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$Ni(OAc)_2$: a highly efficient catalyst for the synthesis of enaminone and enamino ester derivatives under solvent-free conditions

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$Ni(OAc)_2$ was found to be an efficient catalyst for the synthesis of β-enamino ketones or esters from β-dicarbonyl compounds and amines under solvent-free conditions. The reusability of the catalyst was successfully examined without noticeable loss of its catalytic activity.

Keywords: β-dicarbonyl compounds; amines; enaminones; enamino esters; nickel acetate

Introduction

Enamination of β-dicarbonyl compounds forming β-enamino ketones and esters is an important and widely used transformation in organic synthesis.[1] The latter compounds are a highly versatile class of intermediates for the synthesis of heterocycles and pharmaceutical compounds, such as dopamine auto-receptor agonists,[2] acetylcholinestersase inhibitors, oxytocin antagonists[3] and anticonvulsants.[4] Owing to their wide range of activity and importance, many synthetic methods have been developed for the preparation of these compounds.[5–11] Among the plethora of methods, the direct condensation of 1,3-dicarbonyl compounds with amines is the most simple and straightforward route for their synthesis. However, the azeotropic removal of water is usually required using a Dean–Stark trap in a refluxing aromatic solvent.[12] Several improved procedures have been reported using a variety of catalysts such as trimethylsilyl trifluoromethanesulfonate (TMSTf),[13] montmorillonite K10 under microwave irradiation[14] or ultrasound,[15] I_2,[16] $BF_3{\bullet}OEt_2$,[17] Al_2O_3,[18] $Zn(ClO_4)_2{\bullet}6H_2O$,[19] $Zn(OAc)_2{\bullet}2H_2O$,[20] $InBr_3$,[6a] $CoCl_2{\bullet}6H_2O$,[6b] $CeCl_3{\bullet}7H_2O$,[21] $ZrOCl_2{\bullet}8H_2O$,[22] $NaAuCl_4$,[23] $Bi(OTf)_3$,[24] $Sc(OTf)_3$,[25] CAN,[26] $NaHSO_4$,[27] $HClO_4{\bullet}SiO_2$,[28] silica gel,[29] natural clays,[30] L-Proline,[31] silica chloride,[32] silica-supported sulfuric acid,[33] silica-supported antimony(III) chloride,[34] phosphotungstic acid,[35] sulfated zirconia,[36] tin tetrachloride,[37] CAN,[38] K-7 $PW_{11}CoO_{40}$,[39] copper(II) nitrate trihydrate[40] and $ZrCl_4$.[41] Recently, this condensation reaction has also been performed in water,[24a,42] PEG-water[43] or ionic liquid medium.[21,24b] Although these methods are suitable for certain synthetic conditions, many of these procedures suffer from one or more limitations, such as long reaction time,[29] use of non-available and expensive reagents[23–25] and high catalyst loading.[16,20,21] Thus, the development of new catalytic methods is highly desirable.

In recent years, $Ni(OAc)_2$ has been discovered to be a new type of water-tolerant Lewis acid catalyst for organic synthesis with highly chemo-, regio- and stereoselective results.[44] Compared with conventional Lewis acids, it has the advantages of commercial availability, low price (7×10^{-3} \$/g), recyclability, operational simplicity, strong tolerance to oxygen- and nitrogen-containing reaction substrates and functional groups.[45] As a part of our program aiming to develop selective and environmental friendly methodologies for the preparation of fine chemicals and in continuation of our interest in Lewis acid-catalyzed organic reactions,[46] we herein report a green, mild and efficient method for the regio- and chemoselective enamination of β-dicarbonyl compounds using a catalytic amount of $Ni(OAc)_2$ under solvent-free conditions (Scheme 1).

Experimental

Melting points were measured on an X4 Micro-melting Point apparatus without correction. NMR spectra were performed in $CDCl_3$ and recorded on a Bruker Avance 300 spectrometer. IR spectra were obtained using a Bruker-Tensor 27 spectrometer. The mass spectra were recorded on Thermo Finnigan LCQ Advantage spectrometer in ESI mode-I. Elemental analyses were performed on a Yamaco CHN corder MT-3 apparatus equipped with two heaters. All of the obtained β-enamino ketones or esters are known compounds and were well characterized.

