Monatsh Chem (2012) 143:831–834
DOI 10.1007/s00706-011-0669-1

ORIGINAL PAPER

One-pot three-component synthesis of β-acetamido carbonyl compounds catalyzed by heteropoly acids

Ali Javid · Majid M. Heravi · Fatemeh F. Bamoharram

Received: 17 June 2010 / Accepted: 3 October 2011 / Published online: 9 November 2011

Abstract A simple one-pot method for a new Mannich-type reaction is reported. In this method a heteropoly acid is used as a catalyst for the synthesis of β-acetamido carbonyl compounds via a three-component reaction of an aldehyde, acetamide, and dimedone in acetonitrile at room temperature. This method offers several advantages such as good yields, simple procedure, low cost, and ease of workup.

Keywords Multicomponent reaction (MCR) · Dimedone · Aldehyde · β-Acetamido ketones · Solid acid catalyst · Mannich-type reaction

Introduction

Multicomponent reactions (MCRs) are one of the most important protocols in organic synthesis and medicinal chemistry. In these reactions, three or more compounds are used as starting materials. These processes consist of two or more synthetic steps in a one-pot reaction without necessity to isolate any intermediates. Thus, they are facile and simple procedures, very fast, efficient, eco-friendly, and acceptable for green chemistry. Therefore, the design of novel MCRs and modification of them have attracted much attention in medicinal chemistry and drug discovery. The development of new MCRs is an ideal target of research in current organic chemistry [1]. The Biginelli [2, 3], Ugi [4, 5], Passerini [6], and Mannich [7, 8] reactions are some examples of MCRs. Mannich reaction is an aminoalkylation reaction of aldehydes and is a very useful method for the preparation of β-amino compounds. Also, it is a very important basic reaction in organic synthesis [9].

β-Acetamido carbonyl compounds can be used as precursors of 1,3-amino alcohols, β-amino acids, and γ-lactams [10–13]. Some of them also have shown biological and pharmaceutical properties and were used in the preparation of antibiotic drugs such as nikkomycin or neopolyoxins [14]. Recently it was reported that β-acetamido ketones can act as α-glucosidase inhibitors [15]. In 1928, Dakin et al. [16] first reported the synthesis of these kinds of compounds via the so-called Dakin–West reaction. This reaction involves the condensation of an α-amino acid and acetic anhydride in the presence of a base. In recent years, Iqbal et al. [17–19] synthesized this class of compounds by one-pot MCRs that involve an aldehyde, enolizable ketone or keto ester, acetonitrile, and acetyl chloride in the presence of $CoCl_2$ and montmorillonite K-10 clay as a catalyst. Afterwards, a number of catalyst systems were reported for the synthesis of β-acetamido carbonyl compounds via the same reaction, including $ZrOCl_2{\cdot}8H_2O$ [20], silica-supported sulfuric acid [21], $Cu(OTf)_2$ [22], $SiCl_2$–$ZnCl_2$ [23], Amberlyst 15 [24], I_2 [25], heteropoly acids (HPAs) [26, 27], ZnO [28], and $SnCl_2{\cdot}2H_2O$ [29]. Recently, cellulose sulfuric acid [30] was also used to accelerate this reaction. Because β-acetamido carbonyl compounds have become increasingly useful and important in the field of pharmaceuticals, introduction of new and green catalysts is still much in demand.

A. Javid (✉)
Department of Chemistry, Ahvaz Branch,
Islamic Azad University, Ahvaz, Iran
e-mail: alijavids@yahoo.com

M. M. Heravi
Department of Chemistry, Alzahra University,
Vanak, Tehran, Iran

F. F. Bamoharram
Department of Chemistry, Mashhad Branch,
Islamic Azad University, Mashhad, Iran

Theoretically, because amines are able to produce β-amino ketones and keto esters through Mannich reaction, acetamide could similarly afford corresponding β-acetamido ketones and keto esters through this type of reaction. However, in fact the classical Mannich reaction using amides is not promising and fruitful, probably due to the low reactivity and nucleophilicity of amides compared with amines. Previously, amides were used as nucleophiles in reactions with aldehyde in order to form *N*,*N*′-(methylene)diacetamide through a Mannich-type reaction in the presence of Lewis acids such as CF_3SO_3H [31] and trimethylchlorosilane (TMSCl) [32], or in the absence of catalyst with long reaction times under reflux conditions [33]. Recently, Mao and co-workers reported an efficient Mannich-type MCR to prepare β-acetamido carbonyl compounds from aldehydes, acetamide, and enolizable ketones (acetylacetone or acetophenone) or β-keto esters in the presence of TMSCl as a catalyst and 5–10 h reflux conditions [34].

