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Ultrasound promoted efficient and green synthesis of β-amino carbonyl compounds in aqueous hydrotropic medium

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ABSTRACT

Ultrasound promoted synthesis of β-amino carbonyl compounds in aqueous hydrotropic medium at ambient temperature is reported. The remarkable features of the new procedure are shorter reaction time, excellent yields in aqueous medium, cleaner reaction profile and simple experimental and work-up procedure.

1. Introduction

β-Amino carbonyl compounds are valuable synthetic intermediates for pharmaceutical and natural products [1]. Owing to the importance as valuable building blocks for the preparation of 1,3-amino alcohols, β-amino acids as well as for the synthesis of various bioactive molecules such as the antibiotic nikkomycins and neopolyoxines [2–4], several methods have been reported in literature for the synthesis of β-amino carbonyl compounds. Over the past few years, various catalysts such as dodecylbenzene sulphonic acid, polystyrene-SO_3H, $NbCl_5$, $Re(PFO)_3$, $NaBAr_4$, SiO_2–$OAlCl_2$, etc have been exploited with various degrees of success [5]. However, most of the reported methods suffer from serious drawbacks such as use of large excess of catalyst, expensive reagents, long reaction time, low yields and ecologically unsafe organic solvents. Thus, an efficient, economical and environmentally benign protocol is highly desirable for the synthesis of β-amino carbonyl compounds.

Ultrasound irradiation in organic synthesis is considered as a clean and energy conserving protocol as compared to the traditional methods and has been established as a versatile technique in synthetic chemistry [6–9]. It has been well established that ultrasound, when compared with conventional methods enhance the rate of reactions and product yields in addition to sometimes changing the reaction pathway [10].

Organic reactions in aqueous media have attracted increasing interest because of environmental issues. As a reaction solvent, aqueous medium offers many practical and economic advantages including low cost, safe handling and environmental compatibility [11,12]. The term hydrotropes refers to a diverse class of water soluble surface active compounds that enhance the solubilities of organic reactants in the aqueous phase at higher concentration. They are capable of increasing the solubilities of organic compounds up to 200 times in water. Hydrotropes usually comprise of hydrophilic and hydrophobic moieties, with the latter being typically too small to induce micelle formation. Their solubilizing power was recognized as early as 1916 by Neuberg [13]. The potential use of hydrotropes in industry was stressed in 1946 by McKee [14]. Aqueous hydrotropic solutions represent the unique alternative reaction media for organic synthesis. We have recently established the compatibility of aqueous hydrotropic solution as safer solvent for microwave assisted reactions [15]. In continuation of our effort to tap the barely exploited potential of hydrotropes in organic synthesis, we report herein an efficient synthesis of β-amino carbonyl compounds in aqueous hydrotropic solution under ultrasonic irradiation.

2. Methods

^1H NMR and ^{13}C NMR spectra were recorded on a Brucker AC (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR) spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded on a Perkin–Elmer FTIR spectrometer. The samples were examined as KBr discs. Melting points were determined with a DBK melting point apparatus and are uncorrected. All the chemicals were obtained from local suppliers and were used without further purification. The hydrotropes

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were prepared following the literature procedure [16]. Sonication was performed in SPECTRALAB-UCB-30 ultrasonic bath with a frequency of 40 kHz and a nominal power of 100 W. The reaction flask was located in the maximum energy area in the water bath. The temperature of the water bath was maintained at 25–30 °C.

3. General procedure

A mixture of aldehyde (1 mmol), amine (1 mmol) and acetophenone (1 mmol)/cyclohexanone (1 mmol)/aliphatic ketone (1 mmol) in 5–10 mL of aq. 50% hydrotropic solution was stirred until a clear solution was formed. The mixture was irradiated under ultrasonic waves at ambient temperature. After completion of reaction, the crude product obtained by addition of cold water was filtered, washed with water and recystallised from ethanol to afford pure β-amino carbonyl compound.

