Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. 78 (9) 1291–1299 (2013)
JSCS–4497
UDC 547.815+542.9:547.7+
542.913:546.185'226–32
Original scientific paper

Phosphosulfonic acid, an efficient solid acid catalyst for the one-pot preparation of 14-aryl-14*H*-dibenzo[*a,j*]xanthenes and 1,8-dioxooctahydroxanthenes under solvent-free conditions

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(Received 8 October 2012, revised 16 January 2013)

Abstract: An expeditious procedure for the synthesis of 14-aryl-14*H*-dibenzo[*a,j*]xanthenes and 1,8-dioxooctahydroxanthenes through a one-pot pseudo three component condensation of *β*-naphthol or dimedone with various aromatic aldehydes is described. This green protocol is catalyzed by phosphosulfonic acid, and proceeds efficiently in the absence of any organic solvent under optimized, mild, green and environmentally benign reaction conditions in high yields within 20–55 min.

Keywords: xanthenes; one-pot reaction; dimedone; *β*-naphthol; solvent-free; phosphosulfonic acid.

INTRODUCTION

The synthesis of new heterocyclic compounds has always been a subject of great interest due to their wide applicability. Among a large variety of heterocyclic compounds, heterocyclic compounds with oxygen-containing moieties are industrially very important as they serve as precursors. Xanthene derivatives, which have one oxygen atom in a fused ring system, possess antibacterial,[1] antiviral[2] and anti-inflammatory[3] activities. Moreover, these compounds have been used as leuco dyes[4] and found application in laser technology[5] and as sensitizers in photodynamic therapy.[6] Thus, the synthesis of xanthenes is of paramount importance in organic synthesis.

A literature search revealed that many procedures have been developed for the preparation of the biologically important xanthene derivatives, 14-aryl-14*H*--dibenzo[*a,j*]xanthenes, through the dehydration of *β*-naphthol and aromatic alde-

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doi: 10.2298/JSC121108008K

hydes in the presence of various catalysts, such as AcOH–H_2SO_4,[7] selectfluor (1-(chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)),[8] wet cyanuric chloride,[9] $Sc[N(SO_2C_8F_{17})_2]_3$ in a fluorine-containing solvent,[10] silica gel supported $H_6P_2W_{18}O_{62}\cdot 24H_2O$ or $H_3PW_{12}O_{40}\cdot 6H_2O$,[11] I_2,[12] sulfamic acid,[13] a Preyssler-type heteropolyacid ($H_{14}[NaP_5W_{30}O_{110}]$),[14] potassium dodecatungstocobaltate trihydrate ($K_5CoW_{12}O_{40}\cdot 3H_2O$),[15] poly(4-vinylpyridinium) hydrogen sulfate,[16] an acid-functionalized mesoporous silica sieve (SBA-15)[17] and sulfonic acid-functionalized silica (SiO_2–Pr-SO_3H).[18]

In the same manner, the synthesis of 1,8-dioxooctahydroxanthenes was achieved through the dehydration of dimedone (5,5-dimethylcyclohexane-1,3--dione) and aromatic aldehydes in pseudo three-component reactions in the presence of a catalyst, such as, tetrabutylammonium hydrogen sulfate,[19] Sc^{3+}–montmorillonite,[20] $HClO_4$–SiO_2 and polyphosphoric acid (PPA)–SiO_2,[21] phosphomolybdic acid (PMA)–SiO_2,[22] acidic ionic liquids,[23] heteropoly tungstic acid (HPWA) loaded Si-mobile crystalline material (HPWA–MCM-41) mesoporous molecular sieves,[24] silica-supported Preyssler nanoparticles (SPNP),[25] MCM--41–RSO_3H,[26] acid functionalized SBA-15 and MCM-41,[27] and silica-bonded *N*-propylsulfamic acid (SBNPSA).[28]

Although these methods may be effective, some of them have relatively long reaction times and unsatisfactory yields. Due to their wide application, further development of an efficient and useful method for the synthesis of xanthenes derivatives were considered advantageous. These findings prompted further investigations in the search for a new catalyst that would assist in the synthesis of 14*H*-dibenzo[*a*,*j*]xanthenes and 1,8-dioxooctahydroxanthenes under a simpler experimental set up and eco-friendly conditions.

