ICC
Iranian Chemical Communication
Original Research Article
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Phthalimide-*N*-sulfonic acid and Isatin-*N*-sulfonic acid as highly efficient catalysts for the synthesis of bis-coumarins

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Received: 14 January 2018, Accepted: 29 April 2018, Published: 29 September 2018

Abstract

Two highly efficient protocols for the production of bis-coumarins under solvent-free conditions have been introduced. The reaction of 4-hydroxycoumarin (2 eq.) with arylaldehydes (1 eq.) using phthalimide-*N*-sulfonic acid (PhtSA) or isatin-*N*-sulfonic acid (IsSA), as solid-acid catalysts, afforded the mentioned compounds with good to excellent yields in short times.

Keywords: 4-Hydroxycoumarin; arylaldehyde; bis-coumarin; phthalimide-*N*-sulfonic acid (PhtSA); isatin-*N*-sulfonic (IsSA); SO_3H-bearing solid acid.

Introduction

The compounds bearing coumarin moiety are significant in medicinal and industrial chemistry. For instance, they have a variety of biological activities; including cytotoxicity and enzyme inhibitory [1,2], urease inhibitory [3], anti-cancer [4], antinociceptive [4], antibacterial [4], anti-HIV [5,6], anticoagulant [7], antioxidant [8] and antimicrobial [8] properties. Fluorescence and optical emission activities of coumarin derivatives have been also reported [9-11]. Bis-coumarins are an important member of coumarin derivatives, and are prepared by the reaction of 4-hydroxycoumarin (2 eq.) with arylaldehydes (1 eq.). Some catalysts have been used to promote this transformation, e.g. melamine trisulfonic acid [12], poly(4-vinylpyridine)-supported ionic liquid [13], starch-sulfuric acid [14], CuO-CeO_2 nanocomposite [15], RuCl3.nH2O [16], choline hydroxide [17], acetic acid functionalized poly(4-vinylpyridinum)bromide [18], trityl bromide [19], [Fe_3O_4@SiO_2@$(CH_2)_3$-Im-SO_3H]Cl [19], and ethylene glycol [20]. Although some catalysts have been reported for the production of bis-coumarins; many of them are associated with at least one of these disadvantages: relatively long reaction times, moderate yields, utilization of volatile organic solvents as reaction media, application of expensive, non-available or toxic catalysts, harsh conditions, and poor compliance with the green chemistry protocols.

Recently, SO_3H-bearing solid acids have attracted much attention to utilize catalysts in synthetic organic chemistry. Some advantages of this class of catalysts include: (a) easy work-up procedure, (b) availability of the reactants for the catalyst preparation, (c) increased efficacy and selectivity, (d) capability to catalyze various kinds of organic

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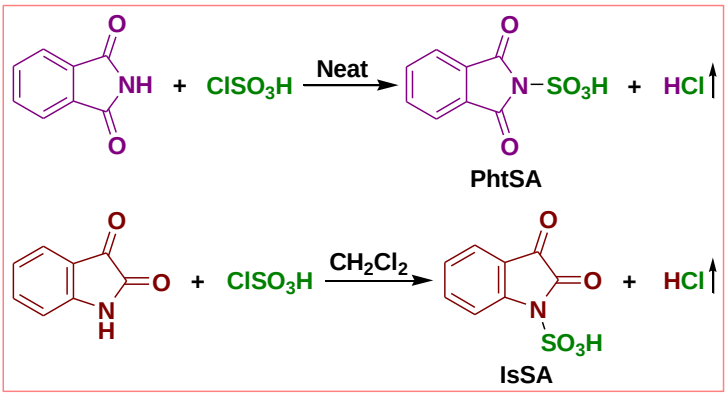
transformations, (e) green reaction conditions, and (f) easy production of catalyst [21-26].

One of the green techniques in synthetic organic chemistry is to perform reactions in solvent-free conditions. This technique has numerous advantages in comparison to solution protocol; some of these advantages consist of higher yield, higher selectivity, shorter reaction time, fewer energy requirement, safer reaction conditions, easier workup, and preventing or decreasing generation of by-products/waste [27-30].

Bearing the above topics in mind, we introduce two SO_3H-bearing solid-acid catalysts namely phthalimide-*N*-sulfonic acid (PhtSA) and isatin-*N*-sulfonic acid (IsSA) for the solvent-free production of bis-coumarins from 4-hydroxycoumarin (2 eq.) and arylaldehydes (1 eq.). It is noteworthy that our catalysts have none of the above-mentioned drawbacks at all.

