Efficient One-Pot Synthesis of β-Acetamido Carbonyl Compounds Using Fe_3O_4 Nanoparticles

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A new, one-pot condensation of aldehydes, enolizable ketones and esters, AcCl, and MeCN, in the presence of Fe_3O_4 nanoparticles (nano-Fe_3O_4) as an efficient catalyst, for the preparation of β-acetamido carbonyl compounds at room temperature is described.

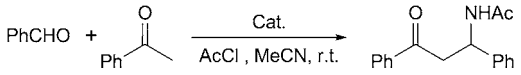
Introduction. – The conventional synthesis of β-amino/β-acetamido carbonyl compounds involves the *Dakin–West* reaction [1], in which an α-amino acid is condensed with Ac_2O in the presence of a base to provide the α-acetamido ketones *via* an intermediate aza-lactone [1b]. However, the direct *Mannich* reaction of aldehydes, ketones, and aromatic amines for the synthesis of β-amino carbonyl compounds, and of aldehydes, ketones, and MeCN in the presence of AcCl for the synthesis of β-acetamido carbonyl compounds by acid catalysis have been reported. Many catalysts such as nano-ZnO [2], $ZrOCl_2 \cdot 8\,H_2O$ [3], $SnCl_2 \cdot 2\,H_2O$ [4], $CeCl_3 \cdot 7\,H_2O$ [5], silica sulfuric acid [6], $H_6P_2W_{18}O_{62}$ [7], sulfamic acid [8], $Sc(OTf)_3$ [9], P_2O_5-HMDS [10], $FeCl_3$ [11], BiOCl [12], I_2 [13], montmorillonite K-10 clay [14], *Nafion-H*® [15], $La(OTf)_3$ [16], and *Amberlyst-15*® [17] have been used in this one-pot reaction.

Recently, metal nanoparticles have attracted a great attention as heterogeneous catalysts because of their interesting structure and high catalytic activities in comparison with the corresponding bulky materials. They can have different melting points, vapor pressures, heat capacities, and optical, electronic, and magnetic properties [18]. Of metal nanocatalysts, nano-Fe_3O_4 is the most promising catalyst because of its simple handling, ease of recovery with an external magnetic field, high catalytic activities, and reactivities in various organic transformations [19].

Results and Discussion. – To develop a nontoxic, heterogeneous, reusable, and potentially eco-friendly catalyst, we considered using Fe_3O_4 nanoparticles (nano-Fe_3O_4) for the one-pot synthesis of β-acetamido carbonyl compounds. Initially, to find the optimal conditions, we set up a model reaction with benzaldehyde (1 mmol), acetophenone (1 mmol), AcCl (1 mmol), and MeCN (2.5 ml) under various reaction conditions at room temperature (*Table 1*).

As can be seen from *Table 1*, in the absence of any catalyst, the acetamido product was obtained in a very low yield after 1.5 h, while better results were obtained in the presence of catalysts like $RuCl_3$, $MgCl_2$, and nano-CuO (*Table 1*, *Entries 2–4*). With nano-Fe_3O_4 as catalyst, good results were achieved within a short reaction time (1 h) at

Table 1. *Optimization of the Reaction Conditions for the Formation of* N-*(3-Oxo-1,3-diphenylpropyl)-acetamide at Room Temperature*



Entry	Catalyst ([mol-%])	Time [h]	Yield [%][a])
1	–	1.5	17
2	$RuCl_3$ (5)	5	47
3	$MgCl_2$ (5)	7	30
4	nano-CuO (5)	24	81
5	nano-Fe_3O_4 (3)	1	69
6	nano-Fe_3O_4 (5)	1	87
7	nano-Fe_3O_4 (7)	1	86
8	nano-Fe_3O_4 (10)	1	86
9	nano-Fe_3O_4 (5)	1	46[b])
10	bulk-Fe_3O_4 (5)	1	51

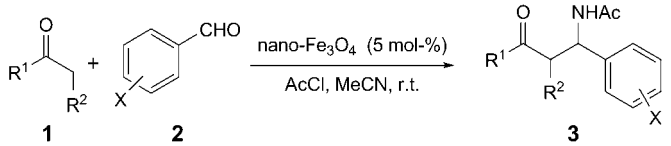
[a]) Yield of isolated product. [b]) At 60°.

room temperature (*Table 1*, *Entries 5–8*). The minimum load of nano-Fe_3O_4 was found as 5 mol-% (*Table 1*, *Entries 5–8*). A lower yield (46%) was observed, when the reaction was carried out at an elevated (60°) temperature (*Table 1*, *Entry 9*). Also commercially available bulk Fe_3O_4 was evaluated. Obviously, under the same reaction conditions, nano-Fe_3O_4 gave higher yield than bulk Fe_3O_4 (87% *vs.* 51%; *Table 1*, *Entries 6* and *10*). Therefore, the condition of *Entry 6* was regarded as optimal. Also, it was observed that during the course of the reaction the magnetic heterogeneous catalyst disappeared; this may be due to the formation of homogeneous $FeCl_3$ in reaction of nano-Fe_3O_4 with AcCl.

