



Full paper/Mémoire

Microwave-assisted green synthesis of dibenzo[*a,j*]xanthenes using *p*-dodecylbenzenesulfonic acid as an efficient Bronsted acid catalyst under solvent-free conditions

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ABSTRACT

The *p*-dodecylbenzenesulfonic acid (DBSA) has been successfully applied as an efficient acidic catalyst for the microwave-assisted synthesis of a series of 14-aryl- or alkyl-14*H*-dibenzo[*a,j*]xanthenes (**3a-m**) via a one-pot condensation-cyclization reaction of β -naphthol with various aliphatic or aromatic aldehydes under solvent-free conditions. Operational simplicity, short reaction times, excellent yields and environmentally-benign conditions are other advantages of this protocol.

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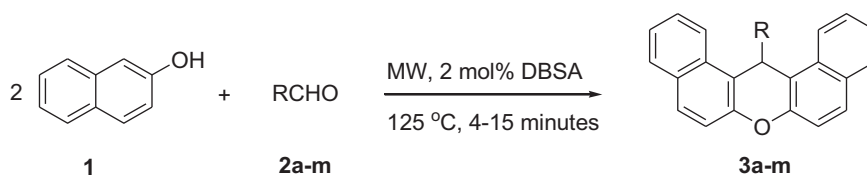
1. Introduction

Xanthenes are pharmaceutically useful oxygen heterocycles that occupy an important place in the realm of medicinal and material chemistry. They are known to exhibit a wide range of biological properties such as antibacterial [1], anti-proliferative [2], anticancer [3], anti-inflammatory [4], antiviral agents [5] and photosensitizers in photodynamic therapy for the treatment of localized tumours [6]. In addition, various xanthene derivatives have also been utilized as fluorescent dyes [7], pH-sensitive fluorescent materials for the visualization of bio-molecular scaffolds [8], substrates for the construction of heteroatoms containing positively charged polycyclic aromatic hydrocarbons [9] and in laser technology [10]. Consequently, the synthesis of various xanthene derivatives has drawn notable attention. A number of diverse approaches are available for the synthesis of these molecules such as intramolecular

trapping of benzynes by phenols [11], reaction of aryloxymagnesium halides with triethylorthoformate [12], condensation of primary alcohols with resorcinol [13], heating of sodium or potassium 2-naphthyl oxide under CO and CO₂ pressure [14] or condensation cyclization reaction of salicylaldehydes with 2-tetralone [15]. However, the synthesis of dibenzoxanthenes via one-pot condensation of β -naphthol with aldehydes has been widely studied. This reaction has been catalyzed by a wide range of catalysts including pTSA [16], P₂O₅/Al₂O₃ [17], ruthenium chloride hydrate [18], ionic liquids [19], methanesulfonic acid [20], LiBr [21], silica sulphuric acid [22], K₅CoW₁₂O₄₀·3H₂O [23], HClO₄ [24], sulfamic acid [25], alum [26], In(OTf)₃ [27], or Sc[N(SO₂C₈F₁₇)₂]₃ [28] etc. Though each of above mentioned methods has demonstrated its own merits, several of these protocols suffer from one or more drawbacks such as prolonged reaction times, use of hazardous solvents, necessity of excess reagents or catalysts, harsh reaction conditions or low yields of the desired products. Hence, there is a scope for the development of an efficient, economical and eco-friendly synthetic strategy for the preparation of these important heterocyclic molecules.

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Scheme 1.

In recent years, *p*-dodecylbenzenesulfonic acid (DBSA) has gained considerable popularity as an efficient Bronsted-acid surfactant combined catalyst for carrying out various organic transformations in water as well as under solvent-free conditions [29]. Additionally, the microwave-accelerated synthesis has been recognized in constituting eco-friendly protocols as it offers several advantages such as high efficiency, short reaction times, minimum energy consumption, high yields and better purity of the products [30]. Hence, the combination of a catalytic system with microwave irradiation under solvent-free conditions could afford an entirely greener approach to assemble diverse biologically relevant compounds in short reaction times [31]. Keeping this in mind, we envision the possibility to synthesize dibenzoxanthenes in the presence of a catalytic amount of DBSA using microwave irradiation under solvent-free conditions. To the best of our knowledge, DBSA has not been employed yet to synthesize 14-aryl- or alkyl-14*H*-dibenzo[*a,j*]xanthenes under solvent-free microwave conditions.

