available at www.sciencedirect.com

journal homepage: www.elsevier.com/locate/chnjc

Article

In(OTf)₃ as a powerful and recyclable catalyst for Pechmann condensation without solvent

Bahador Karami*, Mahtab Kiani, Mohsen Ahmad Hoseini

Department of Chemistry, Yasouj University, Yasouj 75918-74831, Iran

ARTICLE INFO

Article history:

Received 15 December 2013

Accepted 21 March 2014

Published 20 July 2014

Keywords:

In(OTf)₃

Lewis acid catalyst

Pechmann condensation

Coumarin

Solvent-free condition

ABSTRACT

In(OTf)₃ plays the role of a Lewis acid catalyst in the Pechmann condensation of phenols with β -ketoesters under solvent-free conditions to give coumarin derivatives. This novel and inexpensive method has advantages such as short reaction time, excellent product yields, and avoids the use of organic solvents in agreement with green chemistry principles. Catalyst loadings can be as low as 1 mol% to give high yields of the corresponding coumarins at 80 °C. The catalyst can be recovered after the reaction, and reused with only a slight decrease in the yield.

© 2014, Dalian Institute of Chemical Physics, Chinese Academy of Sciences.

Published by Elsevier B.V. All rights reserved.

1. Introduction

2H-Chromen-2-ones (coumarins) continue to be investigated owing to their importance to medicinal chemists because of their variety of biological activity [1]. They are widely used as additives in food, perfumes, cosmetics [2], pharmaceuticals [3], optical brighteners [4] and dispersed fluorescent and laser dyes [5]. Thus, the synthesis of this heterocyclic nucleus is of much interest.

Various methods are known for the synthesis of substituted coumarins, including Pechmann, Perkin, Knoevenagel, Claisen, Reformatsky, and Wittig reactions [6]. Some of these reactions have disadvantages such as harsh conditions, long reaction time, low product yields, and the use of expensive and toxic reagents or organic solvents [7–11].

In recent years, Lewis acids such as polyvinylpyrrolidone [4], nanocrystalline sulfated tin oxide [5], Zr-TMS-TFA-25 [9], ZrOCl₂·8H₂O/SiO₂ [12], and mesoporous zirconium phosphate (m-ZrP) [13] have been used to catalyze the Pechmann

reaction. This method is suitable and better than the other methods to synthesize coumarins in terms of the amount of the catalyst used, reaction time, and product yields. In this study, continuing our work on catalyzed reactions [12], a new application of In(OTf)₃ as a Lewis acid catalyst in the synthesis of coumarins was reported.

2. Experimental

2.1. General

The chemicals were purchased from Aldrich, Fluka, and Merck chemical companies and were freshly used after purification by standard procedures (distillation and recrystallization). The products were isolated and identified by comparing their physical and spectral data with those in the literature. Infrared (IR) spectra were recorded on a JASCO-680 Fourier transform IR spectrometer using KBr disks and the ¹H-NMR spectra were recorded on a Bruker NMR spectrometer (400

* Corresponding author. Tel: +98-7412223048; Fax: +98-7412224167; E-mail: karami@mail.yu.ac.ir

DOI: 10.1016/S1872-2067(14)60090-5 | http://www.sciencedirect.com/science/journal/18722067 | Chin. J. Catal., Vol. 35, No. 7, July 2014

MHz model) as CDCl_3 solutions. The chemical shifts are expressed in δ with $(\text{CH}_3)_4\text{Si}$ (TMS) as the internal standard.

2.2. General procedure for the preparation of coumarin derivatives **1–15a**

In a typical experimental procedure, β -ketoester (1 mmol) was added to a mixture of substituted phenol (1 mmol) and $\text{In}(\text{OTf})_3$ (0.056 g, 1 mol%) in a solvent-free tube. The reaction mixture was stirred in a preheated oil bath (80 °C). After completion of the reaction, the solid product was suspended in water (20 mL). The resulting crude product was filtered off and recrystallized from hot ethanol to give a white crystalline solid.

2.3. Preparation of 7-hydroxy-4-methyl-2H-chromen-2-one (**1a**)

Compound **1a** was prepared according to the general procedure using ethyl acetoacetate (0.13 g, 1 mmol), resorcinol (0.11 g, 1 mmol), and $\text{In}(\text{OTf})_3$ (0.056 g, 1 mol%). The reaction progress was monitored by thin-layer chromatography (TLC). After completion of the reaction, the solid product was suspended in water (20 mL). The resulting crude product was filtered off and recrystallized from hot ethanol to give a white crystalline solid.