Experimental

All starting materials and solvents were obtained from Merck, Fluka or Acros Chemical Companies. Phthalimide-*N*-sulfonic acid and isatin-*N*-sulfonic acid were produced according to our reported methods (Scheme 1) [21,22]. The known compounds were identified by comparing their melting points/spectroscopic data with those reported in the literature. Monitoring progress of the reactions was achieved by thin layer chromatography (TLC). The melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. ^{1}H NMR (250 or 400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance DPX, FT-NMR spectrometer.



Scheme 1. The synthesis of phthalimide-*N*-sulfonic acid (PhtSA) and isatin-*N*-sulfonic acid (IsSA)

General procedure for the production of bis-coumarins

A mixture of 4-hydroxycoumarin (0.324 g, 2 mmol), arylaldehyde (1 mmol) and PhtSA (0.045 g, 0.20 mmol) [or IsSA (0.045 g, 0.20 mmol)] was initially stirred magnetically at 80 °C (for PhtSA) or 85 °C (for IsSA), and after that the reaction mixture was solidified. Besides, it was stirred by a small rod at the same temperatures. Progressing the reaction was monitored by TLC (*n*-hexane/ethyl acetate: 3/1). When the reaction was completed, EtOAc (2 mL) was added, stirred for 2 min, and filtered (to separate the unsolved catalyst). The filtrate was evaporated, and the resulting precipitate was recrystallized from ethanol (96%) to give the pure product.

Selected NMR data of bis-coumarins

Product 3

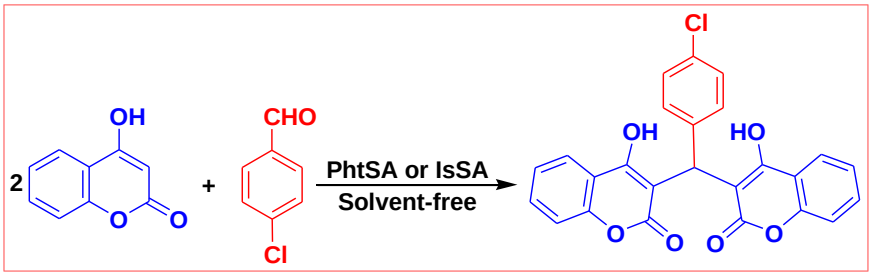
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.26 (s, 3H, CH_3), 5.47 (br., 2H, 2OH), 6.34 (s, 1H, Ar-CH), 7.04 (s, 4H, H_{Ar}), 7.33-7.40 (m, 4H, H_{Ar}), 7.62 (t, *J* = 7.8 Hz, 2H, H_{Ar}), 7.91 (d, *J* = 7.9 Hz, 2H, H_{Ar}); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.0, 36.0, 105.1, 116.6, 117.7, 124.3, 124.6, 127.1, 129.2, 132.7, 135.4, 136.1, 152.5, 164.9, 165.5.

Product 5

^{1}H NMR (250 MHz, DMSO-d_6): δ 5.05 (br., 2H, 2OH), 6.35 (s, 1H, Ar-CH), 7.22-7.31 (m, 4H, H_{Ar}), 7.46-7.60 (m, 4H, H_{Ar}), 7.83 (d, *J* = 7.8 Hz, 2H, H_{Ar}), 7.89 (s, 1H, H_{Ar}), 7.98 (d, *J* = 7.8 Hz, 1H, H_{Ar}).

Results and discussion

To optimize the reaction conditions, the condensation of 4-hydroxycoumarin (2 mmol) with 4-chlorobenzaldehyde (1 mmol) was examined in the presence of different mole percents of PhtSA as well as IsSA at range of 70-90 ºC in the absence of solvent (Scheme 2); the resulting data are summarized in Tables 1 and 2. According to the data, the best catalyst amount and temperature for PhtSA were 20 mol% and 80 ºC (Table 1, Entry 2), and for IsSA were 20 mol% and 85 ºC (Table 2, Entry 2).



