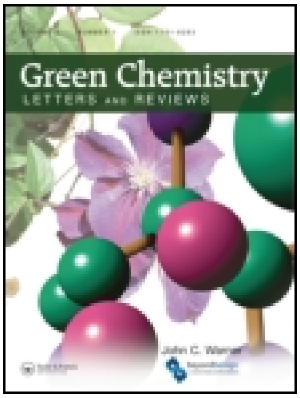

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RESEARCH LETTER

IBX promoted one-pot condensation of β-naphthol, aldehydes, and 1,3-dicarbonyl compounds

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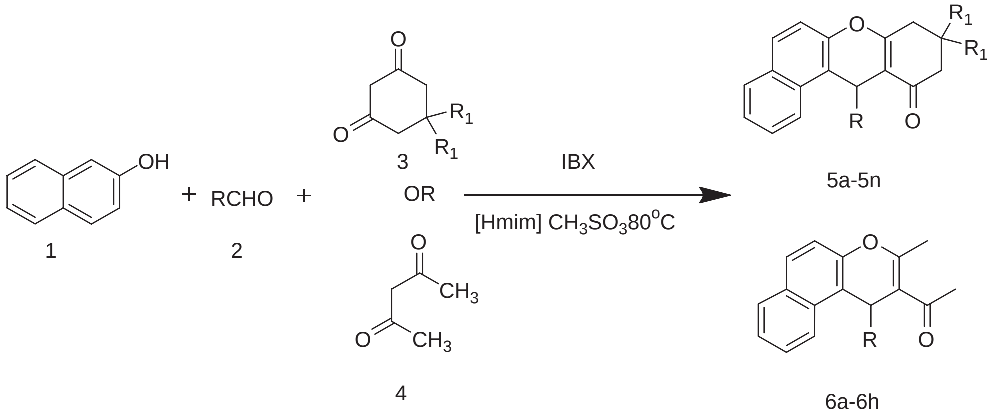
An efficient and mild protocol has been developed for one-pot condensation of *β*-naphthol, aldehydes, and 1,3-dicarbolyl compounds in presence of *o*-iodoxybenzoic acid has been found to be an excellent catalyst for the synthesis of tetrahydrobenzo[a]xanthen-one, 1*H*-benzo[*f*]chromen-2-yl)-one via one-pot three-component condensation of β-naphthol, aldehydes, and 1,3-dicarbonyl compounds. Short reaction time, ambient conditions, simple workup, and high yield with selective manner are some of the striking features of the present protocol.



Keywords: *o*-iodoxybenzoic acid; multicomponent reaction; benzoxanthenes; benzochromenone; *β*-naphthol; aldehydes; 1,3-dicarbonyl compounds; ionic liquid

Introduction

Multicomponent reaction (MCR) is the tool in the synthesis of molecular libraries with high degree of structural diversity. They have gained importance because of their merits over two-component reactions, including the simplicity of a one-pot procedure and wide variety of applications in organic, medicinal chemistry (*1*), and in drug discovery as well as "green chemistry" (*2*). MCRs are one-pot processes in which three or four easily accessible components react to form a single product without isolation of any intermediate (*3*). Recently, there has been tremendous development in three- and four-component reactions viz. Biginelli (*4*), Ugi (*5*), Passerini (*6*), Bucherer-Bergs (*7*) and Mannich (*8*) reactions. Nevertheless, the development and discovery of new MCR's is still in demand.

Molecules with heterocyclic structures are attractive targets for synthesis since they often exhibit diverse and important biological properties. Xanthenes, benzoxanthenes, and benzochromenone have been reported to possess anti-inflammatory (*9*), antiviral (*10*), and antibacterial (*11*) activities. Some of them have been used as antagonists for paralyzing the action of zoxazolamine (*12*) and in photodynamic therapy (*13*). Furthermore, these compounds can be used as dyes (*14*), pH-sensitive fluorescent materials for the visualization of biomolecular assemblies (*15*), and in laser technologies (*16*). Therefore, the

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synthesis of xanthenes and chromen derivatives is of prime interest. The synthesis of tetrahydrobenzo[a]xanthen-ones has been reported in the presence of $Sr(OTf)_2$ (*17*), $NaHSO_4$-SiO_2 (*18*), TBAF (*19*), and solvent-free condition (*20*). However, despite the potential utility of these catalysts, many of these methodologies are associated with several shortcomings, such as use of organic solvent, longer reaction time, low yield of the product, etc. Therefore, the development of a cost-effective, safe, and environment friendly reagent system is highly desirable.

