Indian Journal of Advances in Chemical Science

Article

2-Pyrrolidin-2yl-1H-benzimidazole (PBI): An efficient organocatalyzed synthesis of β-sulphido carbonyl compounds

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ABSTRACT

An efficient and organocatalytic synthetic protocol has been developed involving 2-Pyrrolidin-2yl-1H-benzimidazole (PBI) catalyzed synthesis of β-sulfido carbonyl compounds through reaction of thiophenols with α,β-unsaturated carbonyl compounds in good and excellent yield under mild reaction conditions. The synthetic process for PBI organocatalyst has also been developed. The synthesized organocatalyst was further employed for the synthesis of β-sulfido carbonyl compounds using α,β-unsaturated carbonyl compounds as substrates. We investigated the appropriated reaction condition by screening different solvents and conditions. The optimized reaction conditions further utilized to generate the library of β-sulfido analogues. All the synthesized analogs were characterized using spectroscopic and spectrometric techniques.

Key words: 2-Pyrrolidin-2yl-1H-benzimidazole, Conjugate addition, Thio-Michael reaction, Organocatalysis.

1. INTRODUCTION

Conjugate addition reaction of thiols to α,β-unsaturated carbonyl compounds is among the most widely used methods for carbon-sulfur bond formation in synthetic organic chemistry [1-3]. Conjugate addition of thiols to activated olefins or α,β-unsaturated carbonyl compounds, is called thio-Michael reaction. Thio-Michael reaction is one of the classical carbon-sulfur bond forming processes in organic chemistry [4-8]. Thio-Michael addition reactions have been used as key steps in the synthesis of numerous biologically active compounds [9-11] as well as in biosynthesis [12]. Nucleophilic activation and electrophilic activation are two different pathways available for synthesis of β-sulfido carbonyl compounds [13]. A number of efficient methods for the preparation of β-sulfido carbonyl compounds have been developed [14-21]. Recently, there were also some reports of this reaction conducted in water [22] and ionic liquids [23-26]. Although a variety of reagents such as Copper (II) tetrafloroborate [27], cyclodextrin [28], polyethylene glycol [29], azaphosphtrane nitrate [30], $HClO_4/SiO_2$ [31], and sodium dodecyl sulphate [32] have been used but due to their high cost and non-availability, they are not used for large scale production. However, above methods are often associated with several drawbacks such as use of expensive catalyst [17,20], long reaction time [17,30], high temperature [23,24], and using toxic chemicals [25,26]. The development of new, simple, convenient, and environmentally benign synthetic protocol remains an active research area in the field of medicinal chemistry.

The use of organocatalyst in organic synthesis has been increasing form past few years [33,34]. In recent years, organocatalyst has attracted much interest in organic synthesis because of their low toxicity, ready availability, stability, and operational simplicity. Meanwhile broad spectrums of organic transformations [35-39] are performed through organocatalysis and the research is still in the focus of interest. Over the past few years, proline derivatives [40] have been studied extensively due to their usefulness as organocatalyst in various asymmetric transformations. To the best of our knowledge, there are no convenient methods for the synthesis of a β-sulfido carbonyl compounds. Here in, we wish to report a novel, general, and efficient method that employs a organocatalyzed thio-Michael addition reaction of thiophenol to α,β-unsaturated carbonyl compound for the synthesis of a β-sulfido carbonyl compounds.

2. EXPERIMENTAL

All the reagents were purchased from Sigma-Aldrich Chemical Co, Lancaster and were used directly without further any purification. NMR spectra were obtained using the Brucker DRX 200 MHz spectrometer. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. Mass spectra were obtained using JEOL SX-102 (FAB+) instrument. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light.

2.1. Preparation of Organocatalyst

The mixture of 1 (1 mol eq.) and 2 (1 mol eq.) was dissolved in a solution of 5 N HCl (25 ml). The mixture was refluxed at 100°C for 4–5 days and cool down to room temp. The reaction mixture was then neutralized with a 5 N solution of NaOH in water, then extracted with ethyl acetate and the resulting organic layer dried over Na_2SO_4. The solvent was evaporated in vacuo to give pure 2-Pyrrolidin-2yl-1H benzimidazole as a light brown powder.

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ISSN NO: 2320-0898 (p); 2320-0928 (e)
DOI: 10.22607/IJACS.2022.1004007

Received: 18th October 2022;
Revised: 21th October 2022;
Accepted: 25th October 2022

2.2. 2-Pyrrolidin-2yl-1H benzimidazole

13C NMR (300 MHz, DMSO-d6): δ: 157.69, 134.10, 120.26, 116.48, 113.74, 55.21, 45.68, 31.21, 24.62, MS (ESI) m\z: 211 (M+23)

MP: 102-105ºC.

