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Synthesis of β-aminoketone by reaction of amine and activated chalcone in microwave irradiation

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A simple and efficient protocol has been developed for the aza-Michael addition of amines to a variety of activated olefins or chalcones under microwave irradiation. Under these conditions, there is a significant decrease in the reaction time while considerable increase in the yield and purity of the products can be obtained.

Keywords: β-Aminoketone, aza-Michael addition, microwave irradiation, solvent free, multicomponent reaction

β-Aminoketones are important intermediates for the synthesis of natural product, γ-aminoalcohol and auxiliaries[1]. The Michael reaction and its modified form such as aza-Michael, thio-Michael and carba-Michael reaction was one of the most exploited reactions in organic chemistry[2]. Michael addition reactions have attracted much attention as the most important carbon-carbon and carbon-heteroatom bond forming reactions. Some bioactive alkaloids, antibiotics and drugs were synthesized *via* the addition of electrophiles to α,β-unsaturated carbonyl compounds[3]. Although β-aminoketones can be prepared by the classical Mannich reaction, it has several drawbacks such as harsh reaction conditions and longer reaction time. Therefore, a variety of methods appeared in the literature for the synthesis of β-aminoketones[4].

In the past few years, alternative procedures have been developed using various Lewis acid-induced reactions. Lewis acids such as $AlCl_3$, $TiCl_4$, $SnCl_4$, $CeCl_3.7H_2O$-NaI, $LiClO_4$ and system of clay were used. Interestingly, microwave-assisted chemistry offers new possibilities for the development of any chemical reaction that is thermally possible. It typically produces faster reaction and higher yields, and minimizes the formation of by-products. In addition, there exists the possibility that the reaction that fails under conventional heating could give the desired products under microwave irradiation[5]. Some recently reported examples have included one pot reaction[6] and particular organic reactions such as Suzuki coupling[7], Claisen rearrangement, Mitsunobu reaction[8] and Michael addition[9].

Hence, the Michael reaction is one of the most versatile reactions in organic synthesis and this has been further reinforced through the use of microwaves[10]. One of the most useful applications of this process of 1,4-addition is the synthesis of β-amino ketones and their derivatives which can be carried out under microwave irradiation catalyzed by Et_3N.

Results and Discussion

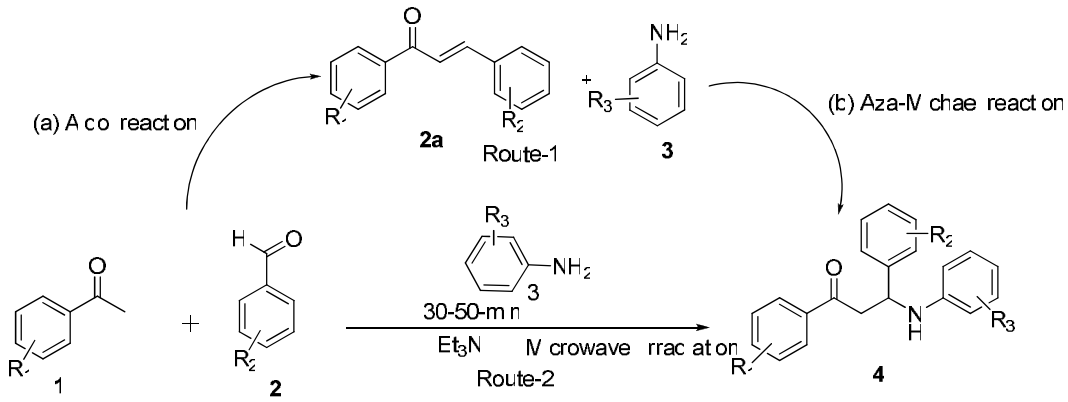
Several research groups have reported many different catalysts for this aza-Michael addition and Aldol reaction. But, most of these catalysts are transition metal salts or other metal salts like $InCl_3$, $CeCl_3.7H_2O$-NaI, Yb(OTf), $Bi(NO_3)_3$, Cu-salts, $LiClO_4$, SmI_2, $FeCl_3.7H_2O$, $CrCl_3.6H_2O$, and $SnCl_4$ (Ref 11). However, both of these reactions require cumbersome work-up and purification steps. Most of these procedures take longer reaction time and produce a lot of waste product.