Hypervalent iodine reagents have attracted increasing interest during the past decade owing to their selective, mild, and environment friendly properties as oxidizing agents in organic synthesis (*21*). *o*-iodoxybenzoic acid (IBX) has gained great popularity as a mild oxidant for the conversion of alcohols to aldehydes or ketones (*22*). In the past few years, an explosive growth has occurred in the demonstration and use of IBX as a selective reagent for dehydrogenation of *N*-heterocycles to heteroaromatics, oxidative cleavage of dithioacetals and dithioketals, and selective deprotection of triethylsilyl ethers in the presence of tert-butyldimethylsilyl (TBDMS) ethers (*23*) that also have relatively low toxicity (*24*).

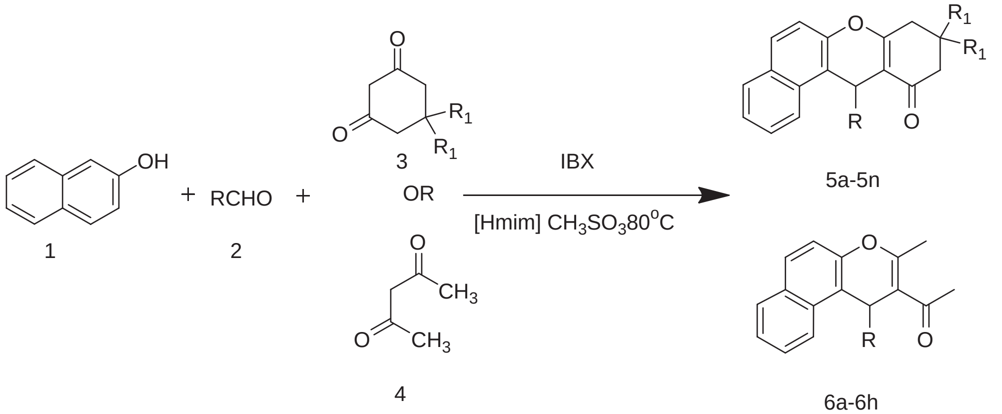
Thus, considering the above reports, advantages and applications of IBX, and as part of our ongoing project to explore the green methodologies for organic transformations (*25–27*), we hereby report the effective and practical one-pot three-component synthesis of tetrahydrobenzo[a]xanthen-ones, 1*H*-benzo[*f*]chromen-2-yl)-one derivatives via condensation reaction between *β*-naphthol, aldehydes, and 1,3-dicarbonyl compounds in the presence of IBX in ionic liquid (3-methylimidazolinium methane sulfonated) as ‘‘green’’ recyclable substitute to the traditional volatile organic solvents at 80°C (Scheme 1). Ionic liquids experienced impetus in recent years. Their negligible vapor pressure makes them easily confinable and also enables an easy recyclability. Moreover, the solvophobic properties of ionic liquids are able to generate an internal pressure and promote the association of reactants in the solvent cavity during the activation process (*28*). Thus, ionic liquids are well suited as reaction media for MCRs in which the entropy of the reaction is decreased in the transition state.

Results and discussion

In order to elucidate the role of the solvents, various solvents were used to evaluate the scope and limitations of the reaction. After screening different solvents, it was found that the best solvent in terms of fast conversion and quantified yield is ionic liquid (Table 1).

A possible mechanism was outlined in Scheme 2. The ortho-quinone methide intermediate is formed by the nucleophilic addition of 2-naphthol to aldehyde in presence of IBX catalyst. Michael addition of ortho-quinone methides with 1,3-dicarbonyl compounds formed cyclic hemiketal which on dehydration afforded the corresponding products.

To investigate the feasibility of this synthetic methodology for above transformation, we have extended the reaction of β-naphthol and 1,3-dicarbonyl compounds with various aldehydes under similar conditions to furnish the respective tetrahydrobenzo[a]xanthen-ones and 1*H*-benzo[*f*]chromen-2-yl)-one derivatives in high yields. The optimized results are summarized in Table 2. In absence of IBX, the reactions proceeded with moderate yields (70–76%) of the products.



