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Phenylboronic acid-Catalyzed Synthesis of 9,9-Dimethyl-12-phenyl-9,10-dihydro-8*H*-benzo[a] xanthen-11(12*H*)-one Derivatives

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ABSTRACT

A simple and efficient method has been described for the synthesis of 9,9-Dimethyl-12-phenyl-9,10-dihydro-8H-benzo [a] xanthen-11(12H)-one derivatives from aromatic aldehydes, β-naphthol and 5,5-dimethylcyclohexane-1,3-dione using a mild phenylboronic acid as a catalyst in good yields.

Keywords: Xanthene, multicomponent reaction, aromatic aldehyde, β-naphthol, phenylboronic acid, 5,5-dimethylcyclohexane-1,3-dione.

INTRODUCTION

Xanthenes and its derivatives are known as an important class of heterocyclic compounds [1] widely used as leco-dye [2], in laser technology [3], and pH sensitive fluorescent materials [4]. They possess a broad range of useful pharmacological activities, including anti-bacterial [5] and antiviral activities [6]. Consequently, the development of novel methods for the synthesis of these heterocyclic compounds has been received considerable interest in both organic and medicinal fields. The three-component reaction of aryl aldehydes, β-naphthol and cyclic 1,3-dicarbonyl compounds has appeared as a novel alternative method for preparation of tetrahydroxanthenones [7].

A few methods have been developed for the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo [a] xanthen-11-one derivative; the most common method is the condensation of an aryl aldehyde, β-naphthol and cyclic 1,3-dicarbonyl compound catalyzed by strontium triflate [8], surfactant [9], iodine [10], Caro's acid–silica gel (CA-SiO_2) [11], $HClO_4$-SiO_2 [12], *p*-TSA [13], $InCl_3$ [14], BNBTS [15], Chlorosulphonic acid ($ClSO_3H$) [16], Cu/SiO_2 [17]. However, in spite of their potential utility, some of these methods suffer drawbacks such as the use of toxic and hazardous solvents, unsatisfactory product yields, expensive catalyst, and prolonged reaction times.

Synthesis of xanthene derivatives is a continuing significant area because these moieties are privileged pharmacophores as well as valuable reactive intermediates for both synthetic and medicinal chemists. On the other hand, multi-component reactions (MCRs) offer noteworthy advantages over conventional linear step synthesis, in terms of simple work-up and purification, less time, energy and raw-material consuming. Thus, MCRs provide benefits in both economic and environment [18].

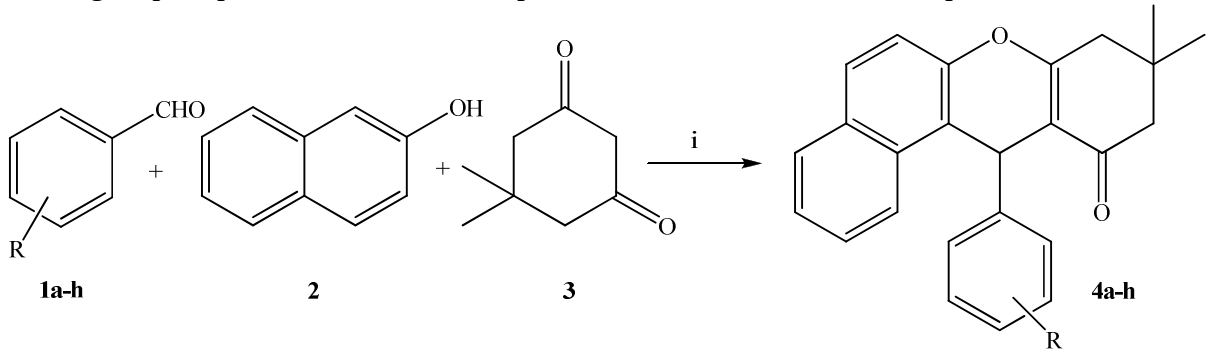
In continuation on the application of eco-friendly materials as catalysts for developing of new synthetic methodology, Here in we describe a novel one-pot three-component synthesis of xanthene derivatives starting from β-naphthol, aromatic aldehyde and 5,5-dimethylcyclohexane-1,3-dione using phenylboronic acid as a catalyst at ambient temperature conditions (**Scheme 1**).

