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ORIGINAL PAPER

L-Proline catalyzed condensation of salicylaldehydes with ethyl nitroacetate: an efficient access to 3-nitrocoumarins

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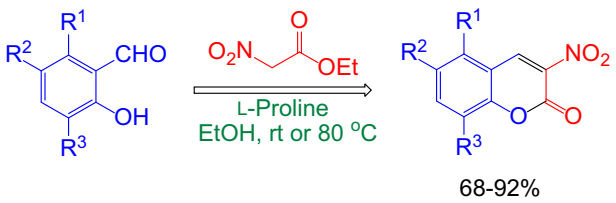
Abstract L-Proline catalyzed condensation of salicylaldehydes and ethyl nitroacetate afforded 3-nitrocoumarins in good to high yields under mild conditions. This organocatalyzed process offers a much improved yield of 3-nitrocoumarins and well tolerates both electron-donating and electron-withdrawing substituents on the phenyl ring.

Graphical abstract



Keywords Coumarins · 3-Nitrocoumarins · L-Proline · Organocatalysis · Salicylaldehyde

Introduction

Coumarin is a well-known structural motif found in a variety of natural products and synthetic molecules. Coumarin compounds exhibit a broad range of biological activities [1–3] and are also widely employed as materials because of their remarkable optical properties [4, 5]. Therefore, the development of synthetic protocols that enable the synthesis of these compounds has attracted a great deal of interest; especially over the past decade. The Pechmann, Perkin, Knoevenagel, and Wittig reactions involving condensation of phenols with carbonyl compounds are some of the well established classic methods [6, 7] for their synthesis. Recently, a number of transition metal-catalyzed routes have also been developed for the obtention of functionalized coumarins [8]. It is well established that the properties of coumarin compounds depend largely on the nature and position of substituents [1, 2]. In particular it has been shown that the presence of nitrogen-containing substituent at 3-position of coumarin moiety induces specific properties [9–11]. For instance, coumarins bearing 3-nitro substituent are important scaffolds having pharmaceutical and synthetic utility. They have been reported as an efficient inhibitor of phospholipase C enzyme and as promising antifungal and antimicrobial agents [10–15]. Moreover, they are also used as precursors of aminocoumarins and other important molecules [16–22]. The methods reported in the literature for the synthesis of 3-nitrocoumarins are commonly based on direct nitration of unsubstituted coumarin with nitric acid and condensation reaction of salicylaldehydes with active methylenes [12, 23–27]. However, these methods suffer from several drawbacks such as use of strong acids or bases, long reaction times, complicated purification process, low functional group tolerance, and low yield (Scheme 1a). Therefore, it is strongly desirable to develop improved methodologies for the synthesis of 3-nitrocoumarins.

L-Proline has been reported as a promising catalyst in various chemical transformations such as Knoevenagel, Aldol, and Michael reactions. L-Proline is a bifunctional

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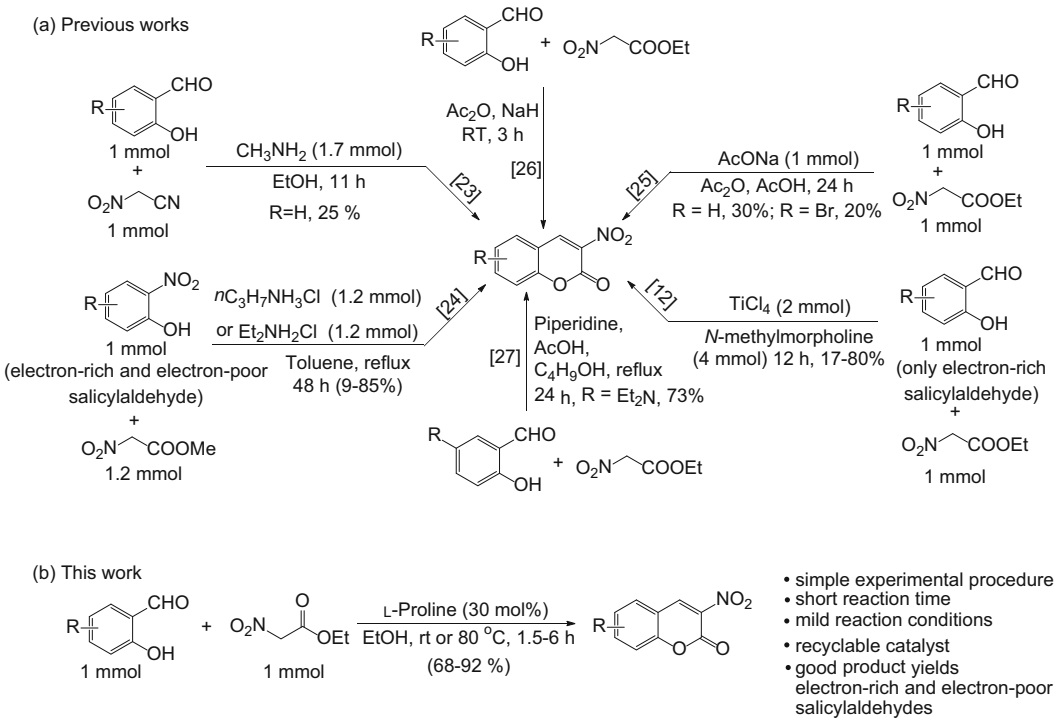
Scheme 1