4. Spectral data of representative compounds

3-Anilino-1,3-diphenylpropan-1-one (Table 2, Entry 4a): IR (KBr): υ 3385, 3025, 2917, 1669, 1600, 1509, 1291, 861 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.41–3.58 (m, 2H, CH_2), 5.00–5.04 (dd, 1H, CH), 6.57 (d, 2H, Ar–H), 6.60–6.71 (m, 1H, Ar–H), 7.01–7.10 (m, 2H, Ar–H), 7.22–7.64 (m, 1H, Ar–H), 7.43 (t, 2H, Ar–H), 7.53 (t, 4H, Ar–H), 7.55 (d, 1H, Ar–H), 7.90 (d, 2H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): 46.1, 55.0, 114.0, 118.0, 126.3, 127.3, 128.1, 128.6, 128.7, 129.0, 133.2; DEPT of CH_2 at 46.1.

3-(4-Chlorophenylamino)-3-(4-methoxyphenyl)-1-phenylpropane-1-one (Table 2, Entry 4e): IR (KBr): υ 3383, 3062, 2929, 1668, 1603, 1505, 1256, 808 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.33 (s, 3H, OCH_3), 3.49 (dd, 1H, CH_2), 3.78 (dd, 1H, CH_2), 4.90 (s, 1H, NH), 6.45 (t, Ar–H, 2H), 6.85 (d, Ar–H, 2H), 7-04 (t, Ar–H, 2H), 7.32 (t, Ar–H, 2H), 7.47 (t, Ar–H, 2H), 7.59 (s, Ar–H, 1H), 7.91 (d, Ar–H, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 46.0, 54.6, 55.1, 96.1, 114.2, 115.2, 127.3, 128.1, 128.6, 128.9, 133.3, 136.7, 145.2, 158.9, 197.9; DEPT of CH_2 at 46.0.

1-Anilino-1-phenylpentan-3-one (Table 2, Entry 4t): IR (KBr): υ 3427, 3350, 3042, 2914, 1687, 1652, 1560, 1227, 1144, 1028, 885 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.97–0.99 (m, 2H), 2.31–2.35 (m, 2H), 2.90–2.92 (m, 2H), 4.70 (brs, 1H, NH), 4.79–4.83 (m, 1H), 6.52–6.55 (m, 2H), 6.60–6.63 (m, 1H), 7.07–7.10 (m, 2H), 7.25–7.38 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): 7.5, 7.7, 12.3, 15.9, 26.2, 34.1, 36.7, 52.1, 53.7, 58.9, 59.5, 114.3, 115.2, 118.7, 126.2, 127.4, 127.8, 129.2, 129.8, 141.5, 146.2, 146.7, 213.5.

2-(α-Anilinobenzyl)cyclohexanone (Table 3, Entry 6a): IR (KBr): υ 3382, 3055, 3026, 2944, 1694, 1603, 1511, 1260, 869 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.63–1.94 (m, 6H, 3 × CH_2), 2.29–2.49 (m, 2H, CH_2), 2.76 (d, 1H, CH), 4.62 (d, 0.87 H, anti isomer), 4.79 (d, 0.13 H, syn isomer), 6.54 (d, 2H, Ar–H), 6.65 (d, 1H, Ar–H), 7.02 (s, 2H, Ar–H), 7.18 (d, 1H, Ar–H), 7.27 (s, 2H, Ar–H), 7.48 (s, 2H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): 23.7, 27.7, 31.2, 41.6, 57.3, 58.3, 113.8, 117.8, 127.2,127.2, 128.4, 129.0, 141.9, 147.5, 213.1.

2-[(4-Hydroxy-3-methoxyphenyl)(phenylamino)methyl)]cyclohexanone (Table 3, Entry 6d): IR (KBr): υ 3474, 3354, 3052, 2937, 1702, 1606, 1533, 1437, 1265, 1166, 1033, 865, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.66–1.73 (m, 2H), 1.85–1.92 (m, 4H), 2.34–2.44 (m, 2H), 2.68–2.70 (m, 1H), 3.85 (s, 3H), 4.51 (d, 0.96 H, anti isomer), 4.54 (d, 0.14H, syn isomer), 5.53 (s, 1H, NH), 6.52–6.54 (m, 2H), 6.51–6.65 (m, 2H), 6.81–6.84 (m, 3H), 6.90 (s, 1H), 7.03–7.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 23.5, 27.7, 31.0, 55.8, 57.5, 58.1, 109.1, 113.8, 114.0, 117.7, 120.4, 129.0, 133.4, 144.8, 146.7, 147.0, 212.7.