In the last few decades, HPAs have found numerous applications as useful and versatile acid catalysts for some acid-catalyzed reactions. HPAs are more reactive catalysts than conventional inorganic and organic acids for reactions in solution. They are solids which are insoluble in nonpolar solvents but highly soluble in polar ones. HPAs can be used in bulk or supported forms in both homogeneous and heterogeneous systems. HPAs are nontoxic, highly stable towards humidity, air stable, recyclable, nonexplosive, easy to handle, compatible with the environment, and experimentally simple [35].

Results and discussion

In this study and in continuation of our works with HPAs as a catalyst in organic reactions [36–44], we wish to report the synthesis of a family of β-acetamido carbonyl compounds (**4a**–**4i**) via a Mannich-type three-component condensation of an aldehyde (**1**), acetamide (**2**), and dimedone (**3**) in the presence of the Keggin-type HPAs $H_n[XM_{12}O_{40}]$ ($n = 3, 4$; $X = P^V, Si^{IV}$; $M = W^{VI}, Mo^{VI}$) at room temperature (Scheme 1).

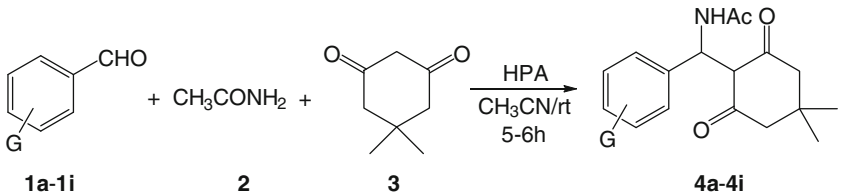
The mechanism of the Mannich reaction has been extensively investigated [45, 46]. The reaction can proceed under both acidic and basic conditions, but acidic conditions are more common. Under acidic conditions the first step is the reaction of the amine component with the protonated nonenolizable aldehyde (or ketone) to give a hemiaminal. After proton transfer and elimination of a water molecule, the electrophilic iminium ion is obtained. The formed iminium ion then reacts with the enolized carbonyl compound (nucleophile) at its α-carbon in an aldol-type reaction to give rise to the Mannich base. HPA might promote the reaction by accelerating the formation of the C=N bond in the iminium ion in the rate-determining step (Scheme 2). It is worth noting that the ^{1}H NMR spectra of the products show that in the keto–enol tautomerization, the enol is the dominant form. However, this is compatible with the fact that 1,3-dicarbonyl compounds exist predominantly in the enol form in acidic conditions. This is due to the generation of a conjugated π system and the formation of an intramolecular hydrogen bond that stabilizes the enol form [47].

The three-component condensation reaction of benzaldehyde (**1a**), acetamide (**2**), and dimedone (**3**) in the presence of a catalytic amount of several acids was chosen as a model reaction (Table 1). The reaction does not occur in the absence of the catalyst (Table 1, entry 1). Also, no target product was formed when HCl was used as a catalyst (Table 1, entry 2). However, the reaction was completed when HPAs were used as a catalyst (Table 1, entries 3–5). Our further investigation showed that Keggin-type 12-tungstophosphoric acid, $H_3[PW_{12}O_{40}]$, has higher catalytic activity than the other Keggin-type HPAs ($H_4[SiW_{12}O_{40}]$ and $H_4[SiMo_{12}O_{40}]$). Although it is difficult to offer an explanation for the different activities of these HPAs, there is a complex relationship between the activity and structure of the polyanion. By changing the constituent elements of the polyanion (both hetero and addenda atoms), the acid strength of HPA as well as its catalytic activity is varied over a wide range [35]. This behavior is in agreement with the acid strength of Keggin-type HPAs that decreases in the series $H_3[PW_{12}O_{40}] > H_4[SiW_{12}O_{40}] > H_4[SiMo_{12}O_{40}]$ [35]. The best molar ratio of aldehyde/acetamide/dimedone/HPA was found to be 2:2.2:2.2:0.05.

Because of the complexity of the behavior of this catalyst in a solvent, we also studied the rate and yield of the reaction in different solvents such as acetonitrile, ethanol, dichloromethane, and water (Table 2). We concluded that acetonitrile is the most suitable solvent for this reaction.

