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Tetrahedron 63 (2007) 2404–2408
Tetrahedron

Stereoselective synthesis of β-amino ketones via direct Mannich-type reaction catalyzed with silica sulfuric acid

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Received 23 November 2006; revised 10 January 2007; accepted 11 January 2007
Available online 13 January 2007

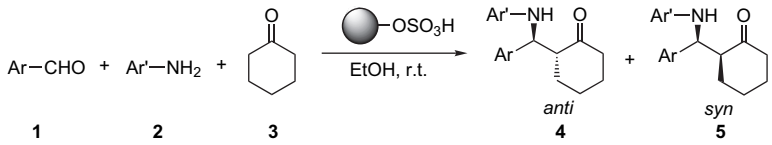
Abstract—At room temperature, the direct Mannich-type reaction of a variety of in situ generated aldimines using aldehydes and anilines with ketones in a three-component reaction was efficiently catalyzed by silica sulfuric acid (SSA) in EtOH. This rapid reaction afforded the corresponding β-amino ketones in good yields with excellent stereoselectivities and catalyst was recyclable.

1. Introduction

Mannich reactions are among the most important carbon–carbon bond forming reactions in organic synthesis.[1] They provide β-amino carbonyl compounds, which are important synthetic intermediates for various pharmaceuticals and natural products.[2] Therefore, the development of new synthetic methods leading to β-amino carbonyl compounds or their derivatives has attracted much attention. However, the classic Mannich reaction has limited applications. To overcome the drawbacks of the classic method, numerous modern versions of the Mannich reaction using performed electrophiles, such as imines and stable nucleophiles, such as enolates, enol ethers, and enamines[3] have been developed. But the preferred route is to use a one-pot three-component strategy that gives a wide range of structural variations. Furthermore, only a few one-pot procedures on the use of unmodified aldehydes or ketones have been reported in the literature and a variety of catalysts, $Zn(OTf)_2$,[4] $H_3PW_{12}O_{40}$,[5] $ZrOCl_2\cdot 8H_2O$,[6] (*S*)-serine,[7] DBSA,[8] SDS–HCl,[9–11] $Bi(OTf)_3\cdot 4H_2O$,[12] sodium tetrakis(3,5-trifluoromethylphenyl)borate,[13] PS–SO_3H,[14] L-proline,[3h] have been investigated. However, these methods have some drawbacks such as long reaction time, use of costly and non-recoverable catalysts, use of toxic reagents, and requirement of special effort for catalyst preparation. Silica sulfuric acid is an excellent acidic catalyst, which is frequently used to promote some important reactions.[15–18] We report herein full details of a novel, convenient, and simple procedure to realize a one-pot three-component reaction of aldehydes, amines, and ketones, catalyzed by SSA, for the preparation of β-amino carbonyl compounds in EtOH (Scheme 1).

2. Results and discussion

Initially, the three-component Mannich reaction of benzaldehyde (2.0 mmol), aniline (2.0 mmol), and cyclohexanone (2.1 mmol) was examined. To optimize reaction condition, some solvents were screened in the model reaction. The results are shown in Table 1. Entries 1a–1f showed the effect of various solvents. Interestingly, the Mannich reaction



Scheme 1. Direct Mannich-type reactions of aromatic aldehydes, anilines, and cyclohexanone.

Keywords: Direct Mannich-type reaction; β-Amino ketones; Silica sulfuric acid; Synthesis.
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doi:10.1016/j.tet.2007.01.015

Table 1. Mannich reactions of benzaldehyde (2.0 mmol), aniline (2.0 mmol), and cyclohexanone (2.1 mmol) under different conditions