In continuation of our ongoing work to develop eco-friendly methods [32] for the synthesis of various bioactive heterocycles, we wish to report herein a microwave-assisted green protocol for the synthesis of 14-aryl- or alkyl-14*H*-dibenzo[*a,j*]xanthenes through one-pot condensation of β -naphthol with alkyl or aryl aldehydes in the presence of DBSA as an efficient Bronsted acid catalyst at 125 °C under solvent-free conditions (Scheme 1).

2. Results and discussion

Previously, Jin et al. [33] have synthesized 14-aryl- or alkyl-14*H*-dibenzo[*a,j*]xanthenes in aqueous medium by using DBSA as an acidic catalyst under conventional heating conditions but the reported procedure is restricted to using the higher load of catalyst (20 mol% DBSA) to generate the desired products after prolonged heating (16–24 h) at reflux temperature. In contrast, the present methodology requires only 2 mol% DBSA to afford various 14-aryl- or alkyl-14*H*-dibenzo[*a,j*]xanthenes in good to excellent yields (78–99%) within 4–15 min under solvent-free microwave conditions.

To obtain the optimum conditions for the synthesis of these molecules, we initiated our investigation by heating β -naphthol and benzaldehyde as model substrates at 125 °C in the presence of 2 mol% DBSA under solvent-free conditions. Interestingly, the reaction afforded the corresponding 14-phenyl-14*H*-dibenzo[*a,j*]xanthene (**3a**) in 90% isolated yield after 180 min (Table 1, entry 1). In contrast, the reaction performed under microwave irradiation provided the desired product (**3a**) in quantitative

Table 1

Optimization of the reaction conditions for microwave-assisted synthesis of 14-phenyl-14*H*-dibenzo[*a,j*]xanthene (**3a**) under solvent-free conditions.

Entry	Catalyst	Catalyst load (mol%)	Temperature (°C)	Time (min)	Yield (%) ^a
1	DBSA	2	125	180	90 ^b
2	DBSA	2	125	4	99
3	–	–	125	30	NR
4	DBSA	2	100	4	82
5	DBSA	2	80	4	37

NR: no reaction; DBSA: *p*-dodecylbenzenesulfonic acid.

^a Isolated yields.

^b Conventional heating.

yield within 4 min (Table 1, entry 2). Indeed, no product formation was observed even after 30 min in the absence of the catalyst under microwave irradiation (Table 1 entry 3), indicating the crucial role of DBSA in the synthesis of dibenzoxanthenes. Furthermore, the effect of temperature on the rate of reaction was examined. We found that 125 °C is the optimal temperature and the reaction was incomplete at lower temperatures (Table 1, entries 4 and 5). Hence, 2 mol% DBSA at 125 °C temperature was chosen as optimal catalyst load to carry out the solvent-free synthesis of target dibenzoxanthene derivatives under microwave irradiation.

After optimization, the scope and generality of this condensation reaction was investigated by synthesizing a series of 14-aryl- or alkyl-14*H*-dibenzo[*a,j*]xanthenes (**3a–m**) via microwave-assisted one-pot condensation of β -naphthol with various alkyl or aryl aldehydes at 125 °C temperature under solvent-free conditions. All the desired products were obtained in good to excellent yields (78–99%) with high purity within 4–15 min (Table 2). In general, the reaction proceeded well with high rate of conversion in the case of benzaldehyde or aryl aldehydes having electron withdrawing substituents such as F, Br and NO₂ on the *meta*-position of aromatic ring (Table 2, entries 1–4) while the aromatic aldehyde bearing electron donating substituent such as CH₃ afforded comparatively lower yield of the desired product **3e** (Table 2, entry 5). On the other hand, the sterically hindered *ortho*-substituted aryl aldehydes reacted with slow rate in comparison to *meta*-substituted aromatic aldehydes to afford the corresponding products (**3f–h**) in 90–95% yields (Table 2, entries 6, 7 and 8). In addition, *p*-formylbenzaldehyde and less reactive aliphatic aldehydes provided the desired dibenzoxanthenes (**3i–m**) in slightly lower yields (Table 2, entries 9–13).

