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RAPID AND CONVENIENT MICROWAVE-ASSISTED SYNTHESIS OF AZA MICHAEL TYPE ADDITION OF SUBSTITUTED ANILINE TO α, β - UNSATURATED ESTER

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Abstract: The rapid, simple microwave-assisted synthesis of N-aryl functionalized β-amino esters using aza Michael addition reaction is presented. Reactions are performed neat at 200°C for 20 minutes under microwave irradiation and are catalyzed by acetic acid.

Key words: Aza-Michael addition, aniline, α, β-Unsaturated ester, Microwave etc.

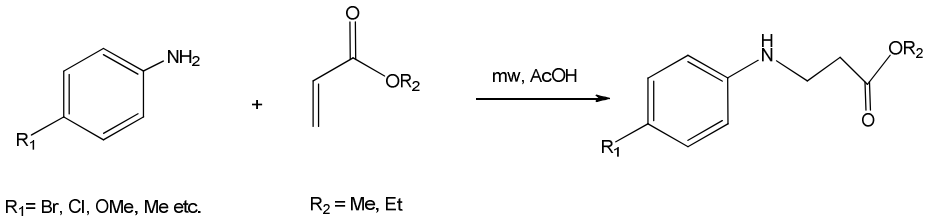
Introduction

The aza-Michael reaction is an important reaction in organic chemistry, especially for the synthesis of C-N heterocycles [i-v] containing the β-aminocarbonyl functionality, which not only constitutes a component of biologically active natural products but also serves as an essential intermediate in the synthesis of β-amino ketones, β-amino acids, β-lactam antibiotics and amides which find applications in the synthesis of natural products, chiral auxiliaries, bioactive compounds, pharmaceuticals, fine chemicals, etc.[vi-xii] Generally, aza-Michael additions have been catalyzed by strong bases and acids, and some side reactions occurred. Therefore, chemical researchers have paid more attentions to the development of more mild catalytic systems for the aza-conjugate reaction. With the goal of avoiding the typical disadvantages resulting from the presence of such catalysts, a large number of alternative procedures have been developed in the past few years.[xiii-xix] Microwave-assisted chemistry offers new possibilities for the development of any chemical reaction that is thermally possible.[xx-xxi] This technique can reduce the time of chemical reaction from hours to minutes. Conventional methods of synthetic reactions need longer heating time, elaborate and tedious apparatus set up which result in higher cost and environmental pollution. The reaction rate of microwave induced organic reaction increases 10-1000 times and the yield of the product increases by 10-30 % compared to that by the conventional methods. In this paper we report the synthesis of a variety of β-aminoketones of potential biological interest under environmentally friendly conditions, using microwave-assisted aza Michael-addition.

Result and discussion:

The rapid, simple microwave-assisted synthesis of N-aryl functionalized β-amino esters using aza Michael addition reaction is presented. The experimental procedure is very simple. Mixture of aromatic amine and α, β-unsaturated ester was heated at 200°C for 20 minutes under microwave irradiation and was catalyzed by acetic acid. The product was isolated by short column chromatography of the reaction mixture over silica gel. Several structurally

varied aromatic amines react with a variety of α, β-unsaturated ester compounds by this procedure to produce the corresponding β-amino derivatives in excellent yields. The reaction sequence leading to the formation of desired heterocycle is outlined in Scheme 1.



Scheme-1

Conclusion: In summary, rapid and convenient methodology for the aza Michael addition of aromatic amines to α, β- unsaturated esters has been reported. The use of microwave irradiation afforded the addition products in a low reaction time and good yield, in comparison with traditional methods.

Experimental Section:

The melting points were taken in open glass capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer IR^{TM} spectrometer model BX-II in KBr pellets, whereas ^{1}H NMR spectra were recorded on Bruker 300-MHz instrument with TMS as internal standard. ^{13}C NMR were recorded on the same instrument at 75.47 MHz in chloroform-d and DMSO-d_6. All chemical shifts are reported in δ downfield from tetramethylsilane. Microwave irradiation was carried out in a domestic microwave at 200 W.

General procedure for aza-Michael reaction of aromatic amines with α, β-unsaturated compounds (Scheme-1):

A mixture of substituted p-aniline (1.5 mmol), α, β-unsaturated compound (1.5 mmol) and acetic acid (1.5 mmol), was irradiated in a microwave in an open vessel for 20 minutes. The reaction mixture showed a major spot on thin-layer chromatography (TLC) in (hexane/ethyl acetate 3:1)**.** The products were purified by column chromatography and recrystallized from ethanol.