EXPERIMENTAL SECTION

Melting points were determined in open capillary tube and are uncorrected. The purity of the compounds has been checked by TLC. The IR spectra were recorded on Varian FTIR 640 spectrometer. ^{1}H NMR spectra were recorded on Burker 300 MHz spectrometer in $CDCl_3$ as a solvent and TMS as an internal standard.

Typical procedure for synthesis of 9,9-Dimethyl-12-phenyl-9,10-dihydro-8*H*-benzo [a] xanthen-11(12*H*)-ones (4a-h):

Aromatic aldehyde (10 mmol), β-naphthol (10 mmol), 5,5-dimethylcyclohexane-1,3-dione (11 mmol) were mixed in ethyl alcohol (15 ml) and catalytic amount of phenylboronic acid (20 mol %) was added and reaction mixture was stirred at room temperature for appropriate time (Table 3). After the completion of reaction indicated by thin layer chromatography (pet ether: ethyl acetate; 8:2), reaction mixture was poured into crushed ice. Obtained precipitate was filtered and dried to give pure product. All of the compounds are identified from their spectral data.



Scheme 1: Reaction condition i) Phenylboronic acid, ethanol, room temperature, 82-93 %.

Spectral data of representative compounds:

9,9-dimethyl-9,10-dihydro-12-(3-nitrophenyl)-8H-benzo[a]xanthen-11(12H)-one (4a): IR (KBr, cm^{-}1): 3073, 2952, 1648, 1528, 1376, 1356, 1228, 1167, 1028, 809; ^{1}H NMR (300 MHz, CDCl3): δ = 8.21 (s, 1H), 7.85–7.90 (m, 3H), 7.50–7.55 (m, 2H), 7.35–7.45 (m, 4H), 5.41 (s, 1H), 2.32 (s, 2H), 2.26 (d, 1H), 2.21 (d, 1H), 1.21 (s, 6H); ^{13}C NMR (75 MHz, CDCl3): δ 196.2, 164.8, 148.5, 147.6, 146.7, 134.9, 131.7, 130.1, 129.2, 129.0, 128.4, 127.1, 125.3, 123.4, 123.0, 121.3, 117.4, 115.7, 113.1, 50.5, 41.2, 34.3, 32.3, 29.2, 27.3; Mass (LC/MS): *m/z* 400.114 (M+), Elem. Anal for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 75.26; H, 5.41; N, 3.66.

9,9-dimethyl-9,10-dihydro-12-(4-methoxyphenyl)-8H-benzo[a]xanthen-11(12H)-one (4e): IR (KBr, cm^{-}1): 3051, 2949, 1652, 1224, 1182, 1028; ^{1}H NMR (300 MHz, CDCl3): δ = 7.90 (d, 1H), 7.68–7.72 (m, 2H), 7.32–7.52 (m, 5H), 6.70 (d, 2H), 5.56 (s, 1H), 3.46 (s, 3H), 2.45 (s, 2H),

2.28 (d, 1H), 2.21 (d, 1H), 1.15 (s, 6H); ^{13}C NMR (75 MHz, CDCl3): δ 196.2, 163.3, 155.7, 146.7, 135.9, 133.4, 130.3, 130.1, 128.5, 127.1, 126.6, 125.4, 124.1, 121.9, 117.0, 116.5, 115.8, 113.1, 112.6, 53.4, 49.5, 40.2, 32.3, 31.1, 28.1, 25.9. Mass (LC/MS): *m/z* 385.214 (M+), Elem. Anal for $C_{26}H_{24}O_3$: C, 81.22; H, 6.29; O, 12.48 Found: C, 81.28; H, 6.21; O, 12.42.

