Preliminary communication/Communication

Use of a highly efficient and recyclable solid-phase catalyst based on nanocrystalline titania for the Pechmann condensation

Seyyed Vahid Atghia *, Somayyeh Sarvi Beigbaghlou

Young Researchers Club, Rasht Branch, Islamic Azad University, Rasht, Iran

ARTICLE INFO

ABSTRACT

Nanocrystalline titania-based sulfonic acid was used as an efficient and reusable catalyst for the synthesis of coumarins. The clean, mild acidity condition, the quantitative yields of products, the short reaction time, and the low reaction temperature are attractive features of this method, making it suitable for heat- or acid-sensitive substrates, particularly in drug synthesis. In practice, this method affords an advantageous combination of satisfactory yields, easy product isolation and purification.

© 2014 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved.

1. Introduction

Coumarins are one of the important classes of heterocyclic compounds whose synthesis has been the focus of attention from many organic and medicinal chemists. Many products, which contain the subunit of coumarin, exhibit useful and variant biological activities, such as inhibition of platelet aggregation [1], antibacterial [2] and anticancer [3] properties, inhibition of steroid 5α-reductase [4] and of HIV-1 protease [5]. Coumarins also serve as intermediates for the synthesis of fluorocoumarins, chromenes, coumarones, and 2-acylresorcinols [6].

Many routes have been used for the synthesis of coumarins, such as Baylis–Hillman [7], Knoevenagel [8–10], Perkin [11], Reformatsky [12], and Wittig reactions [13], but, between these routes, the Pechmann method is a much simple method for the synthesis of coumarins based on a two-component (phenol and β-ketoester) coupling under acid catalysis [14]. In the past decades, more than 60 methodologies with different catalysts were used for the Pechmann condensation. In the conventional method, concentrated sulfuric acid is used as the catalyst [15]. In addition, several other acid catalysts, including Lewis acids, such as $InCl_3$ [16], $BiCl_3$ [17], $ZrCl_4$ [18], VCl_3 [19], and $Sm(NO_3)_3 \cdot 6H_2O$ [20], are known to affect this condensation. Butyl methylimidazolium ionic liquids also have been utilized as catalysts for this reaction [21–23], but these methods also generated strongly acidic wastes and highly expensive and non-recyclable reagents. To solve these problems, a number of heterogeneous alternatives, such as $SBA-15-SO_3H$ [24], Amberlyst-15 [25], montmorillonite clays [26–28], and other solid acids [29–32] have been employed for this purpose in the Pechmann condensation. Although these methods are improvements, most of them suffer from disadvantages, such as harsh reaction conditions, long reaction times, poor yields, poor selectivity, use of toxic or expensive reagents, and use of large amounts of catalyst. Thus, the searches for new reagents and methods that utilize ecofriendly protocols are still in demand.

In recent years, there has been considerable growth of interest in the catalysis of organic reactions by solid acid catalysts. Solid acids provide numerous opportunities for recovering and recycling from reaction environments;

---

* Corresponding author.
*E-mail address:* atghia@yahoo.com (S.V. Atghia).
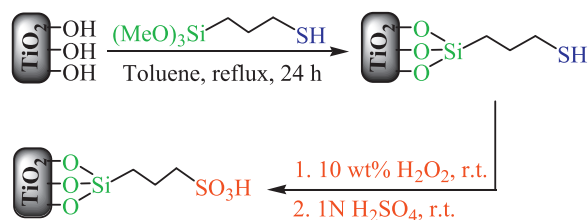
Scheme 1. Preparation of nanocrystalline titania-based sulfonic acid (TiO₂–Pr–SO₃H).