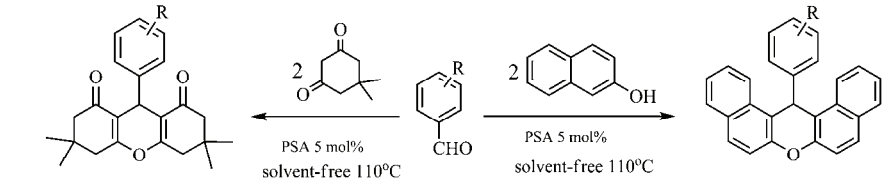
Furthermore, the application of environmentally benign, solid acid catalysts, especially under solvent-free conditions, in organic synthesis provides some advantages, such as ease of handling, mild reaction conditions, decreasing reactor and plant corrosion problems, easier work-up and ease of transportation and storage.[29]

Thus, in continuation of previous studies on the applications of reusable acid catalysts in organic synthesis,[30,31] it was decided to investigate the synthesis of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes and 1,8-dioxooctahydroxanthenes in the presence of catalytic amounts of phosphosulfonic acid under solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSION

Phosphosulfonic acid, PSA, was easily prepared by simple mixing of diammonium hydrogen phosphate and chlorosulfonic acid in CH_2Cl_2 at room temperature (Scheme 2).[32]

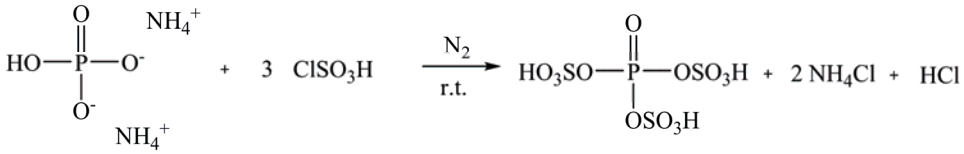
The FT-IR spectrum of the catalyst (Fig. 1) was recorded using the KBr disc technique. The O=S=O asymmetric and symmetric stretching modes of the sulfonic acid functional groups were found in the ranges 1141–1316 and 1010–1020 cm^{-1}, respectively, and that of the S–O stretching mode at 695 cm^{-1}. The spectrum also showed a broad OH stretching absorption around 2700 and 3600 cm^{-1}.



1,8-dioxooctahydroxanthenes **5a-h**

14- aryl-14H-dibenzo[*aj*]xanthenes **3a-l**

Scheme 1. One-pot preparation of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes (**3a**–**l**) and 1,8-dioxooctahydroxanthenes (**5a**–**h**).



Scheme 2. Preparation of phosphosulfonic acid.

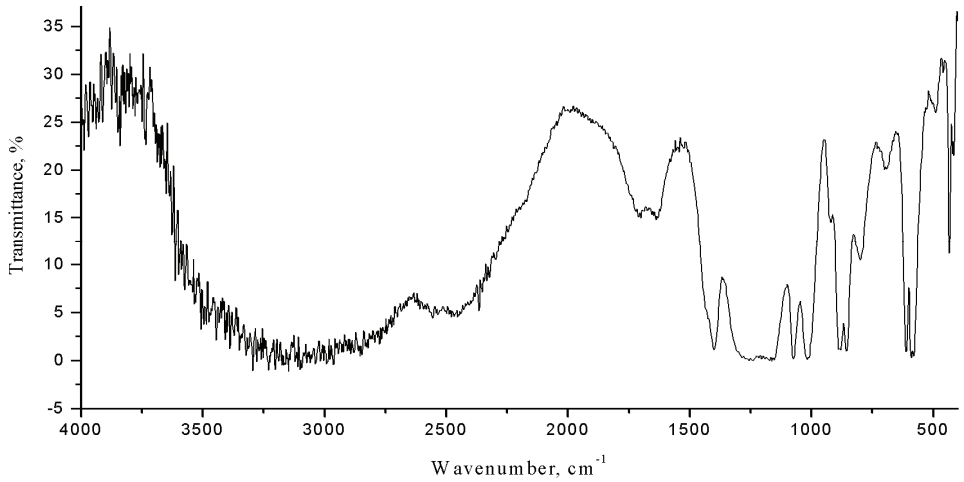


Fig. 1. The FT-IR spectrum of phosphosulfonic acid (KBr disc).

