available at www.sciencedirect.com journal homepage: www.elsevier.com/locate/chnjc

Article

Succinimide-*N*-sulfonic acid catalyzed synthesis of bis(indolyl)methane and coumarin derivatives under mild conditions

Farhad Shirini*, Nader Ghaffari Khaligh

Department of Chemistry, Faculty of Sciences, University of Guilan, Rasht 41335, Post Box: 1914, I.R. Iran

ARTICLE INFO

Article history:

Received 16 June 2013

Accepted 15 July 2013

Published 20 October 2013

Keywords:

Succinimide-*N*-sulfonic acid

Multi-component reaction

Bis(indolyl)methane

Coumarin

Mild reaction condition

ABSTRACT

A mild and simple procedure is described for the synthesis of bis(indolyl)methane and coumarin derivatives using succinimide-*N*-sulfonic acid as an efficient, cheap, and reusable catalyst under mild conditions.

© 2013, Dalian Institute of Chemical Physics, Chinese Academy of Sciences.

Published by Elsevier B.V. All rights reserved.

1. Introduction

Indole is an important heterocyclic compound with a variety of natural and synthetic derivatives that have diverse pharmaceutical properties [1–3]. Among these, bis(indol-3-yl)methanes (BIMs) constitute an old but privileged class of bioactive metabolites [4–6]. Oxidized forms of BIMs are utilized as dyes [7] and colorimetric sensors [8]. Thus there is much interest in the synthesis of this class of compounds, and many approaches and a variety of reagents for their synthesis have been devised [9–11]. In some cases, more than the stoichiometric amounts of many Lewis acids are required because the acids are deactivated by the nitrogen atom of the indoles [12]. The use of lanthanide triflates for this purpose has shown promise [13]. However, lanthanide triflates are rather expensive, thus their use for large scale operation is not economical and some lanthanide triflates suffer from the formation of byproducts, long reaction time, and corrosion as well as waste acid pollution

problems. Therefore, there is still a large demand for the development of mild synthesis conditions using stable, recoverable, and reusable catalysts.

Coumarin and its derivatives are widely used as additives in food, perfumes, agrochemicals, cosmetics, and pharmaceuticals [14]. Coumarins also act as intermediates for the synthesis of furocoumarins, chromenes, coumarones, and 2-acylresorcinols [15]. Moreover, coumarin-based dyes and pigments are used for dye lasers, anion sensors, organic light emitting diodes, and solar cells [16]. The use of various catalysts for their synthesis has been reported in the literature [17]. Most of these methods suffer from severe drawbacks including the use of a large amount of catalysts (for example, sulfuric acid was used in a 10–12 equivalent excess), long reaction time in some cases, low yields, formation of side products, and usually temperatures up to 150 °C (e.g., an aluminum chloride catalyst required a temperature of 130 °C in nitrobenzene). These shortcomings show the need for a safer, more convenient, and efficient method.

* Corresponding author. Tel/Fax: +98-131-3233262; E-mail: shirini@guilan.ac.irDOI: 10.1016/S1872-2067(12)60669-X | <http://www.sciencedirect.com/science/journal/18722067> | Chin. J. Catal., Vol. 34, No. 10, October 2013

2. Experimental

2.1. General

All chemicals were purchased from Merck, Aldrich, or Fluka Chemical Companies and were used without further purification. Products were characterized by their physical constants and comparison with model samples. The purity of the substrates and reaction monitoring were performed by thin-layer chromatography (TLC) using silica gel SIL G/UV 254 plates. The MS spectra were measured using 70 eV electrons. The IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. In all the cases, ^1H NMR spectra were recorded with a Bruker Avance 400 or 300 MHz instrument. The ^{13}C NMR data were collected on a Bruker Avance 100 or 75 MHz instrument. All chemical shifts are given in parts per million (ppm) relative to TMS using a deuterated solvent. Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus with open capillary tubes.