Entry	Solvent	SSA (mol %)	Yields[a] (%)	*anti*/*syn*
1a	MeOH	0.04	53	80:20
1b	CH_3CN	0.04	60	99:1
1c	CH_2Cl_2	0.04	50	82:12
1d	Ethyl acetate	0.04	20	99:1
1e	H_2O	0.04	nr[b]	—
1f	EtOH	0.04	96	85:15
1g	EtOH	0.02	77	84:16
1h	EtOH	0.06	59	80:20
1i	EtOH	0.08	55	80:20
1j	EtOH	0.1	18	81:19

[a] Yield of isolated products.
[b] No reaction.

showed an intriguing solvent effect; excellent *anti* selectivity was observed in CH_3CN and ethyl acetate, whereas the yields of the reaction exhibited were low (20% and 60%). Compared with MeOH, CH_2Cl_2, and H_2O, EtOH showed high yield and good stereoselectivity. Therefore, we chose EtOH as the solvent for high yield and good *anti* selectivity of the reaction. The optimum amount of catalyst (0.04 mol %) was determined from experiments corresponding to entries 1f–1j. When the amount of SSA was higher than 0.04 mol %, the yield gradually decreased.

In our initial experiments, we found that aromatic aldehydes **1**, anilines **2**, and cyclohexanone **3** in EtOH were stirred in the presence of a catalytic amount (0.04 mol %) of SSA at room temperature for 3–6 h to give the corresponding β-amino carbonyl compounds **4**. As shown in Table 2, the reaction of different aromatic aldehydes, anilines, and cyclohexanone gave the β-amino ketone adduct in good to high yield with good to excellent *anti* selectivity at room temperature, but the benzaldehyde with strong electron withdrawing group almost did not work (Table 2, entry 2h).

High *anti* selectivity was obtained with various substituted benzaldehydes except for 4-chlorobenzaldehyde (Table 2, entry 2l).

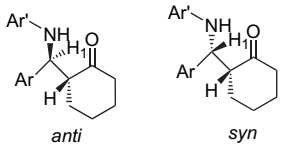
Table 2. Direct Mannich-type reactions of aromatic aldehydes, anilines, and cyclohexanone[a]

Entry	Ar^1	Ar'^2	Time (h)	Yields[b] (%)	*anti*/*syn*[c]
2a	2-$OCH_3C_6H_4$	H	5	89	99:1
2b	2-ClC_6H_4	H	6	83	86:14
2c	2-BrC_6H_4	H	6	81	99:1
2d	2,3-$OCH_3C_6H_3$	H	6	91	95:5
2e	4-$OCH_3C_6H_4$	H	4	90	99:1
2f	4-$CH_3C_6H_4$	H	6	80	99:1
2g	2,5-$OCH_3C_6H_3$	H	6	75	99:1
2h	4-$NO_2C_6H_4$	H	6	nr[d]	—
2i	H	H	3	96	85:15
2j	H	4-$CH_3C_6H_4$	4	89	99:1
2k	H	2-ClC_6H_4	5	82	99:1
2l	H	4-ClC_6H_4	6	83	75:25
2m	H	3-ClC_6H_4	6	92	99:1
2n	H	3-$CH_3C_6H_4$	6	85	11:89

[a] Reaction conditions: aldehydes (2 mmol), anilines (2 mmol), cyclohexanone (2.1 mmol), and SSA (0.04 mol %).
[b] Yield of isolated products.
[c] Diastereomeric ratio measured by ^1H NMR spectroscopy analysis of the crude reaction mixture.
[d] No reaction.

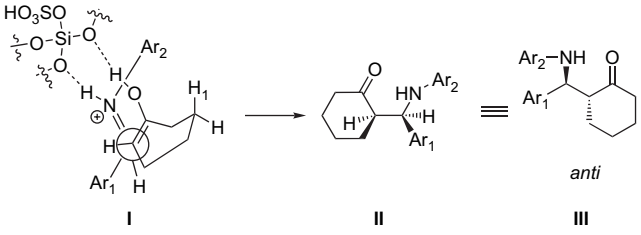
It has to be mentioned that our protocol used stoichiometric cyclohexanone, while other protocols took excessive cyclohexanone (1.7–6.0 equiv), for example, when $H_3PW_{12}O_{40}$,[5] $ZrOCl_2\cdot 8H_2O$,[6] DBSA,[8] SDS–HCl,[9–11] etc. were used as catalysts.