Route-2: Three component reaction catalyzed by Et_3N under microwave irradiation.

Several structurally varied amines react with a variety of β-unsaturated ketones or chalcones by this procedure to produce the corresponding β-aminoketone derivatives in excellent yields (**Scheme I**). The results are summarized in **Table I**.

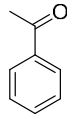
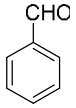
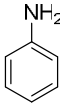
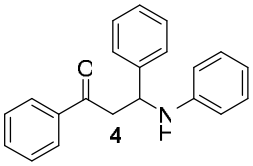
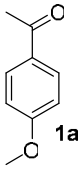
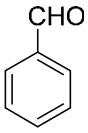
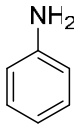
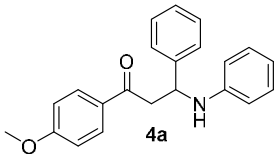
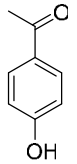
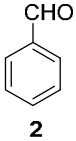
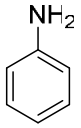
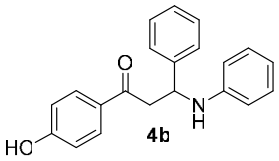
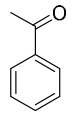
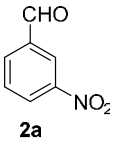
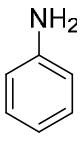
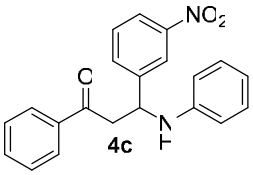
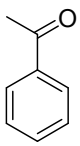
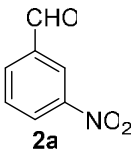
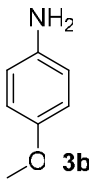
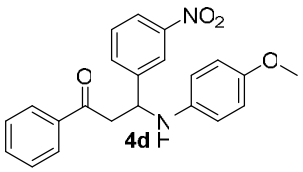
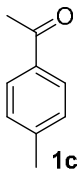
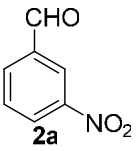
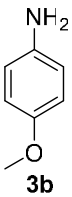
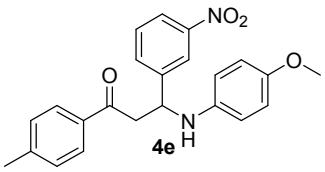
Based on this promising result, we subsequently studied the effect of various catalyst and different time durations to optimize the reaction conditions (**Table II**). A preliminary reaction of aldehyde with amine in the presence of Na_2CO_3 as a catalyst gave trace of product (Entry 1). However, the use of $SnCl_4$ furnished a slight increase in the yield of product to 30% (**Table II**, entry **3**). Surprisingly, when Et_3N was used as a catalyst at 30 min, the yield of product was improved significantly to 90% (**Table II**, Entry **5**). Optimum conditions were observed when the reaction was performed for 30 min in the presence of Et_3N as a catalyst affording a product yield of 90% (**Table II**, Entry **5**).

The experimental procedure employed in the present work is very simple. A mixture of aldehyde,