2.2. General procedure for the synthesis of bis(indolyl)methane derivatives

Succinimide-*N*-sulfonic acid (SuSA, 5.0 mg, 0.05 mmol) was added to a stirred solution of an aldehyde (1 mmol) and indole or 2-methyl indole (2 mmol) in CH_3CN (2 mL). The mixture was vigorously stirred at room temperature. After completion of the reaction (monitored by TLC), the product was extracted with 3×10 mL of cold ethylacetate. The solvent was evaporated at reduced pressure and the remaining solid was recrystallized from a mixture of ethanol-water to afford the pure product. After extraction of the product, the volatiles were removed by evacuation under vacuum and the remaining SuSA was collected and reused for the next run. All the known products gave spectral and physical data consistent with those reported in the literature and samples prepared using previously reported methods. The new products were characterized by their melting point, IR, ^1H NMR, and mass spectrometry. The spectral data of selected products are as follows.

6-(1*H*-indol-3-yl)benzo[*b*]carbazole. Yellow solid; mp: 130–132 °C; IR (KBr) $\nu = 3400, 1620, 1453, 1204\text{ cm}^{-1}$; ^1H NMR (CDCl_3 , 400 MHz) $\delta = 7.31\text{--}7.35$ (m, 7H), 7.62 (t, $J = 7.8$ Hz, 2H), 7.83 (s, 1H), 7.88 (s, 1H, -NH), 8.06 (d, $J = 8.0$ Hz, 1H), 8.16 (d, $J = 8.0$ Hz, 1H), 8.28 (d, $J = 7.8$ Hz, 1H), 8.57 (s, 1H), 8.66 (s, 1H); MS (m/z): 332.0 [M^+].

4-[Bis(1*H*-indol-3-yl)methyl]benzaldehyde. Pink solid; mp: 205–207 °C; IR (KBr) $\nu = 3406, 1736, 1651, 1363, 1215\text{ cm}^{-1}$; ^1H NMR (CDCl_3 , 400 MHz) $\delta = 5.93$ (s, 1 H), 6.65 (t, $J = 1.6$ Hz, 2H), 7.04 (m, 2H), 7.22 (m, 2H), 7.36 (m, 4H), 7.43 (d, $J = 8.2$ Hz, 2H), 7.54 (d, $J = 6.6$ Hz, 2H), 8.05 (br s, 2H), 9.86 (s, 1H); MS (m/z): 350.1 [M^+].

1,4-Bis[di(1*H*-indol-3-yl)methyl]benzene. Pink solid; mp: 139–141 °C; IR (KBr) $\nu = 3405, 3049, 1622, 1455, 1216\text{ cm}^{-1}$; ^1H NMR (CDCl_3 , 400 MHz) $\delta = 5.79$ (s, 2 H), 6.31 (s, 4H), 7.04 (dd, $J = 8.0$ and 7.2 Hz, 4H), 7.18 (dd, $J = 7.6$ and 7.2 Hz, 4H),

7.25 (s, 4H), 7.29 (d, $J = 8.0$ Hz, 4H), 7.40 (d, $J = 7.6$ Hz, 4H), 7.45 (br s, 4H); MS (m/z): 556.2 [M^+].

Tri(1*H*-indol-3-yl)methane. Orange solid; mp: 244–246 °C; IR (KBr) $\nu = 3386, 1624, 1428\text{ cm}^{-1}$; ^1H NMR (CDCl_3 , 400 MHz) $\delta = 6.70$ (s, 1H), 7.34–7.38 (m, 6H), 7.42–7.49 (m, 3H), 7.88 (s, 3H), 8.35 (m, 3H, $J = 7.8$ Hz), 8.80 (s, 3H); MS (m/z): 362.1 [$\text{M}+1$] $^+$.

3,3-Bis(1*H*-indol-3-yl)indolin-2-one. Pale yellow needles; mp: 311–313 °C; IR (KBr) $\nu = 3440, 3399, 1695\text{ cm}^{-1}$; ^1H NMR (CDCl_3 , 400 MHz) $\delta = 6.94\text{--}6.99$ (m, 6H), 7.13 (dd, 3H, $J = 7.6, 8.0$ Hz), 7.31–7.38 (m, 5H), 7.74 (s, 1H), 8.11 (s, 2H); MS (m/z): 363.1 [$\text{M}+1$] $^+$.