5. Results and discussion

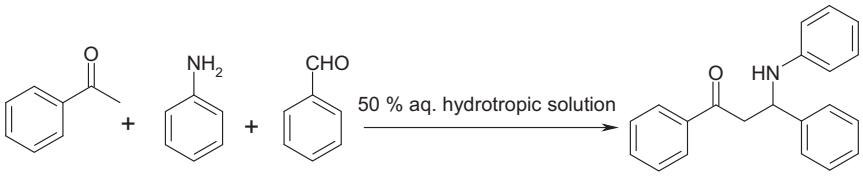
We initially focused our attention on the selection of appropriate hydrotrope for the present work. The different hydrotropes such as sodium benzene sulphonate (NaBS), sodium *p*-xylene sulphonate (NaXS) and sodium *p*-toluene sulphonate (NaPTS) were selected for this purpose. We opted to use 50% (*w*/*v*) aqueous solutions of selected hydrotropes as a solvent, since this concentration was suitable for the maximum solubilization of organic compounds. Our next task was to assess the efficiency of the aqueous hydrotropic solutions in the synthesis of β-amino carbonyl compounds. Accordingly, a model reaction between acetophenone, benzaldehyde and aniline in 50% of aq. NaBS, NaXS and NaPTS was carried at ambient temperature under ultrasound irradiation. On the completion of reaction as monitored by thin layer chromatography (TLC), the reaction mixture was diluted with cold water during which the product separated. The filtration of reaction mixture followed by recrystallization afforded the corresponding product of a high purity, which gave correct spectral analysis. The

Table 2
Ultrasound promoted synthesis of β-amino carbonyl compounds in 50% aq.NaPTS solution[a]

Entry	R_1	R_2	R_3	Time (h)	Yield[b] (%)	M.P. (°C)	Lit. M.P. [18,19] (°C)
4a	Ph	H	H	0.75	91	167–168	169–170
4b	Ph	H	3-NO_2	1.70	87	138–140	140–142
4c	Ph	H	4-CH_3	1.10	86	162–165	167–168
4d	Ph	H	4-COOH	2.00	90	187–188	190–192
4e	Ph	4-OCH_3	4-Cl	1.10	93	113–115	116–118
4f	Ph	4-Cl	4-Cl	1.70	95	117–119	118–119
4g	Ph	4-OCH_3	H	1.75	90	136–138	142–143
4h	Ph	4-Cl	4-CH_3	1.30	89	114–117	118–119
4i	Ph	3-NO_2	4-Cl	1.70	91	149–152	153–155
4j	Ph	4-Cl	4-COOH	2.25	92	156–158	159–160
4k	Ph	4-Cl	H	1.50	92	110–112	114–115
4l	4-ClC_6H_4	3-NO_2	4-Cl	2.00	92	138–140	141–143
4m	4-ClC_6H_4	H	H	2.50	88	116–119	119–120
4n	4-ClC_6H_4	H	4-CH_3	1.70	85	135–137	141–142
4o	4-Cl C_6H_4	H	4-Cl	2.25	83	126–127	130–132
4p	n-C_3H_7	H	H	2	81	90–92	87–88
4q	n-C_3H_7	H	4-CH_3	2	82	96–98	97–98
4r	n-C_3H_7	H	4-Cl	2	81	88–90	85–86
4s	n-C_3H_7	H	4-NO_2	3.5	70	104–106	101–103
4t	C_5H_9O	H	H	2	82	114–116	118–119

[a] All products were characterized by IR, ^1H NMR and ^{13}C NMR spectroscopy.
[b] Isolated yields after recrystallization.

Table 1
Screening of various hydrotropes for synthesis of β-amino carbonyl compound.



Entry	Hydrotrope	With US		Silent	
		Time (h)	Yield (%)[a]	Time (h)	Yield (%)[a]
1	Sodium *p*-toluene sulphonate (NaPTS)	0.75	90	5	75
2	Sodium *p*-xylene sulphonate (NaXS)	0.75	65	5	57
3	Sodium benzene sulphonate (NaBS)	0.75	48	5	43

[a] Isolated yield.