To explore the utility of this multicomponent reaction, a series of β-acetamido carbonyl compounds was prepared in high yields according to the above protocol (*Table 2*). As shown in *Table 2*, aromatic aldehydes and acetophenone derivatives containing electron-donating or electron-withdrawing substituents gave the corresponding β-acetamido ketones without the formation of any side-products in high-to-excellent yields (*Table 2*, *Entries 1–13*). The present protocol is applicable to other enolizable ketones such as butanone, propiophenone, and methyl acetoactate (a β-keto ester) (*Table 2*, *Entries 14–18*). With butanone, propiophenone, and methyl acetoacetate, mixtures of *syn*- and *anti*-diasteroisomers were obtained with the *anti*-isomer as the major product (*Scheme* and *Table 2*). The vicinal coupling constant ^3J (H–C(1),H–C(2)) for the *anti*-isomer is generally 7–9 Hz, while it is typically 3–5 Hz for the *syn*-isomer [20].

Conclusions. – In summary, we have presented a highly efficient and convenient procedure for the synthesis of β-acetamido carbonyl compounds from a variety of aromatic aldehydes, enolizable ketones, AcCl, and MeCN, using Fe_3O_4 nanoparticles as catalyst. The notable feature of the present method lies in the availability, low cost, and nontoxicity of the catalyst. The method offers also some other advantages such as low

Table 2. *One-Pot Synthesis of β-Acetamido Carbonyl Compounds*

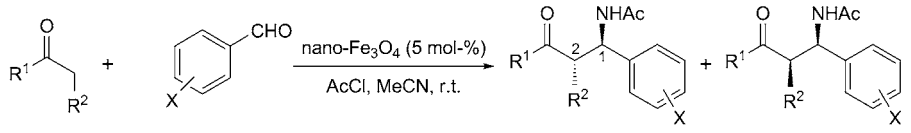


1 **2** **3**

Entry	R^1	R^2	X	Product[a])[b])	Time [h]	Yield [%][c])
1	Ph	H	H	**3a** [14]	1	85
2	Ph	H	2-Cl	**3b** [21]	0.67	90
3	Ph	H	3-NO_2	**3c** [22]	1	87
4	Ph	H	3-Me	**3d** [22]	1	70
5	Ph	H	4-OH	**3e** [22]	1	72
6	Ph	H	4-MeO	**3f** [21]	1	80
7	4-MeO–C_6H_4	H	H	**3g** [21]	1	91
8	4-Cl–C_6H_4	H	H	**3h** [23]	1.17	90
9	4-NO_2–C_6H_4	H	4-MeO	**3i** [24]	1.17	85
10	4-Cl–C_6H_4	H	2,4-Cl_2	**3j** [23]	1.17	86
11	4-Cl–C_6H_4	H	4-Me	**3k** [23]	1.17	87
12	4-MeO–C_6H_4	H	2-Cl	**3l** [23]	0.75	92
13	4-Br–C_6H_4	H	2-MeO	**3m** [25]	0.67	95
14	Me	Me	4-Me	**3n** (84 : 16) [26]	0.75	82
15	Ph	Me	4-Me	**3o** (73 : 27) [26]	0.75	89
16	Ph	Me	4-NO_2	**3p** (64 : 36) [26]	1	83
17	Ph	Me	4-Cl	**3q** (72 : 28) [26]	1	89
18	Me	COOMe	H	**3r** (81 : 19) [26]	0.75	0

[a]) The *anti*/*syn* ratio was determined from the ^{1}H-NMR spectrum of the crude product. [b]) References for known compounds. [c]) Yields of isolated products.

Scheme



R^1 = Me, Ph X = 4-Me, 4-NO_2, 4-Cl, H
R^2 = Me, COOMe

anti (major isomer) *syn* (minor isomer)

loading (5 mol-%) of the catalyst, clean reaction, short reaction times, and high yield of products.

Experimental Part

General Procedure. A soln. of aldehyde (1 mmol), enolizable ketone (1 mmol), AcCl (1 mmol), and MeCN (2.5 ml), in the presence of Fe_3O_4 nanoparticles (0.05 mmol, 5 mol%), was stirred at r.t. After completion of the reaction (monitored by TLC), the mixture was poured into ice-H_2O. The solid was separated, filtered, and recrystallized with either AcOEt/hexane or EtOH/H_2O.