To evaluate the catalytic activity of PSA in the preparation of 14-aryl-14*H*--dibenzo[*a*,*j*]xanthenes derivatives, a model reaction of 2 mmol of *β*-naphthol and 1 mmol of benzaldehyde under solvent-free conditions at 110 °C in the

absence and presence of PSA was examined. It was found that in the absence of solid acid catalyst, only a trace amount of the desired product was produced even after 6 h of heating (Table I). When the reaction was performed in the presence of PSA, it proceeded rapidly to give the desired product.

TABLE I. Determination of the optimum conditions for the pseudo three-component coupling reaction of *β*-naphthol (2 mmol) and benzaldehyde (1 mmol) under thermal solvent-free conditions

Entry	Catalyst, mol %	Temperature, °C	Time, min	Yield, %
1	0	100	360	11
2	3.5	100	55	65
3	3.5	110	45	65
4	5	110	35	93
5	7	110	30	90
6	9	110	30	80

In order to evaluate the appropriate catalyst loading, the model reaction was performed using 3.5 to 9 mol % PSA at 110 °C without solvent (Table I). It was found that 5 mol % of the catalyst afforded the maximum yield in minimum time. Higher percentages of catalyst loading (7 and 9 mol %) neither increased the yield nor lowered the conversion time. Next, the effect of temperature was evaluated for the model reaction. 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.

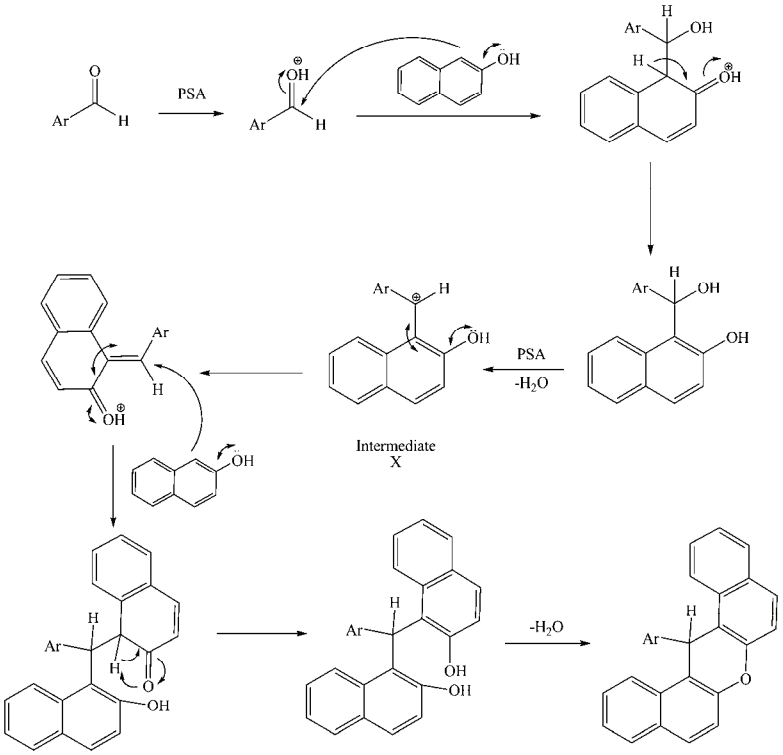
To investigate the feasibility of this synthetic methodology for the synthesis of xanthenes derivatives, the reaction of *β*-naphthol was extended to a range of aromatic aldehydes under similar conditions, furnishing the respective 14-aryl--14*H*-dibenzo[*a*,*j*]xanthenes derivatives in high to excellent isolated yields. The optimized results are summarized in Table II. The method has the ability to tolerate a variety of functional groups, such as fluro-, chloro-, nitro- and methoxy-substituents. The products were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR and physical constants. The results of the characterization of the synthesized xanthenes are given in the Supplementary material to this paper. The physical and spectral data of the known compounds were in agreement with those reported in the literature.