The *anti* and *syn* isomers were identified by the coupling constants (*J*) of the vicinal protons adjacent to C=O and NH in their ^1H NMR spectra.[19] *J* signal of *anti* isomer is higher than that of the *syn* one. The *anti*/*syn* ratio was determined by ^1H NMR judged by the intensity of the H_1 (Scheme 2).

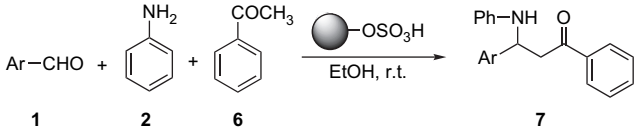


Scheme 2. Identification of *anti* and *syn* isomers by ^1H NMR spectroscopy.

Interestingly, the β-amino ketones in Table 2 show that the *anti* isomer is much more favored than *syn* isomer with the exception of entry 2n (*anti*/*syn*=11:89). The possible transition states are proposed in Scheme 3. If hydrogen bonds are formed among SSA, the imine and the enol form of cyclohexanone, the aryl groups of aldimine would be *anti* to each other and there should be less steric repulsion in I, between the methylene groups of cyclohexanone and aryl group on the carbon atom, as well as SSA and H_1. So the most stable transition state I would produce the *anti* isomer III (Scheme 3). The encouraging results prompted us to use other ketones such as acetophenone (Scheme 4). When 0.06 mol % SSA was used, β-amine ketones **7** were obtained in high yields. Table 3 clearly demonstrates that SSA is a good catalyst for Mannich reaction in EtOH. Acetophenone was less reactive than cyclohexanone and needed more catalyst, longer reaction time to afford the desired products. It was found that the electronic effect of substitutes had some influence on the yields. For example, when there was an electron withdrawing group of aromatic aldehyde (entry 3d), the reaction time was longer (17 h), and the yield was lower (60%).



Scheme 3. Possible transition states.



Scheme 4. Mannich-type reactions of aromatic aldehydes, anilines, and acetophenone.

Table 3. Mannich-type reactions of aromatic aldehydes, anilines, and acetophenone[a]

Entry	Ar	Time (h)	Yields[b] (%)
3a	C_6H_5	12	92
3b	4-$CH_3C_6H_4$	15	80
3c	4-$OCH_3C_6H_4$	14	81
3d	4-BrC_6H_4	17	60
3e	2-ClC_6H_4[c]	14	70
3f	2,3-$OCH_3C_6H_3$	13	71

[a] Reaction conditions: aldehydes (2 mmol), amine (2 mmol), acetophenone (2.1 mmol), and SSA (0.06 mol %).
[b] Yield of isolated products.
[c] SSA (0.08 mol %) was used.

3. Conclusion

In summary, good *anti* selectivity has been observed in the SSA-catalyzed direct-type Mannich reaction in EtOH. The significant features of this procedure include: (1) high yields; (2) good stereoselectivities; (3) facile operations; (4) recyclable catalysts; and (5) non-toxic solvents.

4. Experimental

4.1. General

All reagents were purchased from commercial sources and used without further purification. TLC analysis was performed with glass backed plates precoated with silica gel and examined under UV (254 nm). NMR spectra were measured in $CDCl_3$ with Me_4Si as the internal standards on a Bruker Advance DPX-400 at room temperature. IR spectra were recorded on Bruker FTIR spectrometer, absorbances are reported in cm^{-1}. Elemental analyses were performed on a Perkin–Elmer-2400 elemental analyzer.

