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Original Research article

2,6-pyridinedicarboxylic acid as an efficient and mild organocatalyst for the one-pot synthesis of xanthene derivative

Sobhan Rezayati[a,*], Ehsan Mirzajanzadeh[b], Hamed Seifournia[b]

[a] *Department of Chemistry, Payame Noor University, PO BOX 19395-4697 Tehran, Iran*

[b] *Department of Chemistry, Qaemshahr Branch, Islamic Azad University, Qaemshahr, Iran*

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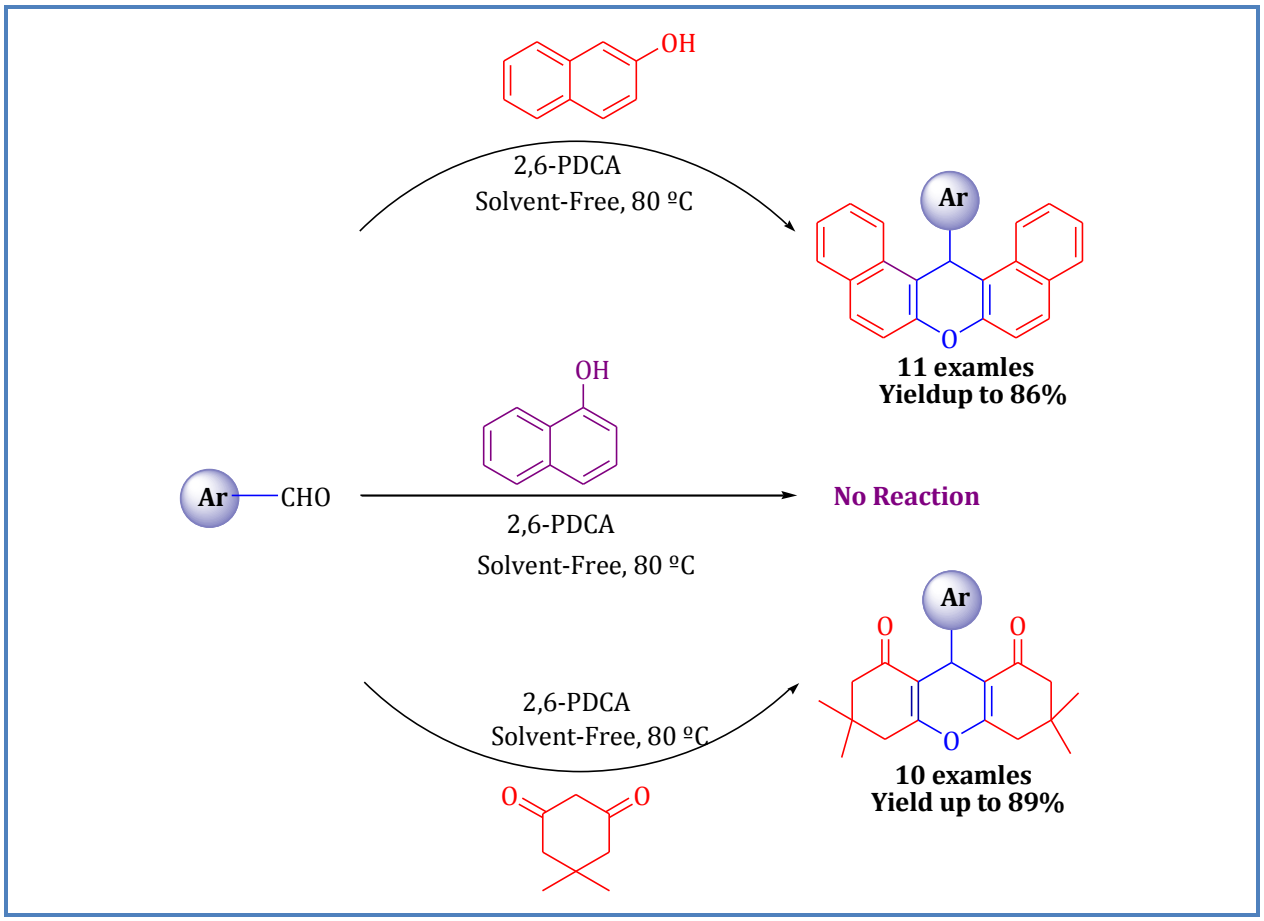
ABSTRACT

Simple and efficient protocols have been developed for the one-pot synthesis of aryl-14H-dibenzo[a,j]xanthenes and 1,8-dioxo-octahydro-xanthenes. (**i**) A cost-effective, simple and convenient procedure for the synthesis of aryl-14H-dibenzo[a,j]xanthenes has been developed *via* a one-pot condensation from substituted benzaldehydes (**1** equiv) and *β*-naphthol (**2** equiv) in the presence of 2,6-pyridinedicarboxylic acid (2,6-PDCA) under solvent-free conditions. **(ii**) The one-pot condensation of substituted benzaldehydes (**1** equiv) and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (**2** equiv) in the presence of 2,6-pyridinedicarboxylic acid (2,6-PDCA) under solvent-free conditions leads to 1,8-dioxo-octahydro-xanthenes. In these protocols several advantages such as: excellent yields, very short reaction times, easy work-up, simple methodology are offered.

