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Indium Triflate-Catalyzed One-Pot Synthesis of 14-Alkyl or Aryl-14*H*-dibenzo[*a*,*j*]xanthenes in Water

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ABSTRACT: *A mild, efficient, and environment friendly method has been developed for the synthesis of 14-alkyl or aryl-14H-dibenzo[a, j]xanthenes by condensation of 2-naphthol and aldehydes in the presence of a catalytic amount of indium(III) triflate (2 mol%) in water at 100°C. Different types of aromatic and aliphatic aldehydes are used in the reaction, and in all cases the products synthesized in moderate to excellent yields.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:232–234, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20539

INTRODUCTION

Lewis acids promoted organic reactions in water or aqueous media have recently attracted great interest [1]. Water has aroused considerable attention in synthetic community and proved to be a promising solvent in organic synthesis due to its economic, environment friendly, and polar nature [2]. In relation to this, significant efforts have been dedicated to develop organic reactions in water with many inherent advantages over reactions in conventional organic solvents. Generally, typical Lewis acids such as BF_3, $AlCl_3$, $TiCl_4$, and $SnCl_4$ are immediately hydrolyzed by atmospheric moisture, and therefore they should be treated strictly in dry conditions to prevent the loss of their catalytic activities. Because of the increasing awareness of environmental problems in chemical research and industry, water-accessible Lewis acid catalysts have attracted much attention [3]. In the course of our studies to develop a new synthetic methodology based on green synthesis, we have become interested in a Lewis acid catalyst that can be used in pure water, not in aqueous media [4].

Indium(III) compounds have evolved as mild and water-tolerant Lewis acids, imparting high regio-, stereo-, and chemoselectivity in various organic transformations [5]. In contrast to classical Lewis acids, which often are required in stoichiometric quantities, indium(III) compounds readily promote a wide variety of organic reactions in catalytic quantities soluble both in organic solvents and in aqueous media. Particularly, in accordance with the recent surge of interest in moisture-stable metal triflates, $In(OTf)_3$ has emerged as a promising catalyst for various types of organic reactions [6].

The synthesis of xanthenes, especially benzoxanthenes, has been of great interest to chemists because of their wide range of biological and pharmaceutical properties such as antiviral, antibacterial, and anti-inflammatory activities as well as efficiency in photodynamic therapy and antagonists for the paralyzing

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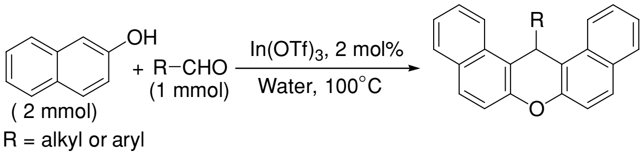


SCHEME 1

action of zoxazolamine [7]. Thus, the synthesis of benzoxanthene derivatives currently is of great interest.

For the synthesis of benzoxanthenes, various methods have been reported including the reaction of β-naphthol with formamide, 2-naphthol-1-methanol, and carbon monoxide [8]. Furthermore, 14*H*-dibenzo[*a,j*]xanthenes and its analogues are prepared by using the condensation reaction of the mixture of 2-naphthol with aldehydes in the presence of a catalyst, such as silica sulfuric acid [9], Dowex-50W [10], $NH_4H_2PO_4$ [11], I_2 [12], sulfamic acid [13], $HClO_4$–SiO_2 [14], PW acid [15], cyanuric chloride [16], $Yb(OTf)_3$ [17], alum [18], and $BF_3.SiO_2$ [19]. However, the above-mentioned catalysts have several disadvantages because they are corrosive, toxic, or volatile and generate large amounts of waste material. Thus, search for eco-friendly catalyst as well as green solvent is highly desirable.

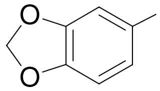
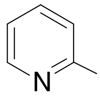
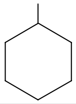
In continuation of our work to apply indium(III) compound as catalyst to organic reactions [20], herein, we report an efficient and environment friendly method for the synthesis of 14-aryl or alkyl-14*H*-dibenzo[*a*, *j*]xanthene derivatives catalyzed by indium triflate in water (Scheme 1).