Scheme 2. The condensation of 4-hydroxycoumarin with 4-chlorobenzaldehyde

Table 1. Optimization of conditions for the reaction of 4-hydroxycoumarin with 4-chlorobenzaldehyde using PhtSA

Entry	Mol% of PhtSA	Temp. (ºC)	Time (min)	Yield (%)[a]
1	15	80	20	84
2	20	80	10	97
3	22	80	10	97
4	20	70	25	91
5	20	85	10	97

[a]Isolated yield

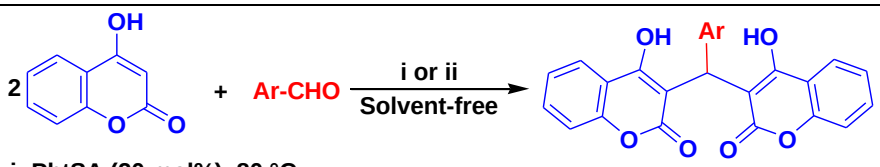
Table 2. Optimization of conditions for the reaction of 4-hydroxycoumarin with 4-chlorobenzaldehyde using IsSA

Entry	Mol% of IsSA	Temp. (ºC)	Time (min)	Yield (%)[a]
1	17	85	10	92
2	20	85	10	96
3	22	85	10	96
4	20	80	15	89
5	20	90	10	96

[a]Isolated yield

After obtaining the optimal conditions, evaluating efficiency and generality of PhtSA as well as IsSA for the synthesis, 4-hydroxycoumarin reacted with arylaldehydes bearing electron-releasing, electron-withdrawing and halogen substituents on ortho, meta and para positions in the presence of these catalysts; the results are given in Table 3. As the data in this Table illustrate, the two catalysts effectively promoted the reactions to provide the relevant bis-coumarins with high to excellent yields in short times when arylaldehyde possessing electron-releasing and halogen substituents were utilized. Nevertheless, arylaldehydes bearing NO_2-substituent afforded the products in lower yields and in longer reaction times in comparison to the other aldehydes (Table 3, products 5 and 6).