also, they can lead to improved processing steps, better process economics, and environmentally friendly industrial manufacturing. Amongst solid acids, metal oxides have been used extensively either as catalysts or as supports in conjunction with other active components for many industrial oxidation, reduction and acid–base-catalyzed reactions. Among semiconducting oxides, TiO₂, due to its low cost and long-term stability, has been widely used as a solid acid catalyst in organic transformations, such as Friedel–Crafts alkylation of indoles [33], synthesis of bis(indolyl) methanes [34], Mannich synthesis of β-aminocarbonyls [35], and esterification of free fatty acids [36]. But traditional TiO₂ has many limitations in the nature of its active sites, because TiO₂ nanoparticles can lonely catalyze the organic reactions by their weak Lewis acidity, so with surface modification of TiO₂ by acidic moieties, we can benefit from the dual acidity of titanium and acidic groups. To solve this problem, for the first time, we successfully prepared sulfonic acid-functionalized nanocrystalline titania (TiO₂–Pr–SO₃H) by modification of TiO₂ with sulfonic acid moieties [37,38]. The preparation strategy for the nanoreactor is shown in Scheme 1. In our first report, we used this reagent as an efficient catalyst for the preparation of quinoxaline derivatives [37], our procedure provided better activity with high yields and turnover compared to the previously reported heterogeneous ones. Also, we used this reagent for the promotion of the N-Boc protection of amines successfully [38]. Herein and in continuation of the above-mentioned studies, we are reporting the promoting effect of TiO₂–Pr–SO₃H as a new catalyst for the preparation of coumarin derivatives (Scheme 2).

2. Experimental

2.1. Materials

Chemicals were purchased from Merck (Darmstadt, Germany) and Sigma–Aldrich (St. Louis, MO, USA). All of
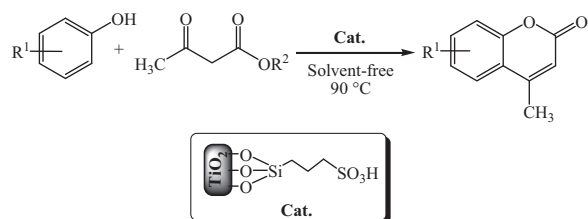
the yields refer to the isolated products. Identification of the products was confirmed by comparison of their physical constants with those of authentic samples. The purity determination of the substrate and reaction monitoring were accompanied by thin-layer chromatography (TLC) on silica gel POLYGRAM SILG-UV₂₅₄ (Carl Roth GmbH, Karlsruhe, Germany) plates.

2.2. Catalyst preparation

2.2.1. Synthesis of 3-mercaptopropyltitania

To 20 g of TiO₂ (anatase, from Sigma–Aldrich) in dry toluene, 25 mL of (3-mercaptopropyl) trimethoxysilane were added, and the reaction mixture was refluxed for 24 h. After this period, the mixture was filtered to obtain 3-mercaptopropyltitania (MPT), which was washed with acetone and dried.

2.2.2. Oxidation of 3-mercaptopropyltitania

MPT was oxidized with 10 wt% H₂O₂ in methanol (20 mL) for 24 h at room temperature. The prepared sample was then treated with 1 N H₂SO₄ at ambient temperature for complete protonation, and then, the mixture was filtered and washed with H₂O and acetone to obtain TiO₂–Pr–SO₃H catalyst (Scheme 1).

2.3. Catalyst characterization

The synthesized catalyst was characterized by Fourier transform–infrared spectroscopy (FT–IR), X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and thermogravimetric analysis (TGA). Also, the acidic property of the synthesized catalyst was evaluated by the calculation of the Hammett acidity function [37,38].

2.4. General procedure

A mixture of substrate (1 mmol), methyl or ethyl acetoacetate (1 mmol) and TiO₂–Pr–SO₃H (8 mg) was taken in a 25-mL round bottomed flask equipped with a condenser. The mixture was heated in an oil bath at 90 °C under stirring and the reaction was monitored by TLC. After completion, the mixture was allowed to cool, ethyl acetate (5 mL) was added and the catalyst was recovered by filtration, washed with ethyl acetate (5 mL), dried and reused according to the procedure mentioned above. Evaporation of the solvent from the filtrate and recrystallization of the solid residue from hot ethanol afforded the requested coumarins in high yields. The results are given in Table 2 and spectral data and melting points are in good agreement with those reported in the literature [24–29].

3. Results and discussion

In order to optimize the reaction conditions, we conducted the preparation of 4,7-dimethylcoumarin from the reaction of m-Cresol (1 mmol) and ethylacetoacetate (1 mmol) in the presence of various amount of TiO₂–Pr–SO₃H at different temperatures and in solventless media

Scheme 2. Preparation of coumarins in the presence of TiO₂–Pr–SO₃H.

