Iranian Journal of Catalysis 5(2), 2015, 149-153

IRANIAN JOURNAL OF CATALYSIS

L-Proline catalyzed synthesis of Betti bases and biscoumarin derivatives

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Received 20 June 2014; received in revised form 25 July 2014; accepted 27 November 2014

ABSTRACT

The direct three component modified Mannich reaction via condensation of aldehydes, 2-naphthol or 2,7-naphthalendiol and piperidine to generate Betti bases has been carried out over L-proline (20 mol%) with high efficiency under solvent-free conditions at 70°C. Also, the reaction of aromatic aldehyde and 4-hydroxycoumarin in the presence of L-proline (20 mol%) in the ethanol under reflux conditions, lead to biscoumarin derivatives.

***Keywords**: Mannich type reaction; Betti base; L-proline; Biscoumarin; Multicomponent reaction.*

1. Introduction

Multicomponent reactions [1–3] have become important tools for the rapid generation of molecular complexity and diversity with predefined functionality in chemical biology and drug discovery [4-6]. These reactions are often discovered by serendipity, but rational design strategies are now playing an increasing role because of their convergent nature, superior atom economy, and straightforward experimental procedures in the construction of target compounds by the introduction of several diversity elements in a single operation, resulting in substantial minimizations of waste, labor, time, and cost [7]. Further, chemo and stereoselectivities of MCRs have been widely accepted as a significant challenging task for synthetic organic chemists [8]. A consequence of the necessity to minimize the amount of toxic waste and by-products from chemical processes is a need for the development of more environmentally friendly and resource-saving synthetic methods in which fewer toxic substances are used. Nowadays in the development of new syntheses, ecological points of view must also be taken into consideration due importance in the assessment of viability [9,10]. The ideal Mannich reaction would involve a catalytic process employing directly the unmodified carbonyl donor, amine, and acceptor aldehyde in one pot [11]. The aminonaphthol product became known in the literature as a Betti base, and the protocol as the Betti reaction [12,13]. The syntheses of a wide-ranging library of racemic and nonracemic Betti base derivatives were recently reviewed, with especial attention to the possibilities of their application as building blocks [14]. These compounds can be transformed into derivatives having antibacterial, hypotensive, and bradycardiac activities [15]. There are very few reports available using Brønsted acid surfactant [16], neutral and efficient non-ionic surfactant [17], nanocrystalline MgO [18] and $Cu(OTf)_2{\cdot}SiO_2$ catalyst [19]. However, some of these methods suffer from at least one of the following disadvantage: high cost and toxicity of the reagent and solvent. Also, the coumarin derivatives have received considerable attention because they possess several types of pharmacological properties, such as antibacterial, anticancer, anti-HIV, anticoagulant, antioxidant and spasmolytic activities [20]. A number of methods have been reported for the synthesis of biscoumarins by reaction of 4-hydroxycoumarin and various aldehydes [21-28]. Fortunately, L-proline, an inexpensive and readily available biomimetic, has become a mostly promising catalyst in many reactions [29-31]. Herein, we wish to report the use of L-proline catalyzed one-pot three component synthesis of Betti bases (Scheme 1) and biscoumarin derivatives.

2. Experimental

2.1. General

All chemicals were purchased from Merck chemical company. Melting points were recorded on an electro-

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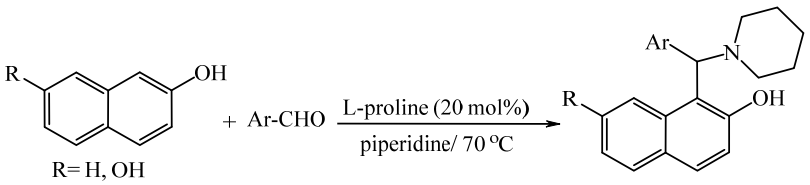


Scheme 1. L-proline catalyzed synthesis of Betti bases.

thermal melting point apparatus. The NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 with TMS as an internal standard on a Bruker Avance DRX 400 MHz spectrometer. IR spectra were determined on an SP-1100, P-UV-Com instrument.