The results of our work are presented in Table 3. It is clear that aromatic aldehydes with both electron-donating

Scheme 1



Scheme 2

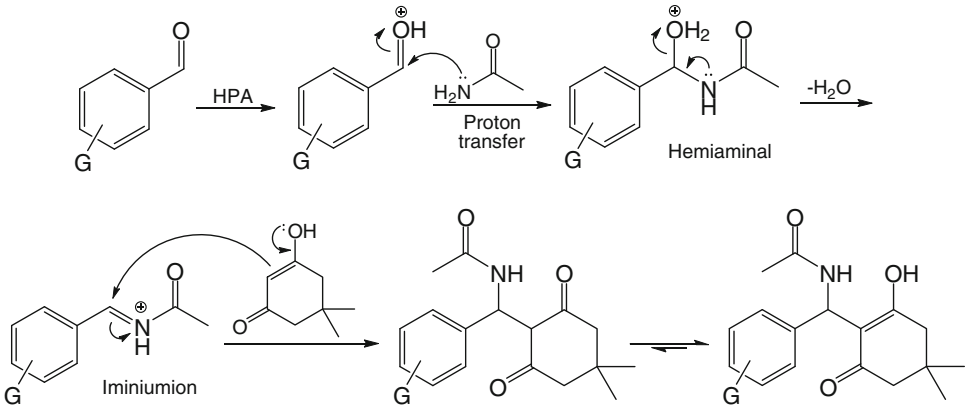


Table 1 Synthesis of *N*-[(4,4-dimethyl-2,6-dioxocyclohexyl)(phenyl)methyl]acetamide in the presence of various acid catalysts

Entry	Catalyst	Time/h	Yield/%[a]
1	None	24	0
2	HCl	24	0
3	$H_3[PW_{12}O_{40}]$	5	78
4	$H_4[SiW_{12}O_{40}]$	6	56
5	$H_4[SiMo_{12}O_{40}]$	10	38

Reaction of benzaldehyde (2 mmol), acetamide (2.2 mmol), and dimedone (2.2 mmol) in 10 cm^3 acetonitrile as solvent, in the presence of different acid catalysts (0.05 mmol) at room temperature

[a] Isolated yields

Table 2 Effect of various solvents in the synthesis of *N*-[(4,4-dimethyl-2,6-dioxocyclohexyl)(phenyl)methyl]acetamide

Entry	Solvent	Yield/%[a]
1	H_2O	No reaction
2	EtOH	32
3	CH_2Cl_2	Trace
4	CH_3CN	78

Reaction of benzaldehyde (2 mmol), acetamide (2.2 mmol), and dimedone (2.2 mmol) in 10 cm^3 solvent, in the presence of $H_3[PW_{12}O_{40}]$ catalyst (0.05 mmol) at room temperature

[a] Isolated yields after 5–6 h

and electron-withdrawing groups readily undergo the reaction giving good yields of corresponding Mannich reactions, except for an aldehyde containing a nitro group at the *para* position. We think that it gives the Knoevenagel condensation product rather than our desired product [34]. Steric demands of *ortho*-substituted aromatic aldehydes are also well tolerated.

Conclusion

We have used Keggin-type HPAs as efficient and green catalysts for the synthesis of a family of *β*-acetamido carbonyl compounds that were prepared via a new Mannich-type three-component reaction of aryl aldehydes, acetamide, and dimedone in acetonitrile at room temperature in good yields and relatively short reaction time.

Table 3 Mannich-type three-component synthesis of *β*-acetamido carbonyl compounds using a catalytic amount of $H_3[PW_{12}O_{40}]$

Entry	Aldehyde	Product	Yield/%[a]	M.p./°C	Ref. m.p./°C
1	C_6H_5CHO	**4a**	78	208–210	200 [30]
2	4-$CH_3C_6H_4CHO$	**4b**	74	190–193	105 [30]
3	4-ClC_6H_4CHO	**4c**	82	198–201	195 [30]
4	3-ClC_6H_4CHO	**4d**	78	193–195	147 [30]
5	4-$CH_3OC_6H_4CHO$	**4e**	85	212–215	188 [30]
6	2-$CH_3OC_6H_4CHO$	**4f**	86	196–199	198 [30]
7	4-HOC_6H_4CHO	**4g**	80	192–194	–
8	3-HOC_6H_4CHO	**4h**	74	189–192	–
9	2-HOC_6H_4CHO	**4i**	76	195–197	–

[a] Isolated yields after 5–6 h

Experimental

All chemicals were obtained from Merck and used as received. Melting points were measured by using the capillary tube method with an electrothermal 9200 apparatus. ^1H NMR spectra were recorded on a Bruker AQS AVANCE-500 MHz spectrometer using TMS as an internal standard. Thin-layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254, was used to monitor the progress of reactions.