Table 1
The Pechmann condensation reaction between *m*-Cresol and ethylacetoacetate in different conditions.

Entry	Catalyst	Catalyst (mg)	Temperature (°C)	Time (min)	Yield (%)[a]
1	–	–	100	120	NR[b]
2	TiO_2	20	100	120	trace
3	TiO_2–Pr–SO_3H	20	100	30	92
4	TiO_2–Pr–SO_3H	15	100	30	90
5	TiO_2–Pr–SO_3H	10	100	30	93
6	TiO_2–Pr–SO_3H	8	100	30	95
7	TiO_2–Pr–SO_3H	5	100	45	80
8	TiO_2–Pr–SO_3H	8	95	30	90
9	**TiO_2–Pr–SO_3H**	**8**	**90**	**30**	**95**
10	TiO_2–Pr–SO_3H	8	80	60	75

The bold elements in the table show the optimized conditions of the reaction.
[a] Isolated yield.
[b] No reaction.

(Table 1). As shown in Table 1, the above-mentioned reaction in the absence of catalyst and in the presence of 20 mg bare TiO_2 did not produce any product in 120 min at 100 °C (entries 1, 2). However, using 20 mg of TiO_2–Pr–SO_3H at 100 °C yielded 92% of 4,7-dimethylcoumarin in 30 min (entry 3). Decreasing the amount of catalyst show better results in the yield of the product and also decreasing the reaction temperature from 100 °C to 90 °C did not affect the duration of the reaction and the product yield (entry 9).

After optimization of the reaction conditions, the reaction of other phenols with ethyl acetoacetate or methyl acetoacetate in the presence of TiO_2–Pr–SO_3H is carried out and the results are presented in Table 2. It can easily be seen that the Pechmann condensation proceeded smoothly under solvent-free conditions and gave good to high yields ranging from 81% to 95%. Many phenols, such as resorcinol, hydroquinone, pyrogallol, 3-methoxy phenol, *m*-Cresol, orcinol and phloroglucinol could be converted into the corresponding coumarins in high yields. As shown in Table 2, the reaction of 2-naphthol is slower than with other phenols and the yields of the products are fewer due to steric hindrance around the reaction centre (entries 13,

14). Phenols that have more than two hydroxyl groups in their structure are slightly more active compared to other phenols because hydroxyl groups activate the aromatic ring and their reaction is faster with higher yields (entries 4, 5, 11 and 12) [30]. It is noticeable that only one product can be obtained by these phenols, because the new produced ring deactivates other hydroxyl groups by resonance and the reaction cannot continue farther.

The possible mechanism for the preparation of coumarins in the presence of TiO_2–Pr–SO_3H as a promoter is shown in Scheme 3. On the basis of this mechanism, intermediate **I** is generated from the transesterification of phenol with ethyl acetoacetate or methyl acetoacetate. Then, Michael addition reaction generates a new ring to afford species **II**. Rearomatization leads to the formation of the coumarin skeleton **III**. At last stage, TiO_2–Pr–SO_3H can be regenerated by dehydration.

The recycling performance of TiO_2–Pr–SO_3H was investigated in the reaction of pyrogallol and ethyl acetoacetate. After performing one reaction under the conditions described in Table 1, the catalyst was recovered by filtration, washed with ethyl acetate (5 mL), dried at 100 °C and reused for a consecutive run under the same

Table 2
Pechmann synthesis of coumarins in the presence of TiO_2–Pr–SO_3H.

Entry	R^1	R^2	Time (min)	Yield[a] (%)
1	3-OH	Et	32	93
2	3-OH	Me	45	85
3	4-OH	Et	30	92
4	2,3-$(OH)_2$	Et	28	91
5	2,3-$(OH)_2$	Me	33	95
6	3-OMe	Et	24	86
7	3-OMe	Me	38	92
8	3-Me	Et	30	95
9	3-Me	Me	60	90
10	3-Me-5-OH	Et	26	93
11	3,5-$(OH)_2$	Et	22	93
12	3,5-$(OH)_2$	Me	23	90
13	2-naphthol	Et	75	83
14	2-naphthol	Me	90	81