2.2. General Method for the Synthesis of Betti bases

A mixture of 2–naphthol (1 mmol) or 2,7-naphthalendiol (1mmol), aromatic aldehyde (1mmol), piperidine (1 mmol) and L-proline (20 mol%) was stirred at 70 °C for the appropriate time, as shown in Table 1. Completion of the reaction was indicated by TLC monitoring. The reaction mixture was cooled to ambient temperature, and the crude solid residue was recrystallized from ethanol to afford pure crystals of the proper 1-(aryl(piperidin-1-yl)methyl)-naphthalen-2-ol in 90-96% yields. The products were characterized by FT-IR, ^{1}HNMR, ^{13}CNMR and by comparison of their physical constants with those of authentic samples.

Selected spectral data

Table 1, entry 8:

FT-IR (KBr): $\bar{\nu}$ = 3446, 2933, 2852, 1616, 1558, 1506, 1458, 1355, 1315, 1265, 1151, 875 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.29-2.20 (m, 10H), 5.04 (s, 1H), 7.17-7.85 (m, 10H), 14.17 (brs, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ= 24.1, 26.0, 51.9, 54.9, 72.1, 109.5, 115.8, 116.4, 119.0, 121.1, 122.8, 128.0, 128.9, 129.4, 129.7, 129.8, 130.6, 130.9, 139.3, 155.9 ppm. White solid; m.p.= 115-117°C.

Table 1, Entry 9:

FT-IR (KBr): $\bar{\nu}$ = 3453, 2856, 1623, 1558, 1504, 1456, 1363, 1309, 1220, 1139, 835 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.48-2.32 (m, 10H), 4.99 (s, 1H), 6.77-7.57 (m, 10 H), 9.5 (brs, 1H), 13.67 (brs, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ= 23.5, 25.6, 45.5, 52.3, 70.7, 103.4, 114.3, 114.5, 115.9, 116.1, 122.6, 127.6, 128.6, 129.03, 130.1, 133.6, 139.9, 155.3, 155.8 ppm. White solid; m.p.= 209-210°C.

Table 1, Entry 10:

FT-IR (KBr): $\bar{\nu}$ = 3396, 2945, 2856, 1627, 1558, 1510, 1456, 1433, 1373, 1272, 1218, 833 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.45-2.34 (m, 10H), 5.14 (s, 1H), 6.81-7.61 (m, 8 H), 7.2 (brs, 1H), 9.67 (brs, 1H) ppm. ^{13}CNMR (100 MHz, DMSO-d_6): δ= 23.52, 25.51, 52.14, 52.21, 68.85, 103.4, 114.6, 116, 122.6, 127.10, 127.17, 127.32, 127.51, 129.4, 130.26, 133.54, 134.16, 155.32, 156.11 ppm. White solid; m.p. = 188-190 °C.

Table 1, Entry 11:

FT-IR (KBr): $\bar{\nu}$ = 3365, 2933, 2858, 1618, 1558, 1508, 1458, 1361, 1209, 1128, 831 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.48-2.33 (m, 10H), 4.86 (s, 1H), 6.68-7.57 (m, 9 H), 9.02 (brs, 1H), 13.76 (brs, 1H) ppm; ^{13}CNMR (100 MHz, DMSO-d_6): δ= 23.5, 25.6, 45.2, 52.3, 70.2, 103.5, 114.9, 115.1, 116.1, 122.6, 128.5, 129.0, 129. 9, 130.0, 133.7, 155.2, 155.7, 156.8 ppm. White solid; m.p. = 210-211°C.

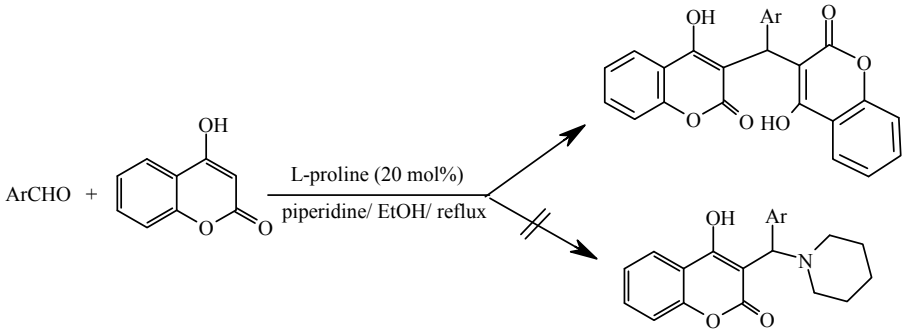
2.3. General procedure for the synthesis of biscomarin derivatives

A solution of aromatic aldehyde (1 mmol), 4-hydroxycoumarin (2 mmol), and L-proline (0.02 g) in 5 mL ethanol (96%) was stirred at reflux temperature for the appropriate times (Table 2). Upon completion of the reaction, monitored by TLC, the reaction mixture was allowed to cool to room temperature. The solid was filtered off and washed with water and purified by recrystallization from ethanol. The structures of all products were characterized by FT-IR, ^{1}H-NMR and by comparison of their physical constants with those of authentic samples.