Scheme 1. Synthesis of tetrahydrobenzo[a]xanthen-ones, 1*H*-benzo[*f*]chromen-2-yl)-one derivatives.

Table 1. Solvent effect on the preparation of tetrahydrobenzo[a]xanthen-ones, 1*H*-benzo[*f*]chromen-2-yl)-one derivative.[a]

Entry	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	Water	90	8	13
2	Methanol	55	5	25
3	Ethanol	75	5	15
4	Chloroform	55	4	64
5	Dichloromethane	35	4	69
6	DMF	120	4	73
7	Acetonitrile	75	6	20
8	None	100	10	Trace
9	[Hmim]CH_3SO_3	80	1	97
10	Toluene	100	7	65

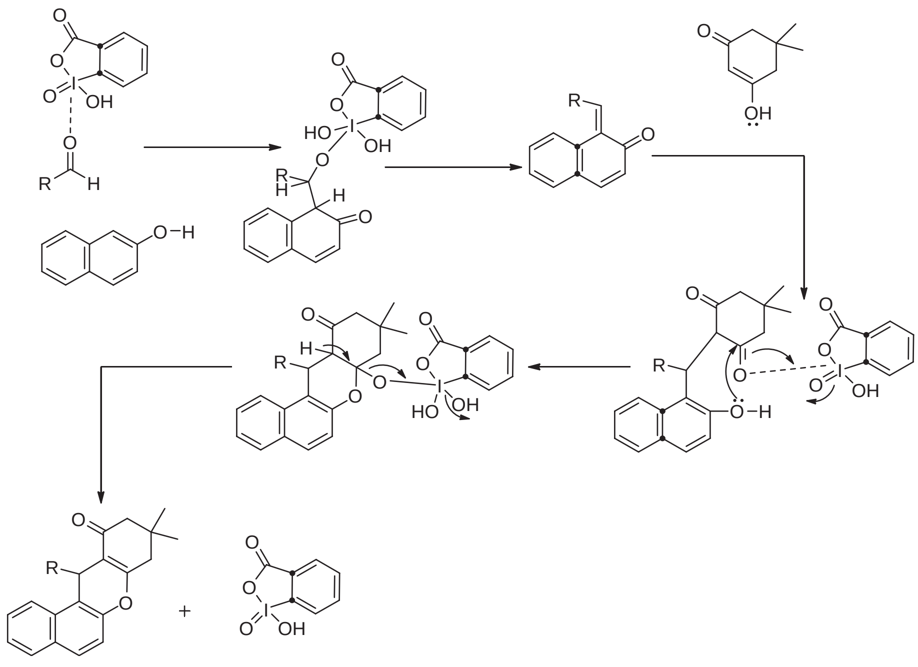
[a] Reaction condition: β-naphthol (1mmol), benzaldehyde (1mmol), cyclohexane1,3-dione (1.2 mmol), IBX (10 mol%), and solvent (5 mL).
[b] Yield: isolated.

The results of Table 2 clearly indicate the feasibility of three-component reaction in ionic liquid. The method has the ability to tolerate a variety of functional groups, such as bromo-, chloro-, nitro-, and methoxy-. The products were synthesized in good to excellent yields and characterized by ^{1}H NMR, ^{13}C NMR, mass, and physical constants. Physical and spectral data of known compounds are in agreement with those reported in the literature (*17–20*).

Recovery and reusability of the solvent is demanded for an eco-friendly process. In this protocol, we used recyclable ionic liquid as a solvent. After completion, the reaction was allowed to cool at room temperature and the product was extracted with diethyl ether to separate the ionic liquid with IBX from the reaction mass. The crude product was purified using column chromatography to yield tetrahydrobenzo[a]xanthen-ones (*5*), 1*H*-benzo[*f*]chromen-2-yl)-one (*6*) derivatives. After completion of reaction, ionic liquid with IBX was recovered (95%) and further reused for two more processes.

Experimental

All commercial reagents were used as received without purification and all solvents were reagent grade.



Scheme 2. Possible mechanism for the condensation reaction between aldehyde, 2-naphthol, and 1,3-dicarbonyl compounds.

Table 2. Synthesis of tetrahydrobenzo[a]xanthen-ones, 1*H*-benzo[*f*]chromen-2-yl)-one derivatives.