General Procedure for the Preparation of β-Enamino Ketones or Esters

A mixture of the β-dicarbonyl compound (1 mmol), the amine (1 mmol) and $Ni(OAc)_2$ (0.05 mmol) was stirred at room temperature for the appropriate time (Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate (10 ml) was added and the heterogeneous mixture was filtered. The filter cake was washed with diethyl ether and the catalyst was recovered. The organic phase was washed with water (2×15 ml) and dried over anhydrous $MgSO_4$. The solvent

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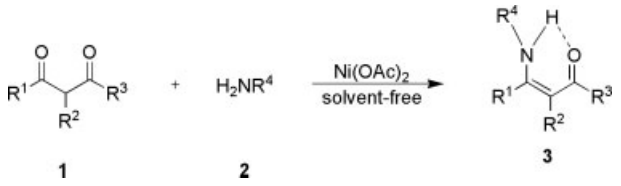


1 2 3

Scheme 1. $Ni(OAc)_2$ catalyzed enamination of β-dicarbonyl compounds.

was evaporated under reduced pressure to provide the crude product. Further purification was carried out by column chromatography on SiO_2 with ethyl acetate–petroleum ether (1 : 4) to afford pure β-enamino ketones or esters in moderate to excellent yields.

Physical and Spectral Data for the Selected Compounds

*Methyl 3-(allylamino)but-2-enoate (**3d**)*

A yellow oil. IR (neat): ν = 3295, 3080, 1654, 1609, 1500, 1287, 1169, 1063, 928 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.89 [s, 3H, =C(CH_3)], 3.61 (s, 3H, –OCH_3), 3.82–3.87 (m, 2H, =CHCH_2 NH–), 4.96 (s, 1H, C=*CH*CO), 5.12–5.23 (m, 2H, =CH_2), 5.80–5.92 (m, 1H, CH_2=*CH*–CH_2), 8.65 (br s, 1H, *NH*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.5 [=C(CH_3)], 44.7 (=CHCH_2 NH–), 49.9 (–OCH_3), 82.2 (=CH_2), 115.5 (CH_2=*CH*CH_2), 134.6 (–NHC=CH), 161.5 (C=*CH*CO), 170.9 (–*CO*–). ESI-MS: *m/z* = 156 $(M + 1)^+$.

Anal. calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.07; H, 8.28; N, 8.91.

*Methyl 3-[3-(2-methoxycarbonyl-1-methyl-vinylamino)-propylamino]-but-2-enoate (**3h**)*

A pale yellow solid, m.p. 69–70 °C. IR (KBr): ν = 3439, 2944, 1651, 1600, 1266, 1176, 1055, 787 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.81 (quin, *J* = 6.3 Hz, 2H, –$CH_2CH_2CH_2$–), 1.93 (s, 6H, =C–CH_3), 3.31 (q, *J* = 6.3 Hz, 4H, –$CH_2CH_2CH_2$–), 3.64 (s, 6H,–OCH_3), 4.45 (s, 2H, –COC*H*=), 8.58 (br s, 2H, *NH*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.1 (–$CH_2CH_2CH_2$–), 31.2 (=C–CH_3), 39.4 (–$CH_2CH_2CH_2$–), 49.6 (–OCH_3), 82.5 (=*C*–CH_3), 161.9 (–COC*H*=), 170.5 (–*CO*CH=). ESI-MS: 271 $(M + 1)^+$. Anal. calcd for $C_{13}H_{22}N_2O_4$: C, 57.76; H, 8.20; N, 10.36. Found: C, 57.59; H, 8.40; N, 10.29.