2.4. Reusability of the catalyst

At the end of the reaction of ethyl acetoacetate (1 mmol), resorcinol (1 mmol), and $\text{In}(\text{OTf})_3$ (1 mol%), the catalyst was filtered, washed with chloroform, and dried at 120 °C for 1 h. The catalyst was used for five times in the model reaction (i.e., recycling four times).

Specific detailed data for each of the compounds are given below.

7-Hydroxy-4-methyl-2H-chromen-2-one (**1a**). Colorless prisms, mp 183–185 °C; Yield 92%. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ = 10.138 (s, 1H), 7.373 (m, 5H), 6.722 (s, 1H), 6.470 (s, 1H), 5.957 (s, 1H), 2.292 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, DMSO-d_6): δ = 160.09, 156.05, 155.96, 155.51, 143.93, 139.75, 128.34, 127.92, 127.75, 113.88, 112.52, 108.19, 105.44, 21.65. IR (KBr, cm^{-1}): 3050, 2900, 1690, 1615, 1590, 1500, 1080.

7-Hydroxy-4-phenyl-2H-chromen-2-one (**2a**). Colorless prisms, mp 251–253 °C; Yield 83%. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 5.905 (s, 1H), 6.56 (m, 2H), 7.04 (d, 1H), 7.28 (t, 1H), 7.322 (m, 3H), 10.65 (s, 1H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 103.12, 110.10, 111.08, 113.68, 128.54, 128.79, 129.29, 130.07, 135.52, 155.9. IR (KBr, cm^{-1}): 3050, 1690, 1600, 1250, 1150.

5-Hydroxy-4,7-dimethyl-2H-chromen-2-one (**4a**). Colorless prisms, mp 253–255 °C; Yield 95%. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ = 10.52 (s, 1H), 6.62 (d, 1H, J = 1.2 Hz), 6.57 (d, 1H, J = 1.2 Hz), 6.03 (d, 1H, J = 1.2 Hz), 2.54 (d, 3H, J = 1.2 Hz), 2.27 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, DMSO-d_6): δ = 160.29, 156.90, 155.28, 154.04, 143.18, 112.37, 112.3, 108.15, 106.96, 23.91, 21.56. IR (KBr, cm^{-1}): 3393 (OH), 1655 (C=O).

5-Hydroxy-7-methyl-4-phenyl-2H-chromen-2-one (**5a**). Colorless prisms, mp 211–213 °C; Yield 80%. $^1\text{H-NMR}$ (400

MHz, DMSO-d_6): δ = 10.14 (s, 1H), 7.35 (m, 5H), 6.72 (s, 1H), 6.47 (s, 1H), 5.96 (s, 1H), 3.01 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, DMSO-d_6): δ = 160.09, 156.05, 155.96, 155.51, 143.93, 139.75, 128.34, 127.92, 127.75, 113.88, 112.52, 108.19, 105.44, 21.65. IR (KBr, cm^{-1}): 3180 (OH), 1680 (C=O).

5,7-Dihydroxy-4-methyl-2H-chromen-2-one (**7a**). White solid, mp 288–290 °C; Yield 98%. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ = 10.51 (1H, s), 10.28 (1H, s), 6.24 (1H, s), 6.15 (1H, s), 5.83 (1H, s), 2.49 (3H, s). $^{13}\text{C-NMR}$ (100 MHz, DMSO-d_6): δ = 16.51, 160.55, 158.39, 156.96, 155.43, 109.22, 102.55, 99.45, 94.98, 23.88. IR (KBr cm^{-1}): 3400, 3070, 2940, 1670, 1600, 1480, 1080.

7-Methoxy-4-methyl-2H-chromen-2-one (**10a**). Colorless prisms, mp 165–167 °C; Yield 96%. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 7.50 (d, 1H, J = 8.8 Hz), 6.87 (dd, 1H, J = 8.8, 2.4 Hz), 6.83 (d, 1H, J = 2.4 Hz), 6.14 (d, 1H, J = 1.2 Hz), 3.88 (s, 3H), 2.40 (d, 3H, J = 1.2 Hz). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 162.83, 160.59, 155.24, 153.86, 126.88, 113.56, 112.54, 111.58, 101.16, 56.36, 18.58. IR (KBr, cm^{-1}): 3400 (OH), 1705 (C=O).

