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K_3PO_4-catalyzed one-pot synthesis of β-amino ketones

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Abstract A new strategy which uses cheap K_3PO_4 as a very effective catalyst has been developed for synthesis of β-amino ketones by one-pot reaction of an aryl aldehyde, acetophenone derivative, and amine in EtOH at room temperature.

Keywords Aza-Michael reaction · One-pot reaction · Potassium phosphate · Chalcones · Conjugate addition

Introduction

The β-amino carbonyl functionality is not only a segment of biologically active natural products but also serves as key intermediate for synthesis of important nitrogen-containing compounds such as β-amino acids, β-lactams, and β-amino alcohols [1–6]. Over the past few decades, synthesis of β-amino carbonyl compounds has become a field of increasing interest in organic synthesis [7, 8]. Mannich-type reaction is one of the classical and powerful methods for construction of this functionality [9–15]. However, this type of reaction suffers from harsh reaction conditions and long reaction times. Another approach for preparing β-amino carbonyl compounds is based on conjugate addition of amines to α,β-unsaturated carbonyl compounds (aza-Michael addition).

Owing to its operational simplicity and mildness, aza-Michael reaction has attracted much attention in recent years. It also has a prominent advantage over the Mannich reaction in covering a wide range of nitrogen nucleophiles including amides, carbamates, and sulfonamides, which can hardly be utilized using conventional Mannich condensation. In recent years a number of Lewis acid catalysts, solid acids, and Brønsted acids, i.e., $LiClO_4$ [16], $Bi(OTf)_2$ [17], $Yb(OTf)_3$ [18], SmI_2 [7], $Bi(NO_3)_2$ [19], $CeCl_3{\cdot}7H_2O$ [20], $InCl_3$ [21], $Cu(OTf)_2$ [22], boric acid [23], silica gel [24], Amberlyst-15 [25], and others, have been employed. Some drawbacks such as high cost and toxicity of catalysts and harsh reaction conditions associated with the above methods led to development of several other catalysts or promoters in conjugate addition, including $ZrOCl_2{\cdot}8H_2O$ on montmorillonite K10 [26], β-cyclodextrin [27], ceric ammonium nitrate (CAN) [28], iodine [29], sodium dodecylsulfate (SDS) [30], $[HP(HNCH_2CH_3)_3N]NO_3$ [31], $Cu(acac)_2$/ionic liquid [32], silica gel supported $TaBr_5$ [33], $FeCl_3$/TMSCl [34, 35], KF/Al_2O_3 [36], alkaline Al_2O_3 [37], [Bmim]OH [38], and Cu–Al hydrotalcite [39]. Unfortunately, most of these procedures suffered from some disadvantages such as the requirement for large excess of reagents or catalysts, long reaction times, use of expensive heavy-metal salts, and toxic solvents such as 1,2-dichloroethane, dichloromethane, or acetonitrile. Also, most of the reported procedures were only applicable to aliphatic amines and failed to work with aromatic amines [24, 26, 27, 31–33, 36]. Although the recent protocols made this route attractive, the development of fast, simple, and environmentally friendly approaches that could be performed at ambient temperature for aza-Michael addition is highly desirable.

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Table 1 Optimization of the K_3PO_4-catalyzed reaction

Entry	Solvent	Catalyst/mol%	Time/h	Yield[a]/%
1	EtOH (abs.)	10	3	50
2	EtOH (abs.)	15	0.83	77
3	EtOH (abs.)	20	1.5	68[b]
4	EtOH (abs.)	30	1	65[b]
5	EtOH (98%)	15	1	68
6	MeOH	15	3	70
7	*t*-BuOH	15	6	65
8	CH_3CN	15	10	24
9	DMF	15	12	30
10	DMSO	15	10.5	15
11	–	15	24	10

[a] Isolated yields

[b] Several by-products were observed

Results and discussion

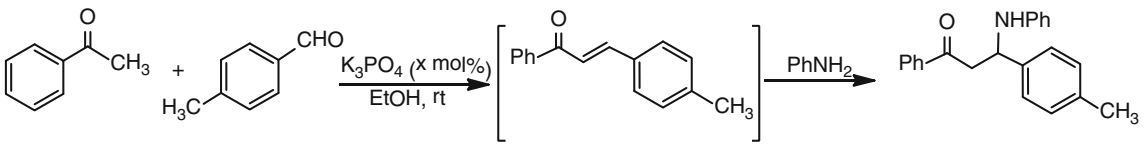
Very recently, we reported a simple and very efficient one-pot three-component procedure for synthesis of *β*-sulfido ketones from aldehydes, acetophenones, and thiols via Claisen–Schmidt/Michael addition reactions catalyzed by potassium *tert*-butoxide at room temperature [40]. Tripotassium phosphate, K_3PO_4, is nontoxic, cheap, and a strong inorganic base, used as an alternative nonnucleophilic base in several reactions [41–45]. We have now developed an easy and highly convenient methodology for synthesis of *β*-amino ketones by one-pot reaction of an aryl aldehyde, acetophenone derivative, and amine in the presence of a catalytic amount of anhydrous K_3PO_4 in EtOH at room temperature. To the best of our knowledge, there is no report of construction of *β*-amino ketones by one-pot aza-Michael-type reaction.

To find the optimal conditions, a mixture of acetophenone (2.0 mmol), *p*-tolualdehyde (2.0 mmol), and aniline (2.6 mmol) was stirred under different reaction conditions catalyzed by K_3PO_4 at room temperature (Table 1). The best result was obtained when 15 mol% K_3PO_4 in absolute EtOH was used (Scheme 1).

