J. Iran. Chem. Soc., Vol. 7, No. 1, March 2010, pp. 95-99.

JOURNAL OF THE
Iranian
Chemical Society

$Zr(HSO_4)_4/SiO_2$: An Effective Heterogeneous Alternative for One-Pot Synthesis of *β*-Acetamido Ketones

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(Received 6 April 2008, Accepted 30 January 2009)

In a one-pot procedure, enolizable ketones reacted with aromatic aldehydes, acetyl chloride and acetonitrile at room temperature in the presence of $Zr(HSO_4)_4/SiO_2$ to furnish the corresponding *β*-acetamido ketones in improved yields.

Keywords: $Zr(HSO_4)_4/SiO_2$, β-Acetamido ketones, One-pot method, Multi-component reaction, Room temperature

INTRODUCTION

β-Acetamido ketones are valuable building blocks for the preparation of *β*-amino ketones or *β*-amino alcohols such as antibiotic nikkomycins [1,2] and neopolyoxines [3]. *α*-acetamido ketones in Dakin-West reaction [4] and *β*-acetamido ketones in Iqbal route are obtained [5,6]. Iqbal route is based on one-pot reaction of aromatic aldehydes, enolizable ketones and acetonitrile in the presence of the acetyl chloride and catalytic amount of an acid. Many catalysts such as $CeCl_3.7H_2O$ [7], silica sulfuric acid [8], $H_6P_2W_{18}O_{62}$ [9], $K_5CoW_{12}O_{40}.3H_2O$ [10], ZnO [11], sulfated zirconia [12], $FeCl_3$ [13], some heteropoly acids [14-16], silica supported $H_3PW_{12}O_{40}$ [17], nano ZnO [18], sulfamic acid [19], $Sc(OTf)_3$ [20], $SnCl_2.2H_2O$ [21], Zeolite Hβ [22], $ZrOCl_2.8H_2O$ [23] and Nafion-H [24] have been applied in this one-pot reaction. With reference to solid acid utilization in organic synthesis [25-34], herein, we wish to report the application of $Zr(HSO_4)_4/SiO_2$, an alternative protocol, for the synthesis of *β*-acetamido ketones [32-35].

EXPERIMENTAL

Chemical

Chemicals were purchased from Fluka, Merck and Aldrich chemicals companies. Using the previously reported procedure, $Zr(HSO_4)_4$ was synthesized according to the literature [23]. The products were characterized by their spectral data (IR and ^1H NMR) in some cases, and comparison with authentic samples.

Preparation of Silica-Supported $Zr(HSO_4)_4$

A mixture of 0.6 g of $Zr(HSO_4)_4$ and 0.4 g of preheated silica gel was ground into fine particles. A suspension of this mixture and 0.5 ml of HCl 0.5 M was stirred for 20 min at room temperature. The suspension was allowed to heat at about 80-90 ºC until the obtained solid was almost dry which in turn was further dried and calcinated in a domestic microwave oven for 20 min in power 100.

General Procedure for One-Pot Synthesis of β-Acetamido Ketones Using $Zr(HSO_4)_4/SiO_2$

Enolizable ketone (1 mmol), aromatic aldehyde (1 mmol), acetyl chloride (0.3 ml), acetonitrile (1 ml) and 60%

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$Zr(HSO_4)_4/SiO_2$ (0.04 g, 0.05 mmol) were placed in a round bottom flask. The materials were mixed at an ambient temperature. The progress of the reaction was followed by TLC (eluent:*n*-hexane:ethylacetate). After completion of the reaction, crushed ice (40 ml) was added to the reaction mixture and stirred. The oily solid was isolated and washed with diethyl ether to remove any residual starting materials. The crude mixture was solidified from ethanol and water mixture. The pure product was obtained by recrystalization from ethyl acetate and *n*-hexane or column chromatography (ethyl acetate:*n*-hexane as eluent).