*Methyl 3-(p-tolylamino)but-2-enoate (**3k**)*

A pale yellow solid, m.p. 58–59 °C. IR (KBr): ν = 3259, 2946, 1652, 1590, 1484, 1385, 1363, 1271, 1185, 1163, 1052, 910 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.94 (s, 3H, =C–CH_3), 2.35 (s, 3H, C_6H_4–CH_3), 3.68 (s, 3H, –OCH_3), 4.65 (s, 1H, C=*CH*–CO), 6.98 (d, *J* = 8.1 Hz, 2H, –*Ar*), 7.12 (d, *J* = 8.1 Hz, 2H, –*Ar*), 10.23 (br s, 1H, *NH*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.3 (=C–CH_3), 20.8 (C_6H_4–CH_3), 50.2 (–OCH_3), 85.1 (*C*=CH–CO), 124.3 (C=*CH*–CO), 129.6 (–*Ar*), 130.6 (–*Ar*), 136.8 (–*Ar*), 159.3 (–*Ar*), 170.9 (–*CO*–). ESI-MS: *m/z* = 206 $(M + 1)^+$. Anal. calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.27; H, 7.40; N, 6.69.

*Methyl 3-(o-tolylamino)but-2-enoate (**3l**)*

A pale yellow solid, m.p. 26–28 °C. IR (KBr): ν = 3440, 3113, 1596, 1401, 1265, 1162, 1059, 915, 787 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.84 (s, 3H, =C–CH_3), 2.25 (s, 3H, C_6H_4–CH_3), 3.67 (s, 3H, –OCH_3), 4.72 (s, 1H, C=*CH*–CO), 7.03–7.22(m, 4H, *Ar*), 10.15 (br s, 1H, *NH*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.7 (=C–CH_3), 19.8 (C_6H_4–CH_3), 50.3 (–OCH_3), 84.5 (*C*=CH–CO), 126.0 (C=*CH*–CO), 126.3 (–*Ar*), 130.6 (–*Ar*), 133.8 (–*Ar*), 137.7 (–*Ar*), 159.8 (–*Ar*), 170.7 (–*CO*–). ESI-MS: *m/z* = 206 $(M + 1)^+$. Anal. calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.09; H, 7.57; N, 6.65.

*Methyl 3-(4-ethoxy-phenylamino)-but-2-enoate (**3m**)*

A pale yellow solid, m.p.: 63–64 °C. IR (KBr): ν = 3440, 3112, 2943, 1647, 1595, 1511, 1481, 1395, 1359, 1248, 1164, 1058, 1004,956 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.45 (t, *J* = 7.2 Hz, 3H, CH_3CH_2–), 1.92 (s, 3H, =C–CH_3), 3.73 (s, 3H, –OCH_3), 4.02 (q, *J* = 7.2 Hz, 2H, CH_3CH_2O), 4.65 (s, 1H, COC*H*=), 6.85 (d, *J* = 8.7 Hz, 2H, *Ar*), 7.05 (d, *J* = 8.7 Hz, 2H, *Ar*), 10.13 (br s, 1H, *NH*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.6 (CH_3CH_2–), 20.1 (=C–CH_3), 50.0 (–OCH_3), 63.7 (CH_3CH_2O), 84.5 (*C*=CH–CO), 114.4 (C=*CH*–CO), 126.5 (–*Ar*), 131.8 (–*Ar*), 156.8 (–*Ar*), 160.0 (–*Ar*), 170.9 (–*CO*–). ESI-MS: *m/z* = 236 $(M + 1)^+$. Anal. calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.52; H, 7.08; N, 5.87.

*Methyl 3-(4-chlorophenylamino)but-2-enoate (**3n**)*

A pale yellow solid, m.p. 60–62 °C. IR (KBr): ν = 3271, 2950, 1654, 1591, 1489, 1350, 1273, 1165, 1054, 940, 785 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.96 (s, 3H, =C–CH_3), 3.67 (s, 3H, –OCH_3), 4.72 (s, 1H, COC*H*=), 7.00 (d, *J* = 8.4 Hz, 2H, *Ar*), 7.26 (d, *J* = 8.4 Hz, 2H, *Ar*), 10.32 (br s, 1H, *NH*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.2 (=C–CH_3), 50.1 (–OCH_3), 86.2 (*C*=CH–CO), 125.5 (C=*CH*–CO), 129.0 (–*Ar*), 137.5 (–*Ar*), 158.5 (–*Ar*), 162.2 (–*Ar*), 170.7 (–*CO*–). ESI-MS: 226 $(M + 1)^+$. Anal. calcd for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.36; N, 6.21. Found: C, 58.39; H, 5.50; N, 6.30.