3,3-Bis(2-methyl-1*H*-indol-3-yl)indolin-2-one. Yellow solid; mp: 300–301 °C; IR (KBr) $\nu = 3400, 3250, 1700\text{ cm}^{-1}$; ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) $\delta = 1.97$ (s, 3H), 2.11 (s, 3H), 6.47 (d, $J = 7.4$ Hz, 1H), 6.62–6.66 (m, 2H), 6.73 (d, $J = 8.0$ Hz, 1H), 6.83–6.91 (m, 3H), 6.96 (d, $J = 7.6$ Hz, 1H), 7.16 (d, $J = 7.4$ Hz, 1H), 7.21–7.24 (m, 3H), 10.57 (s, 1H), 10.87 (s, 1H), 10.90 (s, 1H); MS (m/z): 391.1 [M^+].

Tris(2-methyl-1*H*-indol-3-yl)methane. Orange solid; mp: 335–337 °C; IR (KBr) $\nu = 3397, 1618, 1461, 1427, 1340, 1297, 1218\text{ cm}^{-1}$; ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) $\delta = 1.93$ (s, 9H), 6.10 (s, 1H), 6.62 (t, $J = 8.0$ Hz, 3H), 6.78 (d, $J = 8.0$ Hz, 3H), 6.85 (t, $J = 8.0$ Hz, 3H), 7.18 (d, $J = 8.1$ Hz, 3H), 10.61 (br s, 3H); MS (m/z): 390.1 [$\text{M}+1$] $^+$.

2.3. General procedure for the preparation of coumarins

A mixture of the phenol derivative (1 mmol), β -keto ester (1 mmol), and SuSA (25 mg, 0.096 mmol) was stirred at 50 °C under solvent-free conditions. After completion of the reaction (monitored by TLC), EtOAc (2×10 mL) was added to the resulting solidified mixture, and the catalyst was separated by decantation. The organic phase was washed with water (2×5 mL) and dried over MgSO_4 . Evaporation of the solvent under reduced pressure yielded the crude product, which was purified by recrystallization in ethanol or ethanol-water to give the pure product as colorless prisms, pale yellow, or white powders. The recovered catalyst, after drying, was reused in the next run without further purification. All of the synthesized coumarin derivatives were identified by their physical and spectral data. In addition, the melting points were measured for all of the products and were compared with the corresponding reported melting points. The spectral data of the selected products are as follows.

6,5-Hydroxy-3,4,7-trimethylcoumarin. White crystals; mp: 249–251 °C (ethanol); IR (KBr) $\nu = 3216, 3028, 2986, 1675, 1620, 1283, 1120, 1062\text{ cm}^{-1}$; ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) $\delta = 2.04$ (s, 3H), 2.27 (s, 3H), 2.53 (s, 3H), 6.57 (s, 2H), 10.32 (brs, 1H, OH); MS (m/z): 204 [M^+].

5,7-Dihydroxy-3,4-dimethylcoumarin. White crystals; mp: 290–293 °C (ethanol/water); IR (KBr) $\nu = 3269, 2920, 1675, 1615, 1561, 1383, 1358, 1285, 1167, 1056\text{ cm}^{-1}$; ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) $\delta = 1.24$ (s, 1H), 2.06 (s, 3H), 2.56 (s, 3H), 6.20 (dd, $J = 9.05$ Hz, $J = 3.01$ Hz, 2H), 9.75 (s, 1H); MS (m/z): 206 [M^+].

7,8-Dihydroxy-4-methylcoumarin. Colorless crystals; mp

240–242 °C (ethanol/water); IR (KBr) ν = 3417, 3231, 1675, 1620, 1584, 1441, 1155, 810 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ = 2.36 (s, 3H), 6.12 (s, 1H), 6.86 (d, J = 8.6 Hz, 1H), 7.11 (d, J = 8.6 Hz, 1H), 9.42 (s, 1H), 10.01 (s, 1H); MS (m/z): 192 [M^+].

3. Results and discussion

In a continuation of our ongoing research program on the development of new catalysts and methods for organic transformations, an earlier report from our laboratory described the synthesis of SuSA and its application in the chemoselective trimethylsilylation of alcohols and phenols [18], *N*-Boc protection of amines [19], synthesis of the xanthenes derivatives [20], and the acetylation reactions [21]. Here, we report the use of this catalyst for the synthesis of bis(indolyl)methane and coumarin derivatives under mild conditions (Scheme 1).