Selected Spectroscopic Data

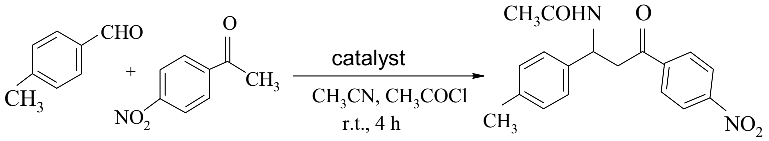
β-Acetamido-*β*-(2-chloro)-4-chloropropiophenone: ^1H NMR ($CDCl_3$, 400 MHz): δ 2.1 (s, 3H), 3.5 (dd, J = 16.8 and 5.6 Hz, 1H), 3.8 (dd, J = 16.8 and 6 Hz, 1H), 5.8 (sbr, 1H), 7.1 (sbr, 1H), 7.2 (m, 2H), 7.4 (d, J = 7.6, 1H), 7.6 (m, 3H), 7.9 (d, J = 8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.27, 42.88, 49.17, 128.28, 128.73, 129.46, 130.0, 130.18, 131.09, 133.59, 135.86, 139.13, 141.27, 173, 196. IR (KBr, cm^{-1}) 3292, 1688, 1653, 1552, 1353, 1200, 814, 753.

RESULS AND DISCUSSION

In order to utilize $Zr(HSO_4)_4$ as a catalyst in the synthesis of *β*-acetamido ketones, the reaction of 4-methyl benzaldehyde and 4-nitro acetophenone was examined in the presence of several mmol of acetyl chloride, acetonitrile and catalysts (Table 1).

Then, various aromatic aldehydes and ketones were transformed to the corresponding *β*-acetamido ketones in the presence of $Zr(HSO_4)_4$ as catalyst without the formation of any

Table 1. Optimization of the Reaction Conditions for One-Pot Reaction of 4-Methyl benzaldehyde (1 mmol) and 4-Nitro Acetophenone (1 mmol)



Entry	Acetylchloride (ml)	Acetonitrile (ml)	Catalyst (mmol)	Yield (%)
1	0.3	0.3	$Zr(HSO_4)_4$ (0.08)	74
2	0.3	0.7	$Zr(HSO_4)_4$ (0.08)	81
3	0.3	1.0	$Zr(HSO_4)_4$ (0.08)	94
4	1.0	0.3	$Zr(HSO_4)_4$ (0.08)	69
5	0.3	1.0	$Zr(HSO_4)_4$ (0.06)	46
6	0.3	1.0	$Zr(HSO_4)_4$ (0.1)	95
7	0.3	1.0	$Al(HSO_4)_3$ (0.08)	70
8	0.3	1.0	$ZrCl_4$ (0.08)	60
9	0.3	1.0	$NaHSO_4$ (0.08)	80
10	0.3	1.0	H_2SO_4(0.08)	60
11	0.3	1.0	40% $Zr(HSO_4)_4/SiO_2$ (0.033)	81
12	0.3	1.0	60% $Zr(HSO_4)_4/SiO_2$ (0.05)	94
13	0.3	1.0	80% $Zr(HSO_4)_4/SiO_2$ (0.06)	95
14	0.3	1.0	60% $Zr(HSO_4)_4/SiO_2$ (0.0375)	65
15	0.3	1.0	60% $Zr(HSO_4)_4/SiO_2$ (0.075)	95
16	0.3	1.0	-	20

side products with improved yields (Table 2).

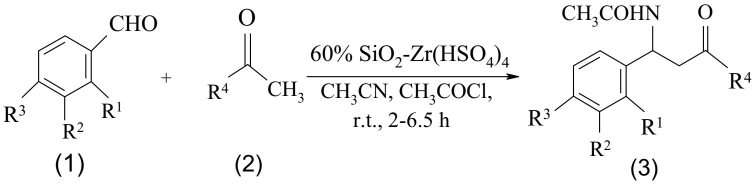
Acetylation of an aromatic hydroxyl group was observed while using *p*-hydroxy benzaldehyde or vanillin. 4-dimethylamino benzaldehyde, however, was inert to the present reaction conditions. The preparative efficiency of this one-pot synthesis was further checked by scaling-up (5 folds) of the reaction of benzaldehyde with acetophenone and other ingredients which proceeded with 90% yield.