Corresponding author, email: sobhan.rezayati@yahoo.com (S. Rezayati)
Tel.: +9884 33339303; Fax: +9884 33332742.

Graphical Abstract



Introduction

Xanthenes and Benzoxanthenes are an important category of organic compounds which recently received much attention of organic and medical chemists due to of their wide range of therapeutic and biological properties such as antiviral [1], antibacterial [2] and anti inflammatory activities [3]. Furthermore, these compounds are used in laser technologies [4], fluorescent material in the visualisation of biomolecules [5], as well as being widely used as dyes [6].

Many methods using the synthesis of xanthene and benzoxanthene have been reported in the literature, including cyclodehydration [7-10], cyclization of polyclic aryl triflate esters [11], trapping of benzynes by phenols [12], intermolecular phenyl carbonyl coupling reactions of benzaldehydes and acetophenones [13] and cyclocondensation between 2-hydroxy aromatic aldehydes and 2-tetralone [14].

Different reagents have been employed for the synthesis of xanthenes and benzoxanthenes such as ZnO-NPs [15], PVPP-BF_3 [16], $H_5PW_{10}V_2O_{40}$ [17], imidazol-1-yl-acetic acid [18], succinimide-*N*-

sulfonic acid [19], ceric ammonium nitrate (CAN) [20], SAFIS [21] and 1,3-disulfonic acid imidazolium hydrogen sulfate [22] as catalysts. However, many of these methods, from certain drawbacks suffer including longer reaction times, unsatisfactory yields and conditions, use of high heat and the use of toxic catalysts [23-26].

2,6-Pyridinedicarboxylic acid (2,6-PDCA), also known as dipicolinic acid, is an organocatalyst and a weak protic acid having acidic hydrogens with pK_1 = 2.16 and pK_2 = 4.76. It can be believed that 2,6-PDCA activates the reacting substrate by proton donation as well as by H-bonding and therefore it is employed as an important catalyst in organic synthesis. Several advantages such as its non-metallic nature, solubility, lower toxicity, cost-effectiveness, air stability and ready availability have made it a significantly suitable catalyst to carry out organic transformations.

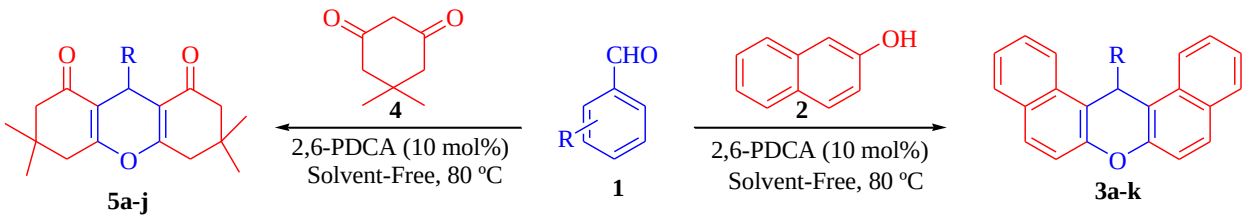
In recent years, the use of solid acidic catalysts and solid-state reactions (or solvent-free reactions) has many advantages in organic synthesis. For example, high efficiency and selectivity, operational simplicity, environmental compatibility, nontoxic, reusability, low cost, ease of isolation and benefit for industry as well as environment [27-30].

In the present work, we report a new and simple method for the synthesis of aryl-14H-dibenzo[a,j]xanthenes 3 and 1,8-dioxo-octahydro-xanthene 5 using 2,6-Pyridinedicarboxylic acid as an efficient, green, and organocatalyst under solvent-free conditions (Scheme 1).