4.2. General procedure for the synthesis of β-amino carbonyl compounds 4

A mixture of benzaldehyde (2.0 mmol), aniline (2.0 mmol), cyclohexanone (2.1 mmol), and SSA (0.11 g, 0.04 mol %) was stirred in EtOH (3 mL) at room temperature for 3–6 h. The reaction was monitored in TLC. Upon and on completion, CH_2Cl_2 was added and catalyst was removed by filtration. Filtrates were washed with saturated $NaHCO_{3(aq)}$ and brine, dried with anhydrous Na_2SO_4, and concentrated to dryness. The crude mixture was subjected to flash column chromatography.

4.3. General procedure for the synthesis of β-amino carbonyl compounds 7

A mixture of benzaldehyde (2.0 mmol), aniline (2.0 mmol), acetophenone (2.0 mmol), and SSA (0.17 g, 0.06 mol %) was stirred in EtOH (3 mL) at room temperature for 12–17 h. The reaction was monitored in TLC. Upon and on completion, CH_2Cl_2 was added and catalyst was removed by filtration. Filtrates were washed with saturated $NaHCO_{3(aq)}$ and brine, dried with anhydrous Na_2SO_4, and concentrated to dryness. The crude mixture was subjected to flash column chromatography.

4.4. Preparation and recycling of SSA

SSA was prepared according to Mohammad Ali Zolfigol's procedure.[20] The catalyst was separated in the first stage of the above work up procedure. The residue was washed with 95% EtOH and dried at 110 °C for 12 h to give pure SSA for further runs.

The known compounds (entries 2f, 2i, and 2l in Table 2 and entries 3a–3d in Table 3) have been identified by comparison of spectral data with those reported.[4–6,19d]

4.5. Spectral data of new products

4.5.1. 2-((2-Methoxyphenyl)(phenylamino)methyl)cyclohexanone (4a). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, J=6.4 Hz, 1H), 7.20 (t, J=8.0 Hz, 1H), 7.08 (t, J=8.0 Hz, 2H), 6.87–6.92 (m, 2H), 6.58–6.65 (m, 2H), 5.02 (d, J=6.8 Hz, 1H), 2.90–2.94 (m, 1H), 2.33–2.47 (m, 2H), 1.59–1.99 (m, 6H); IR (KBr, ν, cm^{-1}): 3349.19, 1698.92, 1600.50, 1516.68, 854.14; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.50, 156.92, 147.06, 129.13, 128.75, 128.71, 127.93, 127.75, 120.52, 116.93, 113.12, 109.91, 55.71, 55.10, 52.20, 41.57, 31.47, 27.95, 23.38; Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.60; H, 7.53; N, 4.50.

4.5.2. 2-((2-Chlorophenyl)(phenylamino)methyl)cyclohexanone (4b). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, J=7.2 Hz, 1H), 7.35 (d, J=7.2 Hz, 1H), 7.09–7.22 (m, 2H), 5.36 (d, J=3.6 Hz, 0.14H), 5.26 (br s, 1H), 4.92 (d, J=4.4 Hz, 0.86H), 2.95–2.99 (m, 1H), 2.30–2.41 (m, 2H), 1.96–2.14 (m, 4H), 1.59–1.85 (m, 2H); IR (KBr, ν, cm^{-1}): 3396.45, 1697.69, 1601.76, 1502.64, 809.08; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.91, 146.67, 138.92, 133.05, 129.57, 129.24, 129.03, 128.91, 128.77, 128.72, 127.97, 126.80, 126.68, 117.74, 117.28, 113.81, 113.07, 55.15, 55.10, 53.84, 53.03, 42.58, 42.06, 32.43, 27.86, 27.25, 26.86, 24.66, 24.55; Calcd for $C_{19}H_{20}ClNO$: C, 72.72; H, 6.42; N, 4.46. Found: C, 72.68; H, 6.32; N, 4.40.