Previously, three types of mechanisms for the Iqbal procedure of *β*-acetamido ketone formation have been proposed [6,7,9,11,18,19]. In some cases [7,18,19], *β*-acetoxy ketone was offered as an intermediate product that converted into *β*-acetamido ketone with acetonitrile. In our investigation, when the reaction was not subjected to acetonitrile, no *β*-acetoxy ketone was formed and only crossed aldol condensation reaction occurred. Meanwhile, in the preparation of *β*-acetamido ketones, no *β*-acetoxy ketones were obtained as by-product. Besides, a mixture of chalcone, acetyl chloride and acetonitrile in the presence of catalyst failed to generate any *β*-acetamido ketones. In the absence of acethyl chloride or benzoyl chlorid, the reaction failed to provide the desired product, 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 such as *β*-phenylacetamido ketone or *β*-benzamido ketone were obtained. Note that neither a mixture of 4-methyl benzaldehyde, 4-nitro acetophenone, acetic anhydride and acetonitrile in the presence of $Zr(HSO_4)_4/SiO_2$, nor a mixture of 4-methyl benzaldehyde acylal, 4-nitro acetophenone and $Zr(HSO_4)_4/SiO_2$ in acetonitrile could produce any of the corresponding *β*-acetamido ketones (Scheme 1).

CONCLUSIONS

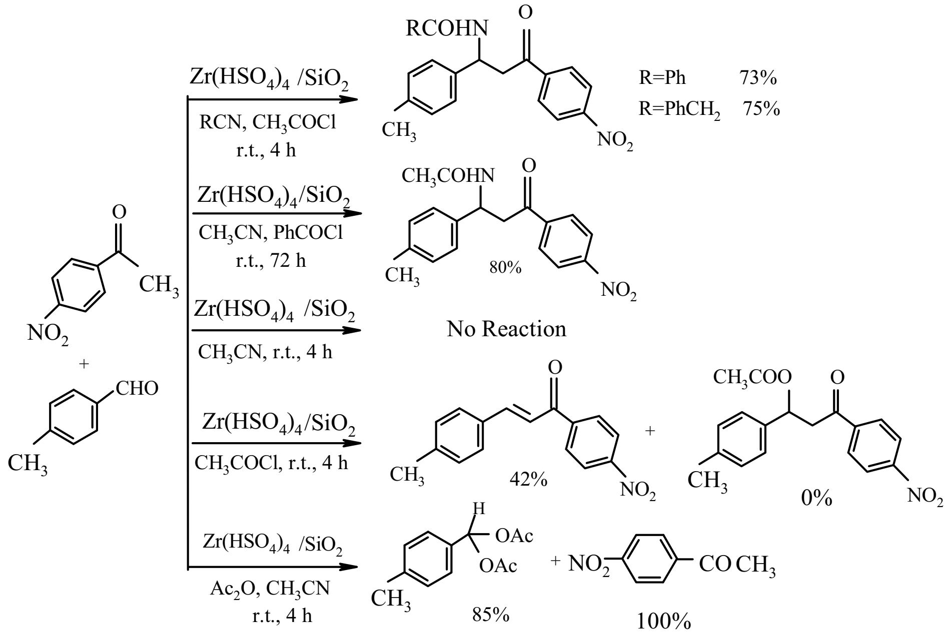
In sum, catalytic activity of $Zr(HSO_4)_4/SiO_2$ as a non-

Table 2. One-Pot Condensation of Aldehydes, Ketones, Acetyl Chloride and Acetonitrile to Give the Corresponding *β*-Acetamido Ketones Catalyzed by $Zr(HSO_4)_4/SiO_2$[a]