Table 3. The production of bis-coumarins using PhtSA and IsSA

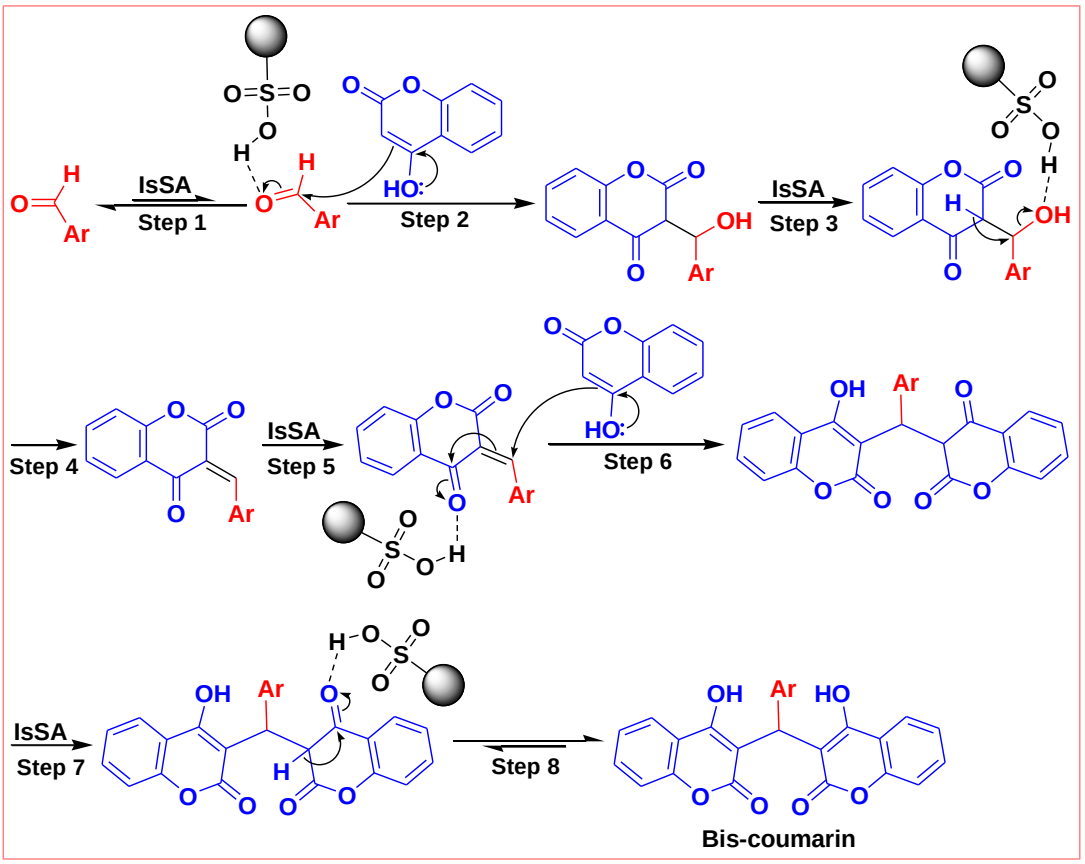


i: PhtSA (20 mol%), 80 °C
ii: IsSA (20 mol%), 85 °C

Product No.	Ar	PhtSA	IsSA	M.p. °C (Lit.)
		Time[a]/Yield[b]	Time[a]/Yield[b]	
1	C_6H_5	10/96	10/96	227-229 (227-230) [12]
2	4-$MeOC_6H_4$	15/95	20/94	249-251 (251-253) [15]
3	4-MeC_6H_4	10/96	10/91	265-268 (268-270) [12]
4	3-$MeOC_6H_4$	15/90	20/92	234-236 (232-234) [31]
5	3-$O_2NC_6H_4$	20/85	20/88	235-237 (236-238) [13]
6	4-$O_2NC_6H_4$	20/81	20/83	230-232 (232-233) [15]
7	2-BrC_6H_4	20/90	15/86	257-259 (259-261) [12]
8	4-FC_6H_4	10/94	10/95	216-218 (214-216) [15]
9	4-ClC_6H_4	10/97	10/96	256-257 (258-260) [13]
10	2,4-$Cl_2C_6H_3$	10/96	15/91	260-262 (262-264) [12]

[a]Time in min
[b]Isolated yield in %

A plausible mechanism, based on the literature [32], was proposed for the synthesis (Scheme 3). PhtSA and IsSA achieve three roles in the reaction by their acidic hydrogens: (i) activation of carbonyl groups to accept nucleophilic attack (steps 2 and 6), (ii) assistance for removing H_2O (step 4), and (iii) acceleration of tautomerization (step 8).



Scheme 3. The proposed mechanism for the production of bis-coumarins

In another study, the results and reaction conditions of PhtSA and IsSA were compared with those in some reported catalysts; the results are given in Table 4. As it can be seen in this table, PhtSA and IsSA afforded better results (in terms of yield, temperature and/or solvent and/or time) in comparison to the other catalysts.

Table 4. Comparison of the results and reaction conditions of PhtSA and IsSA with the reported catalysts

Catalyst	Conditions	Time range	Yield range	Ref.
PhtSA	Solvent-free, 80 °C	10-20	81-97	This work
IsSA	Solvent-free, 85 °C	10-20	83-96	This work
Melamine trisulfonic acid	H_2O, 80 °C	12-46	75-97	[12]
Poly(4-vinylpyridine)-supported ionic liquid	Toluene, 80 °C	36-60	90-95	[13]
Starch-sulfuric acid	Solvent-free, 80 °C	5-15	80-95	[14]
CuO-CeO_2 nanocomposite	H_2O, Reflux	8-45	89-94	[15]
$RuCl_3.nH_2O$	H_2O, 80 °C	25-35	75-95	[16]
Choline hydroxide	H_2O, 50 °C	60-180	81-99	[17]
Trityl bromide	Solvent-free, 100 °C	18-35	76-92	[19]

$[Fe_3O_4@SiO_2@(CH_2)_3$-Im-$SO_3H]Cl$	Solvent-free, 100 °C	10-27	79-94	[19]
Ethylene glycol	90 °C	60-120	83-91	[20]
W-doped ZnO nanocomposite	H_2O, 80 °C	15-120	90-98	[31]
Sulfonic-acid-functionalized pyridinium chloride	Solvent-free, 80 °C	12-21	80-93	[32]

Conclusion

Briefly, we have introduced two SO_3H-bearing solid-acid catalysts, namely phthalimide-*N*-sulfonic acid and isatin-*N*-sulfonic acid, for the preparation of bis-coumarins. The advantages of the presented protocols include: high efficacy and generality of the catalysts, good to excellent yields, short reaction times, simple synthesis of the catalysts from available and inexpensive starting materials, easy work-up and purification of the products, relatively mild conditions, application of solvent-free technique, and good compliance with the green chemistry protocols.

Acknowledgements

We thank Research Council of Payame Noor University for the financial support of this work.

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How to cite this manuscript: Abdolkarim Zare, Jalal Sanjideh. "Phthalimide-*N*-sulfonic acid and Isatin-*N*-sulfonic acid as highly efficient catalysts for the synthesis of bis-coumarins". *Iranian Chemical Communication*, 2019, 7(2), 139-145.