[a] Isolated yields.
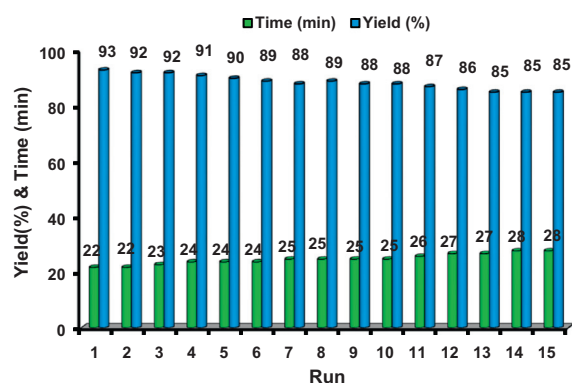
Fig. 1. (Color online.) Reusability of the catalyst in the synthesis of 7,8-dihydroxy-4-methylcoumarin.
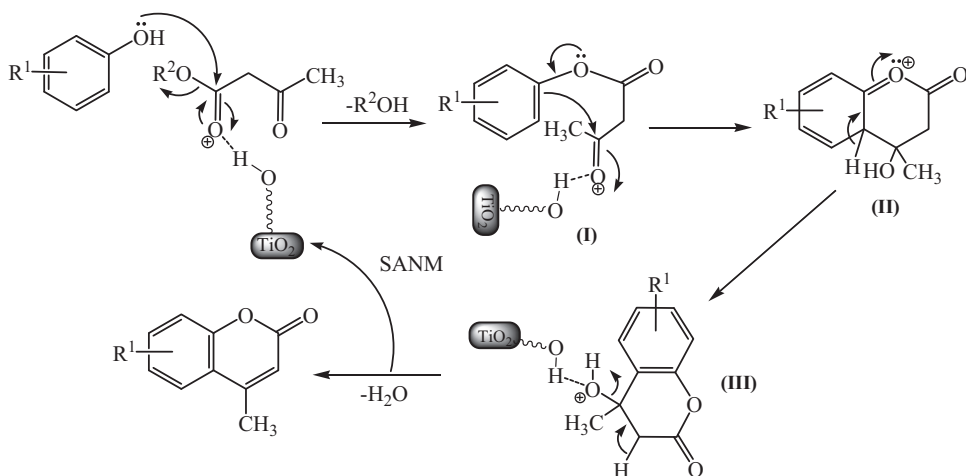
Scheme 3. Proposed mechanism for the Pechmann condensation using TiO$_2$–Pr–SO$_3$H.

reaction conditions. Thus, after the first run, which gave the corresponding coumarin with 91% yield, and after recovery, the catalyst was subjected to a second reaction affording the product obtained with 89% yield; the average time for 15 consecutive runs was 25 min and 88.5% yield for all (Fig. 1). Also, TEM and SEM images of TiO$_2$ and of the recycled catalyst demonstrated that the morphology of the catalyst did not change after the fifth run (Figs. 2 and 3). This reusability shows the high stability and turnover of solid titania-based sulfonic acid (TiO$_2$–Pr–SO$_3$H) under the conditions employed. It should be noted that the recyclability test was stopped after 15 runs.

To illustrate the efficiency of the present method, Table 3 compares our result in the synthesis of 7-hydroxy-4-methylcoumarin with the same results reported by the relevant reagents in the literature. By comparing with different homogeneous Lewis acid catalysts [16–20], ionic liquids [22,30] and other solid acids with different supports such as montmorillonites [27], polymers [31] and silica [32], TiO$_2$–Pr–SO$_3$H give the 7-hydroxy-4-methylcoumarin with using a lower amount of catalyst and with an excellent yield. Also, our synthesized catalyst can be reused 14 times without noticeable decrease in its catalytic activity (Table 3, last column).
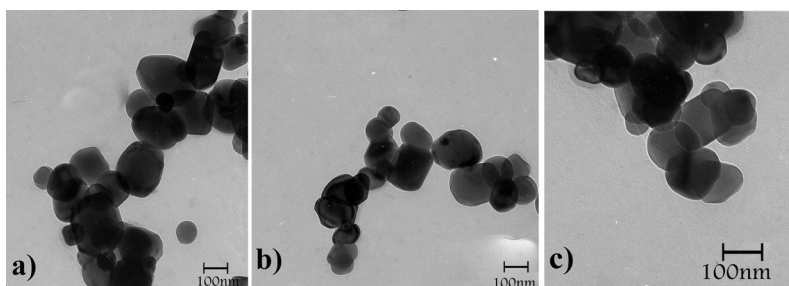