Entry	Product (3)	Time (h)	Ref.	Yield (%)[b]	m.p. (°C)
1	$R_1,R_2,R_3 = H$, $R_4 = Ph$	3.0	[17]	96	104-105
2	$R_1,R_2,R_3 = H$, $R_4 = 4\text{-}NO_2\text{-}C_6H_4$	4.0	[12]	87	97-98
3	$R_1 = Cl$, $R_2,R_3 = H$, $R_4 = Ph$	2.5	[8]	70	135-136
4	$R_2 = NO_2$, $R_1,R_3 = H$, $R_4 = Ph$	2.5	[9]	81	129-130
5	$R_1 = H$, $R_2 = OCH_3$, $R_3 = OCOCH_3$, $R_4 = Ph$	3.0	[23]	85	89-91
6	$R_1,R_2 = H$, $R_3 = CH_3$, $R_4 = 4\text{-}Cl\text{-}C_6H_4$	6.5	[11]	67	-
7	$R_1,R_2 = H$, $R_3 = CH_3$, $R_4 = 4\text{-}NO_2\text{-}C_6H_4$	3.0	[15]	94	84-85
8	$R_1,R_2 = H$, $R_3 = CO_2CH_3$, $R_4 = Ph$	3.5	[24]	68	156-158
9	$R_1,R_3 = H$, $R_2 = OCH_3$, $R_4 = Ph$	2.0	[20]	80	87-89
10	$R_1,R_3 = H$, $R_2 = NO_2$, $R_4 = 4\text{-}NO_2\text{-}C_6H_4$	2.0	[17]	93	105-106
11	$R_1,R_3 = H$, $R_2 = NO_2$, $R_4 = 4\text{-}Cl\text{-}C_6H_4$	2.0	[11]	88	145-146
12	$R_2,R_3 = H$, $R_1 = Cl$, $R_4 = 4\text{-}Cl\text{-}C_6H_4$	3.0	-	75	168-169

[a] Molar ratio of aldehyde (mmol):ketone (mmol):acetyl chloride (ml) :acetonitrile (ml):60% $Zr(HSO_4)_4/SiO_2$(g)[mmol] equal to 1:1:0.3:1:0.04[0.05]. [b] Isolated yield.



Scheme 1

corrosive, easily producible and cheap material has been studied for the synthesis of *β*-acetamido ketones. A mild reaction condition, a simple experimental procedure, an easy work-up and improved yields of products are some major features of this reported method.

ACKNOWLEDGEMENTS

Financial support for this work by the Research Affairs of Yazd University is gratefully acknowledged.

REFERENCES

[1] J. Barluenga, A.L. Viado, E. Aguilar, S. Fustero, B. Olano, J. Org. Chem. 58 (1993) 5972.

[2] D.P. Henderson, M.C. Shelton, I.C. Cotterill, E.J. Toone, J. Org. Chem. 62 (1997) 7910.

[3] M. Uramoto, K. Kobinata, K. Isono, T. Higashijima, T. Miyazawa, E.E. Jenkins, J. McCloskey, A. Tetrahedron Lett. 21 (1980) 3395.

[4] H.D. Dakin, R. West, J. Biol. Chem. 78 (1928) 745.

[5] M.M. Reddy, B. Bhatia, J. Iqbal, Tetrahedron Lett. 36 (1995) 4877.

[6] D. Bahulayan, S.K. Das, J. Iqbal, J. Org. Chem. 68 (2003) 5735.

[7] A.T. Khan, L.H. Choudhury, T. Parvin, M. Asif Ali, Tetrahedron Lett. 47 (2006) 8137.

[8] M.M. Khodaei, A.R. Khosropour, P. Fattahpour, Tetrahedron Lett. 46 (2005) 2105.

[9] M.M. Heravi, L. Ranjbar, F. Derikvand, F. Bamoharram, Catal. Commun. 8 (2007) 289.

[10] L. Nagarapu, S. Kantevari, V.N. Cheemalapati, S. Apuri, V. Kumari, J. Mol.Catal. A: Chem. 264 (2006) 22.

[11] M.T. Maghsoodlou, A. Hassankhani, H.R. Shaterian, S.M. Habibi-Khorasani, E. Mosaddegh, Tetrahedron Lett. 48 (2007) 1729.

