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An Efficient and Eco-Friendly Solvent-Free Synthesis of β-Acetamido Ketones Using L-Proline As a Green and Reusable Catalyst

M. ROSHANI*, S. ALLAMEH and E. DARKOOTI

Department of Chemistry, Mashhad Branch, Islamic Azad University, 91735-413, Mashhad, Iran

*Corresponding author: E-mail: drmina.roshani@yahoo.com

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A simple and efficient catalytic protocol for the synthesis of β-acetamido ketones *via* the one-pot, four component condensation of aryl aldehydes, enolizable aryl ketones, acetyl chloride and acetonitrile using L-proline is reported. The present method offers several advantages such as high yields, short reaction times, recovery and reusability of catalyst and easy workup procedures.

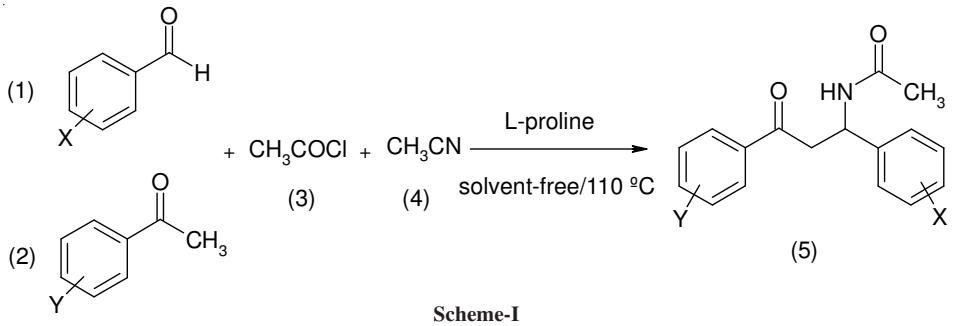
Key Words: β-Acetamido ketones, Enolizable aryl ketones, Aryl aldehydes, Reusable catalyst.

INTRODUCTION

Most attention has been focused on the use of proline due to its ready availability in either L- or D-form and the highly versatile nature of its reactivity[1-3]. The natural amino acid L-proline is one such small molecule, which given rich dividends in ees and yields in several asymmetric transformation, such as Aldol[4], Mannich[5] and Michael[6] reactions, Robinson annulations[7], synthesis of amino acids[8] α-amination of aldehydes and ketones[9], α-oxidation[10] and α-alkylation of aldehydes[11].

β-Acetamido ketones are versatile intermediates, in that their skeletons exist in a number of biologically or pharmacologically active compounds[12,13]. They could easily be converted to 1,3-amino alcohols[14], which are utilized for the synthesis of several antibiotics[15]. β-Acetamido ketones are usually prepared through of β-aminoketones[16], Michael addition to α,β-unsaturated ketones[17] or photoisomerization of phthalimides[18]. The best-known route for the synthesis of these compounds is the one-pot condensation of an aldehyde, an enolizable ketone, acetyl chloride and acetonitrile, originally reported by Iqbal and co-workers. A few catalysts including $CoCl_2$[19], cobalt(II) acetate[20], SiO_2-H_2SO_4[21], triflate salts[22], zeolite[23], iodine[24], $BiCl_3$[25], $ZrOCl_2 \cdot 8H_2O$[26] and heteropolyacids[27] have already been applied for the synthesis of β-acetamido ketones, using this method. Although various procedures are reported for synthesis of β-acetamido ketones, some drawbacks such as low yields, prolonged reaction time, use of costly reagents or catalysts and use of toxic organic solvents, exist. Thus, the development of an environmentally benign methodology for the synthesis of β-acetamido ketone derivatives is in great demand.

It is therefore of interest to examine the behavior of L-proline as catalyst in solvent-free conditions for synthesis of β-acetamido ketones. To the best of our knowledge, condensation of aryl aldehydes, enolizable aryl ketones, acetyl chloride and acetonitrile in the presence of a catalytic amount of L-proline for the synthesis of β-acetamido ketones has not been reported in literature. In this paper we wish to report the use of L-proline for synthesis of β-acetamido ketone derivatives (**Scheme-I**).