*Methyl 3-(2,6-diisopropylphenylamino)but-2-enoate (**3p**)*

A white crystalline solid, m.p. 130–132 °C. IR (KBr): ν = 3248, 2957, 1655, 1604, 1487, 1440, 1318, 1267, 1151, 1055, 911, 806 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.16 [d, *J* = 6.6 Hz, 6H, –CH(CH_3)$_2$], 1.21 [d, *J* = 6.6 Hz, 6H, –CH(CH_3)$_2$], 1.63 (s, 3H, =C–CH_3), 3.05–3.15 [m, 2H, –*CH*(CH_3)$_2$], 3.72 (s, 3H, –OCH_3), 4.66 (s, 1H, COC*H*=), 7.17 (d, *J* = 7.8 Hz, 2H, *Ar*), 7.29–7.33 (m, 1H, *Ar*), 9.81 (br s, 1H, *NH*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.5 [–CH(CH_3)$_2$], 22.7 [–CH(CH_3)$_2$], 24.5 (=C–CH_3), 28.4 [–*CH*(CH_3)$_2$], 50.2 (–OCH_3), 82.6 (*C*=CH–CO), 123.5 (C=*CH*–CO), 128.2 (–*Ar*), 133.9 (–*Ar*), 147.0 (–*Ar*), 162.0 (–*Ar*), 171.1 (–*CO*–). ESI-MS: 276 $(M + 1)^+$. Anal. calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.32; H, 9.25; N, 4.94.

*(R)-4-(1-phenylethylamino)pent-3-en-2-one (**3 w**)*

A yellow oil; $[\alpha]_D^{20}$: −836 (*c* = 0.66, EtOH). IR (neat): ν = 3448, 2973, 2925, 1610, 1578, 1506, 1438, 1355, 1295, 1137, 1017, 858, 746 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.54 (d, *J* = 6.9 Hz, 3H, –CHCH_3), 1.76 (s, 3H, =C–CH_3), 2.04 (s, 3H, –COCH_3), 4.60–4.69 (m, 1H, CH_3*CH*NH), 4.99 (s, 1H, COC*H*=), 7.22–7.34 (m, 5H, *Ar*), 11.26 (br s, 1H, *NH*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.8 (–CHCH_3), 24.2 (=C–CH_3), 28.6 (–COCH_3), 52.5 (CH_3*CH*NH), 95.5 (*C*=CH–CO), 125.4 (C=*CH*–CO), 126.9 (*Ar*), 128.4 (*Ar*), 144.1 (*Ar*), 162.5 (*Ar*), 194.8 (–*CO*–). Anal. calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.85; H, 8.50; N, 6.83.

Table 1. Synthesis of β-enamino ketones and β-enamino esters using Ni(OAc)2 under solvent-free conditions

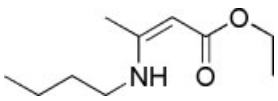
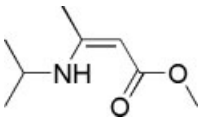
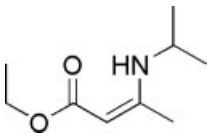
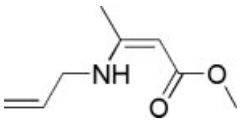
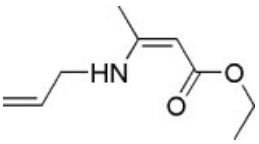
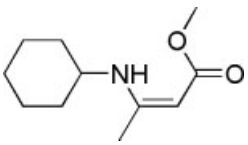
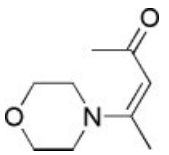
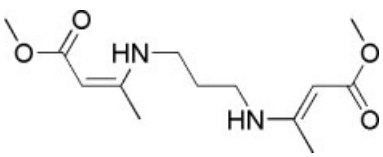
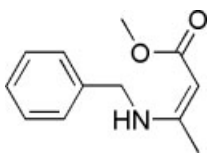
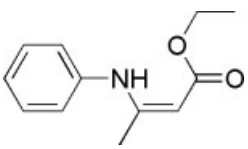
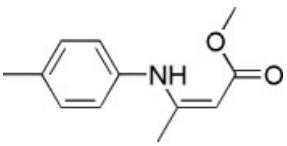
Entry	Product	Time (min)	Yield (%)[a]	Reference
a		4	99	31
b		5	98	6a
c		5	95	6a
d		8	95	6a
e		8	96	22
f		9	90	6a
g		300	74	6a
h		9	96	6a
i		5	97	31
j		18	97	28
k		17	94	31