[12] B. Das, M. Krishnaiah, K. Laxminarayana, K.R. Reddy, J. Mol. Catal. A: Chem. 270 (2007) 284.

[13] A.T. Khan, T. Parvin, L.H. Choudhury, Tetrahedron 63 (2007) 5593.

[14] E. Rafiee, F. Tork, M. Joshaghani, Bioorg. Med. Chem. Lett. 16 (2006) 1221.

[15] M.M. Heravi, L. Ranjbar, F. Derikvand, F.F. Bamoharram, J. Mol. Catal. A:Chem. 271 (2007) 28.

[16] E. Rafiee, F. Paknezhad, S. Shahebrahimi, M. Joshaghani, S.

Eavani, S. Rashidzadeh, J. Mol. Catal. A: Chem. 282 (2008) 92.

[17] E. Rafiee, F. Shahbazi, M. Joshaghani, F. Tork. J. Mol. Catal. A: Chem. 242 (2005) 129.

[18] Z. Mirjafary, H. Saeidian, A. Sadeghi, F. Matloubi Moghaddam, Catal. Commun. 9 (2008) 299.

[19] M. Heravi, L. Ranjbar, F. Derikvand, F.F. Bamoharram, J. Mol. Catal. A:Chem. 276 (2007) 226.

[20] G. Pandey, R.P. Singh, A. Garg, V.K. Singh, Tetrahedron Lett. 46 (2005) 2137.

[21] L. Nagarapu, R. Bantu, R. Puttireddy, Appl. Catal. A: Gen. 332 (2007) 307.

[22] R.P. Bhat, V.P. Raje, V.M. Alexander, S.B. Patil, S.D. Samant, Tetrahedron Lett. 46 (2005) 4801.

[23] R. Ghosh, S. Maiti, A. Chakraborty, S. Chakraborty, A. K. Mukherjee, Tetrahedron 62 (2006) 4059.

[24] T.V. Yakaiah, B.P. Lingaiah, G. Venkat Reddy, B. Narsaiah, P. Shanthan Rao, ARKIVOC 13 (2007) 227.

[25] S. Besoluk, M. Kucukislamoglu, M. Nebioglu, M. Zengin, M. Arslan, J. Iran. Chem. Soc. 5 (2008) 62.

[26] F. Shirini, M.A. Zolfigol, A.-R. Abri, J. Iran. Chem. Soc. 5 (2008) 96.

[27] A. Bamoniri, B.F. Mirjalili, M.A. Zolfigol, I. Mohammadpoor-Baltork, J. Iran. Chem. Soc. 4 (2007) 332.

[28] K. Niknam, M.A. Zolfigol, T. Sadabadi, A. Nejati, J. Iran. Chem. Soc. 3 (2006) 318.

[29] M.A. Zolfigol, M. Bagherzadeh, K. Niknam, F. Shirini, I. Mohammadpoor-Baltork, A. Ghorbani Choghamarani, M. Baghbanzadeh, J. Iran. Chem. Soc. 3 (2006) 73.

[30] K. Niknam, M.A. Zolfigol, T. Sadabadi, J. Iran. Chem. Soc. 4 (2007) 199.

[31] A. Bamoniri, M.A. Zolfigol, I. Mohammadpoor-Baltork, B.F. Mirjalili, J. Iran. Chem. Soc. 3 (2006) 85.

[32] F. Shirini, M.A. Zolfigol, A. Safari,; I. Mohammadpoor-Baltork, B.F. Mirjalili, Tetrahedron Lett. 44 (2003) 7463.

[33] B.F. Mirjalili, M.A. Zolfigol, A. Bamoniri, N. Sheikhan, J. Chin. Chem. Soc. 53 (2006) 955.

[34] B.F. Mirjalili, M.A. Zolfigol, A. Bamoniri, M.A. Karimi-Zarchi, Z. Zaghaghi, M. Parvaideh, J. Iran. Chem. Soc. 4 (2007) 340.

[35] F. Shirini, M.A. Zolfigol, P. Salehi, M. Abedini, Cur. Org. Chem. 12 (2008) 183.