Scheme-I

Initially, in order to find the optimal amount of catalyst, the reaction of *p*-nitrobenzaldehyde (1 mmol), acetophenone (1 mmol), acetyl chloride (1.5 mmol 0.3 mL) and acetonitrile (3 mL) under solvent-free condition at 110 ºC in the presence of various amount of L-proline were used as a model reaction. The best result has been obtained at 35 mol % of catalyst (Table-1).

TABLE-1
COMPARISION OF THE AMOUNT OF L-PROLINE AND YIELDS FOR SYNTHESIS OF N-[1-(4-NITROPHENYL)-3-OXO-3-PHENYLPROPYL]ACETAMID (**5h**)

Entry	Catalyst (mol %)	Time (min)	Yield (%)
1	0	300	Nil
2	5	120	30
3	15	80	46
4	30	30	72
5	35	30	85
6	40	40	70

The generality of this process was demonstrated by the wide range of substituted aryl aldehydes and enolizable aryl ketones to synthesize the corresponding products in high yields (Table-2). Unlike some previously reported methods, the present method does not require toxic organic solvents to produce the β-acetamido ketone derivatives. All the products were characterized by NMR, IR and melting point and also by comparison with the data reported in literature.

The suggested mechanism of the reaction can be followed according to the steps in **Scheme-II**.

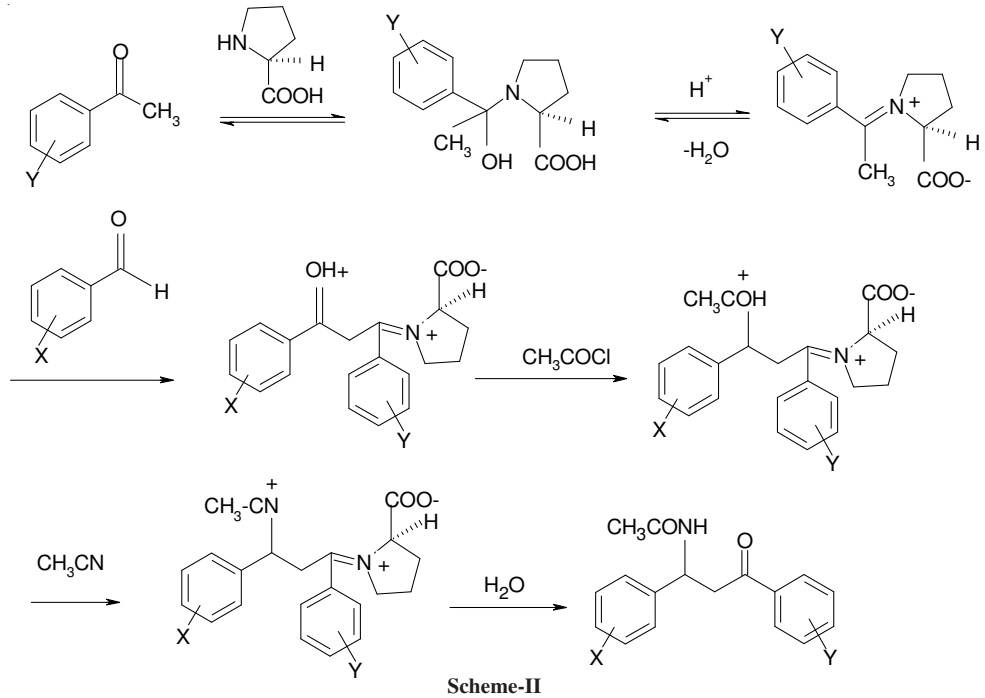
We also investigated the reusability of the catalyst. For this purpose after completion of the model reaction, the cold water was added. The catalyst is soluble in cold water and could therefore be recycled as the filtrate. The catalyst was recovered by evaporation of the water and washed with diethylether and reused in model reaction without appreciable reduction in the catalytic activity.