4.5.3. 2-((2-Bromophenyl)(phenylamino)methyl)cyclohexanone (4c). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, J=8.0 Hz, 1H), 7.53 (dd, J=1.2, 8.4 Hz, 1H), 7.24 (t, J=7.6 Hz, 1H), 7.05–7.13 (m, 3H), 6.66 (t, J=7.2 Hz, 1H), 6.54 (d, J=8.0 Hz, 1H), 5.50 (br s, 1H), 2.98–3.01 (m, 1H), 2.96–3.02 (m, 2H), 2.29–2.96 (m, 2H), 1.99–2.20 (m, 2H), 1.75–1.85 (m, 2H); IR (KBr, ν, cm^{-1}): 3390.40, 1697.71, 1600.70, 1501.84, 806.92; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.89, 146.69, 140.43, 132.31, 129.01, 128.90, 128.28, 127.34, 123.61, 117.23, 113.11, 57.59, 54.99, 42.80, 32.74, 27.85, 24.80; Calcd for $C_{19}H_{20}BrNO$: C, 63.70; H, 5.63; N, 3.91. Found: C, 63.60; H, 5.69; N, 3.96.

4.5.4. 2-((2,3-Dimethoxyphenyl)(phenylamino)methyl)-cyclohexanone (4d). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.11 (t, J=8.0 Hz, 2H), 7.05 (d, J=7.6 Hz, 1H), 7.00 (t, J=8.0 Hz, 1H), 6.79 (t, J=7.6 Hz, 1H), 6.62–6.68 (m, 3H), 5.22 (d, J=4.2 Hz, 0.05H), 4.96 (d, J=7.6 Hz, 0.95H), 3.95 (s, 3H), 3.87 (s, 3H), 2.90–3.00 (m, 1H), 2.30–2.44 (m, 2H), 1.70–1.96 (m, 6H); IR (KBr, ν, cm^{-1}): 3334.72, 1703.50, 1601.57, 1528.75, 813.21; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.24, 151.97, 147.11, 146.53, 134.68, 128.10, 128.74, 123.53, 119.76, 117.07, 113.72, 113.26, 110.79,

60.24, 56.29, 55.34, 53.00, 41.88, 31.95, 27.97, 23.78; Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.21; H, 7.48; N, 4.15.

4.5.5. 2-((4-Methoxyphenyl)(phenylamino)methyl)cyclohexanone (4e). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, J=8.4 Hz, 2H), 7.12 (d, J=7.6 Hz, 2H), 7.10 (t, J=8.0 Hz, 2H), 6.64 (t, J=7.2 Hz, 1H), 6.65 (d, J=8.4 Hz, 2H), 4.71 (br s, 1H), 4.62 (d, J=7.2 Hz, 1H), 2.72–2.76 (m, 1H), 2.42–2.47 (m, 1H), 2.34–2.38 (m, 1H), 1.83–1.93 (m, 4H), 1.68–1.75 (m, 3H); IR (KBr, ν, cm^{-1}): 3332.42, 1707.26, 1600.92, 1532.21, 800.33; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.74, 147.01, 138.36, 136.45, 128.91, 128.77, 126.86, 117.16, 113.34, 57.39, 57.30, 41.43, 30.92, 27.92, 23.28, 20.81; Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.44; H, 7.59; N, 4.54.

4.5.6. 2-((2,5-Dimethoxyphenyl)(phenylamino)methyl)-cyclohexanone (4g). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.08 (t, J=8.0 Hz, 2H), 6.95 (d, J=7.6 Hz, 1H), 6.8 (d, J=8.4 Hz, 1H), 6.70 (dd, J=2.8, 9.6 Hz, 1H), 6.62 (t, J=7.2 Hz, 1H), 6.56 (t, J=8.0 Hz, 2H), 5.99 (d, J=7.2 Hz, 1H), 5.85 (br s, 1H), 3.89 (s, 3H), 3.74 (s, 3H), 2.81–2.86 (m, 1H), 2.41–2.47 (m, 1H), 2.31–2.35 (m, 1H), 1.85–2.00 (m, 4H), 1.58–1.79 (m, 2H); IR (KBr, ν, cm^{-1}): 3353.70, 1702.06, 1602.54, 1531.01, 813.29; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.41, 153.41, 151.24, 146.98, 130.47, 128.25, 117.01, 114.72, 114.05, 113.16, 112.00, 110.76, 55.87, 55.56, 55.28, 52.14, 41.46, 31.30, 27.93, 23.26; Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.30; H, 7.53; N, 4.12.