IR (KBr): 3190, 2964, 2365, 1622, 1429, 1326, 1273, 1089, 749 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d6): 7.48-7.45 (m, 2H), 7.18-7.08 (m, 2H), 6.52-6.35 (m,1H), 4.37-4.32 (m, 1H), 3.01-2.88 (m, 2H), 2.51-2.50 (m, 1H), 2.20-2.08 (m, 1H), 2.03-1.89 (m, 1H), 1.84-1.68 (m, 2H).

MS (ESI) m\z: 211 (M+23)

2.3. General experimental procedure for thio-Michael reaction

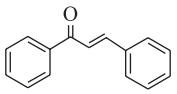
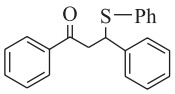
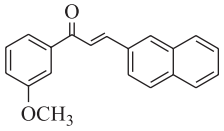
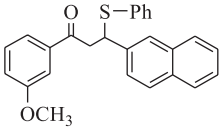
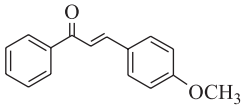
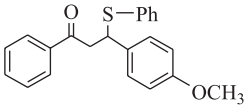
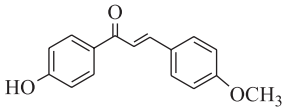
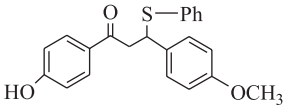
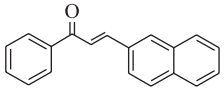
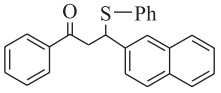
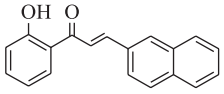
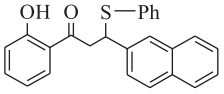
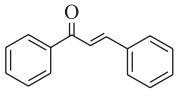
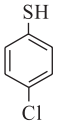
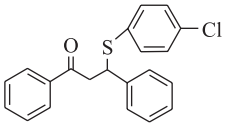
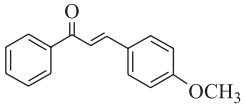
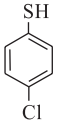
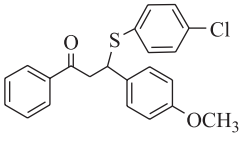
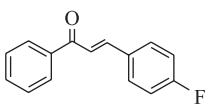
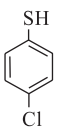
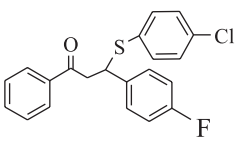
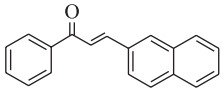
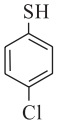
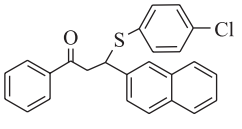
To a stirred solution of the α, β-unsaturated compound (1 mmol) in methanol (2 mL), 2-Pyrrolidine-2yl-1H-benzoimidazole (5 mol%) followed by addition of thio phenols (1.9 mmol) and the reaction mixture was vigorously stirred at room temperature for the specified time (Table 1). After completion of the reaction, as indicated by TLC, the solvent was removed under vacuum and the residue was washed with water, hexane and then distilled ethanol. The residue was dried under vacuum to afford the β-sulfido carbonyl compounds in 80–90% yield.

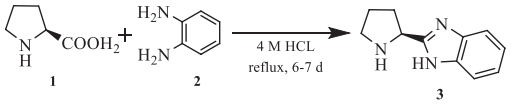
2.4. Spectral data of selected compounds

2.4.1. 3-(4-Chloro-phenylsulfanyl)-1-(2-hydroxy-phenyl)-3-phenyl-propan-1-one (entry 1, Table 1)

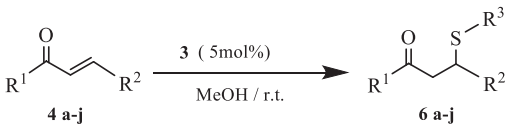
White solid; mp 112–115°C; IR (KBr): 696, 820, 1230, 1336, 1677, 2894, 3062 ν cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.3–3.8 (m, 2H), 4.8–5.0 (m, 1H), 7.1–7.4 (m, 8H), 7.4–7.5 (m, 3H), 7.9 (d, 2H, J = 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.27, 47.27, 126.22, 126.50, 126.79,

Table 1: Results of 2-Pyrrolidin-2yl-1H benzimidazole catalyzed thio-Michael reaction of thiophenols to α,βunsaturated compounds.