Fig. 2. TEM images of fresh TiO$_2$–Pr–SO$_3$H (a) and TiO$_2$–Pr–SO$_3$H after the first (b) and fourth (c) runs.
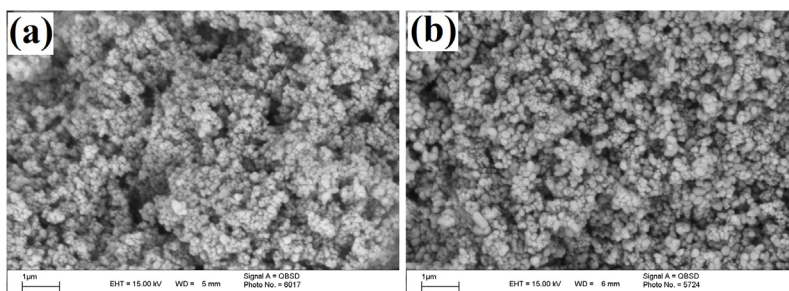
Fig. 3. SEM images of fresh TiO$_2$–Pr–SO$_3$H (a) and TiO$_2$–Pr–SO$_3$H after the fourth (b) run.

Table 3

Compared performance of various catalysts in the synthesis of 7-hydroxy-4-methylcoumarin.

Catalyst	Catalyst loading (mg)	Reaction Temp. (°C)	Time (min)	Yield (%)	Time of runs[a]
TiO$_2$–Pr–SO$_3$H (this work)	8	90	32	93	15
InCl$_3$ [16]	22.2	Reflux in 65 °C under N$_2$	30	98	–
BiCl$_3$ [17]	15.8	75	60	92	–
ZrCl$_4$ [18]	24	RT	5	92	–
VCl$_3$ [19]	15.8	50–55	120	92	–
Sm(NO$_3$)$_3$·6H$_2$O [20]	24	Reflux in 80 °C	20	98	–
Chloroaluminate [22]	265	130	35	90	–
Mont-K10 [27]	72	150	240	96	5
Mont-KSF [27]	72	150	300	88	5
[Msim]HSO$_4$[b] [30]	25	40	25	94	5
PEG-SO$_3$H[c] [31]	11	80	10	91	3
Silica-bonded *S*-sulfonic acid [32]	100	80	15	89	5

All procedures were carried out without use of solvent.

[a] For one reaction.

[b] Msim = 3-methyl-1-sulfonic acid imidazolium.

[c] With methylacetoacetate as β-keto ester.

4. Conclusion

In conclusion, in this article, we have reported the applicability of a new catalyst for the synthesis of coumarins *via* the Pechmann condensation of phenols with methyl or ethyl acetoacetate in the absence of solvent. Our methodology has several advantages: it is green by avoiding toxic catalysts and traditional solvents, the catalyst is very cheap, it proceeds with high reaction rates, affording excellent yields, there is no side reaction, the catalyst is easy to prepare and to handle, it can be effectively recovered and reused with a high turnover rate, it needs only a lower loading and a simple experimental procedure. Further work to explore this novel catalyst in other organic transformations is in progress.