Table 1: Effect of solvents on synthesis of xanthene derivatives

Entry	Phenylboronic acid (mol %)	Solvent	Time (h)	Temperature (°C)	Yield (%)[a]
1	20	DMF	6.0	80	45
2	20	THF	5	reflux	52
3	20	H_2O	8.0	80	-
4	20	CH_3CN	5	30	45
5	**20**	**EtOH**	**3.5**	**30**	**85**

[a]Isolated yield.

Table 2: Effect of catalyst phenylboronic acid for synthesis of xanthene derivatives

Entry	Phenylboronic acid (mol %)	Time (h)	Yield (%)[a]
1	-	12	trace
2	5	5	52
3	10	5	61
4	15	5	65
5	**20**	**3.5**	**85**

Table 3: Synthesis of 9,9-Dimethyl-12-phenyl-9,10-dihydro-8*H*-benzo [a] xanthen-11(12*H*)-ones derivatives

Entry	R	Product	Reaction Time (h)	Mp (°C)	Lit. Mp (°C)	Yield (%)[a]
1	3-NO_2	4a	3.0	168	168-170[15]	88
2	4-Cl	4b	3.5	185	185-186[13]	93
3	4-OH	4c	4.0	224	223-225[15]	87
4	4-OCH_3	4d	4.5	207	206-207[13]	85
5	4-H	4e	4.0	154	151-153[15]	79
6	4-NO_2	4f	3.5	178	178-180[15]	88
7	4-CH_3	4g	4.5	176	176-178[15]	85
8	4-F	4h	3.5	185	184-185[13]	82

[a]*Isolated yield.*

RESULTS AND DISCUSSION

Here in, we report an efficient and environmentally benign protocol for the synthesis of 9,9-Dimethyl-12-phenyl-9,10-dihydro-8*H*-benzo [a] xanthen-11(12*H*)-ones derivatives by the multi-component condensation of β-naphthol, aromatic aldehydes, and 5,5-dimethylcyclohexane-1,3-dione catalyzed by phenylboronic acid in ethanol at ambient temperature conditions. The method offers several advantages such as mild reaction conditions, short reaction time, high yields, and a simple experimental operation leading to a useful and attractive process for the preparation of xanthene derivatives.

To find optimal conditions for the reaction, 3-nitrobenzaldehyde (10 mmol), β-naphthol (10 mmol) and 5,5-dimethylcyclohexane-1,3-dione (11 mmol) was stirred at room temperature in the presence of phenylboronic acid (20 mol %) employing various solvents such as water, acetonitrile, DMF, and THF but these were found to be less effective. It is remarkable that the reaction is carried out in ethanol as a solvent in excellent yield (85%) (Table 1).

We also performed the reaction with varying amounts of phenylboronic acid and found that the reaction was effective with catalytic amount of phenylboronic acid (20 mol%) without diminishing the yield of the desired product (Table 2, entry 5). Only a trace amount of the product was obtained when the reaction was carried out in the absence of catalyst even after 12 h (Table 2, entry 1).

The application of this protocol was extended to a variety of aromatic aldehydes. The reactions proceeded smoothly with different aldehydes substituted with electron-donating or electron-withdrawing groups giving excellent yields (Table 3). It is observed that substituent in the aromatic ring of aldehydes shows a slight effect on the reaction process. Aromatic aldehydes with electron-withdrawing groups reacted faster than those with electron-donating groups.

CONCLUSION

In summary, we have demonstrated a novel and facile method for the synthesis of xanthenes derivatives by using phenylboronic acid as a promoter under mild reaction conditions. The advantages of the present method include high yields of products, simple experimental procedure and non-toxicity of the reagent. The products were obtained in satisfactory yields by conventional work up. Both analytical and spectroscopic data of synthesized compounds are in full agreement with the proposed structures.

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