Entry	α,β Unsaturated Compound		Thiophenols		aProduct		Time(min)	Yield%
1.		4 a	Ph-SH	5 a		6 a	5	94
2.		4 b	Ph-SH	5 a		6 b	30	86
3.		4 c	Ph-SH	5 a		6 c	25	88
4.		4 d	Ph-SH	5 a		6 d	50	85
5.		4 e	Ph-SH	5 a		6 e	35	92
6.		4 f	Ph-SH	5 a		6f	60	89
7.		4 g		5 b		6 g	5	95
8.		4 h		5 b		6 h	40	88
9.		4 i		5 b		6 i	15	95
10.		4 j		5 b		6 j	45	86



Scheme 1: Synthesis of 2-Pyrrolidine-2yl-1H-benzoimidazole.



Scheme 2: Synthesis of β-sulfido analogs.

Table 2: Screening of catalysts.

Entry	Catalyst	Time (min)
1.	Montmorillonite clays, 10% (w/w)	120
2.	$InCl_3$ (10 mol%)	60
3.	Cu $(BF_4)_2 \times H_2O$ (1 mol%)	120
4.	Ionic liquid, [pmIm] Br	120
5.	$Na_2CaP_2O_7$ (0.1 g)	60
6.	NP and KF/NP (0.1 g)	60, 60
7.	Ionic liquid, [bmin] PF_6 in L-Proline	60
8.	PBI	5

Table 3: Screening of solvent.

Entry	Solvent	Time (min)	Yield %
1.	H_2O	2 h	65
2.	CH_3CN	5 h	55
3.	DCM	6 h	50
4.	CH_3OH	5	95

127.25, 127.37, 127.69, 131.37, 132.06, 132.54, 132.97, 135.42, 139.74, 195.46; m\z: 369 (M + H).

2.4.2. 3-(4-Chloro-phenylsulfanyl)-3-(4-fluoro-phenyl)-1-phenyl-propan-1-one (entry 4, Table 1)

White solid; mp 125–127°C; IR (KBr): 684, 731, 823, 1225, 1511, 1682, 2896, 3061 ν cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.4–3.8 (m, 2H), 4.8–5.1 (m, 1H), 6.8–7.1 (m, 2H), 7.1–7.4 (m, 6H), 7.4–7.7 (m, 3H), 7.89 (d, 2H, J = 7.11 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.31, 46.61, 98.71, 113.96, 114.24, 126.76, 127.41, 127.78, 128.06, 128.17, 131.04, 132.16, 132.78, 133.11, 135.31, 135.51, 195.28; m\z: 371 (M + H).

2.4.3. 3-(4-Chloro-phenylsulfanyl)-3-(4-methoxy-phenyl)-1-phenyl-propan-1-one (entry 5, Table 1)

White solid; mp 130–134°C; IR (KBr): 691, 818, 1232, 1332, 1513, 1675, 2958, 3063 ν cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.4–3.6 (m, 2H), 3.7–3.9 (m, 3H), 4.8–5.0 (m, 1H), 6.7–6.9 (m, 2H), 7.1–7.3 (m, 6H), 7.4–7.6 (m, 3H), 7.86 (d, 2H, J = 7.35 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.43, 46.72, 53.94, 112.62, 126.78, 127.36, 127.59, 127.69, 131.57, 131.65, 132.03, 132.43, 132.89, 135.45, 157.57, 195.63; m\z: 383 (M + H).

2.4.4. 3-Naphthalen-2-yl-1-phenyl-3-phenylsulfanyl-propan-1-one (entry 10, Table 1)

White solid; mp 155–158°C; IR (KBr): 687, 739, 874, 1261, 1341, 1596, 1675, 2965, 3069 ν cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.4–3.9 (m, 2H), 5.4–5.9 (m, 1H), 6.9–8.4 (m, 17H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 42.46, 43.57, 122.30, 124.11, 124.72, 125.35, 126.13, 126.47, 126.52, 127.07, 127.14, 127.59, 127.65, 127.79, 127.94, 128.03, 131.63, 132.24, 133.03, 140.74, 189.30, 196.07; m\z: 369 (M + H).

2.4.5. 3-(4-Chloro-phenylsulfanyl)-3-naphthalen-2-yl-1-phenyl-propan-1-one (entry 13, Table 1)

White solid; mp 166–168°C; IR (KBr): 687, 779, 803, 1097, 1255, 1351, 1474, 1595, 1681, 2894, 3061 ν cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.3–4.2 (m, 2H), 5.4–6.0 (m, 1H), 6.8–8.6 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.28, 43.55, 43.84, 44.11, 47.81, 126.63, 128.41, 128.61, 129.30, 129.92, 131.49, 131.74, 132.16, 132.37, 132.46, 134.28, 136.18, 136.91, 137.66, 139.69, 140.05, 200.31; m\z: 403 (M + H).