7,8-Dihydroxy-4-methyl-2H-chromen-2-one (**14a**). White solid, mp 239–241 °C; Yield 87%. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ = 10.1 (s, 1H), 9.35 (s, 1H), 7.07 (d, 1H, J = 8.8 Hz), 6.81 (d, 1H, J = 8.4 Hz), 6.12 (d, 1H, J = 1.2 Hz), 2.4 (d, 3H, J = 1.2 Hz). $^{13}\text{C-NMR}$ (100 MHz, DMSO-d_6): δ = 160.71, 154.35, 149.81, 143.47, 132.60, 115.88, 113.23, 112.56, 110.60, 18.63. IR (KBr, cm^{-1}): 3231 (OH), 1668 (C=O).

7-Amino-4-methyl-2H-chromen-2-one (**15a**). Light yellow solid, mp 223–225 °C; Yield 98%. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ = 7.4 (d, 1H, J = 8.8 Hz), 6.56 (d, 1H, J = 7.2 Hz), 6.39 (s, 1H), 6.09 (s, 2H), 5.89 (s, 1H), 2.39 (s, 3H). $^{13}\text{C-NMR}$ (100 MHz, DMSO-d_6): δ = 160.90, 152.80, 151.00, 148.00, 127.60, 113.00, 112.50, 111.10, 106.70, 21.2. IR (KBr, cm^{-1}): 3439 (N–H), 1684 (C=O).

3. Results and discussion

To study the efficiency of $\text{In}(\text{OTf})_3$ for the Pechmann condensation reaction, the reaction of β -ketoesters and phenol derivatives was selected as the model reaction. The expected coumarins were obtained as pure products in high yield by solvent-free stirring (Scheme 1).

To optimize the reaction conditions, we tested both various temperatures and amounts of the catalyst $\text{In}(\text{OTf})_3$ in the model reaction of resorcinol with ethyl acetoacetate to produce 7-hydroxy-4-methyl-2H-chromen-2-one (**1a**) (Tables 1 and 2). Excellent yields were achieved using only 1 mol% $\text{In}(\text{OTf})_3$ at 80 °C. There was no change in the reaction profile when more than 1 mol% of $\text{In}(\text{OTf})_3$ was used. When similar reactions were carried out in the absence of the catalyst, approximately

Scheme 1. Synthesis of coumarin derivatives using the $\text{In}(\text{OTf})_3$ catalyst.

Table 1

Optimization of the amount of $\text{In}(\text{OTf})_3$ catalyst under solvent-free conditions at 80 °C for the synthesis of **1a**.

Catalyst amount (mol%)	Time (min)	Isolated yield (%)
—	300	10*
1	34	89
5	47	85
10	48	87

* Not completed.

Table 2

Optimization of the reaction temperature under solvent-free conditions using $\text{In}(\text{OTf})_3$ catalyst (1 mol%) for the synthesis of **1a**.

Temperature (°C)	Time (min)	Isolated yield (%)
25	480	10*
60	480	50
80	35	87
120	30	80

* Not completed.

5%–10% conversion was observed after 2 d.

After optimization of the reaction conditions, to extend the scope of this reaction, various phenols, such as resorcinol, pyrogallol and phloroglucinol, were used for the optimized

Pechmann reaction with different β -ketoesters (Table 3). A wide variety of coumarins were obtained through this method in good to excellent yield in short reaction time.

Coumarin **1a** was synthesized in 87% yield in 32 min (CCl_4 :ethylacetate = 5:1). Coumarin **1a** was characterized by IR, NMR and other spectral data. Similarly, resorcinol was treated with ethyl 4-chloroacetoacetate and ethyl benzoylacetate to give coumarins **2a** and **3a** (Table 3, entries 2 and 3), respectively.