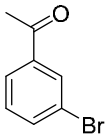
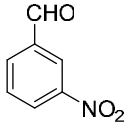
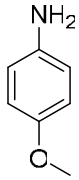
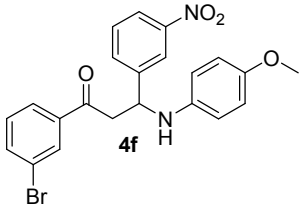
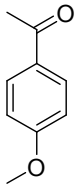
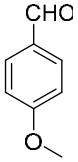
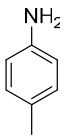
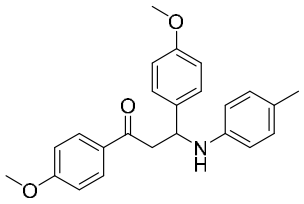
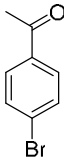
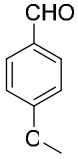
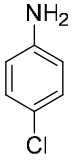
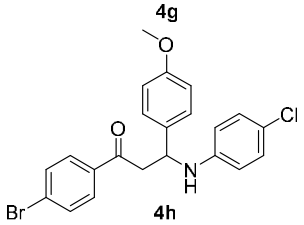
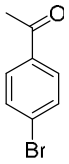
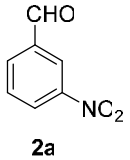
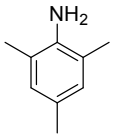
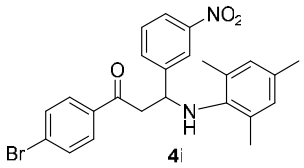
Scheme I — Route-1: (a) Aldol type reaction and (b) Aza-Michael reaction

Table I — Synthesis of β-aminoketone derivatives

Entry	Acetophenone	Aldehyde	Amine	Product	Yield (%)
1	 1	 2	 3	 4	90
2	 1a	 2	 3	 4a	92
3	 1b	 2	 3	 4b	89
4	 1	 2a	 3	 4c	93
5	 1	 2a	 3b	 4d	87
6	 1c	 2a	 3b	 4e	85

Contd —

Table I — Synthesis of β-aminoketone derivatives — *Contd*

Entry	Acetophenone	Aldehyde	Amine	Product	Yield (%)
7	 **1d**	 **2a**	 **3b**	 **4f**	90
8	 **1a**	 **2b**	 **3c**	 **4g**	93
9	 **1e**	 **2b**	 **3c**	 **4h**	78
10	 **1e**	 **2a**	 **3d**	 **4i**	90

Reaction conditions: Aldehyde (1 mmol), Ketone (1 mmol), Amine (1.8 mmol) and Et_3N (0.4 mmol) under microwave irradiation

Table II — Optimization conditions for synthesis of β-aminoketone

Entry	Catalyst	Time (min)	Yield (%)
1	Na_2CO_3	60	Trace
2	K_2CO_3	60	Trace
3	$SnCl_4$	120	30
4	$ZrCl_4$	60	75
5	Et_3N	30	90

acetophenone, amine and Et_3N was stirred homogeneously. The mixture was irradiated for 30 min using microwave reactor. The product was isolated by column chromatography of the reaction mixture over silica gel. In general, the reactions were reasonably fast and clean. No side product was detected in TLC.

Experimental Section

General procedure for the synthesis of 4a-i

Benzaldehyde (1 mmol), acetophenone (1 mmol), aniline (1.8 mmol) and Et_3N (0.4 mmol) were taken in a reaction vessel and homogenized. The mixture was irradiated for 30-50 min using microwave reactor (Samsung Microwave 450 W). The progress of the reaction was monitored using thin-layer chromatography (TLC) and the mixture cooled to RT after completion of the reaction. Then work-up of the reaction with 10 mL of EtOAc was carried out as reported earlier. After purification by column chromatography, the solvent was removed under reduced pressure and the residue was analyzed by NMR, IR and mass spectroscopy and the yield obtained was up to 95%.

Selected spectroscopic data

1,3-Diphenyl-3-(phenylamino)propan-1-one, 4: Yield 90% (colorless solid); m.p. 125-28°C: IR (KBr): 3,470, 3,059, 1,750, 1,542 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.40-3.47 (m, 2H), 3.55 (br, 1H), 4.90 (t, J = 6.1 Hz, 1H), 6.85 (d, J = 8.8Hz, 2H), 7.14-7.38 (m, 4H), 7.44-7.50 (m, 3H), 7.62-7.78(m, 3H) and 7.80(d, J = 8.6Hz, 2H); ^{13}C NMR: δ 57.4, 113.5,

113.8, 114.2, 114.6, 126.7, 126.8, 126.9, 128.2, 128.5, 128.8, 129.0, 129.2, 129.6, 129.8, 135.0, 140.6, 147.6, 199.8; FAB-MS: Calcd for $C_{22}H_{21}N_2O_2$: *m/z* 301.18. Found (M+1): *m/z* 302.22.

