Nano-TiO_2: an Eco-friendly and Re-usable Catalyst for the One-pot Synthesis of β-Acetamido Ketones

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Nano-TiO_2 as an efficient, eco-friendly and reusable catalyst was applied for the one-pot synthesis of β-acetamido ketones. In this improved procedure, an aryl aldehyde, an aryl ketone, acetyl chloride and acetonitrile were condensed in the presence of the catalyst at room temperature.

Key words: Nano-TiO_2, One-pot Reactions, Multi-component Reactions, β-Acetamido Ketones, Re-usable Catalyst

Introduction

β-Acetamido ketones are valuable building blocks for the preparation of β-amino ketones or β-amino alcohols such as the antibiotic nikkomycins [1] and neopolyoxines [2]. α-Acetamido ketones are obtained in the Dakin-West reaction [3] and β-acetamido ketones by the Iqbal route. In the latter, an aromatic aldehyde, an enolizable ketone and acetonitrile are condensed in the presence of acetyl chloride and a catalytic amount of an acid [4]. Recently, many catalysts such as silica sulfuric acid [5], $H_6P_2W_{18}O_{62}$ [6], ZnO [7], sulfated zirconia [8], some heteropoly acids [9], silica-supported $H_3PW_{12}O_{40}$ [10], nano-ZnO [11], sulfamic acid [12], $Sc(OTf)_3$ [13], $SnCl_2{\cdot}2H_2O$ [14], Zeolite *Hβ* [15], $ZrOCl_2 \cdot 8H_2O$ [16], $Mg(HSO_4)_2$ [17], and Nafion-H [18] have been applied in this one-pot reaction. However, some of these methods employ long reaction times [13] or harsh reaction conditions [5 – 7, 10]. Thus, the need for the development of new protocols is evident. TiO_2 as a white pigment is used in the manufacture of paint and of surface coatings on paper and as a filler in rubber and plastics. Fine particles of TiO_2 scatter light so strongly that they can be used to produce films of high capacity. In addition, TiO_2 is chemically inert and its oral LD_{50} for rats is higher than 10000 $mg\,kg^{-1}$ [19].

The high surface area-to-volume ratio of metal oxide nanoparticles is mainly responsible for their catalytic properties. High yield, selectivity and recyclability have been reported for a variety of nanocatalyst-based organic reactions. TiO_2 nanoparticles have been widely investigated in the past decades due to their multiple potential applications, such as solar energy conversion, photocatalysts, sensors, and photochromic devices. TiO_2 has three well-known crystallographic phases in nature: anatase, rutile, and brookite. Among these, anatase has been proved to have excellent chemical and physical properties for environmental purification and many other uses. In continuation of our utilization of solid acids in organic synthesis [20 – 26], we became interested in the synthesis of β-acetamido ketones using nano-TiO_2 as an efficient, re-usable and eco-friendly nano catalyst.

Results and Discussion

To find the optimal conditions, the synthesis of β-acetamido-β-phenyl-propiophenone was used as a model reaction. A mixture of benzaldehyde (2 mmol), acetophenone (2 mmol), acetyl chloride (0.5 mL) and acetonitrile (2 mL) was stirred under various reaction conditions (Table 1). In the presence of 12 mol-% of TiO_2, β-acetamido-β-phenyl-propiophenone was obtained in moderate yield after 12 h, while excellent results were obtained in the presence of 8 mol-% of nano-TiO_2 after 12 h. Using more than 8 mol-% TiO_2 nanoparticles has less effect on the yield and time of the reaction. To generalize this methodology, we subjected a series of aromatic aldehydes and enolizable ketones having electron-donating as well as electron-withdrawing substituents under the optimized reaction conditions (Table 2). Acetylation of an aromatic hydroxyl group was observed when using *p*-hydroxybenzaldehyde. 4-Dimethylamino-benzaldehyde, however, was inert under the present reaction conditions.

The preparative efficacy of this one-pot synthesis was further checked by five-fold scaling-up of the reaction of benzaldehyde with acetophenone and the other ingredients which proceeded with an 88 % yield. The

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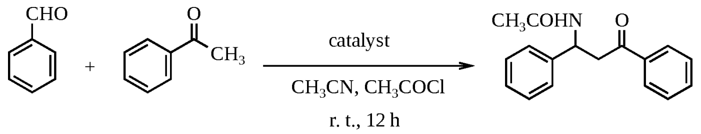
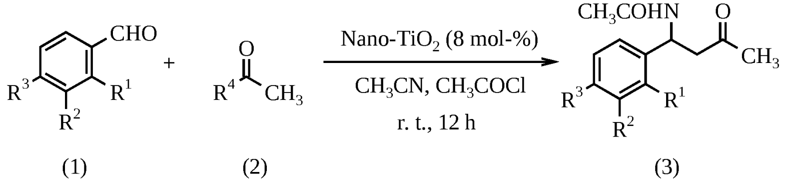
Table 1. Optimization of reaction conditions for one-pot formation of β-acetamido ketones.