References

[1] G. Cravotto, G.M. Nano, G. Palmisano, S. Tagliapietra, Tetrahedron: Asymm. 12 (2001) 707.
[2] O. Kayser, H. Kolodziej, Planta Med. 63 (1997) 508.
[3] C.J. Wang, Y.J. Hsieh, C.Y. Chu, Y.L. Lim, T.H. Tseng, Cancer Lett. 183 (2002) 163.
[4] G.J. Fan, W. Mar, M.K. Park, E.W. Choi, K. Kim, S. Kim, Bioorg. Med. Chem. Lett. 11 (2001) 2361.
[5] S. Kirkiacharian, D.T. Thuy, S. Sicsic, R. Bakhchianian, R. Kurkjian, T. Tonnaire, Il Farmaco 57 (2002) 703.
[6] S.M. Sethna, N.M. Shah, Chem. Rev. 36 (1945) 1.
[7] V.P. Hong, K.J. lee, Synthesis (2005) 33.
[8] A. Shaabani, R. Ghadari, A. Rahmati, A.H. Rezayan, J. Iran Chem. Soc. 6 (2009) 710.
[9] G. Jones, Org. React. 15 (1967) 204.
[10] G. Brufola, F. Fringuelli, O. Piermatti, F. Pizzo, Heterocycles 43 (1996) 1257–1266.
[11] R.L. Shriner, Org. React. 1 (1942) 1.

[12] I. Yavari, R. Hekmat-Shoar, A. Zonouzi, Tetrahedron Lett. 39 (1998) 2391.
[13] J.R. Johnson, Org. React. 1 (1942) 210.
[14] H. Von Pechmann, Chem. Ber. 17 (1884) 929.
[15] E.C. Horning, Organic Synthesis, Vol. III, Wiley, New York, 1955, p. 281.
[16] D.S. Bose, A.P. Rudradas, M.T. Hari Babu, Tetrahedron Lett. 43 (2002) 9195.
[17] S.K. De, R.A. Gibbs, Synthesis (2005) 1231.
[18] G.V.M. Sharma, J.J. Reddy, P.S. Lakshmi, P.R. Krishna, Tetrahedron Lett. 46 (2005) 6119.
[19] B.S. Kumar, P.S. Kumar, N. Srinivasulu, B. Rajitha, Y.T. Reddy, P.N. Reddy, R.H. Udupi, Heterocycl. Compd. 42 (2006) 172.
[20] S.S. Bahekar, D.B. Shinde, Tetrahedron Lett. 45 (2004) 7999.
[21] M.K. Potdur, S.S. Mohile, M.M. Salunkhe, Tetrahedron Lett. 42 (2001) 9285.
[22] A.C. Kandekar, B.M. Khadikar, Synlett (2002) 152.
[23] M.K. Potdar, M.S. Rasalkar, S.S. Mohile, M.M. Salunkhe, J. Mol. Catal. A: Chem 235 (2005) 249.
[24] B. Karimi, D. Zareyee, Org. Lett. 10 (2008) 3989.
[25] E.A. Gunnewegh, A.J. Hoefnegal, H. Van Bekkum, J. Mol. Catal. A: Chem. 100 (1995) 87.
[26] S. Frere, V. Thiery, T. Besson, Tetrahedron Lett. 42 (2001) 2791.
[27] T. Li, Z. Zhang, F. Yang, C. Fu, J. Chem. Res. (1998) 38.
[28] B. Vijayakumar, G. Ranga Rao, J. Porous Mater. 19 (2012) 233.
[29] J.C. Rodriguez-Dominguez, G. Kirsch, Tetrahedron Lett. 47 (2006) 3279.
[30] N.G. Khaligh, Catal. Sci. Technol. 2 (2012) 1633.
[31] G.M. Nazeruddin, M.S. Pandharpatte, K.B. Mulani, C. R. Chimie 15 (2012) 91.
[32] K. Niknam, D. Saberi, M. Baghernejad, Chin. Chem. Lett. 20 (2009) 1444.
[33] M. Lakshmi Kantam, S. Laha, J. Yadav, B. Sreedhar, Tetrahedron Lett. 47 (2006) 6213.
[34] M. Hosseini-Sarvari, Acta. Chim. Slov. 54 (2007) 354.
[35] M.Z. Kassaee, R. Mohammadi, H. Masrouri, F. Movahedi, Chin. Chem. Lett. 22 (2011) 1203.
[36] J.L. Ropero-Vega, A. Aldana-Péreza, R. Gómez, M.E. Nino-Gómez, Appl. Catal. A: Gen. 379 (2010) 24.
[37] S.V. Atghia, S. Sarvi Beighbaghlou, J. Nanostructure Chem. 3 (2013) 38.
[38] S.V. Atghia, S. Sarvi Beighbaghlou, J. Organomet. Chem. 745–746 (2013) 42–49.