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PMA/SiO₂: An Efficient and Reusable Heterogeneous Catalyst for the Synthesis of β-Acetamidocarbonyl Compounds by Multicomponent Reaction

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PMA/SiO₂: An Efficient and Reusable Heterogeneous Catalyst for the Synthesis of β-Acetamidocarbonyl Compounds by Multicomponent Reaction

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Abstract: Phosphomolybdic acid supported on silica (PMA/SiO₂) has been used as an efficient heterogeneous catalyst for the preparation of β -acetamidoketones and esters in good yields. The reaction conditions are mild, and the catalyst can be recycled.

Keywords: β -Acetamidocarbonyl compound, heterogeneous catalyst, multicomponent reaction, PMA/SiO₂

INTRODUCTION

Multicomponent reactions (MCRs) are powerful tool in modern organic synthesis because they have several advantages over conventional multistep synthesis. These processes consist of two or more synthetic steps, which are performed without isolation of any intermediate. Thus MCRs reduce time and save both energy and raw materials. In drug discovery as well as in green chemistry, these processes are the preferred techniques because of their high-throughput synthesis of compounds in a

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Address correspondence to Biswanath Das, Organic Chemistry Division I, Indian Institute of Chemical Technology, Uppal Road, Hyderabad 500 007, Andhra Pradesh, India. E-mail: biswanathdas@yahoo.com cost- and time-effective manner. Hence, the development of MCRs is of current interest in the synthesis of various useful organic products.^[1]

β-Acetamido- or amino-ketones are important for their biological and pharmaceutical properties^[2] and in the preparation of antibiotic drugs such as nikkomycine and neopolyxine.^[3] The best-known synthesis of this class of compounds is the Dakin-West reaction,^[4] which involves the condensation of an α-amino acid with acetic anhydride in the presence of a base via an azolactone intermediate.^[5] The syntheses of β-acetamidoketones by the multicomponent coupling method in the presence of a Lewis acid such as $CoCl_2^{[6]}$ or montmorillonite K-10clay,^[7] silica sulfuric acid,^[8] ZrOCl₂ · 8H₂O,^[9] Sc(OTf)₃,^[10] BiCl₃ generated from BiOCl,^[11] ZnO,^[12] and I₂^[13] have been reported. Because β-acetamidoketones or esters have become increasingly useful and important in the field of pharmaceuticals, the development of clean, high-yielding, and environmentally friendly approaches is still desirable and much in demand.

RESULTS AND DISCUSSION

In recent years, heterogeneous catalysts have gained considerable importance because of environmental and economic considerations. In continuation of our work^[14] on heterogeneous catalysts for the development of useful synthetic methodologies, we have observed that phosphomolybdic acid supported on silica (PMA/SiO₂)^[15] is very suitable to catalyze one-pot coupling of aldehydes, enolizable ketones, or ketoesters and acetylchloride in the presence of acetonitrile to form β -acetamidoketones or esters at room temperature (Scheme 1). PMA/SiO₂ has great potential as an environmentally friendly alternative to the more wasteful traditional catalysts. This catalyst possesses excellent activity, low toxicity, and good stability to humidity. It can be recovered from the reaction mixture and reused.

Initially, we prepared N-(3-oxo-1,3-diphenyl propyl) acetamide in excellent yield from the reaction of benzaldehyde, acetophenone, acetylchloride, and acetonitrile (reactant as well as solvent) in the presence



Scheme 1. Synthesis of β -acetamidocarbonyl compounds using PMA/SiO₂.

Entry	β -Acetamidoketone or ester ^a	Time (h)	Isolated yield (%)	Mp ^[ref] (°C)
1	NHAC O 3a	6.0	94	102–104 ^[7]
2	H ₃ C 3b	6.0	92	170 ^[9]
3	O ₂ N NHAC O 3c	8.0	89	148–149 ^[7]
4	NHAC O NO ₂ 3d	7.5	88	151–153 ^[9]
5	NHAC O 3e	6.0	91	108–111
6	NHAC O OMe 3f	6.5	92	130 ^[9]
7	NHAC O OAC 3g	6.0	90	160–162
8	NHAC O 3h	6.0	92	152–154

Table 1. PMA/SiO₂-catalyzed formation of β -acetamidoketones and esters

(Continued)

Entry	β -Acetamidoketone or ester ^a	Time (h)	Isolated yield (%)	Mp ^[ref] (°C)
9	NHAC O CH ₃ 3i	6.0	85	104–105 ^[9]
10	H ₃ C NHAC O CH ₃ 3j	6.0	82	112 ^[9]
11	NHAc O 3k	6.0	91	174 ^[9]
12	H ₃ C NHAC 0 H ₃ C 31	6.0	89	159 ^[9]
13	Meoc OMe 3m	6.0	90	174–176
14	CI SINGLE SINDLE SINGLE SINGLE SINGLE SINGLE SINGLE SINGLE SINGLE SINGLE SINGLE	7.0	89	162 ^[9]
15	NHAC O O2N 30	8.0	82	143 ^[9]
16	NHAC O OMe 3p	6.0	88	129–131 ^[6c]

