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ORIGINAL PAPER

A facile and efficient method for synthesis of xanthone derivatives catalyzed by HBF_4/SiO_2 under solvent-free conditions

Zhan-Hui Zhang · Hong-Juan Wang · Xiao-Qian Ren · Yan-Yan Zhang

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Abstract HBF_4/SiO_2 was used as an efficient, green, and inexpensive catalytic system for synthesis of 12-aryl or 12-alkyl-8,9,10,12-tetrahydro-11*H*-benzo[*a*]xanthen-11-one derivatives via a one-pot three-component reaction of aldehydes, 2-naphthol, and cyclic 1,3-dicarbonyl compounds. The reactions proceeded rapidly at 80 °C under solvent-free conditions and the desired products were obtained in good to excellent yields.

Keywords Multicomponent reaction · Aldehydes · Heterogeneous catalyst · HBF_4/SiO_2 · Solvent-free conditions

Introduction

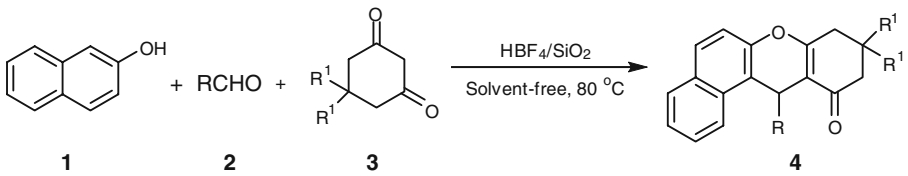
With increasing environmental concerns, the development of clean synthetic procedures has become crucial and demanding research. In this sense, heterogeneous organic reactions have many advantages, for example ease of handling, separation, and recycling, low corrosion, and environmentally safe disposal [1]. Multi-component reactions enable the creation of complicated molecules using only one process in a very fast, efficient, and raw materials and time-saving manner [2]. In addition, solvent-free conditions make synthesis simpler, save energy, and prevent solvent waste, hazards, and toxicity [3–5]. It therefore remains a challenge to develop multi-component reactions with a suitable heterogeneous catalysts and the use of solvent-free conditions.

Z.-H. Zhang (✉) · H.-J. Wang · X.-Q. Ren · Y.-Y. Zhang
The College of Chemistry and Material Science,
Hebei Normal University, 050016 Shijiazhuang, China
e-mail: zhanhui@126.com

Xanthenes are an important class of compounds with remarkable biological and medicinal properties, for example antibacterial, antiviral, and anti-inflammatory activity [6–9]. Furthermore, they are used as dyes, pH-sensitive fluorescent materials, and in laser technologies [10–12]. Among this class of molecules, xanthone is a prominent structural motif found in numerous natural products and synthetic compounds with important biological activity [13–17]. Recently, methodology for synthesis of 12-aryl- or 12-alkyl-8,9,10,12-tetrahydro-11*H*-benzo[*a*]xanthen-11-one derivatives by condensation of aldehydes, 2-naphthol, and cyclic 1,3-dicarbonyl compounds in the presence of $NaHSO_4{\cdot}SiO_2$ in 1,2-dichloroethane under reflux has been described [18]. However, this procedure also is limited in scope, because of relatively long reaction times and the use of a harmful volatile organic solvent. As a consequence, the development of an environmentally benign practical procedure for accessing these xanthones remains an elusive goal.

The use of silica-supported HBF_4 (HBF_4/SiO_2) as a heterogeneous catalytic system to promote various transformations is well documented in the literature [19–24]. In particular, HBF_4/SiO_2 has been found to catalyze efficiently thia-Michael additions to α,β-unsaturated carbonyl compounds [25], Mannich-type reactions [26], and the synthesis of 1,5-benzodiazepines [27] and 14-aryl-14*H*-dibenzo[*a,j*]xanthene derivatives [28]. Considering these topics and our ongoing project on developing several catalytic systems for organic reactions [29–39], we now report a highly efficient procedure for preparation of 12-aryl- or 12-alkyl-8,9,10,12-tetrahydro-11*H*-benzo[*a*]xanthen-11-one derivatives via a one-pot three-component reaction of aldehydes, 2-naphthol, and cyclic 1,3-dicarbonyl compounds in the presence of HBF_4/SiO_2 under solvent-free conditions (Scheme 1).

Scheme 1



Results and discussion

We started our study by examining the reaction of 4-chlorobenzaldehyde (**2m**), 2-naphthol (**1**), and 5,5-dimethyl-1,3-cyclohexanedione. After initial screening of amounts of HBF_4/SiO_2, solvents, and reaction temperatures, we found that use of 10 mol% HBF_4/SiO_2 at 80 °C under solvent-free conditions produced 12-(4-chlorophenyl)-9,9-dimethyl-8,9,10,12-tetrahydro-11*H*-benzo[*a*]xanthen-11-one (**4m**), after 1 h, in 95% yield. Notably, the desired product could not be obtained under similar reaction conditions, even after a long time (2 h) in the absence of the catalyst. This method is superior to available methods with regard to yield and reaction time [18].