Table 1. (*Continued*)

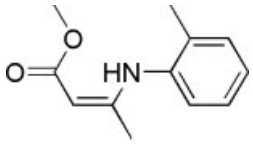
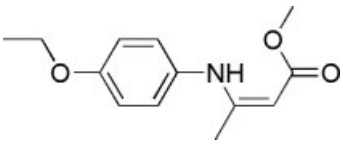
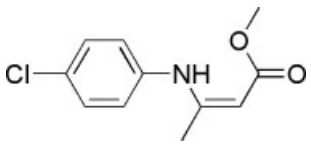
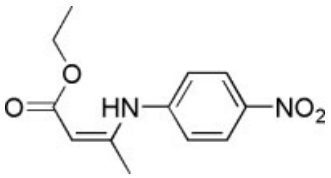
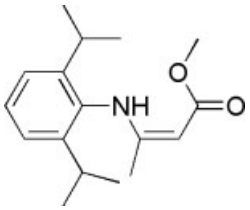
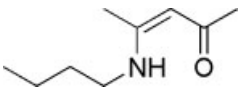
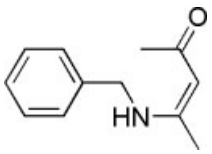
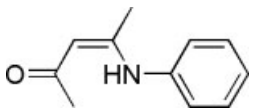
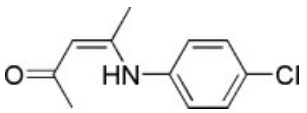
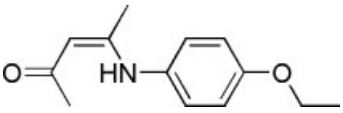
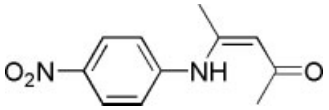
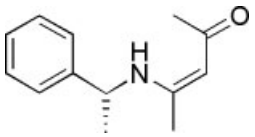
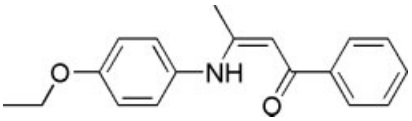
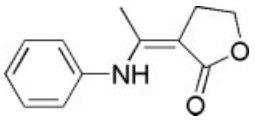
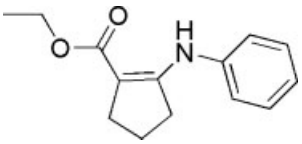
Entry	Product	Time (min)	Yield (%)[a]	Reference
l		21	92	6a
m		11	96	6a
n		240	89[b]	31
o		400	69[b]	6a
p		270	82[b]	6a
q		4	99[b]	24
r		5	98[b]	6a
s		9	98	28
t		240	86[b]	6a
u		10	96	6a
v		420	65[b]	6a

Table 1. (*Continued*)

Entry	Product	Time (min)	Yield (%)[a]	Reference
w		6	95[b]	6a
x		51	79[b]	6a
y		60	95	29
z		87	93	29

[a] Yields are given for isolated products.
[b] The reactions were performed at 60 °C.