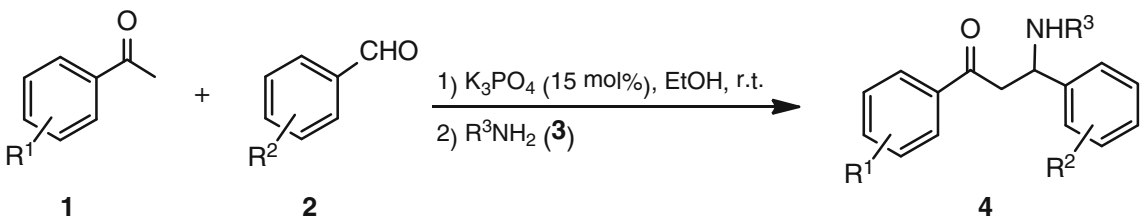
After optimization, a variety of other aromatic aldehydes and acetophenones having electron-donating and electron-withdrawing substituents as well as different amines were shown to undergo the reaction smoothly, giving the desired products in high to excellent yields (Scheme 2). The results are summarized in Table 2.

All products were fully characterized by spectroscopic methods and compared with authentic spectra. As seen in Table 2, aliphatic amines (benzylamine, *n*-butylamine) needed longer reaction times and afforded lower yields (entries 11, 12, and 19) than anilines. Aromatic aldehydes containing a methoxy substituent took longer reaction times and had generally lower yields (entries 2, 8, and 15). The results clearly show that K_3PO_4 is an efficient catalyst in aza-Michael addition reaction. This is because (i) tripotassium phosphate has a strong electron-withdrawing counteranion, namely PO_4^{3-}, to make the K^+ ion oxophilic enough to form a strong coordinate bond with the oxygen atom of the enone and thereby make C_β sufficiently electrophilic, and (ii) K_3PO_4 is basic enough to deprotonate amines (specially the aromatic ones) having pK_A values in the range 7–11 [46] to convert them to their conjugate bases and assist the aza-Michael addition.

In conclusion, we have developed an easy, efficient, and fast protocol for preparation of *β*-amino ketones using K_3PO_4 as catalyst. The salient features of this protocol include operational simplicity, high yields of the products, short reaction times, ready availability, low toxicity of the catalyst, and use of a green solvent.

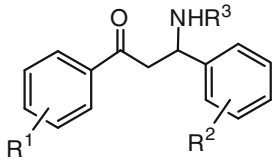


Scheme 1



Scheme 2

Table 2 K_3PO_4-catalyzed one-pot preparation of β-amino ketones **4**



4a-4s

Entry	Comp	R^1	R^2	R^3	Time/min	Yield[a]/%	M.p. (lit. m.p.)/°C
1	**4a**	H	H	C_6H_5	30	95	168–170 (168–170 [49])
2	**4b**	H	4-CH_3O	C_6H_5	70	79	156–158 (150–152 [47])
3	**4c**	H	4-Cl	C_6H_5	40	90	129–130 (131–132 [49])
4	**4d**	H	4-CH_3	C_6H_5	50	77	129–130 (128–130 [49])
5	**4e**	H	4-NO_2	C_6H_5	55	82	105–106 (105–106 [50])
6	**4f**	H	H	4-CH_3O–C_6H_4	35	94	164–165 (165–167 [47])
7	**4g**	H	4-Cl	4-CH_3O–C_6H_4	40	78	170–171 [51]
8	**4h**	H	4-CH_3O	4-CH_3O–C_6H_4	85	60	180–182 (182 [52])
9	**4i**	H	H	4-Cl–C_6H_4	55	85	169–170 (166–167 [48])
10	**4j**	H	H	4-NO_2–C_6H_4	80	81	175–177 (177–178 [49])
11	**4k**	H	H	$C_6H_5CH_2$	300	52	73–74 (75–76 [53])
12	**4l**	H	4-Cl	$C_6H_5CH_2$	330	50	97–98 (98–100 [53])
13	**4m**	H	4-Cl	4-Cl–C_6H_4	60	84	116–118 (118–119 [54])
14	**4n**	4-CH_3	H	C_6H_5	65	83	139–140 (136–137 [48])
15	**4o**	H	4-CH_3O	4-Cl–C_6H_4	75	76	158–160 (159–160 [48])
16	**4p**	4-Cl	H	C_6H_5	45	91	118–119 (118–119 [48])
17	**4q**	4-NO_2	H	4-Cl–C_6H_4	65	78	143–145 (146–148 [15])
18	**4r**	4-CH_3O	H	C_6H_5	75	86	123–125 (123–125 [48])
19	**4s**	H	H	*n*-C_4H_9	480	32	Oil [47]

All products were characterized by infrared (IR), and ^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy as well as melting points

[a] Yields of pure isolated products

Experimental

Chemicals were purchased from Merck chemical company. Yields refer to isolated products. ^1H (300 MHz) and ^{13}C (75 MHz) nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AQS-300 Avance spectrometer. Chemical shifts were determined by reference to residual $CHCl_3$ in $CDCl_3$. Infrared (IR) spectra were obtained using an ABB FTLA 2000 instrument.

General procedure

A suspension of 0.064 g anhydrous K_3PO_4 (15 mol%) in 1 cm^3 absolute ethanol was placed in a flask. While stirring magnetically at room temperature, a mixture of aldehyde (2.0 mmol) and ketone (2.0 mmol) was added to the above suspension and stirring was continued for 15 min. The course of the reaction was monitored by thin-layer chromatography (TLC) until the starting materials disappeared completely. Amine (2.6 mmol) was then added, and the mixture was stirred for the appropriate time (Table 2). On completion of the reaction (TLC), ethanol was evaporated, 10 cm^3 water was added, followed by extraction with CH_2Cl_2 (2 × 10 cm^3) and drying over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was recrystallized from acetone:EtOH = 3:2 to afford the pure product. The spectral data of some representative β-amino ketones are given in the Supplementary Material.

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