Methyl 3-anilinopropionate: MP: 54-56°C; IR(neat): 3380(NH), 1735(C=O), 1500(Ar), 1430(C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.28(t, *J* = 7.5 Hz, 2H), 6.77(t, *J* = 7.3 Hz, 1H), 6.52(d, *J* = 7.7 Hz, 2H), 4.02(br, s,1H), 3.70(s, 3H), 3.58(t, *J* = 6.4 Hz, 2H), 2.64(t, *J* = 6.4 Hz, 2H); ^{13}CNMR ($CDCl_3$): 173.0, 147.5, 129.2, 120.1, 114.3, 51.9, 37.7, 35.4; Anal. Data Calcd for $C_{10}H_{13}NO_2$(179.22): C 67.02, H 7.31, N 7.82; Found C 67.32, H 7.33, N 7.93.

Methyl 3-(4-Methoxyanilino)propionate: MP: 58-60°C; IR(Neat): 3382(NH), 1732(C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.77(d, *J* = 8.8 Hz, 2H), 6.65(d, *J* = 8.8 Hz, 2H), 3.90(br, s, 1H), 3.74(s, 3H), 3.69(s, 3H), 3.50(t, *J* = 6.3 Hz, 2H), 2.61(t, *J* = 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 172.9, 151.4, 140.6, 113.9, 113.6, 55.7, 51.7, 37.5, 35.7; Anal. Data Calcd. For $C_{11}H_{15}NO_3$ (209.24): C 63.14, H 7.23, N 6.69; Found C 63.20, H 7.53, N 6.63.

Methyl 3-(4-Methylanilino)propionate: MP: 54-56°C; IR: 3284(NH), 1732(C=O), 1546(Ar), 1287(C-N) cm^{-1}; ^{1}H-NMR($CDCl_3$): δ 6.99(d, *J* = 8.2 Hz, 2H), 6.55(d, *J* = 8.2 Hz, 2H), 3.91(br, s, 1H), 3.69(s, 3H), 3.43(t, *J* = 6.0 Hz, 2H), 2.62(t, *J* = 6.0 Hz, 2H), 2.24(s, 3H); ^{13}C-NMR: δ 172.7, 144.2, 129.8, 129.6, 113.2, 51.7, 37.9, 35.7, 21.7. Anal. Calcd for $C_{11}H_{15}NO_2$(193.24): C 68.37, H 7.82, N 7.25; Found: C 68.44, H 7.83, N 7.21.

Methyl 3-(4-nitroanilino)propionate: MP: 130-132°C; IR(Neat): 3235(NH), 1731(C=O),1610, 1566(Ar), 1250(C-N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.05(d, *J* = 8.8 Hz, 2H), 6.72(d, *J* = 8.8 Hz, 2H), 4.0(br, s,1H), 3.69(s, 3H), 3.58(t, *J* = 6.6 Hz, 2H), 2.61(t, *J* = 6.6 Hz, 2H); ^{13}CNMR ($CDCl_3$): 173.51, 154.5, 138.2, 127.5, 110.3, 50.9, 37.7, 35.2; Anal. Data Calcd. For $C_{10}H_{12}N_2O_4$ (224.21): C 53.57, H 5.39, N 12.49; Found C 53.02, H 5.33, N 12.23.

Methyl 3-(4-chloroanilino)propionate: MP: 57-59°C; IR(Neat): 3400(NH), 1732(C=O), 1610 (C=O), 1506(Ar), 1432(C-N) cm^{-1}; ^1H NMR($CDCl_3$): δ7.2(d, *J* = 8.8 Hz, 2H), 6.55(d, *J* = 8.8 Hz), 4.0(br, s, 1H), 3.69(s, 3H), 3.41(t, *J* = 7.2 Hz, 2H), 2.61(t, *J* = 7.2 Hz, 2H); ^{13}CNMR ($CDCl_3$): δ 173.0,145.5, 129.2, 126.1, 114.3, 51.9, 37.7, 35.2; Anal. Data Calcd. For $C_{10}H_{12}ClNO_2$(213.66): C 56.21, H 5.66, N 6.56; Found C 56.32, H 5.73, N 6.63.

Methyl 3-(4-bromoanilino)propionate: MP: 65-66°C; IR(Neat) 3338(NH), 1735(C=O), 1570(Ar), 1413(C-N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.25(d, *J* = 8.8 Hz, 2H), 6.55(d, *J* = 8.8 Hz, 2H), 4.0(br, s, 1H), 3.69(s, 3H), 3.51(t, *J* = 7.2 Hz, 2H), 2.61(t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): 173.2, 146.5, 132.5, 116.1, 114.3, 51.9, 37.7, 35.2; Anal. Data Calcd. For $C_{10}H_{12}BrNO_2$(258.11): C 46.53, H 4.69, N 5.43; Found C 46.32, H 4.73, N 5.63.

