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Synthesis of *β*-amino carbonyl derivatives of coumarin *via* Mannich-type reaction catalyzed by Zirconium oxychloride

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ABSTRACT

A series of β-amino carbonyl compounds containing coumarin was synthesized by a three component Mannich reaction of 3-acetyl coumarin, aromatic aldehydes and aromatic amines in the presence of zirconium oxychloride $ZrOCl_2{\cdot}8H_2O$as a catalyst. The present methodology offers several advantages such as high yields, simple procedure, low cost, short reaction times, mild reaction conditions and use of a reusable catalyst.

Keywords: Zirconium oxychloride $ZrOCl_2{\cdot}8H_2O$;Mannich reaction; β-amino ketones;3-acetyl coumarin

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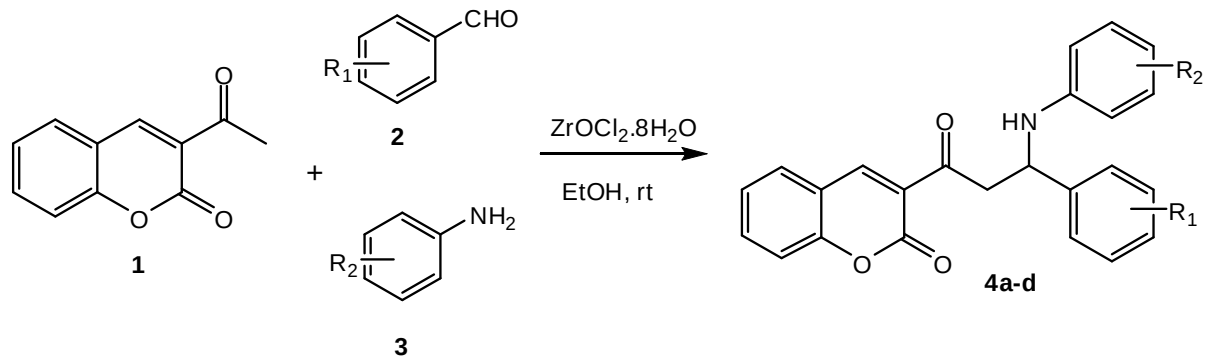
INTRODUCTION

Over the years, coumarin (2-oxo-2*H*-chromene) derivatives have been established as well-known naturally occurring oxygen-heterocyclic compounds isolated from various plants which occupy a special role in nature [1].Coumarin derivatives have attracted intense interest because of their wide variety of biological properties, *viz.*, antibacterial, antifungal, antioxidant, anti-inflammatory, analgesic, anticancer, anthelmintic, and anticonvulsant [2-4].

The Mannich reaction is one of the most important carbon–carbon bond-forming reactions inorganic synthesis because of its atom economy and potential application in the synthesis of biologically active molecules [5–7]. In this reaction, an amine, two carbonyl compounds, and acid(or base) catalysts are used to produce *β*-amino carbonyl compounds, which constitute various pharmaceuticals, natural products, and versatile synthetic intermediates [8,9]. Conventional catalysts for the classic Mannich reaction involve inorganic and organic acids and several Lewis acids [10-16].

Therefore, considering the above and in the development of new carbon-carbon bond formation reactions [17, 18], an efficient and convenient synthesis of 3-(3-phenyl-3-(phenylamino)propanoyl)-2*H*-chromen-2-onederivatives have been accomplished by the multi-component reaction of 3-acetylcoumarin,aromatic aldehydes, and aromatic amines using $ZrOCl_2{\cdot}8H_2O$as an efficient catalyst. The reactions are conducted at room temperature in ethanol (Scheme 1).



Scheme -1 Synthesis of3-(3-phenyl-3-(phenylamino)propanoyl)-2*H*-chromen-2-onederivatives

MATERIALS AND METHODS

Apparatus and analysis

All chemicals were purchased from Merck and Aldrich chemical companies. Analytical thin-layer chromatography was performed with E.merck silica gel 60F glass plates. Visualization of the developed chromatogram was performed on silica gel 90, 200-300 mesh. ^{1}H NMR (300MHz) and ^{13}C NMR (75 MHz) spectra were obtained using a Bruker DRX-500 Advance at ambient temperature, using TMS as an internal standard. Mass spectra were determined on a Varian-Saturn instrument. FT-IR spectra were obtained as KBr pellets on Shimadzu spectrometer.