Entry	Catal. (mol-%)	Time (h)	Cond. / Yield (%)[a]	Ref.
1	$ZrOCl_2 \cdot 8H_2O$ (20)	5	r. t. / 90[b]	[16]
2	Silica sufuric acid (78)	1.1	80 °C / 91	[5]
3	$H_3[PW_{12}O_{40}]$	1	80 °C / 65[b]	[10]
4	ZnO nanoparticles (10)	1	r. t. / 83	[11]
5	ZnO (50)	6	80 °C / 90	[7]
6	Nafion-H (500 mg)	4	r. t. / 96	[18]
7	$Sc(OTf)_3$ (10)	30	r. t. / 82	[13]
8	$H_6P_2W_{18}O_{62}$ (0.14)	0.5	80 °C / 86	[6]
9	–	12	r. t. / 15	–
10	TiO_2 (5)	12	r. t. / 30	–
11	TiO_2 (16)	12	r. t. / 48	–
12	TiO_2 (8)	12	r. t. / 53	–
13	TiO_2 (12)	12	r. t. / 71	–
14	TiO_2 (12)	18	r. t. / 72	–
15	TiO_2 (12)	24	r. t. / 73	–
16	Nano-TiO_2 (5)	12	r. t. / 78	–
17	Nano-TiO_2 (8)	12	r. t. / 93	–
18	Nano-TiO_2 (12)	12	r. t. / 92	–
19	Nano-TiO_2 (16)	12	r. t. / 93	–
20	Nano-TiO_2 (12)	18	r. t. / 94	–
21	Nano-TiO_2 (12)	24	r. t. / 93	–
22	Nano-TiO_2 (12), 2nd run	12	r. t. / 88	–
23	Nano-TiO_2 (12), 3rd run	12	r. t. / 85	–

[a] Isolated yield; [b] yield after chromatographic purification.

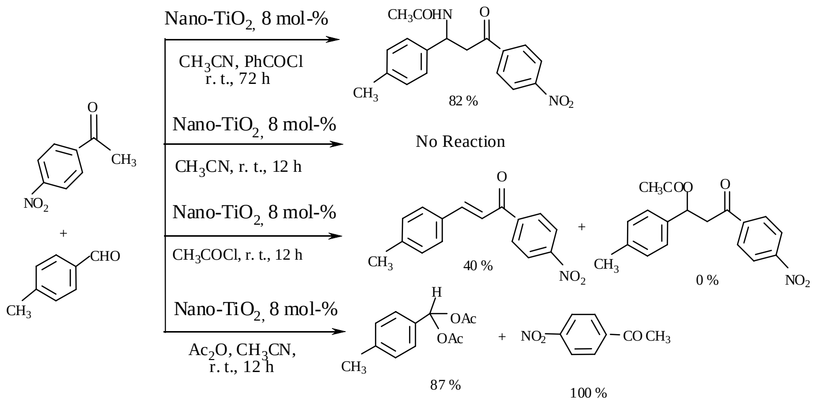
Table 2. Nano-TiO_2-catalyzed formation of β-acetamido ketones.[a]



Entry	Product (3)[b]	Yield (%) Nano-TiO_2/TiO_2	m. p (°C)	reported m. p. (°C)	Crystallization solvent	Ref.
1	R^1, R^2, R^3=H, R^4=Ph	93/53	105 – 106	104 – 105	EtOAc-petroleum ether (20 : 80)	[16]
2	R^1, R^2, R^3=H, R^4=4-NO_2-C_6H_4	92/75	118 – 119	118 – 120	Ethanol-water (30 : 70)	[9, 18]
3	R^1=Cl, R^2, R^3=H, R^4=Ph	94/62	135 – 136	135 – 137	Ethanol-water (40 : 60)	[9]
4	R^2=NO_2, R^1, R^3=H, R^4=Ph	88/57	193 – 194	194 – 195	EtOAc-petroleum ether (20 : 80)	[16]
5	R^1, R^2=H, R^3=CH_3, R^4=Ph	92/60	111 – 113	112	EtOAc-petroleum ether (20 : 80)	[16]
6	R^1, R^2 =H, R^3=CH_3, R^4=4-NO_2-C_6H_4	94/86	84 – 85	83 – 85	Ethanol-water (40 : 60)	[9]
7	R^1, R^2 =H, R^3=CO_2CH_3, R^4=Ph	86/60	234 – 236	236 – 237	Ethanol-water (40 : 60)	[18, 27]
8	R^1, R^2 =H, R^3=OCH_3, R^4=Ph	88/60	109 – 110	110 – 112	EtOAc-petroleum ether (20 : 80)	[16]
9	R^1, R^3 =H, R^2=NO_2, R^4=4-NO_2-C_6H_4	89/68	155 – 157	154 – 157	Ethanol-water (20 : 80)	[6]
10	R^1, R^2=H, R^3=Cl, R^4=4-Cl -C_6H_4	80/53	142 – 143	141 – 143	Ethanol-water (20 : 80)	[5]