We first compared the effect of different solvents in the synthesis of bis(indol-3-yl)methanes using SuSA. The results are summarized in Table 1. Acetonitrile was the best solvent for the synthesis of bis(indol-3-yl)methanes.

In addition, the effect of catalyst amount on reaction yield was explored. The results are shown in Table 2. The best result was obtained using 5 mol% of the catalyst.

After optimizing the conditions, the generality of this method was examined by the reaction of several substituted aryl aldehydes with indole and 2-methylindole. As shown in Table 3, aromatic and heterocyclic aldehydes underwent smooth transformation to the corresponding bis(indolyl)methanes in good to excellent yields in relatively short reaction time. The IR spectra of the bis(1*H*-indol-3-yl)methane derivatives showed the characteristic IR absorption at 3747–3170 (N–H), 1676–1660 (aromatic C=C), and 1613–1580 (C=C–N) cm^{-1} . In addition to substituent, aromatic and/or heteroaromatic proton signals, the ^1H NMR spectra displayed signals at δ = 8.80–8.05 (br s, NH), and at δ = 5.7–4.85 (s, =CH–R, R = aryl, hetaryl) or 3.78–3.77 (t, =CH–R, R = *n*-alkyl), respectively.

It is also worth noting that the reaction is general and is applicable to various aromatic ketones (Table 3, entries 21–23, 25, and 31) to afford the corresponding bis(indolyl)methanes in high yields. Aromatic ketones required increasingly more time for the completion of the reaction because of the steric crowding effect. In addition, the present methodology was found to be applicable for the preparation of bis(indolyl)methanes from 2-methylindole and aldehydes (Table 3, entries 26–32) in excellent yields.

Table 1
Optimization of the solvent.

Entry	Solvent	Isolated yield (%)
1	Toluene	18
2	Dichloromethane	25
3	Methanol	75
4	Ethanol	82
5	Acetonitrile	96

Reaction of 4-chlorobenzaldehyde (1 mmol) with indole (2 mmol) in the presence of SuSA (10 mol%) at room temperature for 1 h.

Table 2
Screening of the amount of catalyst.

Entry	Amount of SuSA (mol%)	Isolated yield (%)
1	—	N.R.
2	2	55
3	5	96
4	10	96

Reaction of 4-chlorobenzaldehyde (1 mmol) with indole (2 mmol) in the presence of SuSA at room temperature for 1 h.

In an attempt to produce the corresponding bis(indolyl)methane, *o*-phthalaldehyde was reacted with indole (in a 1:2 ratio) in dry acetonitrile in the presence of SuSA (Scheme 2). The reaction was completed after 80 min and afforded the 6-(indol-3-yl)benzo[*b*]carbazole in 84% yield (Table 3, entry 13) [22]. Selective condensation of terephthalaldehyde to the corresponding bis(indolyl)methane was achieved by controlling the molar ratio of indole (Scheme 2).

The results showed that the addition of 2 equivalents of indole to terephthalaldehyde gave 4-[bis-(1*H*-indol-3-yl)methyl]benzaldehyde in 86% yield (Table 3, entry 14). 1,4-Bis[di(1*H*-indol-3-yl)methyl]benzene was synthesized in 89% yield (Table 3, entry 15) by the electrophilic substitution reaction of indole with terephthalaldehyde (4:1 molar ratio). It is noteworthy that 1,4-bis[di(1*H*-indol-3-yl)methyl]benzene was obtained as the sole product of the reaction, which was in contrast to our previous procedure [23]. Indole-3-carboxaldehyde reacted smoothly with indole and 2-methylindole to produce tris(indolyl) and tris(methylindole) methane in 95% and 92% yields, respectively (Table 3, entries 24 and 32).

The probable mechanism of the reaction is shown in Scheme 3. In this mechanism, SuSA activates the aldehyde for the electrophilic attack of indole to generate the azafulvaline intermediate (**I**). The reaction is followed by the nucleophilic addition of the second indole molecule onto the azafulvaline intermediate.

Scheme 1. Synthesis of bis(indolyl)methane and coumarin derivatives using SuSA under mild conditions.

Table 3Synthesis of bis(indolyl)methanes in the presence of SuSA under solvent-free conditions ^a.