*3-(4-Ethoxy-phenylamino)-1-phenyl-but-2-en-1-one (**3x**)*

A yellow solid, m.p. 86-87 °C. IR (KBr): ν = 3418, 2976, 1598, 1503, 1475, 1437, 1370, 1321, 825 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.41 (t, J = 6.9 Hz, 3H, $-OCH_2CH_3$), 2.05 (s, 3H, $=C-CH_3$), 4.05 (q, J = 6.9 Hz, 2H, $-OCH_2CH_3$), 5.85 (s, 1H, $-COCH$), 6.89 (d, J = 9.0 Hz, 2H, *Ar*), 7.07 (d, J = 9.0 Hz, 2H, *Ar*), 7.42–7.45 (m, 3H, *Ar*), 7.89–7.92 (m, 2H, *Ar*), 12.94 (br s, 1H, *NH*).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.6 ($-CH_2CH_3$), 20.1 ($=C-CH_3$), 63.8 ($-OCH_2CH_3$), 93.4 ($-COCH$), 114.9 ($=C-CH_3$), 126.6 (*Ar*), 127.2 (*Ar*), 128.3 (*Ar*), 130.9 (*Ar*), 131.4 (*Ar*), 140.5 (*Ar*), 157.6 (*Ar*), 163.5 (*Ar*), 188.2 ($-CO-$). ESI-MS: 282 $(M+1)^+$. Anal. calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 75.69; H, 6.90; N, 5.01.

*Ethyl 2-(phenylamino)cyclopent-1-enecarboxylate (**3z**)*

A yellow oil. IR (KBr): ν = 3288, 2955, 1654, 1620, 1506, 1478, 1264, 1170, 1046, 751 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.31 (t, J = 7.2 Hz, 3H, $-CH_2CH_3$), 1.82–1.91 (m, 2H, $-CH_2CH_2CH_2-$), 2.54 (t, J = 7.5 Hz, 2H, $-CH_2CH_2CH_2-$), 2.78 (t, J = 7.2 Hz, 2H, $-CH_2CH_2CH_2-$), 4.19 (q, J = 7.2 Hz, 2H, $-CH_2CH_3$), 7.01–7.28 (m, 5H, *Ar*), 9.58 (br s, 1H, *NH*). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.5 ($-CH_2CH_3$), 21.8 ($-CH_2CH_2CH_2-$), 28.6 ($-CH_2CH_2CH_2-$), 33.5 ($-CH_2CH_2CH_2-$), 58.8 ($-CH_2CH_3$), 97.6 ($=C-NH$), 120.5 ($=CCO$), 123.1 (*Ar*), 129.3 (*Ar*), 140.8 (*Ar*), 160.1 (*Ar*), 168.5 ($-CO-$). Anal. calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.65; H, 7.39; N, 6.18.

Results and Discussion

To demonstrate the generality and scope of this method, various cyclic and acyclic β-dicarbonyl compounds such as methyl acetoacetate, ethyl acetoacetate, 2-acetybutyrolactone and ethyl 2-oxocyclopentanecarboxylate were treated with a range of primary, secondary, benzylic and aromatic amines in the presence of catalytic amounts of $Ni(OAc)_2$ (5 mol%) under solvent-free conditions and the results are shown in Table 1. The reactions were fast (4 min to 420 min) and clean with moderate to high isolated yield (65–99%). For example, ethyl 3-(butylamino)but-2-enoate (**3a**) and methyl 3-(isopropylamino)but-2-enoate (**3b**) were obtained in 99 and 98% yield, respectively. The nucleophilic addition of amines to carbonyl compounds, catalyzed by $Ni(OAc)_2$, was found to be dependent on steric and electronic factors of β-keto esters and amines. The reaction between aniline and cyclic β-keto esters with a substituent different from hydrogen in the α-position (**3y** and **3z**) took longer compared with the corresponding reaction with ethyl acetoacetate (**3j**) under similar conditions. Since a keto carbonyl group is more electrophilic than an ester group, this reaction was highly chemoselective, evidenced by the formation of **3y–3z** in high yield (93–95%). The presence of electron-donating and electron-withdrawing groups on the aromatic ring of substituted anilines makes an obvious difference to the reaction rate.

Substitution of an electron-withdrawing group onto the aromatic ring severely retards this condensation reaction (**3n** and **3t**). Anilines bearing strong electron-withdrawing groups, such as 4-nitroaniline (**3o** and **3v**), provided the corresponding β-enamino ester and ketone in only 69 and 65% yield at 60 °C, respectively, which showed an obvious electronic effect. *Ortho*-substituted anilines, whatever the nature of the substituted groups, required a longer reaction period. It was suggested that the yields were significantly decreased when the size of the *ortho*-substituent groups was large. For instance, 2,6-diisopropylaniline (**3p**) was found to be less active and gave the desired β-keto esters in 82% yield even after 4.5 h. This may be due to the steric hindrance performed by the 2,6-diisopropyl groups of the aniline towards the approaching β-keto ester.