Table 3
Ultrasound promoted synthesis β-amino carbonyl compounds from cyclohexanone in 50% aq. NaPTS.[a]

Entry	R_2	R_3	Time (h)	Yield[b] (%)	M.P. (°C)	Lit. M.P. [20] (°C)	Anti/Syn [17]
6a	H	H	2.50	90	135–136	139–140	87:13
6b	H	4-Cl	2.70	91	138–140	137–138	65:35
6c	H	4-CH_3	1.50	86	114–116	116–117	87:13
6d	3-OCH_3, 4-OH	H	2.10	82	144–145	146–147	96:14
6e	H	2-Cl	2.30	82	132–133	134–135	77:23

[a] All products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy.
[b] Isolated yields after recrystallization.

results are summarized in Table 1. It is noteworthy that the same reactions in absence of sonication showed significant rate retardation resulting in considerably lower yields of product (Table 1). The plausible reason for the significant rate enhancement observed under sonication can be accounted on the basis of process of acoustic cavitation: the formation, growth and implosive collapse of bubbles in liquid. Cavitation and the subsequent sonochemistry primarily depend on the chemical properties of the fluid medium used. Aqueous hydrotropic solutions provide an interesting approach to control the chemical contents of bubble due to a combination of the low vapour pressure and increased viscosity of the aqueous hydrotropic solutions relative to pure water. Chemical control of the vapour content of the collapsing bubble allows for a stronger collapse that leads to greater compressional heating of reactants leading to reaction rate acceleration.

As excellent results were obtained for NaPTS, we employed this particular hydrotrope for subsequent studies. We have also studied the effect of concentration of aq. NaPTS. The efficiency of model reaction varied dramatically with respect to concentration of hydrotrope and was maximum when 50% of aq. NaPTS was used as a reaction medium (Fig. 1).

After the selection of appropriate hydrotrope and optimized conditions, a series of β-amino carbonyl compounds was synthesized by reacting various acetophenones with differently substituted benzaldehydes and anilines (Scheme 1). In all cases, the reactions proceeded smoothly affording the corresponding products in high yields (Table 2). The acetophenones and benzaldehydes with electron withdrawing substituents gave slightly higher yields than those bearing electron-donating substituents. Aromatic amines bearing variety of substituents were all suitable for this new methodology. In order to show the generality and scope of the new protocol, the reactions of different aliphatic and cyclic ketones were carried out under the same conditions. Several aliphatic ketones underwent reactions yielding corresponding β-amino carbonyl compounds in satisfactorily yield (Table 2, Entry 4p–4t). The reactions of cyclohexanone (Scheme 2) accomplished with anti regioselectivity which was confirmed by ^{1}H NMR spectroscopy (Table 3). The identity of all the compounds was ascertained on the basis of IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The physical and spectroscopic data are in harmony with the proposed structures.

Recycling of hydrotrope is important for large scale operations and industrial point of view. To check the possibility of the hydrotrope recycling, the model reaction was carried out in 50% aq. NaPTS solution under ultrasound irradiation at ambient temperature. After completion of the reaction, the product was separated out from the reaction mixture and the resultant aqueous hydrotropic solution was concentrated and reused for the subsequent reactions. As shown in Fig. 2, the aq. NaPTS solution could be reused for at least five times with modest change in yield of the product.

In order to illustrate the role of hydrotrope, the model reaction was carried out using pure water. The reaction did not give quantitative yield of corresponding product indicating that the use of NaPTS is crucial. NaPTS is short chain organic compound with a polar group that serves as agent to dissolve poorly water soluble substances or organic compounds in water, if added in high concentration. Cooperative aggregation is absent because the hydrophobic moieties are too small for hydrophobic interactions to overcome electrostatic repulsion. Lack of aggregation results in