Encouraged by the above results, other phenolic substrates were subjected to the Pechmann reaction using $\text{In}(\text{OTf})_3$. In all cases, the reactions successfully proceeded to give the corresponding coumarins in good to excellent yield. Electron-donating substituents in the meta position to the phenolic –OH facilitated the cyclization. The reactivity of phloroglucinol (1,3,5-trihydroxybenzene) (Table 3, entry 7) with ethyl acetoacetate was observed to be higher than pyrogallol (Table 3, entry 14) owing to two hydroxyl groups at meta positions in phloroglucinol compared to only one in pyrogallol. The presence of *m*-hydroxy groups strongly activates the substrates because of the resonance effect. *m*-Methoxyphenol (Table 3, entry 10) showed no detectable demethylation under the optimized re-

Table 3

Synthesis of coumarins by Pechmann condensation of phenols with β -ketoesters catalyzed by $\text{In}(\text{OTf})_3$.

Entry	Phenol	β -Ketoester	Product	Time (min)	Mp (°C)	Isolated yield* (%)
1			1a	32	183–185 [6]	87
2			2a	45	251–253 [14]	98
3			3a	12	177–179 [15]	85
4			4a	38	253–255 [6]	87
5			5a	80	211–213 [6]	79
6			6a	15	161–163 [16]	85
7			7a	20	288–290 [6]	80
8			8a	25	236–238 [17]	82
9			9a	10	185–187 [18]	92

(To be continued)

Table 3 (continued)

Entry	Phenol	β -Ketoester	Product	Time (min)	Mp ($^{\circ}\text{C}$)	Isolated yield* (%)
10			10a	87	165–167 [14]	73
11			11a	13	179–181 [19]	87
12			12a	27	153–155 [20]	68
13			13a	44	163–165 [18]	83
14			14a	26	239–241 [19]	75
15			15a	13	223–225 [21]	89

action conditions. Similarly, 1-naphthol (Table 3, entry 12) requires a slightly higher temperature and longer reaction time. These results show that besides of the catalyst acidity and the reactivity of phenolic substrates. Finally, the reactions are remarkably clean, and no chromatographic separation is necessary to obtain the spectra-pure compounds.

The suggested mechanism for the Pechmann condensation reaction of phenols with β -ketoesters in the presence of $\text{In}(\text{OTf})_3$ catalyst has been described using condensation as the probe reaction (Scheme 2). The $\text{In}(\text{OTf})_3$ catalyst would cause dehydration and produce an olefinic bond, and simultaneously ethanol would be eliminated with the formation of the couma-

rin ring.

Comparing this method with other methods, the synthesis of 7-hydroxy-4-methyl-2H-chromen-2-one (Table 1, entry 1) as the model reaction was performed in the presence of other catalysts. The results are shown in Table 4. It shows that our method is suitable and better than other methods to synthesize coumarins in terms of the catalyst amount, the reaction time, and the product yield.

The design and synthesis of recoverable catalysts is a highly challenging interdisciplinary field, which combines chemistry, materials science, and engineering from both economic and environmental perspectives. The main disadvantage of many of

Scheme 2. Suggested mechanism for the Pechmann condensation of phenols with β -ketoesters in the presence of $\text{In}(\text{OTf})_3$.

Table 4Comparison of our method with other methods for the synthesis of **1a** by the condensation of ethyl acetoacetate (1 mmol) with resorcinol (1 mmol).

Catalyst	Catalyst amount	Conditions	Time (min)	Yield (%)	Ref.
In(OTf) ₃	1 mol%	solvent-free, 80 °C	32	87	this work
ZrPW	0.2 g	solvent-free, 130 °C	480	58	[2]
Nanocrystalline sulfated tin oxide	25 wt%	solvent-free, 120 °C	240	95	[5]
Zr-TMS-TFA-25	0.1 g	solvent-free, 100 °C	540	88	[9]
ZrOCl ₂ ·8H ₂ O/SiO ₂	10 mol%	solvent-free, 80 °C	10	98	[12]
Mesoporous zirconium phosphate (m-ZrP)	15 wt%	solvent-free, 160 °C	240	94	[13]
Y(NO ₃) ₃ ·6H ₂ O	10 mol%	solvent-free, 90 °C	45	94	[22]
H ₃ PW ₁₂ O ₄₀ supported on nanoparticle tin oxide	30 wt%	solvent-free, 120 °C	120	78	[23]

Fig. 1. Recyclability of In(OTf)₃ as a catalyst for the synthesis of **1a** in the condensation of resorcinol (1 mmol) and ethylacetoacetate (1 mmol) under solvent-free conditions at 80 °C for 32–38 min.

the reported methods is that the catalysts are destroyed in the procedure and cannot be recovered or reused. In the process described here, as outlined in Fig. 1, the catalyst can be used in up to five times, during which there is negligible loss in the catalytic activity.