Table 1. Continued

(Continued)

Entry	β -Acetamidoketone or ester ^a	Time (h)	Isolated yield (%)	Mp ^[ref] (°C)
17	MeO OMe 3q	6.0	88	142–144 ^[6c]
18	O ₂ N OMe OMe 3r	8.0	78	149–151 ^[6c]
19	NHAC O OCH ₂ CH ₃ 38	7.0	90	105–107
20	AcO OME OME AcO	7.0	89	130–134

Table	1.	Continued
I ante		Commuca

^{*a*}The structures of the products were determined from their spectroscopic (¹H NMR and MS) and analytical data.

of PMA/SiO₂ at room temperature (Table 1, entry 1). In the absence of catalyst, the product was obtained in very poor yield even after 24 h, whereas in the absence of PMA and only with SiO₂ the transformation took a long time and the yield was only 12% after 24 h.

A variety of other aromatic aldehydes with electron-donating groups as well as electron-withdrawing substituents underwent the reaction smoothly, giving the desired products in good yields (the result is summarized in Table 1). An aromatic aldehyde containing a nitro substituent took longer (entry 3). Several enolizable ketones served as good substrates for the present one-pot synthesis of β -acetamidoketones. Thus, the reaction of benzaldehyde with a variety of acetophenones (*p*methoxy, *p*-nitro, *p*-hydroxy, *p*-isopropyl acetophenones), acetylchloride, and acetonitrile proceeded efficiently in the presence of PMA/SiO₂, resulting in the formation of the desired products in impressive yields. The reaction between *p*-hydroxy acetophenone and 2-naphathaldehyde yielded the corresponding β -acetamidoketone (entry 7) as acetylated product. A mixture of acetophenone or *p*-isopropyl acetophenone, hexanal, acetylchloride, and acetonitrile failed to generate the corresponding product in the presence of a catalytic amount of PMA/SiO₂ even after 36 h.

To demonstrate the versatility of the catalyst PMA/SiO₂, we have examined the reaction of benzaldehyde derivatives with ethyl methyl ketone, propiophenone, ethyl acetoacetate, methyl acetoacetate, and ethyl benzoylacetate (Table 1, entries 9–20). With these substrates, the β -acetamidoketones or esters were obtained in good yields, but the *syn*and the *anti*-products were produced in almost equal amounts. The structures of the products were settled from their spectral (¹H NMR and mass spectral, MS) data. The coupling constants between H-2 and H-3 is 6–9 Hz for an *anti*-isomer and 2–5 Hz for a *syn*-isomer.^[5c,12]

CONCLUSION

In conclusion, we have revealed a simple, efficient, and green protocol for the preparation of β -acetamidoketones and esters using PMA/SiO₂ as a heterogeneous catalyst. The salient features of this protocol include operational simplicity, low toxicity, excellent activity, good stability to humidity, and reusability of the catalyst.

EXPERIMENTAL

General

 PMA/SiO_2 (113 mg, 0.005 mol based on PMA) was added to a solution of an aldehyde (1 mmol), an enolizable ketone or ester (1 mmol), and acetylchloride (1.5 mmol) in acetonitrile (4 mL). The mixture was stirred at room temperature, and the reaction was monitored by thin-layer chromatograph (TLC). After completion of the reaction, the mixture was filtered to recover the catalyst and the filtrate was poured onto ice-cold water (25 mL). The precipitated solid was filtered, washed with ice-cold water, and recrystalized from ethylacetate/n-hexane to give the pure product.

The recovered catalyst was recycled three times without affecting the yields of the products.

Spectroscopic (¹H NMR and MS) and Analytical Data of the New Compounds

Compound 3e

¹H NMR (CDCl₃, 200 MHz): δ 7.81 (2H, d, *J* = 8.0 Hz), 7.32–7.10 (6H, m), 6.78 (2H, d, *J* = 8.0 Hz), 5.46 (1H, m), 4.57 (1H, m), 3.56 (1H, dd, *J* = 17.0,

4.4 Hz), 3.22 (1H, dd, J = 17.0, 5.2 Hz), 1.88 (3H, s), 1.31 (6H, d, J = 8.0 Hz); FABMS: m/z 310 [M + H]⁺. Anal. calc. for C₂₀H₂₃NO₂: C, 77.66; H, 7.44; N, 4.53%. Found: C, 77.02; H, 7.29; N, 4.39%.

Compound 3g

¹H NMR (CDCl₃, 200 MHz): δ 7.95 (2H, d, J = 8.0 Hz), 7.89–7.71 (4H, m), 7.55–7.38 (3H, m), 7.16 (2H, d, J = 8.0 Hz), 6.84 (1H, d, J = 8.0 Hz), 5.69 (1H, m), 3.81 (1H, dd, J = 17.0, 4.5 Hz), 3.46 (1H, dd, J = 17.0, 5.5 Hz), 2.30 (3H, s), 2.01 (3H, s); FABMS: m/z 364 [M + H]⁺. Anal. calc. for C₂₂H₂₁NO₄: C, 72.72; H, 5.78; N, 3.85%. Found: C, 71.58; H, 5.69; N, 3.80%.