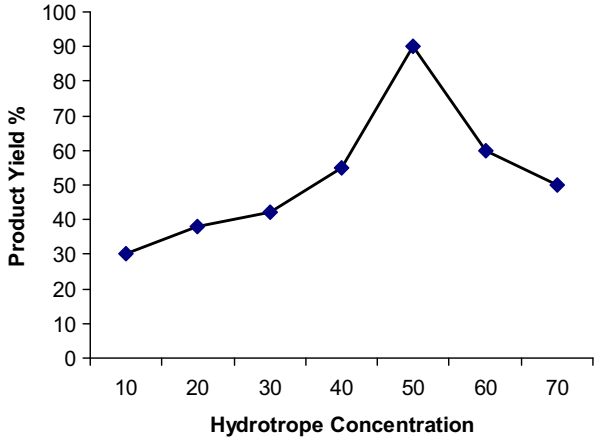
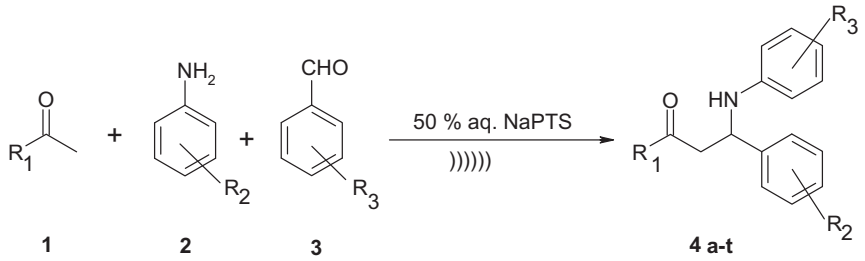
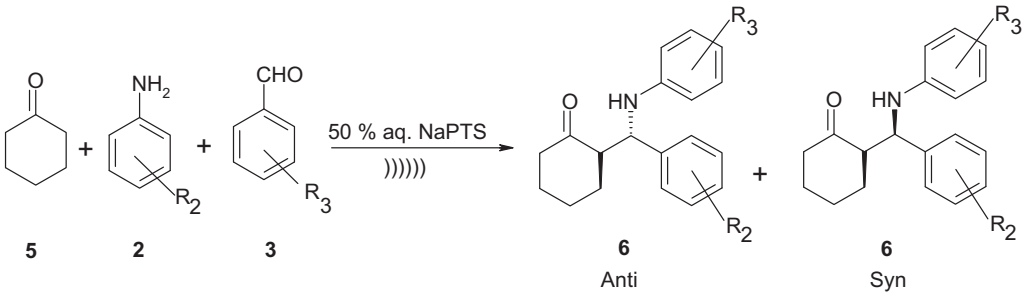


Fig. 1. Effect of NaPTS concentration on the yield of β-amino carbonyl compound.



Scheme 1. Synthesis of β-amino carbonyl compounds in 50% aq. NaPTS.



Scheme 2. Synthesis of β-amino carbonyl compounds from cyclohexanone in 50% aq. NaPTS.

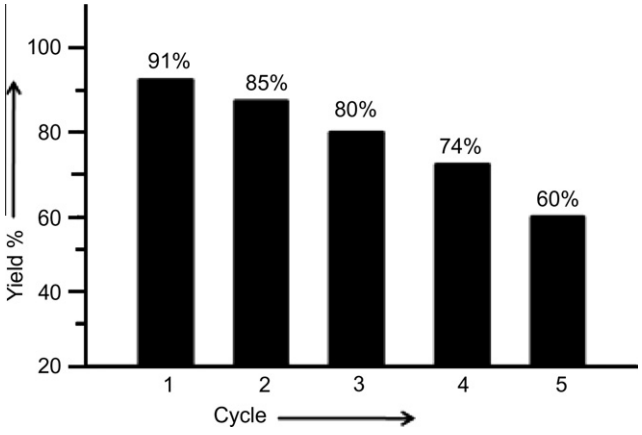


Fig. 2. Recyclability performance of aq. 50% NaPTS in β-amino carbonyl compound synthesis.

high availability of the hydrophobic binding sites, thereby accounting for the high solubilizing power.

6. Conclusion

In summary, a simple, efficient and green protocol for the synthesis of β-amino carbonyl compounds in aqueous hydrotropic solution under ultrasound irradiation is described. The significant aspects of methodology are efficiency, generality, high yield, short reaction time, low cost, greener reaction profile, ease of product isolation and the use of alternative source of energy.

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