Entry	R ²	Substrate	Time (min)	Isolated yield (%)	mp (°C)
1	H	C ₆ H ₅ -CHO	45	96	123–125
2	H	4-Cl-C ₆ H ₄ -CHO	32 (32, 38, 45) ^b	96 (94, 90, 90) ^b	87–89
3	H	2-Cl-C ₆ H ₄ -CHO	34	95	77–78
4	H	4-CH ₃ O-C ₆ H ₄ -CHO	55	92	195
5	H	3,4-(CH ₃ O) ₂ -C ₆ H ₄ -CHO	60	92	197–199
6	H	4-CH ₃ -C ₆ H ₄ -CHO	32	95	99–100
7	H	4-NO ₂ -C ₆ H ₄ -CHO	30	98	245–246
8	H	3-NO ₂ -C ₆ H ₄ -CHO	40	92	261–263
9	H	4-Br-C ₆ H ₄ -CHO	34	96	111–113
10	H	C ₆ H ₅ -CH=CH-CHO	45	92	100–102
11	H	2-OH,4-Cl-C ₆ H ₃ -CHO	40	94	79–81
12	H	2-furaldehyde	28	97	322–324
13	H	1,2-C ₆ H ₄ -(CHO) ₂	80	84	135–137 ^c
14	H	1,4-C ₆ H ₄ -(CHO) ₂	28	86	207–210 ^d
15	H	1,4-C ₆ H ₄ -(CHO) ₂	45	89	139–141 ^e
16	H	4-OH-C ₆ H ₄ -CHO	60	92	210–212
17	H	2-OH-C ₆ H ₄ -CHO	55	91	103–105
18	H	3-CH ₃ O,4-OH-C ₆ H ₃ -CHO	75	89	100–103
19	H	CH ₃ CH ₂ CH ₂ CHO	80	92	oil
20	H	CH ₃ (CH ₂) ₅ -CHO	80	94	68–70
21	H	C ₆ H ₅ -CO-CH ₃	90	84	169–171
22	H	4-Cl-C ₆ H ₅ -CO-CH ₃	85	85	109–110
23	H	4-NO ₂ -C ₆ H ₅ -CO-CH ₃	78	90	274–276
24	H	3-indolecarbaldehyde	62	95	245–247
25	H	isatin	50	96	244–245
26	Me	C ₆ H ₅ -CHO	40	95	244–246
27	Me	3,4-(CH ₃ O) ₂ -C ₆ H ₄ -CHO	60	91	204–206
28	Me	4-NO ₂ -C ₆ H ₄ -CHO	40	96	240–242
29	Me	4-OH-C ₆ H ₄ -CHO	65	88	240–242
30	Me	4-CH ₃ -C ₆ H ₄ -CHO	45	92	175–177
31	Me	isatin	70	92	300–302
32	Me	3-indolecarbaldehyde	75	92	260–262

^a Desired products were characterized by the comparison of their spectral and physical data with those of known compounds. ^b Reusability of the catalyst. ^c 6-(1*H*-indol-3-yl)benzo[*b*]carbazole was obtained [22]. ^d Indole:dialdehyde = 2:1. ^e Indole:dialdehyde = 4:1.

Scheme 2. Selective condensation of *o*-phthalaldehyde and terephthalaldehyde with indole in the presence of SuSA at room temperature.

Some previously reported data on the reaction conditions and the yield of the product in the preparation of 3,3'-bis-in-

dolylphenylmethane (Table 3, entry 1) are compared with our results in Table 4. As can be seen, our results compared very

Scheme 3. Mechanism for the synthesis of bis(indolyl) methane derivatives.

well with the previously reported yield, catalyst amount, and reaction time.

The reusability of SuSA was also studied. The first run gave 94% yield after 32 min. Subsequently, the catalyst was collected by filtration, washed with EtOAc, dried at ambient temperature, and used again. The same procedure was repeated four times. As shown in Table 3 (entry 2), even after three cycles, SuSA still gave excellent yields. This showed that SuSA can be reused without significant loss of activity.

