often afford a mixture of products containing flavones, flavanones and aurones.[18] Furthermore, these procedures require prolonged reaction times, use of harsh organic solvents, high temperatures, expensive catalysts or hazardous reaction conditions. Hence, there is scope for the development of new methods for the synthesis of flavones using easily available, inexpensive and eco-friendly reagents.

Synthesis of flavones from 2′-hydroxychalcone using iodine in dimethyl sulfoxide is reported in the literature.[23] However, molecular iodine is highly corrosive, toxic and expensive, making its use somewhat unattractive. In order to overcome the problems associated with molecular iodine, herein, for the first time, the oxidative cyclization of 2′-hydroxychalcones to flavones by *in situ* generated iodine from ammonium iodide in the presence of air under solvent-free conditions is reported. However, the use of ammonium iodide in organic synthesis is very rare; it is used in the iodination of aromatic compounds with ozone as the oxidizing agent.[35] Recently there was a report on the use of ammonium iodide and H_2O_2 in organic synthesis for iodination of ketones and aromatic compounds, and dethioacetalization.[36] In continuation of ongoing interest in the development of novel synthetic methodologies, particularly of carbon–carbon and carbon–heteroatom bond formation of biologically relevant heterocycles,[37] brief findings are reported herein on the use of ammonium iodide in the oxidative cyclization of 2′-hydroxychalcone to flavones.

EXPERIMENTAL

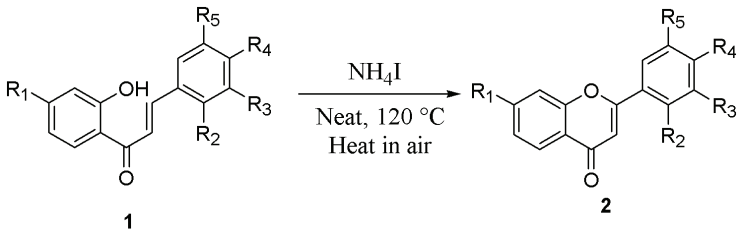
2′-Hydroxychalcones (**1a**–**q**) were prepared by base-catalyzed condensation between 2-hydroxyacetophenone and the appropriate benzaldehyde using a literature procedure.[38] 2-Hydroxyacetophenone, substituted benzaldehydes, ammonium iodide and solvents were purchased from Loba Chemicals, Merck and Sigma–Aldrich. Progress of the reaction was monitored by TLC. All the yields were calculated after purification of the products by column chromatography using EtOAc:petroleum ether (1:4, boiling range 40–60 °C) on silica gel. The melting points of the compounds were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded at room temperature on Bruker AC-250 spectrometers using TMS as an internal standard.

*General procedure for the preparation of flavones (**2a**–**q**)*

A mixture of 1.0 mmol of **1** (2′-hydroxychalcone) and ammonium iodide (0.1 mmol) was heated in air under neat condition at 120 °C for 1 h. After completion of the reaction, the reaction mixture was cooled to room temperature and poured into 20 mL water. The formed precipitate was filtered, washed with 10 % sodium thiosulfate (3×10 mL) and then with 5 mL ice-cold ethanol. The crude product obtained was purified by column chromatography (silica gel, ethyl acetate–petroleum ether (1:4)) to give pure flavone (**2**).

RESULTS AND DISCUSSION

Ammonium iodide gradually turns yellow on standing in moist air, owing to decomposition with liberation of iodine[39] and this was utilized for the oxidative cyclization of 2′-hydroxychalcones to their corresponding flavones (Scheme 1).



1 2

Scheme 1. Synthesis of flavones using NH_4I.

For this purpose, 2′-hydroxychalcones (**1a**–**q**) were synthesized using easily accessible starting materials, substituted 2-hydroxyacetophenones and electronically divergent benzaldehydes in good to excellent yields in presence of base.[38] It was observed that 1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (1 mmol, **1a**) when heated with a solution of ammonium iodide (10 mol %) in DMSO at 120 °C becomes transformed to the corresponding flavone (**2a**) in 1 h in good yield (88 %). The reaction was monitored by TLC and the structure of product was confirmed by spectroscopic data. The ^{1}H-NMR spectra of **2a** showed a singlet at 6.86 due to 1H of 3H, *i.e.*, pyrone ring, which is the characteristic singlet for flavones. Such observed ^{1}H-NMR data and the complete absence of a peak near 12.73 ppm due to an *ortho*-hydroxy group is in agreement with the oxidation of the

chalcone into the corresponding flavone. Among the solvents screened for optimum conditions for the transformation, DMSO was found to be the most suitable, as is obvious from the data presented in Table I. Of the tested solvents, ethanol (reflux) and diethylene glycol (120 °C) gave poor or no yields. The same reaction was explored under neat conditions and, to our utmost satisfaction, product **2a** was obtained in a good isolated yield (92 %).

TABLE I. Cyclization of 2′-hydroxychalcone in different solvents using ammonium iodide; reaction conditions: 2′-hydroxychalcone (1 mmol), NH_4I (0.1 mmol)

Entry	Solvent	Time, h	Yield[a], %	Product
1	DMSO	1	88	Flavone (**2a**)
2	DMF	4	72	Unidentified compound
3	EtOH	12	10	Flavone (**2a**)
4	Diethylene glycol	12	0	No reaction
5	Solvent free	1	92	Flavone (**2a**)

[a]Isolated yield

In the absence of NH_4I, only the starting materials were isolated from the reaction mixture, even after 12 h. This indicates that the reagent exhibits high catalytic activity in this transformation. In order to evaluate the most appropriate reagent loading, the above test reaction was performed using 5, 10 and 20 mol % of NH_4I under solvent-free conditions. It was found that 10 mol % of the reagent showed maximum yield in the minimum time at 120 °C. Further increasing of the reagent loading did not affect the yield.