N-*[1-(2-Chlorophenyl)-3-oxo-3-phenylpropyl]acetamide* (**3b**). M.p. 135–136° ([21]: 134–136°). IR (KBr): 3295 (N–H), 1689 (C=O), 1651 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): 2.04 (*s*, 3 H); 3.48 (*dd*, *J* = 16.7, 5.6, 1 H); 3.75 (*dd*, *J* = 16.7, 6.0, 1 H); 5.85 (*dd*, *J* = 13.2, 5.6, 1 H); 7.11 (br. *d*, *J* = 6.8, 1 H); 7.17–7.23 (*m*, 2 H); 7.35 (*d*, *J* = 7.6, 1 H); 7.44–7.48 (*m*, 3 H); 7.58 (*t*, *J* = 7.2, 1 H); 7.92 (*d*, *J* = 7.6, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.4; 41.5; 48.0; 127.0; 128.2; 128.4; 128.7; 128.8; 129.9; 132.5; 133.7; 136.4; 138.2; 169.5; 198.8.

N-*[3-(4-Methoxyphenyl)-3-oxo-1-phenylpropyl]acetamide* (**3g**). M.p. 128–129° ([22]: 128–131°). IR (KBr): 3270 (N–H), 1676 (C=O), 1646 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): 2.06 (*s*, 3 H); 3.39 (*dd*, *J* = 16.6, 5.6, 1 H); 3.73 (*dd*, *J* = 16.4, 5.2, 1 H); 3.89 (*s*, 3 H); 5.57 (*dd*, *J* = 13.2, 5.6, 1 H); 6.86 (br. *d*, *J* = 7.6, 1 H); 6.94 (*d*, *J* = 8.8, 2 H); 7.23–7.36 (*m*, 5 H); 7.92 (*d*, *J* = 8.8, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.5; 42.9; 50.1; 55.6; 113.9; 126.5; 127.4; 128.6; 129.7; 130.5; 141.2; 163.8; 169.6; 197.1.

N-*[3-(4-Chlorophenyl)-3-oxo-1-phenylpropyl]acetamide* (**3h**). M.p. 106–108° ([23]: 107–109°). IR (KBr): 3302 (N–H), 1689 (C=O), 1646 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): 2.04 (*s*, 3 H); 3.42 (*dd*, *J* = 16.6, 6.4, 1 H); 3.76 (*dd*, *J* = 16.6, 5.2, 1 H); 5.56 (*dd*, *J* = 13.2, 6.0, 1 H); 6.67 (br. *d*, *J* = 7.2, 1 H); 7.26–7.35 (*m*, 5 H); 7.44 (*d*, *J* = 8.4, 2 H); 7.87 (*d*, *J* = 8.4, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.5; 43.3; 50.0; 126.5; 127.6; 128.8; 129.1; 129.6; 134.9; 140.0; 140.6; 169.6; 197.3.

N-*[1-(4-Methoxyphenyl)-3-(4-nitrophenyl)-3-oxopropyl]acetamide* (**3i**). M.p. 89–90° ([24]: 87–89°). IR (KBr): 3279 (N–H), 1695 (C=O), 1649 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): 2.03 (*s*, 3 H); 3.47 (*dd*, *J* = 16.4, 7.2, 1 H); 3.80 (*s*, 3 H); 3.85 (*dd*, *J* = 16.4, 5.2, 1 H); 5.48 (*dd*, *J* = 12.4, 7.2, 1 H); 6.35 (br. *d*, *J* = 7.2, 1 H); 6.87 (*d*, *J* = 8.8, 2 H); 7.27 (*d*, *J* = 8.8, 2 H); 8.11 (*d*, *J* = 8.8, 2 H); 8.31 (*d*, *J* = 8.8, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.4; 44.4; 49.8; 55.3; 114.2; 123.9; 127.9; 129.3; 132.3; 141.0; 150.4; 159.1; 169.7; 196.8.

N-*[1-(2-Chlorophenyl)-3-(4-methoxyphenyl)-3-oxopropyl]acetamide* (**3l**). M.p. 154–155° ([23]: 155–156°). IR (KBr): 3266 (N–H), 1681 (C=O), 1643 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): 2.06 (*s*, 3 H); 3.40 (*dd*, *J* = 16.4, 5.2, 1 H); 3.69 (*dd*, *J* = 16.2, 6.0, 1 H); 3.88 (*s*, 3 H); 5.81 (*dd*, *J* = 13.4, 6.0, 1 H); 6.92 (*d*, *J* = 8.8, 2 H); 7.12–7.29 (*m*, 3 H); 7.35 (*d*, *J* = 8.8, 1 H); 7.45 (*d*, *J* = 7.6, 1 H); 7.89 (*d*, *J* = 8.8, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.4; 40.9; 48.2; 55.6; 113.9; 127.0; 128.2; 128.6; 129.6; 129.9; 130.6; 132.4; 138.3; 164.0; 169.3; 197.5.