After the successful synthesis of the bis(indolyl)methanes, we decided to explore the synthesis of coumarin derivatives using SuSA as the catalyst. At the beginning of this study, resorcinol and ethyl acetoacetate (EAA) were employed as model reactants. The model reaction was tried out using different solvents under reflux reaction conditions as well as the solvent-free system for 1 h reaction time. Also, the model reaction was carried out at many temperatures in the presence of various amounts of SuSA. The results are summarized in Table 5.

The resorcinol conversion increased with increasing temperature up to 50 °C. However, with further increase in temperature, no significant improvement was observed in the yield

and reaction time. There was no significant difference in conversion between 50 and 60 °C (Table 5, entries 8 and 9). The yield of 7-hydroxy-4-methylcoumarin decreased with decreasing amount of SuSA. When 5 mol% SuSA was added, the reaction yield was 94% (Table 5, entry 8), and when 2 mol% SuSA was added, the reaction yield decreased to 69% (Table 5, entry 10). Interestingly, no reaction took place in the absence of catalyst after 1 h (Table 5, entry 1). The best result was achieved under solvent-free conditions because when the reaction was carried out in a solvent under reflux conditions, a longer reaction time was required, which gave a smaller yield. The best result was obtained when 5 mol% SuSA was used at 50 °C in the absence of a solvent. The Pechmann condensation reaction of other phenols and ethyl acetoacetate in the presence of SuSA was accomplished under the optimized reaction conditions (Scheme 1).

It can easily be seen in Table 6 that the Pechmann condensation proceeded smoothly under solvent-free conditions and gave good to excellent yields. The reaction worked well with phenols containing electron-donating and electron-withdrawing substituents on the aromatic ring.

Table 4

Comparison of our results with previously reported data for the synthesis of 3,3'-bis(indolyl)phenylmethane.

Entry	Catalyst	Reaction condition	Time	Catalyst content	Yield (%)	Ref.
1	(PhCH ₂ PPh ₃) ⁺ Br ³⁻ / SiO ₂	solvent-free, 90 °C	16 min	5 mol	80	[23]
2	lanthanide triflate	EtOH/H ₂ O	12 h	solution (0.1 mol/L)	95	[24]
3	indium trichloride	CH ₃ CN	4 h	0.2 mol	96	[25]
4	Zeokarb-225	CH ₃ CN	7.5 h	0.5 g	95	[26]
5	[hmim]HSO ₄	EtOH	1 h	0.01 mol	97	[27]
6	aminosulfonic acid	EtOH/H ₂ O(N ₂ atm)/ultrasound	30 min	1.5 mol	93	[28]
7	SuSA	CH ₃ CN, r.t.	45 min	0.05 mol	96	this work

Table 5

Effect of temperature, solvent, and amount of SuSA catalyst on the synthesis of 7-hydroxy-4-methylcoumarin.

Entry	Amount of catalyst (mol%)	Temperature (°C)	Solvent	Isolated yield (%)
1	—	60	solvent-free	trace
2	5	reflux	toluene	42
3	5	reflux	methanol	66
4	5	reflux	ethanol	68
5	5	reflux	acetonitrile	72
6	5	reflux	dichloromethane	56
7	5	r.t.	solvent-free	88
8	5	50	solvent-free	94
9	5	60	solvent-free	95
10	2	60	solvent-free	69

Reaction of resorcinol (5 mmol) with ethyl acetoacetate (5 mmol) in presence of SuSA as a catalyst for 1 h.

Table 6

Pechmann synthesis of coumarin derivatives in the presence of SuSA under solvent-free conditions.