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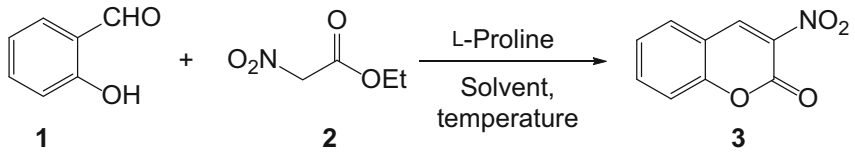
catalyst and its catalytic action mainly involves the easy and rapid formation of iminium ion and enamine intermediates with carbonyl compounds [28, 29]. To the best of our knowledge, no example of L-proline catalyzed synthesis of 3-nitrocoumarins has been reported so far. Herein we wish to report a simple and efficient protocol for the synthesis of 3-nitrocoumarins via L-proline catalyzed condensation of salicylaldehydes and ethyl nitroacetate (Scheme 1b).

Results and discussion

The commercially available ethyl nitroacetate (**2**) is very expensive; we have therefore synthesized it economically and in much improved yield by modification of earlier reported method [30]. In an initial investigation, we conducted a model reaction between salicylaldehyde (**1**) and **2** in the presence of 30 mol % of L-proline in acetonitrile at rt (40–42 °C) for 6 h to afford desired product **3** in 30 % yield (Table 1, entry 1). To further improve the reaction yield, a series of solvents were examined. When the reaction was performed in DCM, 68 % conversion was observed (6 h; Table 1, entry 2). To our delight, the reaction proceeded well in ethanol in a much shorter reaction time of 4 h, affording the desired product **3** in 85 % yield (Table 1, entry 3). Notably, the reaction did not occur satisfactorily in toluene, THF, and DMF and no product formation was detected in case of water (Table 1, entries 4–7). Further, the yield of the product **3** remained almost the same with an increased catalyst loading of 40 mol % (Table 1, entry 8) and declined remarkably when the reaction was performed at lower catalyst loadings of 20, 10, and 5 mol % (Table 1, entries 9–11). In addition, increase in the reaction temperature resulted in the formation of some unidentified side products and low yields of coumarin **3** (Table 1, entries 12–15).12

With the optimized reaction conditions in hand, the substrate scope of this methodology was explored by varying salicylaldehyde **4** (Table 2). A variety of salicylaldehydes **4a**–**4h** were compatible with the reaction conditions and the corresponding coumarin products were obtained in good to excellent yields (68–92 %, 1.5–6 h, entries 1–8). Electron-donating substitutents such as 6-hydroxy (**5a**), 6-methyl (**5b**), 8-methoxy (**5c**), 8-ethoxy (**5d**) on the aryl moiety were effectively converted to the corresponding 3-nitrocoumarins in good yields. Electron-withdrawing groups including 6-chloro (**5e**), 6-bromo (**5f**), and 6-nitro (**5g**) were also well tolerated to afford the desired coumarins. However, in case of **5c**–**5g** heating was needed to accelerate the reaction rate. Further, the scope of this reaction could be expanded from the phenyl to

Table 1 Optimization of reaction conditions for the synthesis of **3**



1 2 3

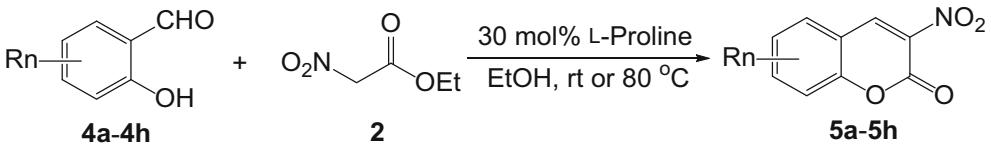
Entry	Proline/mol %	Solvent	Temp./°C	Time/h	Yield/%[a]
1	30	CH_3CN	rt	6	30
2	30	DCM	rt	6	68
3	30	C_2H_5OH	rt	4	85[b]
4	30	Toluene	rt	8	Trace
5	30	THF	rt	8	18
6	30	DMF	rt	8	Trace
7	30	Water	rt	8	0
8	40	C_2H_5OH	rt	4	83
9	20	C_2H_5OH	rt	8	69
10	10	C_2H_5OH	rt	12	57
11	5	C_2H_5OH	rt	20	35
12	30	C_2H_5OH	80	3	75
13	20	C_2H_5OH	80	6	58
14	10	C_2H_5OH	80	5	48
15	5	C_2H_5OH	80	8	32