Preparation of N-[(4,4-dimethyl-2,6-dioxocyclohexyl)(aryl)methyl]acetamides

To a solution of aldehyde (2 mmol), acetamide (2.2 mmol), and dimedone (2.2 mmol) in 10 cm^3 acetonitrile was added HPA (0.05 mmol). The mixture was stirred for 5–6 h at room temperature. After completion of the reaction (the progress of the reaction was monitored by

TLC using *n*-hexane/ethyl acetate as eluent), the resulting solid product was filtered, washed with cold water (3×20 cm^3), and recrystallized from ethyl acetate/hexane to give pure product.

N-[(4,4-Dimethyl-2,6-dioxocyclohexyl)(4-hydroxyphenyl)methyl]acetamide (**4g**, $C_{17}H_{21}NO_4$)
Yield 80%; m.p.: 192–194 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 0.97$ (6H, s, $2CH_3$), 1.87 (3H, s, CH_3CO), 2.26 (4H, br s, $2CH_2$), 6.1 (1H, d, $J = 9.2$ Hz, PhCH), 6.6 (2H, d, $J = 8.4$ Hz, Ph), 6.9 (2H, d, $J = 8.5$ Hz, Ph), 7.8 (1H, d, $J = 9.2$ Hz, NH), 9.09 (1H, s, PhOH), 10.99 (1H, s, OH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 23.36$, 28.35, 32.22, 39.75, 41.51, 45.84, 114.63, 114.93, 127.39, 133.69, 155.94, 168.64 ppm; MS: $m/z = 303$ (M^+), 260, 243, 227, 146, 83, 43.

N-[(4,4-Dimethyl-2,6-dioxocyclohexyl)(3-hydroxyphenyl)methyl]acetamide (**4h**, $C_{17}H_{21}NO_4$)
Yield 74%; m.p.: 189–192 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 0.98$ (6H, s, $2CH_3$), 1.83 (3H, s, CH_3CO), 2.27 (4H, br s, $2CH_2$), 6.2 (1H, d, $J = 9.2$ Hz, PhCH), 6.81–7.25 (4H, m, Ph), 7.9 (1H, d, $J = 9.2$ Hz, NH), 8.73 (1H, s, PhOH), 11.11 (1H, s, OH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 23.41$, 28.51, 32.20, 39.69, 41.12, 46.02, 114.59, 122.71, 125.31, 126.40, 126.73, 130.11, 147.51, 166.04 ppm; MS: $m/z = 303$ (M^+), 260, 243, 227, 146, 83, 43.

N-[(4,4-Dimethyl-2,6-dioxocyclohexyl)(2-hydroxyphenyl)methyl]acetamide (**4i**, $C_{17}H_{21}NO_4$)
Yield 76%; m.p.: 195–197 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 0.95$ (6H, s, $2CH_3$), 1.93 (3H, s, CH_3CO), 2.22 (4H, br s, $2CH_2$), 6.2 (1H, d, $J = 9.3$ Hz, PhCH), 6.89–7.09 (4H, m, Ph), 7.8 (1H, d, $J = 9.2$ Hz, NH), 8.95 (1H, s, PhOH), 11.04 (1H, s, OH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 23.26$, 28.97, 32.51, 39.69, 41.40, 45.77, 114.71, 115.50, 128.12, 136.09, 152.86, 164.31 ppm; MS: $m/z = 303$ (M^+), 260, 243, 227, 146, 83, 43.