As seen from Table II, electron-withdrawing substituents on the aromatic ring retarded the reaction while electron-donating groups promoted it. This effect of the substituents is comprehendible according to the plausible mechanism for the one-pot preparation of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes (Scheme 3). First, the aldehyde is activated by PSA, and subsequently nucleophilic attack of the *β*-naphthol occurs. After stepwise rearrangement and dehydration, the intermediate X is formed. According to this, electron-withdrawing substituents destabilize the positive charge and consequently increase the activation energy and retard

the reaction, while electron-donating groups stabilize the positive charge and promote the reaction.

TABLE II. One-pot preparation of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes promoted by PSA under solvent-free conditions at 110 °C

Entry	R	Time, min	Yield, %	Melting point, °C	
				Found	Literature
3a	H	35	93	183–185	183[8]
3b	4-NO_2	55	88	310–312	312[8]
3c	3-NO_2	55	90	211–212	213[8]
3d	2-Cl	45	95	214–216	215[8]
3e	4-CH_3	30	91	226–228	228[8]
3f	4-Cl	40	98	285–287	287[8]
3g	2-NO_2	40	96	294–295	293[8]
3h	4-OH	30	89	140–142	140[8]
3i	4-CF_3	40	97	258–259	258–259[33]
3j	3-CH_3	40	94	198–200	198[18]
3k	3-F	45	96	258–260	259[8]
3l	4-OMe	45	65	203–205	205[8]



Scheme 3. Plausible mechanism for the one-pot preparation of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes.

After the success of phosphosulfonic acid in the preparation of 14-aryl-14*H*--dibenzo[*a*,*j*]xanthenes, it was decided to explore the catalytic activity of this catalyst in the preparation of 1,8-dioxooctahydroxanthenes. Thus, the condensation of various aromatic aldehydes with dimedone was performed using phosphosulfonic acid as the solid acid catalyst under the above optimized reaction condition. All the aldehydes reacted almost equally well to afford the corresponding 1,8-dioxooctahydroxanthenes in high to excellent yields (Table III).

TABLE III. One-pot preparation of 1,8-dioxo-octahydro-xanthenes promoted by PSA under solvent-free conditions at 110 °C

Product	R	Time, min	Yield, %	Melting point, °C	
				Found	Literature
5a	H	20	96	206–207	204–206[19]
5b	4-NO_2	30	95	220–222	221–223[19]
5c	3-NO_2	30	93	172–174	170–172[19]
5d	2-NO_2	35	95	249–250	248–249[19]
5e	4-CH_3	25	97	216–218	217–218[19]
5f	4-OMe	30	98	241–242	240–242[19]
5g	2-Cl	25	96	224–225	225–227[19]
5h	4-CN	35	88	224–226	217–218[34]

With the increasing interest in human health and environmental protection, more attention is being paid to green chemistry. With this view, the recyclability and reusability of the catalyst were studied. After completion of the reaction, the separated catalyst was washed with hot ethanol and dried. The catalyst was used for two more subsequent cycles. Surprisingly, a consistent performance of the catalyst was observed in all the cycles, Table IV.

TABLE IV. The reusability of the catalyst in the pseudo three-component coupling reaction of *β*-naphthol (2 mmol) and benzaldehyde (1 mmol) under thermal solvent-free conditions at 110 °C

Run	Time, min	Yield, %
1	35	93
2	38	91
3	40	90

To compare the advantage of the use of PSA over other reported catalysts, the pseudo three-component coupling reaction of *β*-naphthol and benzaldehyde was considered as a representative example (Table V). While in most of these cases (except entry 2), comparative yields of the desired product were obtained following the PSA-catalyzed procedure, the reported procedures required long reaction times (entry 1, 2, 4 and 5), or high catalyst loading (entry 1 and 3). These results clearly demonstrate that PSA is an equally or more efficient catalyst for this three-component reaction.