3. RESULTS AND DISCUSSION

Initially, we focused our effort toward the synthesis of organocatalys. To achieve this goal, we utilized the L-Proline and O-Phenylenediamine. Primarily, L-Proline **1** and O-Phenylenediamine **2** were mixed in 4M HCl solution and stirred at 100°C for the preparation of organocatalyst 2-Pyrrolidin-2yl-1*H*-benzimidazole (PBI) **3** in 60% yield (Scheme 1). Reaction took longer time to complete and isolation of -Pyrrolidin-2yl-1*H*-benzimidazole (PBI). The synthesized organocatalyst was characterized by spectroscopic and spectrometric data.

After having the organocatalyst in our hand, we tried to employ the synthesized organocatalyst in thia-micheal addition reaction. To achieve this, we focused the suitable reaction medium for the synthesis of β-sulfido carbonyl compounds. We investigated various green catalysts for the thia-Micheal addition reaction. We screened Montmorillonite clays 10% (w/w), $InCl_3$, $Cu(BF_4)_2.xH_2O$, Ionic Liquid, $Na_2CaP_2O_7$, NP and KF/NP, and PBI. We found the best results using PBI as catalyst, since reaction was completed in only 5 h, the results are summarized in Table 2. Organocatalyst PBI further employed for the thio-Michael addition reactions on α,β-unsaturated compounds (Scheme 2). Common solvents such as H_2O, CH_3CN, DCM, and CH_3OH for the thia-Micheal reaction. We found that the methanol exhibited the best results, so we have chosen methanol as the reaction solvents (Table 3).

A series of β-sulfido carbonyl compounds **6 a-j** were synthesized by reaction of thiolphenols and α,β unsaturated carbonyl compounds. All the synthesized analogs were well characterized using various characterization tools. Thus, we evaluated the addition of thiols **5** onto various α,β-unsaturated compounds **4** in the presence of **3** (Scheme 2). The observations summarized in Table 1 shows that the 2-Pyrrolidin-2yl-1H-benzimidazole is an effective organocatalyst for thio-Michael reaction, and the product is formed with good conversion in short reaction time. The reactions were clean and the products were obtained in high yields without the formation of any side products such as 1,2-conjugate product and disulfides.

This organocatalytic addition protocol offers operational simplicity, does not require exclusion of air, and offers mild conditions. With this optimized procedure, we tested several α,β-unsaturared carbonyl compounds 4a-4j having both electron-donating and electron-withdrawing group at the aryl unit (Table 1). For all the substrates depicted in Table 1, the yields obtained with 3 is very high up to 95% after few minutes, except for the product (entry 2, 3, 4, 6, and 8). In this case, the low reactivity observed may be due to presence of an electron-donor group. Thus, the reaction rate is much slower and needs comparatively larger time for completion. The less nucleophilic thiophenol 5b required a longer reaction time to obtain a good yield comparable to that of 5a (Table 1, entry 7).

We observed that after the completion of reaction a white precipitate appeared and this could be used as indicator for monitoring the reaction visually. As a result of the optimization of the reaction conditions, we found that increased yields were observed when the

reaction was conducted in 2 ml of methanol using 1 mmol of α,β-unsaturared carbonyl compound, 1.9 mmol of thiophenol, and 0.02 g of organocatalyst at room temperature. The procedure does not require any anhydrous conditions and column chromatography. As emerges from Table 2 that the use of $Cu(BF_4)_2.xH_2O$, $Na_2CaP_2O_7$, NP, and KF/NP under similar conditions, the time required for conversion of product is more as compared to 2-Pyrrolidin-2yl-1H-benzimidazole for the reaction of 4a with 5a while $InCl_3$ and Montmorillonite clays take few to several hours for same reaction in different conditions.

4. CONCLUSION

In summary, we have reported an easy synthetic methodology involving organocatalytic approach for synthesis of β-sulphido analogs. The synthesis of organocatalyst has also been developed and scope of catalytic efficiency is shown by thia-Micheal reaction. The synthesized molecules are not only very interesting from synthetic perspective but also very significant due biological potential associated with them.

5. ACKNOWLEDGMENTS

The authors acknowledge the M.L.T. College Saharsa for providing necessary support and IIT Patna for providing spectroscopic data.

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