Entry	Substrate	β -Keto ester	Time (min)	Isolated yield (%)	mp (°C)
1	1,3-(OH) ₂ -C ₆ H ₄	EAA	20 (20, 22, 22) ^a	94 (94, 92, 92) ^a	185–187
		MEAA	25	90	257–259
2	3-CH ₃ -1,5-(OH) ₂ -C ₆ H ₃	EAA	30	90	250–252
		MEAA	40	85	248–250
3	3-CH ₃ O-1,5-(OH) ₂ -C ₆ H ₃	EAA	25	90	122–124
4	3-CH ₃ (CO)-1,5-(OH) ₂ -C ₆ H ₃	EAA	25	84	170–171
5	C ₆ H ₅ -OH	EAA	60	75	78–80
6	1,3,5-(OH) ₃ -C ₆ H ₃	EAA	15	96	288–290
		MEAA	20	90	290–293
7	2-CH ₃ -1,3-(OH) ₂ -C ₆ H ₃	EAA	35	85	138–139
8	4-NO ₂ -C ₆ H ₄ -OH	EAA	40	82	151–154
9	2-NO ₂ -C ₆ H ₄ -OH	EAA	65	62	183–185
10	1,2,3-(OH) ₃ -C ₆ H ₃	EAA	25	90	240–242
		MEAA	30	86	250–252
11	4-CH ₃ O-C ₆ H ₄ -OH	EAA	30	89	167–169
12	4-Cl-C ₆ H ₄ -OH	EAA	40	86	235–237
13	3-CH ₃ O-C ₆ H ₄ -OH	EAA	35	90	158–160
14	3-CH ₃ -C ₆ H ₄ -OH	EAA	32	80	218–220
15	1-naphthol	EAA	40	74	154–156
16	2-naphthol	EAA	38	78	186–188

Reaction conditions: substrate, 5.0 mmol; EAA or MEAA, 5.0 mmol. ^a Reusability of the catalyst. **Scheme 4.** Mechanism for the Pechmann reaction of resorcinol with EAA in the presence of SuSA at 50 °C under solvent-free conditions.

As compared with resorcinol, the yield of the reaction of orcinol (Table 6, entry 2) with EAA was a bit low. This may be due to steric hindrance by the methyl group in the ortho position to hydroxylalkylation, and this was also reflected by the higher yields in entries 1 and 6 as compared, respectively, with entries 2 and 10 in Table 6. In general, substrates having electron-donating groups *para* to the site of the electrophilic substitution gave high yields in the slightly shorter time. This is due to the fact that an electron-donating group enhances the electron density at the *para*-position to it, which in turn makes that position more susceptible to electrophilic attack. The reaction of 1-naphthol with EAA was slow (Table 6, entry 14), and only a moderate yield was obtained. Phenol (Table 6, entry 5) gave a lower yield, and it required longer reaction time because of the lack of an electron-donating group. The present method tolerates a variety of functional groups such as ether, hydroxyl, acetyl, and halo. It was observed that 2-naphthol gave the linear coumarin as the sole product without any angular coumarin or chromone.

The reactivity of two different β -keto esters namely, EAA and α -methyl ethyl acetoacetate (MEAA) was compared under the optimized reaction conditions (Table 6, entries 1, 2, 6, and 10). The reactivity order for β -keto esters was EAA > MEAA.

The suggested mechanism for the synthesis of 7-hydroxy-4-methylcoumarin in the presence of SuSA as a Brönsted acid

catalyst under solvent-free conditions is shown in Scheme 4. In this mechanism, SuSA catalyzes the reaction of hydroxyalkylation by the activation of EAA, making the carbonyl group susceptible to nucleophilic attack by resorcinol. The transesterification and dehydration occur simultaneously at two sites to produce 7-hydroxy-4-methylcoumarin and regenerates the catalyst.

We have also studied the catalytic activity of recycled SuSA for the synthesis of 7-hydroxy-4-methylcoumarin. After separation of the product, the catalyst was washed with EtOAc and evacuated under vacuum to remove EtOAc. The resulting catalyst was reused for the next run. As shown in Table 6 entry 1, the Brönsted acid SuSA can be recycled at least four times without significant decrease in catalytic activity, with yields ranging from 94% to 92%.

4. Conclusions

The Brönsted acid succinimide-*N*-sulfonic acid (SuSA) is a catalyst that has high efficiency in the synthesis of bis(indolyl)methane and coumarin derivatives. The reaction of the condensation of aldehydes with indole or 2-methyl indole in acetonitrile as a solvent at room temperature and phenols with ethyl acetoacetate (EAA) or α -methyl ethyl acetoacetate (MEAA) at 50 °C under solvent-free conditions gave good to

Graphical Abstract

Chin. J. Catal., 2013, 34: 1890–1896 doi: 10.1016/S1872-2067(12)60669-X

Succinimide-*N*-sulfonic acid catalyzed synthesis of bis(indolyl)methane and coumarin derivatives under mild conditions

Farhad Shirini*, Nader Ghaffari Khaligh
University of Guilan, Iran

The present article describes the applicability of succinimide-*N*-sulfonic acid (SuSA), as a newly reported catalyst, in the promotion of the synthesis of bis(indolyl)methanes and coumarin derivatives. All reactions are performed under mild conditions in good to high yields.

excellent yields. The present method has several advantages such as high reaction rates and excellent yields, no side reaction, ease of preparation and handling of the catalyst, cost efficiency (inexpensive catalyst with lower loading), and a simple experimental procedure.