EXPERIMENTAL

Melting points were determined on an Electrothermal type 9100 melting point apparatus. IR spectra were recorded using a 4300 Shimadzu spectrophotometer with KBr plates. ^{1}H NMR spectra were recorded on a Bruker DR X500 spectrometer. The products (**5a-l**) were isolated and characterized by

TABLE-2
SYNTHESIS OF β-ACETAMIDO KETONES USING L-PROLINE UNDER SOLVENT-FREE CONDITIONS

Entry	X	Y	Product	Time (min)	Yield (%)	m.p. (ºC)	Lit. m.p. (ºC)
1	H	H	**5a**	50	67	103-105	104-105[19]
2	2-Cl	H	**5b**	40	85	295-297	295-296[19]
3	4-Cl	H	**5c**	25	90	145-146	149-150[19]
4	3-Br	H	**5d**	25	80	239-242	239-240[19]
5	4-Br	H	**5e**	25	89	160-162	162-164[19]
6	2-NO_2	H	**5f**	30	63	137-140	139-140[19]
7	3-NO_2	H	**5g**	30	74	115-117	119-121[19]
8	4-NO_2	H	**5h**	25	85	152-154	155-156[19]
9	4-Me	H	**5i**	45	45	209-211	210-211[19]
10	4-OMe	H	**5j**	40	55	107-110	109-110[19]
11	4-Cl	4-Cl	**5k**	25	92	140-143	–
12	4-Cl	4-NO_2	**5l**	25	94	115-118	–



Scheme-II

comparison of physical and spectral data with those of known samples.

General procedure for the preparation of β-acetamido ketones (5a-l): A mixture of aryl aldehydes (1 mmol), enolizable aryl ketones (1 mmol), acetyl chloride (1.5 mmol 0.3 mL), acetonitrile (3 mL) and L-proline (35 mol %) was heated at 110 ºC for 25-50 min. After completion of reaction (monitored by TLC), the reaction mass was added to a stirred mixture of ice and water. The product was filtered, washed with diethylether and recrystallized from ethanol/ethylacetate to give compounds (**5a-l**) in high yields.

Selected specteral data

N-[1-(4-Nitrophenyl)-3-oxo-3-phenylpropyl]acetamid (5h): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.2 (s, 3H, CH_3), 3.6 (dd, 1H, CH_2), 3.9 (dd, 1H, CH_2), 5.8 (m, 1H, CH), 7.1 (m, 1H, NH), 7.6-8.5 (m, 9H, Ar-H). IR (KBr disc, ν_{max}, cm^{-1}): 3289 (NH_2), 1686 (CO), 1650 (CO).

N-[1-(4-Methylphenyl)-3-oxo-3-phenylpropyl] acetamid (5i): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.0 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 3.4 (dd, 1H, CH_2), 3.6 (dd, 1H, CH_2), 5.5 (m, 1H, CH), 7.1 (m, 1H, NH), 7.3-8.1 (m, 9H, Ar-H). IR (KBr disc, ν_{max}, cm^{-1}): 3288 (NH_2), 1686 (CO), 1650(CO).

N-[1-(4-Chlorophenyl-4-nitropropiophenone)-3-oxo-3-phenylpropyl]acetamid (5l): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.2 (s, 3H, CH_3), 3.7 (dd, 1H, CH_2), 3.9 (dd, 1H, CH_2), 5.8 (m, 1H, CH), 7.1 (m, 1H, NH), 7.6-8.5 (m, 8H, Ar-H). IR (KBr disc, ν_{max}, cm^{-1}): 3295 (NH_2), 1689(CO), 1650(CO).

Conclusion

It should be noted that, this method is effective for the preparation of β-acetamido ketones from the one-pot, four component condensation of aryl aldehydes, enolizable aryl ketones, acetyl chloride and acetonitrile using L-proline.

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