1-(4-Methoxyphenyl)-3-phenyl-3- (phenylamino)-propan-1-one, 4a: Yield 92% (colorless solid); m.p. 135-37°C; IR (KBr): 3,501, 3,050, 1,745, 1,512 cm^{-1}; ^1H NMR (500 MHz,$CDCl_3$): δ 3.42-3.48 (m, 2H), 3.59 (br, 1H), 3.80(s, 3H), 4.89 (t, *J* = 6.1 Hz, 1H), 6.87 (d, *J* = 8.8Hz, 2H), 7.12-7.36(m, 5H), 7.62-7.78 (m, 5H) and 7.80(d, *J* = 8.6Hz, 2H); ^{13}C NMR: δ 55.5, 57.4, 113.5, 113.8, 114.2, 114.6, 126.7, 126.8, 126.9, 128.2, 128.5, 128.8, 129.0, 129.2, 129.6, 129.8, 135.0, 140.6, 147.6, 199.8; FAB-MS: Calcd for $C_{22}H_{21}N_2O_2$: *m/z* 331.14. Found (M+1): *m/z* 332.20.

1-(4-Bromoyphenyl)-3-(4-chlorophenyl-3-(4-methoxyphenylamino)propan-1-one, 4f: Yield 78% (colorless solid); m.p. 119-22°C; IR (KBr): 3,530, 3,020, 1,755, 1,552 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.44-3.47 (m, 2H), 3.57 (br, 1H), 3.82 (s, 3H), 4.90 (t, *J* = 6.1 Hz, 1H), 6.88 (d, *J* = 8.8Hz, 2H), 7.13-7.37 (m, 3H), 7.40-7.45 (m, 2H), 7.63-7.79 (m, 3H) and 7.81 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR: δ 55.6, 57.4, 113.6, 113.9, 114.4, 114.5, 126.8, 126.9, 126.9, 128.4, 128.6, 128.8, 129.2, 129.4, 129.6, 129.8, 135.2, 140.7, 147.5, 199.9; FAB-MS: Calcd for $C_{22}H_{21}N_2O_2$: *m/z* 444.70. Found (M+1): *m/z* 445.40.

1,3-Bis-(4-methoxyphenyl)-3-*p*-tolylamino-propan-1-one, 4g: Yield 93%; m.p. 120-23°C; IR (KBr): 3,485, 3,050, 1,753, 1,532 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.28 (s, 3H), 3.46-3.56 (m, 2H), 3.50 (br, 1H), 3.73(s, 3H), 3.82 (s, 3H), 4.79 (t, *J* = 6.0Hz, 1H), 6.74 (d, *J* = 8.5Hz, 2H), 6.86 (d, *J* = 8.8Hz, 2H), 7.02 (d, *J* = 7.6Hz, 2H), 7.20-7.24(m, 4H), and 7.81(d, *J* = 8.9 Hz, 2H); ^{13}C NMR: δ 25.3, 55.4, 57.4, 74.5, 113.6, 113.9, 114.4, 114.6, 126.5, 126.9, 127.0, 128.3, 128.6, 128.9, 129.2, 129.2, 129.7, 129.7, 135.2, 140.8, 147.6, 158.8, 199.9; FAB-MS: Calcd for $C_{22}H_{21}N_2O_2$: *m/z* 375.14. Found (M+1): *m/z* 376.40.

Conclusion

A new, efficient and environmentally friendly method for the aza-Michael addition of a variety of amines to α,β-unsaturated ketones under microwave irradiation without using any solvent has been reported. The advantage of microwave radiation offers the addition product faster with better yields when compared with conventional methods.

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