3. Results and Discussion

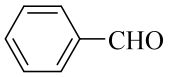
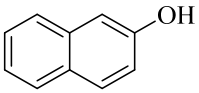
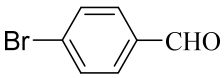
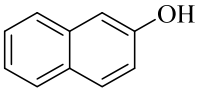
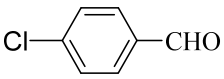
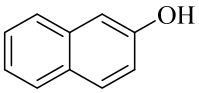
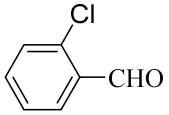
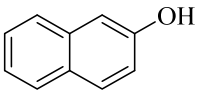
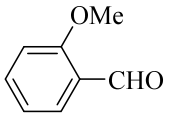
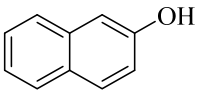
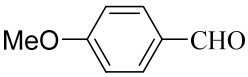
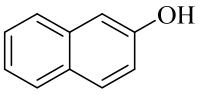
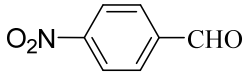
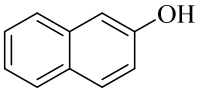
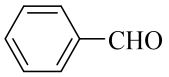
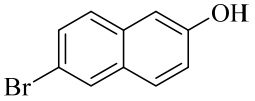
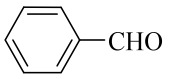
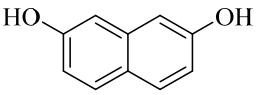
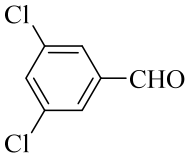
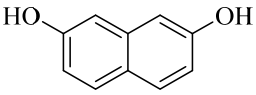
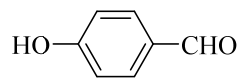
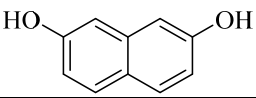
A variety of Betti bases was prepared from aldehydes, piperidine and 2-naphthol in the presence of L-proline (20 mol%) under solvent free conditions at 70°C in excellent yields (Table 1, entries 1-8). Also, this reaction performed with 2,7-naphthalendiol and the corresponding product was achieved in very good yields under similar conditions (Table 1, entries 9-11). It is worth mentioning that the corresponding Betti bases were isolated by crystallization from the crude filtrate.

In addition, the reactions worked well with electron-donating or electron-withdrawing substituent. However, in the absence of L-proline, the reaction proceeds with a low yield after a long reaction time (24 h). The reaction of arylaldehyde, 4-hydroxycoumarin and piperidine in the presence of L-proline lead to biscoumarin derivatives and piperidine remained unchanged (Scheme 2).



Scheme 2. L-proline catalyzed synthesis of biscoumarin derivatives.

Table 1. Synthesis of Betti bases catalyzed by L-proline[a].

Entry	Aldehyde	2-naphthol	Time (h)	Yield %[b]
1			4	91
2			3	95
3			3	94
4			3.5	92
5			4	90
6			3.5	94
7			2.5	96
8			3.5	95
9			3	93
10			3.5	95
11			4	94

[a]Reaction and conditions: 2-naphthol (1 mmol) or 2,7-naphthalendiol (1 mmol), aldehyde (1 mmol), piperidine (1 mmol) and L-proline (20 mol%) at 70 °C under solvent-free conditions.
[b]Isolated yields.

Encouraged by this result, we extended this reaction to preparation of a variety of biscoumarin derivatives from 4-hydroxycoumarin and aldehydes using L-proline (20 mol%) in ethanol under reflux conditions in excellent yields. The results are summarized in Table 2. In a plausible mechanism, is assumed that, the L-proline activated carbonyl group of aldehyde via protonation (I), followed by the nucleophilic attack of piperidine nitrogen on carbonyl group of activated aldehyde leads to intermediate (II), then attacking of 2-naphthol carbon to iminium ion intermediate (II) and subsequent shifting of hydrogen atom (III) leads to the formation of product and release the L-proline (Scheme 3).