Experimental

Matreials and methodes

All reagents were purchased from Aldrich (USA) or Merck Fine Chemicals and were used without further purification. Products were separated and purified by chromatographic techniques and were identified by the comparison of their IR and NMR data with those reported for the authentic samples. The IR spectra of the compounds were obtained on a Perkin-Elmer spectrometer (USA), version 10.03.06 using a KBr disk. ^{1}H NMR spectra were recorded on a Bruker DRX-300 AVANCE (Germany) spectrometer in $CDCl_3$ as a solvent and chemical shift values were recorded in δ relative to TMS as an internal standard. Thin-layer chromatography (TLC) was performed on pre-coated aluminium plates (silica gel 60 F254, Merck, Germany). The chromatographic spots on the plates were visualised under UV light and iodine vapour. Melting points were taken on an electrothermal capillary melting point apparatus (UK) and are uncorrected.



Typical procedure for the preparation of aryl-14H-dibenzo[a,j]xanthenes

A mixture of *β*-naphthol (2 mmol), various aldehydes (1 mmol) and 2,6-PDCA (10 mol%) was added and the mixture was kept in an oil bath at 80 °C for a certain time (Table 3). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and then the residue was purified by chromatography over silica gel (Merck, 230–400 mesh) using an *n*-hexane-AcOEt (*n*-hexane/ethyl acetate, 4:1) mixture as eluant, to afford the pure adducts. After completion of the reaction, the reaction mixture was quenched with H_2O addition (3 mL) and the product was extracted with CH_2Cl_2 (10 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (3 × 10 mL), brine (2 × 10 mL), dried over anhydrous $MgSO_4$, filtered and the solvent from the filtrate evaporated under vacuum. The residue was re-crystallised from ethanol to afford pure products.

Typical procedure for the preparation of 1,8-dioxo-octahydro-xanthenes

The procedure was similar to that described for **3** with the exception that *β*-naphthol was replaced with 5,5-dimethyl-1,3-cyclohexanedione.

Results and discussion

For this purpose, as a model reaction, the condensation of benzaldehyde **1** and **β**-naphthol **2** was tested using different amounts of catalyst under solvent-free conditions at room temperature (Table 1). In order to determine the role of 2,6-PDCA better, when reactions were carried out in the absence of catalyst for long period of time 720 min under solvent-free condition the yields of products were low (<5%) (Table 1, entry 1). Better yield and shorter reaction time were obtained when the reaction was carried out in the presence of 10 mol % of the catalyst under solvent-free conditions (Table 1, entry 5). It is notable that when 15 mol% of catalyst was used, neither increased the yield nor shortened the conversion time (Table 1, entry 6). It was observed that the reaction did not proceed at room temperature. Elevating the reaction temperature proved helpful, and the yield of desired product increased considerably. It was gratifying to find that the reaction

proceeded smoothly and almost complete conversion to the product was observed at 80 °C, affording 14H-dibenzo[a,j]xanthenes in 84% yield within a short time (Table 2, entry 2).

As expected, both aromatic aldehydes containing electron-donating as well as electron-withdrawing groups were utilized in the present case to form corresponding benzoxanthenes 3a-n in high yields. In addition, as seen in Table 3, the reaction was performed with benzaldehyde containing withdrawing as well as electron donating groups, but benzaldehydes by electron donating groups is generally more reactive than its corresponding ones with electron withdrawing groups and it gives the desired product at a short reaction time with excellent yield (Table 3). This observation clearly shows that the preparation of benzoxanthenes is more strongly affected by the electronic factors. This method was general and efficient; all reactions were successfully performed to furnish the corresponding 14-aryl-14H-dibenzo[a,j]xanthenes in high to excellent yields and relatively short reaction times. However, the reaction conducted by α-naphthol instead of β-naphthol did not afford any product.

Table 1. Optimization of the amount of the 2,6-PDCA

Entry	Loading catalyst (mol %)	Time (min)	Yield (%)[a]
1	None	720	<5
2	1	120	58
3	5	50	65
4	7	45	69
5	10	25	74
6	15	25	70

[a] Yield of isolated product

Table 2. Effect of temperature on the synthesis of **3a**[a]

Entry	Temperature (°C)	Yield (%)
1	60	78
2	80	84
3	100	76
4	120	68

[a] Benzaldehyde (1 mmol) and *β*-naphthol (2 mmol) in presence of catalyst (10 mol%), under thermal (80 °C) solvent-free conditions

In Table 4, the results are compared with the results of some other procedures for the synthesis of 14-aryl-14H-dibenzo[a,j]xanthenes. It is clear that in Table 4 the current method is simpler, more efficient, and less time-consuming for the synthesis of 14-aryl-14H-dibenzo[a,j]xanthene derivatives. The data presented in this table show the comparison between the promising features of this method in terms of the molar ratio of the catalyst, reaction time and yield of product with those reported in the literature.