Generally, aliphatic amines are more reactive than aromatic amines. In the case of 1,3-diaminopropane, two equivalents of β-keto ester were used, producing the product with two enamino

Table 2. Comparison of the effect of catalysts for the synthesis of 4-(phenylamino)pent-3-en-2-one (**3s**)

Catalyst/solvent	Catalyst loading	Time	Yield (%)	Reference
$Zn(OAc)_2 \cdot 2H_2O/CH_2Cl_2$	5 mol%	2 days	86	20
$InBr_3$	1 mol%	10 min	94	6a
$Zn(ClO_4)_2 \cdot 6H_2O/CH_2Cl_2$	5 mol%	4 h	95	19
$CoCl_2 \cdot 6H_2O$	5 mol%	15 min	95	6b
Silica gel/solvent-free	10 mg	35 h	95	29
$CeCl_3 \cdot 7H_2O$/solvent-free	10 mol%	35 min	76	21
$ZrOCl_2 \cdot 8H_2O$/solvent-free	2 mol%	10 min	95	22
$Ni(OAc)_2$/solvent-free	5 mol%	9 min	98	

ester groups (**3h**). Optically active amine was converted into the corresponding β-enamino compounds without any racemization or inversion (**3 w**). The less reactive 1-benzoylacetone reacted with ethoxy aniline to obtain exclusively a single regioisomer (**3x**). Additionally, secondary amines also gave low conversion, as confirmed by the fact that the condensation reaction of acetylacetone and morpholine provided the β-enamino ketone product in Generally, aliphatic amines are more reactive than. aromatic amines. In the case of 1,3-diaminopropane, two equivalents of β-keto ester were used producing the product with two enamino ester groups (**3h**). Optically active amine was converted into the corresponding β-enamino compounds without any racemization or inversion (**3 w**). The less reactive 1-benzoylacetone reacted with ethoxy aniline to obtain exclusively a single regioisomer (**3x**). Additionally, secondary amines also gave low conversion as confirmed by the fact that the condensation reaction of acetylacetone and morpholine provided the β-enamino ketone product in 74% yield and required a long reaction time (**3g**). In some cases, the condensation of acetylacetone with aliphatic amines produced a precipitate (**3q** and **3r**), which resulted from the formation of a carbinolamine derivative.[47] These compounds were relatively unstable and they were dehydrated by heating to give β-enamino ketones. In all reactions, the products were obtained with the (Z)-form configuration. The proton of the -NH- group appearing at a lower field ($\delta > 8.2$) indicated the classical intramolecular hydrogen-bonding interactions between the amino proton and the carbonyl oxygen, which stabilized the products (**3** in Scheme 1). Therefore, this condensation reaction was stereospecific.

In comparison with other catalysts such as $Zn(OAc)_2 \bullet 2H_2O$, $InBr_3$, $Zn(ClO_4)_2 \bullet 6H_2O$, $CoCl_2 \bullet H_2O$, silica gel, $CeCl_3 \bullet 7H_2O$ and $ZrOCl_2 \bullet 8H_2O$, which were recently used in the enamination of β-dicarbonyl compounds, $Ni(OAc)_2$ employed here exhibits more effective catalytic activity than those previously reported in terms of the amount of catalyst, yields and reaction time (Table 2).

Recyclability of the catalyst was also studied through a condensation reaction of aniline and ethyl acetoacetate as model substrates. The catalyst was simply filtered from the reaction mixture, and $Ni(OAc)_2 x H_2O$ was recovered after washing with ether and air drying. This was reused for the preparation of **3j** in five runs without significant loss of activity.

Conclusions

In conclusion, $Ni(OAc)_2$ has been employed for the first time as a novel and efficient catalyst for the synthesis of β-enamino ketones and esters under solvent-free conditions. The advantages include mild reaction conditions, enhanced reaction rates, low loading of catalyst, and operational and experimental simplicity.

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