General procedure for the synthesis of mannich base derivatives

A mixture of 3-acetyl coumarin**1**(10mmol), aromatic aldehydes **2** (10mmol), aromatic amine**3**(10mmol) and $ZrOCl_2.8H_2O$ (10 mol%) was stirred in EtOH (10 ml) at room temperature. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled, poured into crushed ice, and neutralized using 10 % $NaHCO_3$ solution. The precipitated product was filtered, dried, and recrystallized from ethanol. The catalyst was removed dried for its next use.

Spectral data for selected compounds

*3-(3-phenyl-3-(phenylamino)propanoyl)-2H-chromen-2-one **(4a)***

IR (KBr, cm^{-1}): 3354 (N-H), 3026 (C-H), 1720 (C=O), 1678 (C=C), 1168 (C-C); ^{1}HNMR(300 MHz, DMSO-d_6): (δ ppm): 8.66 (s, 1H, CH), 6.95–7.98 (m, 14H, Ar-H), 6.25 (d, 1H, NCH), 4.99 (s, 1H, NH), 3.59-3.67 (dd, 2H, $COCH_2$).^{13}C NMR(75 MHz, DMSO-d_6): (δppm): 50.4, 53.1, 116.3, 116.5, 121.6, 124.9, 125.2, 125.4, 127.0, 127.1, 127.5, 128.7, 129.1, 129.5, 131.3, 144.4, 144.6, 155.0, 158.9, 195.3: MS (ESI): m/z 369. Anal. Calcd. For $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found: C, 77.92; H, 5.11; N, 3.70%.

*3-(3-(phenylamino)-3-(p-tolyl)propanoyl)-2H-chromen-2-one **(4d)***

IR (KBr, cm^{-1}): 3358 (N-H), 2914 (C-H), 1732 (C=O), 1656 (C=C), 1178 (C-C); ^{1}HNMR(300 MHz, DMSO-d_6) (δ ppm):8.57 (s, 1H, CH), 6.43–7.97 (m, 13H, Ar-H), 6.20 (d, 1H, NCH), 4.94 (s, 1H, NH), 3.55-3.64 (dd, 2H, $COCH_2$),2.10 (s, 3H, CH_3).^{13}C NMR (75 MHz, DMSO-d_6) (δppm): 21.5, 50.4, 52.9, 113.3, 118.8, 121.4, 124.9, 125.4, 126.0, 126.9, 129.1, 129.2, 129.8, 130.1, 132.1, 136.2, 144.7, 154.9, 154.9, 187.7, 195.4: MS (ESI): m/z 383. Anal. Calcd. for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52; N, 3.65. Found: C, 78.39; H, 5.45; N, 3.59%.

RESULTS AND DISCUSSION

This report describes a very efficient one-pot three-component synthesis ofβ-aminocarbonyl compounds of coumarinderivatives catalysed by $ZrOCl_2{\cdot}8H_2O$in ethanol at room temperature. In order to optimize the conditions, we studied the reaction of reaction of 3-acetyl coumarin, benzaldehyde and aniline as model substrate in various conditions. First, we focused on the catalyst effects. Our studies showed that in the absence of catalyst in ethanol no product was formed (Table 1, entry 1). The model reaction was conducted in the presence of various catalysts (Table 1, entries 2–8). Among the various catalysts, $ZrOCl_2{\cdot}8H_2O$proved to be the best (Table 1, entry 8). Catalyst loading was a future target for the optimization of the reaction parameters. To optimize the catalyst loading, the model reaction was investigated with 8, 5, 3, and 15 mol% of $ZrOCl_2{\cdot}8H_2O$ at room temperature in ethanol. Lower yield was obtained when the same reaction carried out with lower amount of the catalyst (Table 1, entries9-11). Further, an increase in the amount of the catalyst no improvement could be observed in the yield of the product (Table 1, entry 12).