4.5.7. 2-((*p*-Toluidino)(phenyl)methyl)cyclohexanone (4j). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, J=7.2 Hz, 2H), 3.32 (t, J=7.6 Hz, 2H), 7.23 (t, J=7.6 Hz, 1H), 6.90 (d, J=8.0 Hz, 2H), 6.51 (d, J=7.6 Hz, 2H), 4.61 (d, J=7.6 Hz, 1H), 2.80–2.82 (m, 1H), 2.34–2.48 (m, 2H), 2.19 (s, 3H), 1.86–1.95 (m, 6H); IR (KBr, ν, cm^{-1}): 3406.42, 1702.39, 1620.45, 1524.27, 805.21; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.65, 144.61, 141.56, 129.27, 129.17, 126.99, 126.83, 126.40, 113.48, 57.91, 57.26, 41.41, 30.90, 27.61, 23.31, 20.05; Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.80; H, 7.91; N, 4.70.

4.5.8. 2-((2-Chlorophenylamino)(phenyl)methyl)cyclohexanone (4k). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, J=7.6 Hz, 2H), 7.33 (t, J=7.6 Hz, 2H), 7.24–7.26 (m, 2H), 6.96 (t, J=7.6 Hz, 1H), 6.58 (t, J=7.6 Hz, 1H), 6.49 (d, J=8.0 Hz, 1H), 5.5 (br s, 1H), 4.72 (d, J=6.4 Hz, 1H), 2.87–2.89 (m, 1H), 2.20–2.49 (m, 2H), 1.27–2.02 (m, 6H); IR (KBr, ν, cm^{-1}): 3391.50, 1701.95, 1595.43, 1500.10, 811.33; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.77, 142.93, 140.83, 128.78, 128.25, 127.28, 127.02, 126.96, 119.44, 117.14, 112.04, 57.56, 57.13, 41.85, 31.36, 27.65, 23.87; Calcd for $C_{19}H_{20}ClNO$: C, 72.72; H, 6.42; N, 4.46. Found: C, 72.68; H, 6.50; N, 4.40.

4.5.9. 2-((3-Chlorophenylamino)(phenyl)methyl)cyclohexanone (4m). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31–7.38 (m, 4H), 7.25 (t, J=6.8 Hz, 1H), 6.98 (t, J=8.0 Hz, 1H), 6.60 (d, J=7.6 Hz, 1H), 6.52–6.53 (m, 1H), 6.41–6.43 (m, 1H), 4.89 (br s, 1H), 4.57 (d, J=6.4 Hz, 1H), 2.76–2.81 (m, 1H), 2.32–2.47 (m, 2H), 1.91–2.00 (m, 4H), 1.70–1.86 (m, 2H); IR (KBr, ν, cm^{-1}): 3342.02, 1701.50, 1599.60, 1525.80, 829.73; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.46, 148.22, 140.91, 134.49, 129.76, 128.29, 127.07, 126.87, 117.11, 113.01, 111.55, 57.79, 57.07, 41.73, 31.36, 27.68, 23.60; Calcd for $C_{19}H_{20}ClNO$: C, 72.72; H, 6.42; N, 4.46. Found: C, 72.682; H, 6.50; N, 4.41.