[a] Isolated yield; [b] all the products are known and were characterized by IR and ^{1}H NMR spectroscopy and by comparison of their physical properties with those reported in the literature.

re-usability of the nano-TiO_2 catalyst was also examined. To this end, after each run the product was dissolved in ethanol, filtered, and the residue (catalyst) was washed with $CHCl_3$ and re-used. Apparently, the treatment with $CHCl_3$ removed tars more efficiently from the catalyst surface This catalyst was re-usable, although a gradual decline of activity was observed (Table 1, entries 22 and 23).



Scheme 1.

Previously, three types of mechanisms for formation of β-acetamido ketones by the Iqbal procedure have been proposed [6,7,9,11,18,19]. In some cases [7,18,19], a β-acetoxy ketone was offered as an intermediate product that was converted into the β-acetamido ketone with acetonitrile. In our investigation, when no acetonitrile was present in the medium, no β-acetoxy ketone was formed, and only a crossed aldol condensation reaction occurred. In the preparation of β-acetamido ketone, no β-acetoxy ketone was obtained as a by-product. Besides, a mixture of chalcone, acetyl chloride and acetonitrile in the presence of catalyst failed to generate any β-acetamido ketone.

In the absence of acetyl chloride or benzoyl chloride, the reaction failed to provide the desired products, obviously indicating that they play a necessary role in this reaction, although not involved in the final product. When benzyl cyanide or phenyl cyanide was used instead of acetonitrile, the corresponding β-amido ketones, namely a β-phenylacetamido ketone or β-benzamido ketone were obtained. Note that neither a mixture of 4-methylbenzaldehyde, 4-nitroacetophenone, acetic anhydride and acetonitrile in the presence of nano-TiO_2, nor a mixture of 4-methyl benzaldehyde acylal, 4-nitroacetophenone and nano-TiO_2 in acetonitrile could produce any of the corresponding β-acetamido ketones (Scheme 1).

Conclusion

We have reported an efficient procedure for the synthesis of β-acetamido ketones using nano-TiO_2 as a re-usable, eco-friendly and efficient heterogeneous catalyst. Some advantages of this protocol are easy work-up, improved yields, clean reactions, and low loading of catalyst.

Experimental Section

General

The organic materials were purchased from Sigma-Aldrich and Merck and were used without any additional purification. All compounds gave satisfactory spectroscopic data. A Bruker (DRX-400 Avance) NMR spectrometer was used to record the ^1H NMR and ^{13}C NMR spectra. All NMR spectra were determined in $CDCl_3$ at ambient temperature. Nano-TiO_2 which was used as catalyst consists of anatase (plus some amorphous phase) with a specific BET surface area of 90 $m^2\ g^{-1}$ and ellipsoids with a 35 nm long axis and 15 nm diameter. TiO_2 nano-powders were extracted from a TiO_2 sol (TW01, Posshesh-haye Nanosakhtar Co., Iran). The β-acetamido ketone products are known and were characterized by IR and ^1H NMR spetroscopy and comparison of their physical properties with those reported in the literature.

General procedure for the synthesis of β-acetamido ketones

To a stirred suspension of nano-TiO_2 (8 mol-%) in acetonitrile (2 mL) were added an aldehyde (2 mmol), an enolizable ketone (2 mmol) and acetyl chloride (0.5 mL). The reaction mixture was stirred at ambient temperature for 12 h. The progress of the reaction was monitored by TLC. After 12 h, 3 mL of ethanol was added to the cold reaction mixture, stirred for 2 min, and the catalyst was recovered by filtration and washed with ethanol. Then, 50 mL of cold water was added to the filtrate, the precipitated product was filtered and recrystallized from a mixture of ethanol and water.

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