Thus, we selected the optimized reaction condition to examine the universality of this catalyst's application with different electron rich and deficient substrates. Various substituted aromatic aldehydes and aromatic amines with 3-

acetyl coumarin undergo the reaction in the presence of catalytic amount of $ZrOCl_2 \cdot 8H_2O$(10mol%) in ethanol at room temperature to furnish the corresponding β-aminocarbonyl compounds of coumarin(Scheme 1). The results of this study are summarized in Table 2. It was indicated that both electron deficient and electron rich aromatic compounds worked well, giving high yield of the product.

Table 1Effect of catalyst for the synthesis of *β*-amino carbonyl derivatives of coumarin[a]

Entry	Catalyst	Amount of catalyst (mol %)	Time(h)	Yield(%)[b]
1	None	-	10	0
2	$FeCl_3$	10	7	17
3	$InCl_3$	10	6	28
4	$La(OTf)_3$	10	6	44
5	$Nd(OTf)_3$	10	6	58
6	$Yb(OTf)_3$	10	7	82
7	$Al(CH_3SO_3)_3.4H_2O$	10	6	77
8	$ZrOCl_2 \cdot 8H_2O$	10	5	92
9	$ZrOCl_2 \cdot 8H_2O$	8	5	85
10	$ZrOCl_2 \cdot 8H_2O$	5	5	74
11	$ZrOCl_2 \cdot 8H_2O$	3	5	66
12	$ZrOCl_2 \cdot 8H_2O$	15	5	92

[a]Reaction conditions: 3-acetyl coumarin (10 mmol), benzaldehyde (10 mmol), aniline (10mmol) andethanol at room temperature.
[b]Isolated Yields

Table 2Synthesis of *β*-amino carbonyl derivatives of coumarin[a]

Entry	R_1	R_2	Product	Time(h)	Yield (%)[b]
1	H	H	**4a**	5.0	92
2	4-OH	H	**4b**	5.5	85
3	3-NO_2	4-NO_2	**4c**	6.0	80
4	4-CH_3	H	**4d**	6.0	86

[a]Reaction conditions: 3-acetyl coumarin (10mmol), aromaticaldehyde (10mmol), aromatic amines (10mmol) andethanol at room temperature.
[b]Isolated Yields.

Reusability of the catalyst:

Ease of recycling of the catalyst is a valuable advantage of our method. After the separation of the product, the catalyst was washed with dichloromethane and vacuumed to remove CH_2Cl_2, and the recovered catalyst $ZrOCl_2 \cdot 8H_2O$was reused directly for the next run. As shown in Fig. 1, the catalyst can be recycled at least four times without significant decrease in catalytic activity, the yields ranged from92 to 88 %.

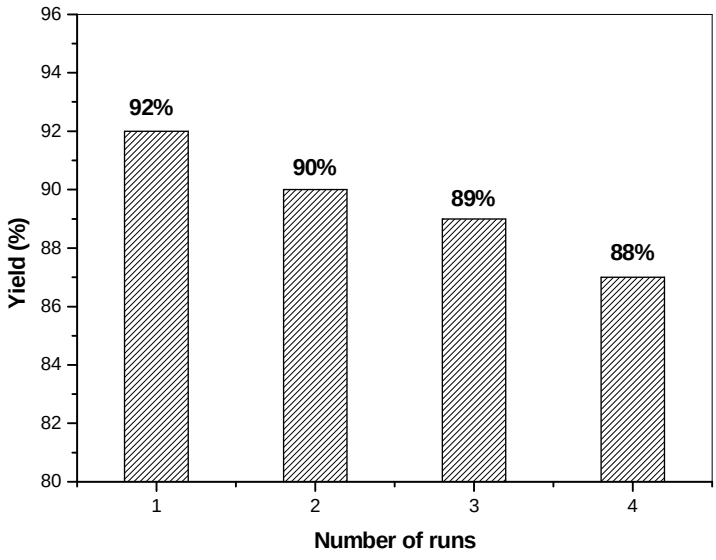


Figure 1 Reusability of catalyst

CONCLUSION

An economic, rapid, and environmentally benign procedure has been developed for one-pot synthesis of *β*-aminocarbonyl compounds of coumarin at room temperature in ethanol by three-component reaction of aromatic

aldehydes, 3-acetyl coumarin and aromatic amines with $ZrOCl_2 \cdot 8H_2O$as catalyst. The method has several advantages, including short reaction times, high yields, and facile workup, which makes it a useful and attractive procedure for synthesis of these compounds.

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