Table 3. Synthesis of aryl-14H-dibenzo[a,j]xanthenes[a]

Entry	Substrate	Product	Time (min)	Yieldb (%)	Mp (ºC)	[Ref.]
1	C_6H_5	**3a**	15	84	178-179	[23]
2	4-BrC_6H_4	**3b**	20	80	291-293	[23]
3	4-$NO_2C_6H_4$	**3c**	25	6	307-308	[23]
4	3-$NO_2C_6H_4$	**3d**	30	88	207-208	[23]
5	2-ClC_6H_4	**3k**	30	86	212-213	[23]
6	4-ClC_6H_4	**3e**	15	80	288-291	[31]
7	2-$NO_2C_6H_4$	**3i**	35	85	290-291	[31]
8	4-$OMeC_6H_4$	**3f**	15	81	204-205	[32]
9	4-OHC_6H_4	**3g**	30	4	141-143	[32]
10	2,4-ClC_6H_4	**3h**	20	76	255-256	[33]
11	3-BrC_6H_4	**3j**	30	81	187-186	[34]

[a] Reaction Condition: *β*-naphthol (2 mmol), aldehyde (1 mmol) in the presence of 2,6-PDCA under solvent-free condition at 80 °C

[b] Yield of isolated products

Table 4. Comparison of efficiency of various catalysts in synthesis of 14-aryl-14H-dibenzo[a,j]xanthenes

Entry	Catalyst	conditions	Time (h)	Yield (%)[a]	[Lit.]
1	*p*-Toluene sulfonic acid	Solvent-free/ 125 °C	2.5-6	80-96	[25]
2	*p*-Toluene sulfonic acid	1,2-Dichloroethanea	15-24	85-95	[25]
3	LiBr	Solvent-free/ 130 °C	1–1.2	80–84	[26]
4	Selectfluor	Solvent-free/ 125 °C	6-12	90-95	[34]
5	Sulfamic acid	Solvent-free/ 125 °C	6-12	90-95	[35]
6	Amberlyst-15	Solvent-free/ 125 °C	0.5-2	80-94	[36]
7	I_2	Solvent-free/ 90 °C	2-5	85-95	[37]
8	Silica sulfuric acid	Solvent-free/ 80 °C	0.5–2	80–96	[38]
9	Dowex-50W	Solvent-free/ 100 °C	1-2	78–91	[39]
10	This work	Solvent-free/ 80 °C	15-35 min	76-86b	-
11	This work	Solvent-free/ 80 °C	40-110 min	75-89c	-