References

1. Zhu J, Bienayme H (2005) Multicomponent reactions. Wiley-VCH, Weinheim
2. Biginelli P (1893) Gazz Chim Ital 23:360
3. Biginelli P (1891) Ber 24:2962
4. Ugi I, Meyr R, Fetzer U (1959) Angew Chem 71:386
5. Ugi I, Steinbruckner C (1960) Angew Chem 72:267
6. Passerini M (1921) Gazz Chim Ital 51:181
7. Mannich C, Krosche W (1912) Arch Pharm 250:647
8. Mannich C (1917) Arch Pharm 255:261
9. Michael A, Bernhard W, Nikolaus R (1998) Angew Chem Int Ed 37:1400
10. Barluenga J, Viado AL, Aguilar E, Fustero S, Olano B (1993) J Org Chem 58:5972
11. Enders D, Moser M, Geibel G, Laufer MC (2004) Synthesis 2040
12. Mukhopadhyay M, Bhatia B, Iqbal J (1997) Tetrahedron Lett 38:1083
13. Rao IN, Prabhakaran EN, Das SK, Iqbal J (2003) J Org Chem 68:4079
14. Dahn U, Hagenmaier H, Hohne H, König WA, Wolf G, Zahner H (1997) Arch Microbiol 107:143
15. Tiwari AK, Kumbhare RM, Agawane SB, Ali AZ, Kumar KV (2008) Bioorg Med Chem Lett 18:4130
16. Dakin HD, West R (1928) J Biol Chem 78:745
17. Rao IN, Prabhakaran EN, Das SK, Iqbal J (2003) J Org Chem 68:4079
18. Bahulayan D, Das SK, Iqbal J (2003) J Org Chem 68:5735
19. Prabhakaran EN, Iqbal J (1999) J Org Chem 64:3339
20. Ghosh R, Maiti S, Chakraborty A, Chakraborty S (2006) Tetrahedron Lett 47:8137
21. Khodaei MM, Khosropour AR, Fattahpour P (2005) Tetrahedron 46:2105
22. Pandey G, Singh RP, Singh VK (2005) Tetrahedron Lett 46:2137
23. Tarek AS, Saad SE, Mohamed AI (2007) Tetrahedron Lett 48:6199
24. Das B, Reddy KR (2006) Helv Chim Acta 89:3109
25. Das B, Reddy KR, Ramu R, Thirupathi P, Ravikanth B (2006) Synlett 11:1756
26. Heravi MM, Ranjbar L, Derikvand F, Bamoharram FF (2007) Catal Commun 8:289
27. Rafiee E, Tork F, Joshaghani M (2006) Bioorg Med Chem Lett 16:1221
28. Maghsoodlou MT, Hassankhani A, Shaterian HR, Habibi SM, Mosaddegh E (2007) Tetrahedron Lett 48:1729
29. Nagarapu L, Bantu R, Puttireddy R (2007) Appl Catal A 332:304
30. Oskooie HA, Heravi MM, Tahershamsi L, Sadjadi S, Tajbakhsh M (2010) Synth Commun 40:1772
31. Fernandez AH, Alvarez RM, Abajo TM (1996) Synthesis 1299
32. Wan JP, Chai YF, Wu JM, Pan YJ (2008) Synlett 19:3068
33. Milenkovicl A, Fachel F, Faure R, Lemaire M (1999) Synth Commun 29:1535
34. Mao H, Wan J, Pan Y (2009) Tetrahedron 65:1026
35. Kozhevnikov IV (2002) Catalysts for fine chemical synthesis: catalysis by polyoxo metalates, vol 2. Wiley, Chichester
36. Heravi MM, Sadjadi S, Mokhtari Haj N, Oskooie HA, Bamoharram FF (2009) Catal Commun 10:1643
37. Heravi MM, Sadjadi S, Mokhtari Haj N, Oskooie HA, Hekmat Shoar R, Bamoharram FF (2009) Tetrahedron Lett 50:943
38. Heravi MM, Sadjadi S, Oskooie HA, Bamoharram FF (2009) Ultrason Sonochem 16:708
39. Bamoharram FF, Heravi MM, Roushani M, Toosi M, Jodeyre L (2009) Green Chem Lett Rev 2:35
40. Heravi MM, Sadjadi S, Oskooie HA, Hekmat Shoar R, Bamoharram FF (2009) Tetrahedron Lett 50:662
41. Heravi MM, Sadjadi S, Mokhtari Haj N, Oskooie HA, Hekmat Shoar R, Bamoharram FF (2009) Tetrahedron Lett 50:943
42. Heravi MM, Sadjadi S, Oskooie HA, Hekmat Shoar R, Bamoharram FF (2008) Catal Commun 9:470
43. Heravi MM, Bakhtiari K, Fatehi A, Bamoharram FF (2008) Catal Commun 9:289
44. Heravi MM, Alimadadi Jani B, Derikvand F, Bamoharram FF, Oskooie HA (2008) Catal Commun 10:272
45. Thampson BB (1968) J Pharm Sci 57:715
46. Bencovic SJ, Bencovic PA, Comfort DR (1969) J Am Chem Soc 91:1860
47. Anslyn EV, Dougherty DA (2006) Modern physical organic chemistry. University Science Books, Sausalito