Reaction conditions: **1** (1 mmol), **2** (1 mmol), L-proline (30 mol %), 3 cm^3 ethanol, rt, 4 h

[a] Isolated yields

[b] M.p.: 141–142 °C (Ref. [12] M.p.: 141–142 °C)

Table 2 Synthesis of 3-nitrocoumarin derivatives



4a-4h 2 5a-5h

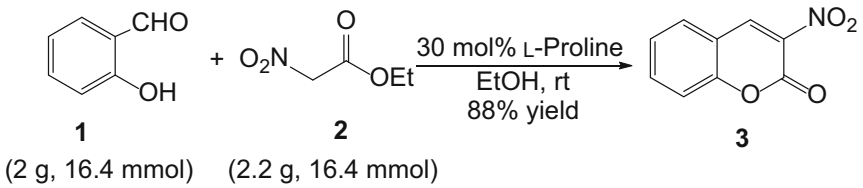
Entry	Substrate Rn=	Time/h	Prod.	Yield/%[a]	M.p./°C (obs)	M.p./°C (lit)
1	5-OH	4	**5a**	75	208–209	215–218 [12]
2	5-CH_3	5	**5b**	82	Sticky solid	–
3	3-CH_3O	4	**5c**[b]	81	179–180	187.5–188.5 [24]
4	3-CH_3CH_2O	5	**5d**[b]	76	180–181	–
5	5-Cl	6	**5e**[b]	82	136–137	176–177 [24]
6	5-Br	6	**5f**[b]	78	182–183	200 [25], 207–208 [24]
7	5-NO_2	6	**5g**[b]	68	174–175	179.5–180.5 [24]
8	5,6-Benzo	1.5	**5h**	92	225–226	–

Reaction conditions: 4 (1 mmol), 2 (1 mmol), L-proline (30 mol %) in 3 cm^3 ethanol at rt for given hours

[a] Isolated yield

[b] Reaction was conducted at 80 °C

Scheme 2



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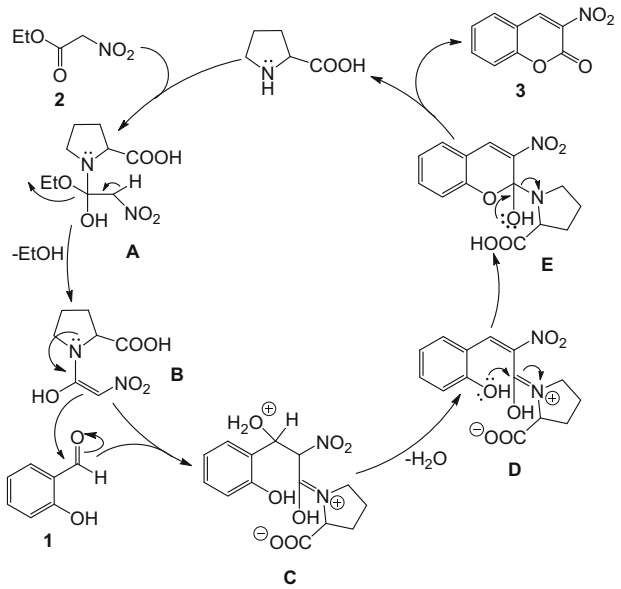
Scheme 3



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naphthyl system, leading to the formation of benzocoumarin **5h** in excellent yield (92 %, Table 2, entry 8) with significantly shorter reaction time than the others. Notably, benzocoumarins are an important class of compounds found in a variety of naturally occurring molecules such as arnottin and gilvocarcin [31].

Furthermore, to demonstrate the synthetic utility of the present protocol, a gram scale synthesis was performed reacting **1** and **2** under the standard reaction conditions to afford the desired product **3** in high yield as shown in Scheme 2.

Finally, recycling experiments carried out during the synthesis of **3** showed that the catalyst can be reused in up to three runs without any appreciable loss of activity.

A plausible mechanism of the reaction is shown in Scheme 3. We assume that the initial interaction of L-proline with **2** generates an enamine intermediate **B**, which undergoes nucleophilic addition to the aldehyde **1** to produce intermediate **C**. Subsequent dehydration provides an intermediate **D**, which undergoes cyclization via intermediate **E** to afford the desired product **3** [32].