To explore the scope and limitations of the procedure, a number of aldehydes were examined under the optimized conditions. As shown in Table 1, aromatic aldehydes substituted with an electron-withdrawing group or an electron-donating group were transformed into the corresponding xanthones in good to excellent yields. Moreover, it was observed that aliphatic aldehydes were viable substrates, although long reaction times were required for slightly lower yields. The products obtained were characterized by IR and ^{1}H NMR spectroscopy; the results were in agreement with those published in the literature [18, 41].

In order to check the recyclability of the catalyst after completion of the reaction, the reaction mixture was dissolved in ethyl acetate and the catalyst was recovered after filtration. The recovered catalyst was reused again for the synthesis of **4m**. The reaction was found to proceed smoothly and afforded comparable yields of 93, 92, 92, and 90%, confirming the recyclability and reusability of the catalyst in this reaction.

In conclusion, we have introduced a new catalyst system for synthesis of various xanthone derivatives via one-pot three-component reaction of aldehydes, 2-naphthol, and cyclic 1,3-dicarbonyl compounds. Advantages of our procedure include simplicity of operation, high yields of products, short reaction time, solvent-free conditions, and the use of an inexpensive and readily available catalyst.

Experimental

Melting points were determined on an X-4 apparatus. IR spectra were obtained using a Shimadzu FTIR-8900 spectrometer. ^{1}H NMR spectra were recorded with a Varian Mercury Plus 400 spectrometer using TMS as internal standard. Elemental analysis was performed on a Vario EL III CHNOS elemental analyzer and the results obtained agreed favorably with calculated values.

Table 1 Preparation of xanthone derivatives in the presence of HBF_4/SiO_2

Compound	R	R^1	Time (min)	Yield (%)[a]	mp (°C)
4a	Ph	H	65	92	189–190 [18]
4b	4-MeO-C_6H_4	H	70	90	180–182 [40]
4c	3-MeO-4-HO-C_6H_4	H	70	89	193–194 [40]
4d	3-Cl-C_6H_4	H	60	92	209–210 [40]
4e	4-Cl-C_6H_4	H	60	93	206–208 [40]
4f	3-NO_2-C_6H_4	H	60	94	235–236 [40]
4g	4-NO_2-C_6H_4	H	60	92	234–235 [40]
4h	CH_3CH_2	H	90	85	Oil [18]
4i	C_6H_{11}	H	90	83	186–187
4j	Ph	Me	65	91	150–151 [40]
4k	4-Me-C_6H_4	Me	70	90	175–176 [41]
4l	4-MeO-C_6H_4	Me	70	89	208–209 [18]
4m	4-Cl-C_6H_4	Me	60	95	187–188 [18]
4n	4-HO-C_6H_4	Me	65	94	150–152 [18]
4o	4-NO_2-C_6H_4	Me	55	92	174–175 [40]
4p	CH_3CH_2	Me	90	84	Oil [18]

[a] Yields refer to isolated products

Representative procedure for the synthesis of xanthones

A mixture of 281 mg **2m** (2 mmol), 288 mg **1** (2 mmol), 350 mg 5,5-dimethyl-1,3-cyclohexanedione (2.5 mmol), and 0.4 g HBF_4/SiO_2 (0.2 mmol) was heated at 80 °C for the appropriate time according to Table 1. After completion of reaction, as indicated by TLC, the mixture was washed with ethyl acetate and filtered to recover the catalyst. The organic filtrate was separated and concentrated under reduced pressure. The crude product was recrystallized from EtOH to afford 737 mg **4m** (95%).

12-Cyclohexyl-8,9,10,12-tetrahydro-11H-benzo[a] xanthen-11-one (**4i**, $C_{23}H_{24}O_2$)
White solid; m.p.: 186–187 °C; IR (KBr): $\bar{\nu} = 2{,}931$, 2,860, 2,848, 1,643, 1,618, 1,595, 1,514, 1,391, 1,256, 1,234, 1,188, 1,134, 993, 949, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.97$–1.10 (m, 6H, cyclohexane), 1.26–1.81 (m, 5H, cyclohexane), 2.10–2.15 (m, 2H, CH_2), 2.32–2.41 (m, 2H, CH_2), 2.57–2.78 (m, 2H, CH_2), 4.68 (d, $J = 4.0$ Hz, 1H, CH), 7.24 (d, $J = 8.8$ Hz, 1H, Ar–H), 7.45 (d, $J = 7.6$ Hz, 1H, Ar–H), 7.56 (d, $J = 7.6$ Hz, 1H, Ar–H), 7.71 (d, $J = 8.8$ Hz, 1H, Ar–H), 7.83 (d, $J = 8.0$ Hz, 1H, Ar–H), 8.12 (d, $J = 8.0$ Hz, 1H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.2$, 26.3, 28.0, 28.5, 31.2, 32.6, 37.2, 45.6, 113.4, 116.8, 119.0, 123.8, 124.8, 126.6, 127.8, 128.5, 131.5, 131.6, 149.2, 168.6, 197.8 ppm.

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