Acknowledgements

We are thankful to the University of Guilan Research Council for the partial support of this work.

References

- [1] El-Gamal A A, Wang W L, Duh C Y. *J Nat Prod*, 2005, 68: 815
- [2] Endo T, Tsuda M, Fromont J, Kobayashi J. *J Nat Prod*, 2007, 70: 423
- [3] Garbe T R, Kobayashi M, Shimizu N, Takesue N, Ozawa M, Yukawa H. *J Nat Prod*, 2000, 63: 596
- [4] Sirisoma N, Pervin A, Drewe J, Tseng B, Cai S X. *Bioorg Med Chem Lett*, 2009, 19: 2710
- [5] Gribble G W. In: *Comprehensive Heterocyclic Chemistry*. Vol. 2. 2nd Ed. New York: Pergamom Press, 1996. 211
- [6] Frost J M, Dart M J, Tietje K R, Garrison T R, Grayson G K, Daza A V, El-Kouhen O F, Miller L N, Li L L, Yao B B, Hsieh G C, Pai M, Zhu C Z, Chandran P, Meyer M D. *J Med Chem*, 2008, 51: 1904
- [7] Novak T J, Kramer D N, Klapper H, Daasch L W, Murr B L. *J Org Chem*, 1976, 41: 870
- [8] Martinez R, Espinosa A, Tarraga A, Molina P. *Tetrahedron*, 2008, 64: 2184
- [9] Pal B, Giri V S, Jaisankar P. *Catal Commun*, 2005, 6: 711
- [10] Bandgar B P, Patil A V, Kamble V T. *ARKIVOC*, 2007, Part (xvi): 252
- [11] Deb M L, Bhuyan P J. *Tetrahedron Lett*, 2007, 48: 2159
- [12] Kobayashi S, Araki M, Yasuda M. *Tetrahedron Lett*, 1995, 36: 5773
- [13] Li X, Wang J Y, Yu W, Wu L M. *Tetrahedron*, 2009, 65: 1140
- [14] O'Kennedy R, Thornes R D. *Coumarins: Biology Application and Mode of Action*. Chichester: Wiley, 1997. 23
- [15] Sethna S M, Shah N M. *Chem Rev*, 1945, 36: 1
- [16] Key J A, Koh S, Timerghazin Q K, Brown A, Cairo C W. *Dyes Pigm*, 2009, 82: 196
- [17] Li T S, Zhang Z H, Yang F, Fu C G. *J Chem Res (S)*, 1998: 38
- [18] Shirini F, Khaligh N G. *Phosphorus, Sulfur Silicon Relat Elem*, 2011, 186: 2156
- [19] Shirini F, Khaligh N G. *Monatsh Chem*, 2012, 143: 631
- [20] Shirini F, Khaligh N G. *Dyes Pigm*, 2012, 95: 789
- [21] Shirini F, Khaligh N G. *Chin J Catal* (催化学报), 2013, 34: 695
- [22] Black D StC, Craig D C, Santoso M. *Tetrahedron Lett*, 1999, 40: 6653
- [23] Shirini F, Langroodi M S, Abedini M. *Chin Chem Lett*, 2010, 21: 1342
- [24] Xia M, Wang S H, Yuan W B. *Synth Commun*, 2004, 34: 3175
- [25] Babu G, Sridhar N, Perumal P T. *Synth Commun*, 2000, 30: 1609
- [26] Magesh C J, Nagarajan R, Karthik M, Perumal P T. *Appl Catal A*, 2004, 266: 1
- [27] Gu D G, Ji S J, Jiang Z Q, Zhou M F, Loh T P. *Synlett*, 2005: 959
- [28] Li J T, Dai H G, Xu W Z, Li T S. *Ultrason Sonochem*, 2006, 13: 24