Conclusion

In conclusion, we have developed an efficient, mild, and environmentally benign method for the preparation of 3-nitrocoumarins from salicylaldehydes and ethyl nitroacetate using a catalytic amount of L-proline. The method yielded 3-nitrocoumarins in good to high yields under mild conditions. Most importantly, both electron rich and electron deficient salicyaldehydes were well tolerated under the reaction conditions. The resulting substituted coumarins can be subjected to different functional group transformations to produce other compounds of chemical and biological importance. The biological evaluation of synthesized compounds and the extension of this methodology to the synthesis of some new bioactive molecules are currently in progress in our laboratory.

Experimental

Unless otherwise stated, all common reagents and solvents were obtained from commercial suppliers (Sigma-Aldrich and Spectrochem Pvt. Ltd.) and were used without further purification. Melting points were determined on a Büchi 510 apparatus. Column chromatography was carried on silica gel (60–120 mesh). Reactions were monitored by thin-layer chromatography (TLC) using pre-coated, glass-backed silica gel plates and visualization of the developed chromatogram was performed by UV absorbance (254 nm) and by iodine vapors. ESI mass spectra were recorded using Quattro II (Micromass). IR spectra were recorded on a JASCO FTIR 5300 in KBr from 400 to 4000 cm^{-1}. NMR spectra were recorded on JEOL FT-NMR spectrometer using tetramethylsilane (TMS) as internal standard. The chemical shift values are on δ scale and the coupling constant (J) are in Hertz (Hz). The data of ^1H NMR was reported in the order: chemical shift, multiplicity

(s = singlet, d = doublet, t = triplet, m = multiplet and br = broad), coupling constant, and integration.

*General procedure for the synthesis of 3-nitrocoumarins **3** and **5***

To the solution of salicylaldehyde (1 mmol) and ethyl nitroacetate (1 mmol) in 3 cm^3 ethanol, L-proline (30 mol %) was added. The reaction mixture was stirred for an appropriate time. After completion of the reaction (as monitored by TLC), the solvent was evaporated and the product so obtained was dissolved in 12 cm^3 $CHCl_3$ and washed with water (3 × 10 cm^3). The organic layer was washed with 10 cm^3 brine, dried over anhydrous $NaSO_4$, and evaporated under reduced pressure. The residue was recrystallized from ethanol (**3**, **5a**, **5b**, and **5h**) or purified by silica gel column using chloroform/methanol (9:1) as eluent (**5c**–**5g**). The combined aqueous layers, containing L-proline, were evaporated, washed with ether, dried at 45 °C, and reused for next run.

6-Methyl-3-nitrocoumarin (**5b**, $C_{10}H_7NO_4$)

Light yellow sticky solid; $R_f = 0.36$ (20 % ethyl acetate/hexane); IR (KBr): $\overline{V}$ = 3083, 2929, 1742, 1620, 1345, 851 cm^{-1}; ESI MS: $m/z = 206$ ($[M + H]^+$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.54$ (s, 1H), 7.34 (m, 3H), 2.47 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.0, 145.3, 140.6, 136.1, 129.6, 129.3, 123.1, 120.1, 118.6, 19.2 ppm.

8-Ethoxy-3-nitrocoumarin (**5d**, $C_{11}H_9NO_5$)

Light yellow solid; $R_f = 0.32$ (20 % ethyl acetate/hexane); IR (KBr): $\overline{V}$ = 3081, 2940, 1746, 1567, 1456, 1341, 863 cm^{-1}; ESI MS: $m/z = 236$ ($[M + H]^+$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.63$ (s, 1H), 7.72 (m, 2H), 7.41 (d, $J = 9.6$ Hz, 1H), 4.16 (q, $J = 6.8$ Hz, 2H), 1.51 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.4, 150.9, 144.3, 138.9, 137.1, 128.6, 121.2, 117.5, 115.0, 64.9, 14.8 ppm.

2-Nitro-3H-benzo[f]chromen-3-one (**5h**, $C_{13}H_7NO_4$)

Yellow solid; $R_f = 0.41$ (20 % ethyl acetate/hexane); IR (KBr): $\overline{V}$ = 3065, 1757, 1598, 1560, 1511, 1345, 822 cm^{-1}; ESI MS: $m/z = 242$ ($[M + H]^+$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.58$ (s, 1H), 8.31 (d, $J = 8.4$ Hz, 1H), 8.24 (d, $J = 9.3$ Hz, 1H), 7.99 (d, $J = 7.8$ Hz, 1H), 7.84 (t, $J = 7.5$ Hz, 1H), 7.69 (m, 1H), 7.53 (d, $J = 9.0$ Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3, 151.4, 138.7, 137.9, 137.6, 129.5, 129.1, 126.4, 121.5, 115.5, 107.1 ppm.

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