RESULTS AND DISCUSSION

To study the reaction in water, we tested the reaction of β-naphthol and 4-chlorobenzaldehyde as a simple model substrate in water in the presence of indium triflate (2 mol%) as a nonhazardous and available catalyst. It was found that the condensation reaction was proceeded very well in water, and the desired product obtained in high yield. The structure of the product was settled from the spectral data. Use of just 2 mol% of $In(OTf)_3$ in water is sufficient to push the reaction forward. Higher amount of $In(OTf)_3$ did not improve the result to a great extent. Presumably, the reaction proceeds by the usual mechanism proposed using Lewis acids [17].

After optimizing the reaction conditions, we next examined the generality of this condition to other substrates using several aromatic and aliphatic aldehydes. The results are summarized in Table 1.

TABLE 1 Synthesis of Alkyl or Aryl-14*H*-dibenzo[*a, j*]xanthenes by the Reaction of 2-Naphthol, and Aldehydes in the Presence of 2 mol% $In(OTf)_3$ in Water

Entry	*R*	*Time (h)*	*Yield (%)*[a]
1	C_6H_5	8	82
2	4-Me-C_6H_4	8	82
3	4-OMe-C_6H_4	8	85
4		9	90
5	4-OH-C_6H_4	13	70
6	3-OH-4-OMe-C_6H_3	11	93
7	4-Cl-C_6H_4	7	80
8	4-Br-C_6H_4	9	80
9	3-NO_2-C_6H_4	12	80
10	4-NO_2-C_6H_4	5	88
11		13	54
12	$(CH_3)_2CH$	12	59
13	$CH_3CH_2CH_2$	15	56
14		15	76

[a]Yields refer to those of pure isolated products fully characterized by spectral and physical data.

The aromatic aldehydes containing electron-donating as well as electron-withdrawing groups underwent the conversion equally. Acid-sensitive substrate such as 2-pyridinecarboxaldehyde produced the desired condensation product in good yield (entry 11, Table 1). Another advantage of this method is its efficiency for the synthesis of alkyl-14*H*-dibenzo[a,j]xanthenes from aliphatic aldehydes (entries 12–14, Table 1). However, the reaction conducted with phenol and 1-naphthol instead of 2-naphthol could not afford any product. The work-up procedure is so simple and includes filtration of the mixture to separate the product. After isolation of the product from the water mixture, the water layer containing indium triflate was washed with ether and was reused. The effectiveness of the catalyst was decreased after each run. In comparison with other reported methods of dibenzoxanthene synthesis, the use of $In(OTf)_3$ as a catalyst and water as a solvent is very much versatile and efficient catalyst for obtaining 14-aryl or alkyl-14*H*-dibenzo[*a*, *j*]xanthenes from different types of aldehydes.

In conclusion, $In(OTf)_3$ is an efficient and versatile catalyst for the preparation of aryl or alkyl 14*H*-dibenzo[a,j] xanthene derivatives. The significant advantages offered by this method are the following: (i) water as solvent, (ii) high yields, (iii) no waste production, (iv) nontoxic metal catalyst, and (v) simple operation. Another advantage of this method is its efficiency for the synthesis of xanthenes from aliphatic aldehydes. Further studies on the application of the present methodology to the synthesis of biologically active compounds are under investigation.

EXPERIMENTAL

Typical Procedure for the Synthesis of 14-Cyclohexyl-14H-dibenzo[a,j]xanthene (entry 14)

A mixture of β-naphthol (577 mg, 4 mmol) and cyclohexanecarboxaldehyde (225 mg, 2 mmol) was stirred in presence of indium triflate (22 mg, 2 mol%) in water (4 mL) at 100°C for 15 h (TLC). After completion of the reaction confirmed by TLC, the mixture was cooled to room temperature and the precipitated product was filtered and recrystallized from ethanol to afford the pure product as white crystals (554 mg, 76%), mp 174–175°C. IR: $\nu = 2927$, 2364, 1622, 1585, 1452, 1234 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.29 (d, $J = 8.4$ Hz, 2H), 7.85 (d, $J = 8.1$ Hz, 2H), 7.75 (d, $J = 8.7$ Hz, 2H), 7.61–7.55 (m, 2H), 7.45–7.23 (m, 4H), 5.39 (d, $J = 3.6$ Hz, 1H), 1.89–1.38 (m, 6H), 1.04–0.76 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.9, 132.2, 131.0, 128.6, 127.9, 126.2, 123.9, 123.9, 123.0, 47.1, 36.3, 30.7, 26.5, 25.9; Anal. Calcd for $C_{27}H_{24}O$: C, 88.97; H, 6.64. Found: C, 88.78; H, 6.47.

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