Furthermore, the catalytic potential of DBSA was compared with other reported catalysts for the synthesis

Table 2

p-dodecylbenzenesulfonic acid (DBSA) catalyzed, microwave-assisted one-pot condensation of β -naphthol with aryl or alkyl aldehydes at 125 °C under solvent-free conditions.

Entry	R	Products	Time (min)	Yields (%) ^a
1	C ₆ H ₅	3a	4	99
2	3-FC ₆ H ₄	3b	4	99
3	3-BrC ₆ H ₄	3c	4	99
4	3-NO ₂ C ₆ H ₄	3d	4	99
5	3-CH ₃ C ₆ H ₄	3e	4	93
6	2-CH ₃ C ₆ H ₄	3f	4	90
7	2-BrC ₆ H ₄	3g	4	90
8	2-CF ₃ C ₆ H ₄	3h	4	95
9	4-CHOC ₆ H ₄	3i	4	84
10	CH ₃ CH ₂ CH ₂	3j	15	80
11	(CH ₃) ₂ CH	3k	15	89
12	CH ₃ CH ₂	3l	15	78
13	CH ₃ (CH ₂) ₇	3m ^b	15	86

^a Isolated yields after chromatographic purification.

^b Oil.

of 14-phenyl-14*H*-dibenzo[*a,j*]xanthene (**3a**) under microwave irradiation. It is evident from Table 3 that DBSA has demonstrated relatively comparable catalytic efficiency with K₅CoW₁₂O₄₀·3H₂O (Table 3, entries 4 and 7) while it can be considered as a better catalyst than *n*-Bu₄NBr, methanesulfonic acid, LiBr and sulfamic acid for the synthesis of **3a** under solvent-free microwave conditions.

3. Conclusion

In summary, we have demonstrated an efficient, economical and eco-friendly protocol for the synthesis of various 14-aryl- or alkyl-14*H*-dibenzo[*a,j*]xanthenes under solvent-free conditions. A variety of aromatic and aliphatic aldehydes reacted successfully with β -naphthol to afford the desired products in good to excellent yields. The notable features of the present methodology include operational simplicity, short reaction times, high yields of the products and the release of water as the only byproduct during the reaction.

Table 3

Comparative study of catalytic potential of *p*-dodecylbenzenesulfonic acid (DBSA) with other reported catalysts for the synthesis of 14-phenyl-14*H*-dibenzo[*a,j*]xanthene (**3a**) under microwave irradiation.

Entry	Catalysts	Catalyst load (mol%)	Temperature (°C)	Time (min)	Yields (%) ^a
1	<i>n</i> -Bu ₄ NBr	10	130	4	94 ^[19]
2	Methanesulfonic acid	10	125	2	86 ^[20]
3	LiBr	15	130	4	83 ^[21]
4	K ₅ CoW ₁₂ O ₄₀ ·3H ₂ O	1	125	2	89 ^[23]
5	Sulfamic acid	4	125	2.5	95 ^[25]
6	DBSA	2	125	4	99 ^b
7	DBSA	2	125	2	95 ^b

^a References.

^b Present work.

4. Experimental

All the chemicals were purchased from Sigma-Aldrich and used without further purification. The progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel 60 F₂₅₄ (pre-coated aluminium sheets) from Merck. TLC spots were visualized by UV-light followed by iodine. NMR spectra were obtained in CDCl₃ or DMSO-*d*₆ on Jeol ECX 400 MHz NMR spectrometer and chemical shifts are expressed in parts per million (ppm). Infrared spectra were recorded on Perkin Elmer IR spectrometer and absorption maxima (ν_{\max}) are given in cm⁻¹. The melting points were determined in open capillary tubes on Buchi M-560 melting point apparatus and are uncorrected. Microwave reactions were carried out in a CEM Discover Microwave by using standard 10 mL Pyrex microwave tube at medium stirring mode.