Compound 3h

¹H NMR (CDCl₃, 200 MHz): δ 7.92 (2H, d, J = 8.0 Hz), 7.86–7.72 (4H, m), 7.53 (1H, t, J = 8.0 Hz), 7.48–7.39 (5H, m), 6.83 (1H, d, J = 8.0 Hz), 5.67 (1H, m), 3.81 (1H, dd, J = 17.0, 4.5 Hz), 3.48 (1H, dd, J = 17.0, 5.0 Hz), 2.03 (3H, s); FABMS: m/z 318 [M + H]⁺. Anal. calc. for C₂₁H₁₉NO₂: C, 79.49; H, 5.99; N, 4.41%. Found: C, 78.98; H, 5.78; N, 4.38%.

Compound 3m (syn)

¹H NMR (CDCl₃, 200 MHz): δ 7.82 (2H, d, J = 8.0 Hz), 7.43–7.31 (4H, m), 6.80–6.72 (3H, m), 5.22 (1H, dd, J = 8.0, 4.0 Hz), 4.05 (1H, m), 3.63 (3H, s), 2.21 (3H, s), 2.02 (3H, s), 1.21 (3H, t, J = 7.0 Hz); FABMS: m/z 370 [M + H]⁺. Anal. calc. for C₂₁H₂₃NO₅: C, 68.29; H, 6.23; N, 3.79%. Found: C, 68.07; H, 6.17; N, 3.69%.

Compound 3m (anti)

¹H NMR (CDCl₃, 200 MHz): δ 7.71 (2H, d, J = 8.0 Hz), 7.53–7.46 (4H, m), 6.84–6.79 (2H, m), 6.62 (1H, d, J = 8.0 Hz), 5.40 (1H, t, J = 8.0 Hz), 4.01 (1H, s), 3.68 (3H, s), 2.22 (3H, s), 2.02 (3H, s), 1.28 (3H, t, J = 7.0 Hz);); FABMS: m/z 370 [M + H]⁺. Anal. calc. for C₂₁H₂₃NO₅: C, 68.29; H, 6.23; N, 3.79%. Found: C, 67.99; H, 6.11; N, 3.68%.

Compound 3s (syn)

¹H NMR (CDCl₃, 200 MHz): δ 7.98 (1H, d, J = 8.0 Hz), 7.87–7.71 (5H, m), 7.61–7.40 (7H, m), 6.02 (1H, dd, J = 7.0, 4.0 Hz), 5.05 (1H, d, J = 4.0 Hz),

4.17 (2H, q, J = 7.0 Hz), 2.05 (3 H, s), 1.20 (3 H, t, J = 7.0 Hz); FABMS: m/z 378 [M + H]⁺. Anal. calc. for C₂₃H₂₃NO₄: C, 73.20; H, 6.10; N, 3.71%. Found: C, 72.93; H, 5.97; N, 3.64%.

Compound 3s (anti)

¹H NMR (CDCl₃, 200 MHz): δ 7.83 (1H, d, J = 8.0 Hz), 7.72–7.61 (5H, m), 7.49–7.32 (7H, m), 5.91 (1H, dd, J = 9.0, 6.0 Hz), 4.99 (1H, d, J = 6.0 Hz), 4.10 (2H, q, J = 7.0 Hz), 2.01 (3 H, s), 1.11 (3H, t, J = 7.0 Hz);); FABMS: m/z 378 [M + H]⁺. Anal. calc. for C₂₃H₂₃NO₄: C, 73.20; H, 6.10; N, 3.71%. Found: C, 72.88; H, 5.90; N, 3.60%.

Compound 3t (syn)

¹H NMR (CDCl₃, 200 MHz): δ 7.82 (2H, d, J = 8.0 Hz), 7.53–7.40 (4H, m), 6.93–6.85 (3H, m), 5.88 (1H, dd, J = 8.0, 4.0 Hz), 4.94 (1H, d, J = 4.0 Hz), 4.18 (2H, q, J = 7.0 Hz), 3.75 (3H, s), 2.22 (3H, s), 2.03 (3H, s), 1.12 (3H, t, J = 7.0 Hz); FABMS: m/z 428 [M + H]⁺. Anal. calc. for C₂₃H₂₅NO₇: C, 64.63; H, 5.85; N, 3.27%. Found: C, 64.03; H, 5.78; N, 3.21%.

Compound 3t (anti)

¹H NMR (CDCl₃, 200 MHz): δ 7.95 (2H, d, J = 8.0 Hz), 7.66–7.51 (4H, m), 7.01–6.90 (3H, m), 5.72 (1H, dd, J = 9.0, 6.0 Hz), 4.90 (1H, d, J = 6.0 Hz), 4.09 (2H, q, J = 7.0 Hz), 3.80 (3H, s), 2.30 (3H, s), 1.98 (3H, s), 1.21 (3 H, t, J = 7.0 Hz); FABMS: m/z 428 [M + H]⁺. Anal. calc. for C₂₃H₂₅NO₇: C, 64.63; H, 5.85; N, 3.27%. Found: C, 64.13; H, 5.65; N, 3.14%.

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