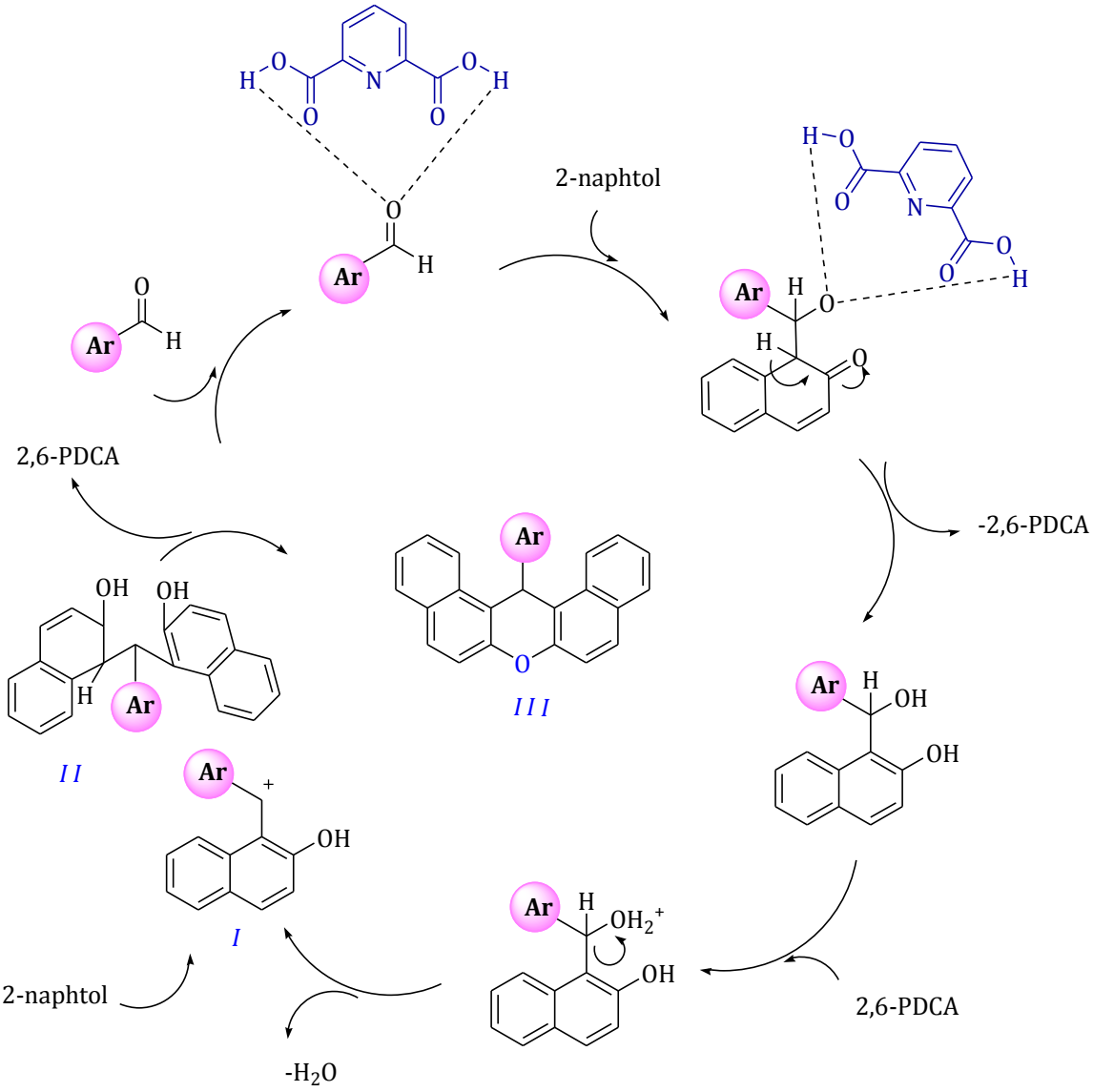
[a] Yield of isolated products

[b] Reaction condition: 2-naphthol (2 mmol), aldehyde (1 mmol) in presence 2,6-PDCA under solvent-free condition at 80 °C

[c] Reaction condition: dimedone (2 mmol), aldehyde (1 mmol) in presence 2,6-PDCA under solvent-free condition at 80 °C

The suggested mechanism of the 2,6-PDCA catalyzed transformation is shown in Scheme 2. Concerning the reaction mechanism, we suggest that, initially a carbocation be formed (structure I) and then aryl-methanebisnaphthols prepared (structure II), which then undergoes dehydration to give the final product (structure III).

In another study, we carried out the reaction of 5,5-dimethyl-1,3-cyclohexanedione **4** instead of *β*-naphthol **2** by various aromatic aldehydes such bearing electron-donating substituents, electron withdrawing substituents or halogens on their aromatic rings under solvent-free conditions at 80 °C, which afforded 1,8-dioxo-octahydro-xanthene derivatives **5** in excellent yields within a short period of time (Scheme 1, Table 5).



Scheme 2. The proposed mechanism for the synthsis of 14-aryl-14H-dibenzo[a,j]xanthenes

Table 5. Synthesis of 1,8-dioxo-octahydro-xanthenes[a]

Entry	Substrate	Product	Time (min)	Yieldb (%)	Mp (°C)	[Lit.]
1	C_6H_5	**5a**	50	86	201-202	[39]
2	4-ClC_6H_5	**5b**	90	89	228-230	[39]
3	3-NO_2C6H_4	**5c**	55	84	172-174	[39]
4	4-HOC_6H_4	**5d**	90	85	242-243	[40]
5	4-OCH_3-C_6H_4	**5e**	40	78	239-240	[40]
6	4-NO_2C6H_4	**5f**	90	79	221-223	[39]
7	2,4-Cl_2-C_6H_4	**5g**	100	81	250-251	[40]
8	4-$Me_2NC_6H_4$	**5h**	85	75	223-225	[40]
9	4-BrC_6H_5	**5i**	100	86	231-232	[39]
10	2-ClC_6H_4	**5j**	85	75	227-228	[39]

[a] Reaction condition: dimedone (2 mmol), aldehyde (1 mmol) in presence 2,6-PDCA under solvent-free condition at 80 °C

[b] Yield of isolated products

Conclusion

In summary, this method is an efficient, economical and 'green' method for the synthesis of xanthenes under solvent free condition using 2,6-pyridinedicarboxylic acid (2,6-PDCA) as a newly organocatalyst. This simple method is significant from both environmental and economical point of views as it creates little waste. The important features of this procedure such as excellent yield, short reaction times, non-toxicity of reagent, eco-friendly, simplicity of reaction are the advantages of the present method. This protocol could serve as a valuable alternative to known reactive systems.

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