Having optimized the reaction parameters (10 mol % NH_4I, heating at 120 °C in open air under neat conditions), this methodology was extended to the other 2′-hydroxychalcones and the results are presented in Table II. The substituents on B ring of 2′-hydroxychalcones were varied from electron donating to electron withdrawing and in all the cases, the studied the transformation went smoothly to yield the corresponding flavones in good yield.[40] Contrary to previously reported methods, this procedure tolerates a wide range of substituents, such as methyl, chloro, methoxy, bromo, hydroxyl, *N*,*N*-dimethylamino and nitro. Generally, it was observed that oxidation of substrates with unprotected hydroxyl groups on the aromatic rings gave poor yields. However, it was found that this new reagent is equally suitable and efficient for the oxidation of such derivatives (entries 15 and 16).

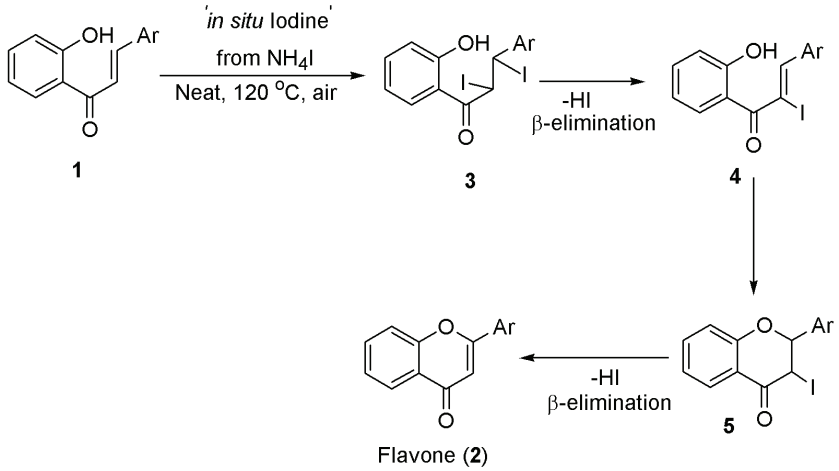
The mechanism of this reaction is still not clear. However, the reaction pathway shown in Scheme 2 is tentatively proposed. Initially, electrophilic addition of iodine to the enone to form **3**, followed by elimination of HI with oxidative cyclization yielding **5**. A β-elimination of HI from **5** gave flavone **2**. In support of this mechanism, the model reaction on a relatively larger scale (10 mmol) was performed and during the course of reaction, the pH of aqueous layer was

measured. The pH was found to be acidic, confirming thereby the elimination product to be HI.

TABLE II. Cyclization of 2′-hydroxychalcone to flavones using NH_4I under solvent free conditions; reaction conditions: 2′-hydroxychalcone (1 mmol), NH_4I (0.1 mmol) under neat condition

Entry	Chalcone	R^1	R^2	R^3	R^4	R^5	Flavone	Yield[a], %	M.p., °C
1	**1a**	H	H	H	H	H	**2a**	92	97[40a]
2	**1b**	H	H	H	OMe	H	**2b**	89	157[40a]
3	**1c**	H	H	OMe	OMe	OMe	**2c**	82	174[40a]
4	**1d**	H	H	H	Cl	H	**2d**	94	189[40b]
5	**1e**	H	H	H	Me	H	**2e**	79	110[40c]
6	**1f**	H	H	OMe	OMe	H	**2f**	82	154[40d]
7	**1g**	H	H	OMe	H	H	**2g**	78	132[40e]
8	**1h**	H	Cl	H	H	H	**2h**	74	118[40f]
9	**1i**	H	Cl	H	Cl	H	**2i**	81	172[40i]
10	**1j**	H	H	H	NO_2	H	**2j**	75	242[40j]
11	**1k**	OMe	H	H	OMe	H	**2k**	79	143[40k]
12	**1l**	H	OMe	H	OMe	H	**2l**	84	95[40k]
13	**1m**	H	H	H	Br	H	**2m**	91	177[40l]
14	**1n**	H	H	Br	H	H	**2n**	93	115[40m]
15	**1o**	OH	H	H	H	H	**2o**	71	240[40g]
16	**1p**	OH	H	H	OMe	H	**2p**	67	264[40h]
17	**1q**	H	H	H	NMe_2	H	**2q**	72	192[40n]

[a]Isolated yield after purification



Scheme 2. Possible mechanism of flavone synthesis using NH_4I *via* oxidative cyclization.

CONCLUSIONS

In conclusion, an efficient general method for the conversion of 2′-hydroxychalcones to the corresponding flavones using *in situ* generated iodine is

reported. The products were obtained in a shorter time, in high yields, and employed a less hazardous and inexpensive reagent than molecular iodine. Other attributes include its applicability to substrates bearing electron donating and electron withdrawing as well as a free hydroxyl group on the B ring of chalcones. Thus, this methodology would serve as attractive alternative to the use of toxic molecular iodine.

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И З В О Д

ЦИКЛИЗАЦИЈА 2′-ХИДРОКСИХАЛКОНА ДО ФЛАВОНА УПОТРЕБОМ АМОНИЈУМ-ЈОДИДА КАО ИЗВОРА ЕЛЕМЕНТАРНОГ ЈОДА – ЕКОЛОШКИ ПРИХВАТЉИВ ПРИСТУП

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Амонијум-јодид се у присуству ваздуха разлаже на амонијак и елементарни јод. Генерисан *in situ* у реакционој смеши, јод омогућава циклизацију 2′-хидроксихалкона до одговарајућих флавона, у одсуству растварача, у одличном приносу. Поступак се може користити као добра алтернатива постојећим методама синтезе флавона.

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