TABLE V. Comparison of PSA with reported catalysts in the pseudo three-component coupling reaction of *β*-naphthol and benzaldehyde

Entry	Catalyst/Temperature, °C	Catalyst loading, mol %	Time, h	Yield, %	Ref.
1	AcOH–H_2SO_4/0 then 80	100	73	60	7
2	Selectfluor/125	10	8	93	8
3	Cyanuric chloride/110	20	0.7	94	9
4	$Sc[N(SO_2C_8F_{17})_2]_3$/110	1	5	93	10
5	I_2/90	10	2.5	90	12
6	Phosphosulfonic acid/110	5	0.6	93	This work

EXPERIMENTAL

All commercially available chemicals were purchased from Fluka or Merck and used without further purification. The IR spectra were recorded on a Bomem MB-Series 1998 FT-IR spectrophotometer. The ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker Advance DPX 400 MHz spectrometer using TMS as an internal standard. Monitoring of the reactions was accomplished by TLC on silica gel polygram SILG/UV 254 plates. Phosphosulfonic acid was prepared according to the recently reported procedure.[32]

Determination of the acidity of the catalyst

The acidity of the catalyst was determined by titration with standard NaOH. Catalyst (0.5 g) required 8.9 mL of 0.05 M NaOH to reach neutralization, as witnessed by an indicator. The titration verified that the amount of base consumed was 3 equivalents per 1 mole of the catalyst.

*Typical procedure for the preparation of 14-aryl-14*H*-dibenzo[*a,j*]xanthenes/1,8-dioxo-octahydroxanthenes derivatives*

A mixture of aromatic aldehyde (1.0 mmol), *β*-naphthol or dimedone (2.0 mmol), and PSA (0.05 g) was heated at 110 °C for 20–55 min. Completion of the reaction was indicated by TLC (ethyl acetate/*n*-hexane, 2:5). After completion of the reaction (as indicated in Tables II and III), the insoluble crude product was dissolved in hot ethanol and the phosphosulfonic acid was filtered off. The filtrate was concentrated to dryness, and the crude product was purified by recrystallization from ethanol.

CONCLUSION

In conclusion, a simple, facile and green protocol is described for the synthesis of 14-aryl-14*H*-dibenzo[*a,j*]xanthenes and 1,8-dioxooctahydroxanthenes by a one-pot pseudo three-component condensation reaction of aromatic aldehydes and *β*-naphthol or dimidone using phosphosulfonic acid as a novel, environmentally safe, heterogeneous solid acid catalyst under solvent-free conditions. This method offers several advantages, including high yields, inexpensive catalyst, short reaction times, easy work-up and realization of the reaction under green, solvent-free conditions.

SUPPLEMENTARY MATERIAL

Spectroscopic data for the prepared xanthenes are available electronically at http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgement. We gratefully acknowledge the support of this work by the Shahid Chamran University Research Council.

И З В О Д

ФОСФОСУЛФОНСКА КИСЕЛИНА: ЕФИКАСАН ЧВРСТ КИСЕЛИ КАТАЛИЗАТОР ЗА СИНТЕЗУ 14-АРИЛ-14*H*-ДИБЕНЗО[*a*,*j*]КСАНТЕНА И 1,8-ДИОКСООКТАХИДРОКСАНТЕНА У ЈЕДНОМ РЕАКЦИОНОМ КОРАКУ У ОДСУСТВУ РАСТВАРАЧА

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Описана је синтеза 14-арил-14*H*-дибензо[*a*,*j*]ксантена и 1,8-диоксооктахидроксантена из псеудо-трокомпонентне реакционе смеше кондензацијом *β*-нафтола или димедона са различитим ароматичним алдехидима. Поступак катализован фосфосулфонском киселином, одиграва се без присуства органских растварача, под оптимизованим, благим и еколошки прихватљивим условима, у високом приносу и током 20–55 min.

(Примљено 8. октобра 2012, ревидирано 16. јануара 2013)

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