N-*[3-(4-Bromophenyl)-1-(2-methoxyphenyl)-3-oxopropyl]acetamide* (**3m**). M.p. 156–157° ([25]: 161–162°). IR (KBr): 3311 (N–H), 1692 (C=O), 1649 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): 2.02 (*s*, 3 H); 3.45 (*dd*, *J* = 15.6, 6.4, 1 H); 3.56 (*dd*, *J* = 15.2, 5.2, 1 H); 3.90 (*s*, 3 H); 5.69–5.75 (*m*, 1 H); 6.84 (br. *d*, *J* = 7.2, 1 H); 6.88–6.95 (*m*, 2 H); 7.23–7.30 (*m*, 2 H); 7.58 (*d*, *J* = 8.0, 2 H); 7.80 (*d*, *J* = 8.0, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.6; 43.2; 48.0; 55.4; 110.8; 120.9; 128.0; 128.4; 128.7; 128.9; 129.8; 131.9; 135.4; 156.6; 169.2; 197.6.

N-*[2-Methyl-1-(4-methylphenyl)-3-oxobutyl]acetamide* (**3n**). Major isomer. M.p. 114–115° ([26]: 112°). IR (KBr): 3295 (N–H), 1711 (C=O), 1648 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.19 (*d*, *J* = 7.2, 3 H); 2.02 (*s*, 3 H); 2.05 (*s*, 2 H); 2.33 (*s*, 3 H); 3.11 (*quint.*, *J* = 6.4, 1 H); 5.15 (*dd*, *J* = 8.6, 6.0, 1 H); 7.01 (*d*, *J* = 8.6, 1 H); 7.10–7.18 (*m*, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.3; 21.1; 23.4; 28.9; 29.8; 51.3; 55.1; 126.2; 129.3; 137.1; 137.6; 169.9; 213.8.

N-*[2-Methyl-1-(4-methylphenyl)-3-oxo-3-phenylpropyl]acetamide* (**3o**). Major isomer. M.p. 147–149° ([26]: 159°). IR (KBr): 3235 (N–H), 1682 (C=O), 1645 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.26 (*d*, *J* = 6.8, 3 H); 1.97 (*s*, 3 H); 2.28 (*s*, 3 H); 4.09 (*quint.*, *J* = 7.2, 1 H); 5.49 (*t*, *J* = 8.4, 1 H); 6.48 (br. *d*, *J* = 8.4, 1 H); 7.08 (*d*, *J* = 7.6, 2 H); 7.22 (*d*, *J* = 8.0, 2 H); 7.45 (*t*, *J* = 7.6, 2 H); 7.56 (*t*, *J* = 7.2, 1 H); 7.90 (*d*, *J* = 7.2, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.0; 21.1; 23.4; 45.7; 54.8; 126.9; 128.2; 128.8; 129.3; 133.2; 136.4; 137.1; 137.6; 169.7; 202.1.

N-[1-(4-Chlorophenyl)-2-methyl-3-oxo-3-phenylpropyl]acetamide (**3q**). Major isomer. M.p. 161–162° ([26]: 162°). IR (KBr): 3268 (N–H), 1682 (C=O), 1651 (C=O). ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.16 (*d*, *J* = 6.8, 3 H); 1.89 (*s*, 3 H); 4.10 (*quint.*, *J* = 6.8, 1 H); 5.28 (*t*, *J* = 8.8, 1 H); 7.29 (*d*, *J* = 8.4, 2 H); 7.35 (*d*, *J* = 8.4, 2 H); 7.48 (*t*, *J* = 8.0, 2 H); 7.59 (*t*, *J* = 7.6, 1 H); 7.83 (*d*, *J* = 8.0, 2 H); 8.44 (*t*, *J* = 9.2, 1 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 15.1; 23.1; 45.6; 54.2; 128.3; 128.6; 129.3; 129.6; 131.9; 133.7; 136.5; 141.5; 169.2; 202.1.

Methyl 2-[(Acetamido)(phenyl)methyl]-3-oxobutanoate (**3r**). Major isomer. M.p. 158–159° ([26]: 129–131°). IR (KBr): 3330 (N–H), 1746 (C=O), 1719 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): 2.01 (*s*,

3 H); 2.17 (*s*, 3 H); 3.71 (*s*, 3 H); 4.11 (*d*, $J = 6.0$, 1 H); 5.77 (*dd*, $J = 9.0$, 6.0, 1 H); 7.08 (br. *d*, $J = 8.8$, 1 H); 7.25–7.35 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 23.4; 30.8; 52.3; 52.8; 62.5; 126.5; 127.8; 128.8; 139.2; 167.8; 169.6; 203.9.

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