4.1. General procedure for the synthesis of 14-aryl- or alkyl-14*H*-dibenzo[*a,j*]xanthenes (**3a–m**)

A mixture of β -naphthol (2 mmol), alkyl or aryl aldehydes (1 mmol) and DBSA (0.02 mmol) was irradiated in a sealed 10 mL Pyrex microwave tube at preset 300 W power, 100 psi pressure and 125 °C temperature for 4–15 min. During the reaction, the power was varied between 117 and 135 W and no pressure was developed. After compressed air cooling to room temperature, a saturated aqueous solution of NaHCO₃ (5 mL) and brine (5 mL) were added to the reaction mixture. The aqueous solution was extracted with ethyl acetate (10 mL × 3) and the combined organic layers were dried over anhydrous Na₂SO₄ and evaporated under vacuum to dryness. The crude products were purified on silica gel (60–120 mesh size) column by using 1% ethyl acetate in heptane as eluent to afford the pure products (**3a–m**).

All the synthesized compounds are known and their physical and spectral data are found in agreement with the reported data [16,18,21,25,28,34]. The characterization data of two representative compounds (**3g** and **3h**) are given below.

4.1.1. 14-(2-Bromophenyl)-14*H*-dibenzo[*a,j*]xanthenes (**3g**)

White solid; mp 215 °C. IR (CHCl₃): ν = 3058, 1593, 1517, 1459, 1431, 1402, 1250, 1242, 1020, 962, 828, 808, 759, 748 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 8.88 (d, *J* = 8.79 Hz, 2H, ArH), 7.80 (t, *J* = 8.79 Hz, 4H, ArH), 7.64–7.60 (m, 2H, ArH), 7.48 (d, *J* = 8.79 Hz, 2H, ArH), 7.44–7.40 (m, 4H, ArH), 6.98–6.94 (m, 1H, ArH), 6.83–6.79 (m, 1H, ArH), 6.73 (s, 1H, CH) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 148.85, 145.39, 133.03, 132.00, 131.70, 130.84, 129.01, 128.56, 128.42, 128.05, 126.71, 124.35, 124.01, 120.86, 118.25, 118.06, 37.10 ppm; Anal. calcd for C₂₇H₁₇BrO: C, 74.15; H, 3.92. Found: C, 74.45; H, 4.02.

4.1.2. 14-(2-(Trifluoromethyl)phenyl)-14*H*-dibenzo[*a,j*]xanthenes (**3h**)

White solid; mp 247 °C. IR (CHCl₃): ν = 3059, 1584, 1519, 1442, 1379, 1245, 1024, 882, 844, 814, 695 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 8.43 (d, *J* = 8.05 Hz, 2H, ArH), 7.82–7.78 (m, 4H, ArH), 7.61–7.55 (m, 3H, ArH), 7.49

(d, $J = 8.79$ Hz, 2H, ArH), 7.46–7.43 (m, 2H, ArH), 7.40 (d, $J = 8.05$ Hz, 1H, ArH), 7.16 (t, $J = 7.32$ Hz, 1H, ArH), 7.08–7.03 (m, 2H, ArH) ppm; ^{13}C NMR (100 MHz, CDCl_3): $\delta = 149.03, 143.68, 132.44, 132.12, 131.44, 130.90, 129.31, 128.68, 127.59, 127.18$ (q, $^3J_{\text{C-F}} = 4.79$ Hz), 126.73, 125.97 (d, $^2J_{\text{C-F}} = 28.75$ Hz), 125.64 (d, $^1J_{\text{C-F}} = 247.28$ Hz), 124.85, 122.35 (d, $^4J_{\text{C-F}} = 2.88$ Hz), 118.14, 117.99, 33.80 (d, $^4J_{\text{C-F}} = 2.88$ Hz) ppm; Anal. calcd for $\text{C}_{28}\text{H}_{17}\text{F}_3\text{O}_0.24\text{H}_2\text{O}$: C, 78.07; H, 4.09. Found: C, 78.25; H, 4.22.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.crci.2012.05.018>.

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