Entry	R	R_1	Product	Yield[b] (%) A	Yield[b] (%) B
1	C_6H_5	H	**5a**	71	92
2	2-BrC_6H_4	H	**5b**	76	97
3	4-BrC_6H_4	H	**5c**	72	95
4	4-$NO_2C_6H_4$	H	**5d**	70	94
5	4-$CH_3C_6H_4$	H	**5e**	70	93
6	4-$CH_3OC_6H_4$	H	**5f**	69	90
7	C_6H_5	CH_3	**5g**	69	91
8	2-BrC_6H_4	CH_3	**5h**	75	97
9	4-BrC_6H_4	CH_3	**5i**	71	92
10	4-$NO_2C_6H_4$	CH_3	**5j**	73	93
11	4-$CH_3C_6H_4$	CH_3	**5k**	68	90
12	4-$CH_3OC_6H_4$	CH_3	**5l**	64	88
13	CH_3-CH_2	CH_3	**5m**	66	89
14	$(CH_3)CH$	CH_3	**5n**	67	91
15	C_6H_5	–	**6a**	63	88
16	2-BrC_6H_4	–	**6b**	71	93
17	3-$NO_2C_6H_4$	–	**6c**	67	90
18	4-$NO_2C_6H_4$	–	**6d**	67	92
19	4-$CH_3C_6H_4$	–	**6e**	73	93
20	4-$CH_3OC_6H_4$	–	**6h**	70	90

[a] Yield: isolated.

Note: Reaction condition for A: *β*-naphthol (1mmol), aldehydes (1mmol), 1,3-dicarbonyl compounds (1.2 mmol), and ionic liquid (5 mL); temperature: 80°C; time: 1 h. Reaction condition for B: *β*-naphthol (1mmol), aldehydes (1mmol), 1,3-dicarbonyl compounds (1.2 mmol), IBX (10 mol%), and ionic liquid (5 mL); temperature: 80°C; time: 1 h.

The reaction was monitored by TLC using 0.25 mm E-Merck silica gel 60 F254 precoated plates, which were visualized with UV light. Melting points were taken in open capillaries. The IR spectra were recorded on a PerkinElmer 257 spectrometer using KBr discs. ^{1}H NMR and ^{13}C NMR spectra were recorded on a VXR-300 MHz instrument using TMS as an internal standard.

General experimental procedure

A mixture of β-naphthol (1 mmol), aldehydes (1 mmol), 1,3-dicarbonyl compounds (1.2 mmol), and IBX (10 mol%) in ionic liquid (5 mL) was heated at 80°C for 1 h. After completion, the reaction was allowed to cool at room temperature and the product was extracted with diethyl ether to separate the ionic liquid and IBX from the reaction mass. Diethyl ether layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to isolate the product. The crude product was purified using column chromatography.

Representative spectral data for products

Compound ***(5i)***. ^{1}H NMR (DMSO-d_6): δ 7.80 (d, 1H), 7.70–7.76 (m, 2H), 7.40–7.45 (m, 2H), 7.29–7.35 (m, 3H), 7.18–7.23 (m, 2H), 5.63 (s, 1H), 2.53 (s, 2H), 2.29 (d, $J = 12$ Hz, 1H), 2.24 (d, J = 12 Hz, 1H), 1.12 (s, 3H), 1.0 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 197, 164, 148.6, 144, 132, 131.5, 131, 130.2, 129.4,129, 127, 125, 124, 120.1, 117, 116.8, 114, 51, 41.2, 34, 32, 30.1, 28; IR (KBr): 2960, 1657, 1600, 1375, 1231, 1190; MS: 433, 435 [M + 2].

Conclusion

We have demonstrated an efficient and versatile one-pot method for the synthesis of tetrahydrobenzo[a]xanthen-ones, 1*H*-benzo[*f*]chromen-2-yl)-one derivatives via cyclocondensation reactions of β-naphthol, aldehydes, and 1,3-dicarbonyl compounds catalyzed by IBX in ionic liquid ([Hmim]CH_3SO_3). The process has several advantages from economical and environmental point of view, such as easy workup, fast reaction rates, mild reaction conditions, and good yields, which made the method an attractive and a useful contribution to the present methodologies.

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