Ethyl 3-anilinopropionate: MP: 57-59°C; IR(neat): 3355(NH), 1740(C=O), 1571(Ar), 1386 (C-N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.23(m, *J* = 7.5 Hz, 2H), 6.77(m, *J* = 7.2 Hz, 1H), 6.58 (d, *J*, = 7.6 Hz, 2H), 4.13(q, *J,* = 7.15Hz, 2H), 4.0(br, s, 1H), 3.56 (t, *J* = 6.3Hz, 2H), 2.62(t, *J* = 6.3Hz, 2H), 1.29(t, *J* = 7.15Hz, 3H); ^{13}CNMR ($CDCl_3$): 171.0, 147.5, 129.5, 120.1, 114.3 , 61.9, 37.7, 35.2, 14.1; Anal. Data Calcd. For $C_{11}H_{15}NO_2$(193.11): C 68.37, H 7.82, N 7.25; Found C 68.20, H 7.83, N 7.23.

Ethyl 3-(4-methoxyanilino)propionate: MP: 60-62°C; IR(neat): 3359(NH), 1624(C=O), 1513 (Ar), 1228(C-N) cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 6.82(d, *J* = 7.1 Hz, 2 H), 6.75(d, *J* = 7.1 Hz, 2 H), 4.0(br, s, 1 H), 4.2(q, *J* = 7.2 Hz, 2 H), 3.54 (s, 3 H), 3.51(t, *J* = 6.15 Hz, 2 H), 2.60(t, *J* = 6.15 Hz, 2 H), 1.27(t, *J* = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 171.0, 151.4, 139.6, 115.9, 113.6, 61.7, 55.7, 37.5, 35.7, 14.1; Anal. Data Calcd. For $C_{12}H_{17}NO_3$(223.27): C 64.55, H 7.67, N 6.27; Found C 64.20, H 7.53, N 6.23.

Ethyl 3-(4-nitroanilino)propionate: MP: 72-75°C; IR (neat): 3392(NH), 1723(C=O), 1503(Ar), 1260(C-N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.0(d, *J* = 9.0 Hz, 2 H), 6.5(d, *J* = 9.0 Hz, 2 H), 4.2 (br, s, 1 H), 4.15(q, *J* = 7.15 Hz, 2 H), 3.52(t, *J* = 6.2 Hz, 2 H), 2.62(t, *J* = 6.2 Hz, 2 H), 1.25(t, *J* = 7.15 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 171.0, 153.4, 136.5, 127.6, 110.9, 113.6, 61.7, 37.5, 35.7, 14.1; Anal. Data Calcd. For $C_{11}H_{14}N_2O_4$(238.24): C 55.46, H 5.92 and N 11.76; Found C 55.40, H 5.72 and N 11.86.

Ethyl 3-(4-chloroanilino)propionate: MP: 123-125°C; IR(neat): 3360(NH), 1560(C=O), 1520(Ar), 1228(C-N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.5(d, *J* = 8.0 Hz, 2 H), 6.54(d, *J* = 8.0 Hz, 2 H), 4.2(br, s, 1H), 4.15(q, *J* = 7.2 Hz, 2 H), 3.56(t, *J* = 6.2 Hz, 2 H), 2.62(t, *J* = 6.2 Hz, 2 H), 1.25(t, *J* = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 171.0, 145.4, 126.5, 129.6, 114.9, 61.7, 37.5, 35.7, 14.1; Anal. Data Calcd. For $C_{11}H_{14}ClNO_2$(227.69): C 58.03, H 6.20, N 6.15: Found C 58.40, H 6.72 and N 6.56.

Ethyl 3-(4-bromoanilino)propionate: MP: 70-74°C; IR(neat): 3375(NH), 1674(C=O), 1526 (Ar), 1250(C-N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.15(d, *J* = 7.8 Hz, 2 H), 6.54(d, *J* = 7.8 Hz, 2 H), 4.0(br, s, 1H), 4.15(q, *J* = 7.2 Hz, 2 H), 3.56(t, *J* = 6.2 Hz, 2 H), 2.62(t, *J* = 6.2 Hz, 2 H), 1.29(t, *J* = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 171.0, 146.4, 134.5, 115.6, 114.5, 61.3, 37.8,

35.7, 14.1;Anal. Data Calcd. For $C_{11}H_{14}BrNO_2$(272.14): C 48.55, H 5.19 and N 5.15: Found C 48.40, H 5.05 and N 5.10.

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