4. Conclusions

We have demonstrated the facile In(OTf)₃-catalyzed synthesis of coumarins by the Pechmann reaction. The important advantages of this method are the short reaction time, high yield,

simple workup, the use of an inexpensive and available catalyst, the nonchromatographic purification of the products, and the use of solvent-free conditions instead of organic solvents in accordance with green chemistry principles.

Acknowledgments

We thank Yasouj University for its support.

References

- [1] Basanagouda M, Jambagi V B, Barigidad N N, Laxmeshwar S S, Devaru V, Narayanachar. *Eur J Med Chem*, 2014, 74: 225
- [2] Ghodke S, Chudasama U. *Appl Catal A*, 2013, 453: 219
- [3] Zhao J Y, Zhou M, Liu Y, Zhang G L, Luo Y G. *Fitoterapia*, 2011, 82: 767
- [4] Mokhtary M, Najafizadeh F. *C R Chim*, 2012, 15: 530
- [5] Ahmed A I, El-Hakam S A, Khder A S, Abo El-Yazeed W S. *J Mol Catal A*, 2013, 366: 99
- [6] Rajitha B, Naveen Kumar V N, Someshwar P, Madhav J V, Reddy P N, Reddy Y T. *Arkivoc*, 2006, (12): 23
- [7] De S K, Gibbs R A. *Synthesis*, 2005: 1231
- [8] Goswami P. *Synth Commun*, 2009, 39: 2271
- [9] Kalita P, Kumar R. *Microporous Mesoporous Mater*, 2012, 149: 1
- [10] Sheng S R, Huang P G, Wang Q, Huang R, Liu X L. *Synth Commun*, 2006, 36: 3175
- [11] Kumar V, Tomar S, Patel R, Yousaf A, Parmar V S, Malhotra S V. *Synth Commun*, 2008, 38: 2646
- [12] Karami B, Kiani M. *Catal Commun*, 2011, 14: 62
- [13] Sinhamahapatra A, Sutradhar N, Pahari S, Bajaj H C, Panda A B. *Appl Catal A*, 2011, 394: 93

Graphical Abstract

Chin. J. Catal., 2014, 35: 1206–1211 doi: 10.1016/S1872-2067(14)60090-5

In(OTf)₃ as a powerful and recyclable catalyst for Pechmann condensation without solvent

Bahador Karami*, Mahtab Kiani, Mohsen Ahmad Hoseini
Yasouj University, Iran

Various coumarin derivatives have been efficiently synthesized by the In(OTf)₃-catalyzed Pechmann condensation reaction of various phenols and β -ketoesters under solvent-free conditions. This novel and inexpensive method has advantages such as short reaction time, excellent product yields, and avoiding the use of organic solvents in agreement with green chemistry principles.

- [14] Sharma G V M, Reddy J J, Sree Lakshmi P, Krishna P R. *Tetrahedron Lett*, 2005, 46: 6119
- [15] Zagotto G, Gia O, Baccichetti F, Uriarte E, Palum M. *Photochem Photobiol*, 1993, 58: 486
- [16] Jung K, Park Y J, Ryu J S. *Synth Commun*, 2008, 38: 4395
- [17] Goswami P. *Synth Commun*, 2009, 39: 2271
- [18] Smitha G, Reddy C S. *Synth Commun*, 2004, 34: 3997
- [19] Bahekar S S, Shinde D B. *Tetrahedron Lett*, 2004, 45: 7999
- [20] Heravi M M, Khorasani M, Derikvand F, Oskooie H A, Bamoharram F F. *Catal Commun*, 2007, 8: 1886
- [21] Xie S S, Wang X B, Li J Y, Yang L, Kong L Y. *Eur J Med Chem*, 2013, 64: 540
- [22] Karami B, Khodabakhshi S, Jamshidi M. *J Chin Chem Soc*, 2013, 60: 1103
- [23] Ahmed A I, El-Hakam S A, Abd Elghany M A, Abo El-Yazeed W S. *Appl Catal A*, 2011, 407: 40