4.5.10. 2-((*m*-Toluidino)(phenyl)methyl)cyclohexanone (4n). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, J=7.2 Hz, 2H), 7.31 (t, J=7.6 Hz, 2H), 7.23 (t, J=7.2 Hz, 1H), 6.98 (t, J=8.0 Hz, 1H), 6.49 (d, J=8.0 Hz, 1H), 6.43 (s, 1H), 6.35 (d, J=8.0 Hz, 1H), 4.82 (d, J=4.0 Hz, 0.89H), 4.64 (d, J=7.2 Hz, 0.11H), 4.47 (br s, 1H), 2.76–2.82 (m, 1H), 2.42–2.46 (m, 1H), 2.28–2.36 (m, 1H), 2.22 (s, 3H), 2.03–2.09 (m, 2H), 1.91 (d, J=6.8 Hz, 1H); IR (KBr, ν, cm^{-1}): 3386.31, 1695.13, 1602.90, 1524.73, 802.64; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.06, 147.21, 141.42, 138.42, 128.67, 128.62, 128.18, 128.08, 127.21, 126.95, 126.84, 126.67, 118.39, 118.23, 114.71, 110.71, 110.22, 57.24, 56.91, 56.39, 42.14, 41.46, 30.98, 28.45, 27.63, 26.77, 24.58, 23.33, 21.32; Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.82; H, 7.99; N, 4.76.

4.5.11. 3-(2-Chlorophenyl)-1-phenyl-3-(phenylamino)-propan-1-one (7e). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.0 (d, J=8.4 Hz, 2H), 7.55–7.61 (m, 2H), 7.50 (t, J=7.6 Hz, 2H), 7.41–7.44 (m, 1H), 7.19–7.21 (m, 2H), 7.10 (t, J=8.0 Hz, 2H), 6.67 (t, J=7.6 Hz, 1H), 6.50 (d, J=8.4 Hz, 2H), 5.33 (t, J=4.0 Hz, 1H), 4.93 (br s, 1H), 3.65 (dd, J=4.0, 14.4 Hz, 1H), 3.20 (dd, J=8.8, 15.6 Hz, 1H); IR (KBr, ν, cm^{-1}): 3400.44, 1675.45, 1599.81, 1519.11, 873.80; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.27, 146.19, 139.23, 136.18, 133.29, 132.07, 129.55, 128.84, 128.45, 128.27, 128.10, 127.81, 127.17, 117.60, 113.32, 51.73, 43.50; Calcd for $C_{21}H_{18}ClNO$: C, 75.11; H, 5.40; N, 4.17. Found: C, 75.01; H, 5.50; N, 4.10.

4.5.12. 3-(2,3-Dimethoxyphenyl)-1-phenyl-3-(phenylamino)propan-1-one (7f). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, J=8.0 Hz, 2H), 7.58 (t, J=7.6 Hz, 1H), 7.47 (t, J=7.6 Hz, 2H), 7.09 (t, J=8.0 Hz, 2H), 7.00 (t, J=8.0 Hz, 2H), 6.85 (d, J=7.6 Hz, 1H), 6.65 (t, J=7.6 Hz, 1H), 6.55 (d, J=8.0 Hz, 2H), 5.20 (t, J=4.4 Hz, 1H), 4.70 (br s, 1H), 4.04 (s, 3H), 3.92 (s, 3H), 3.73 (dd, J=4.4, 8.4 Hz, 1H), 3.18 (dd, J=9.2, 14.8 Hz, 1H); IR (KBr, ν, cm^{-1}): 3400.68, 1683.59, 1600.33, 1523.52, 866.12; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.90, 156.19, 152.60, 152.24, 149.91, 129.68, 129.01, 128.84, 125.65, 124.03, 123.91, 120.76, 118.94, 118.25, 117.83, 114.81, 114.74, 62.11, 61.67, 55.78, 55.65; Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.40; H, 6.53; N, 3.80.

Acknowledgements

We are grateful to the foundation of the 'Natural Science Research Project of University in Jiangsu Province' (No. JH03-038) and the 'Post-doctor Foundation of Xuzhou Normal University' (No. 2003009).

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