4. Conclusions

In conclusion, we have developed a simple, clean, step economic, efficient, and one-pot procedure for the synthesis of Betti bases and biscoumarin derivatives in high yields using L-proline catalyst.

Acknowledgment

We are grateful to Islamic Azad University of Rasht Branch for financial support.

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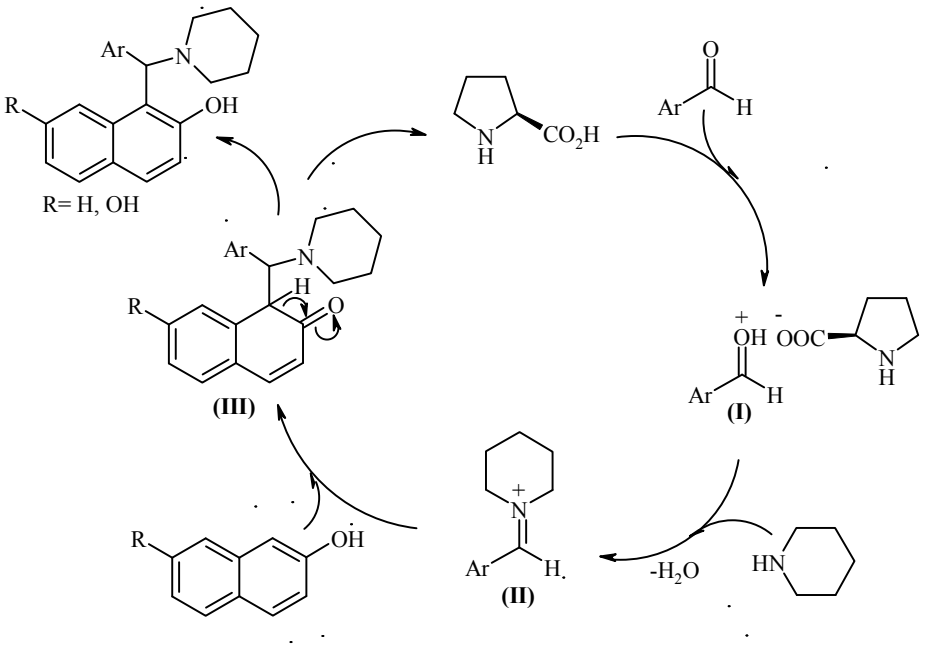
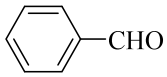
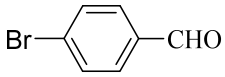
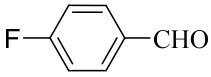
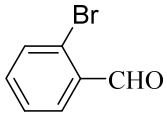
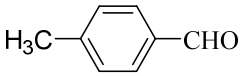
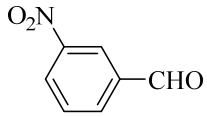
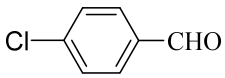
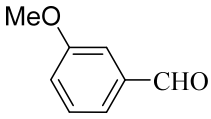
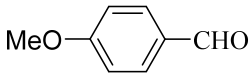
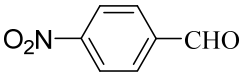


Scheme 3. A plausible mechanism for the synthesis of Betti bases.

Table 2. Synthesis of biscoumarin derivatives catalyzed by L-proline[a].

Entry	Aldehyde	Time (min)	Yield %[b]	m.p. (°C)		Ref.
				Found	Reported	
1		45	94	229-231	230-232	[25]
2		30	95	266-268	265-268	[25]
3		30	96	212-214	213-215	[25]
4		35	94	202-204	203	[21]
5		40	92	265-267	266-268	[25]
6		30	96	233-235	234-236	[25]
7		35	96	254-256	256-258	[25]
8		45	93	236-238	238	[21]
9		45	92	242-244	246-248	[25]
10		30	97	232-234	232-234	[25]

[a]Reaction and conditions: 4-hydroxycoumarin (2 mmol), aldehyde (1 mmol) and L-proline (20 mol%) in ethanol (5 mL) under reflux conditions.
[b]Isolated yields.

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