ULTRASONIC-PROMOTED SYNTHESIS OF FUNCTIONALIZED TETRAHYDROPYRIDINES USING TRIFLATE

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Abstract

An easy, and effective multicomponent synthesis of a highly substituted tetrahydropyridines has been achieved by reaction of different substituted aromatic aldehydes, β-ketoester (methyl acetoacetate), and p-methoxyaniline, in the presence of ytterbium (III) trifluoromethanesulfonate, $Yb(OTf)_3$, as an efficient catalyst under ultrasound irradiation. This method has supplied a different approach for the synthesis of highly substituted tetrahydropyridines in moderate to good yields.

Key words: Heterocycles, tetrahydropyridine, triflate, ultrasound, β-ketoester

TRİFLAT KULLANARAK İŞLEVSELLEŞTİRİLMİŞ TETRAHİDROPİRİDİNLERİN ULTRASONİK DESTEKLİ SENTEZİ

Özet

Yüksek derecede sübstitüe edilmiş tetrahidropiridinler, iterbiyum(III)triflorometansülfonat $Yb(OTf)_3$ katalizörlüğünde, farklı sübstitüe aromatik aldehitler, β-ketoester (metil asetoasetat) ve p-metoksianilinin kolay ve etkili reaksiyonuyla ultrason ışıması altında elde edilmiştir. Bu yöntem yüksek derecede sübstitüe edilmiş tetrahidropiridinlerin iyi verimlerle sentezi için farklı bir yaklaşım sağlamıştır.

Anahtar kelimeler: Heterosiklikler, tetrahidropiridin, triflat, ultrason, β-ketoester

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1. INTRODUCTION

Substituted tetrahydropyridines are significant heterocycles, which form the core part of various natural products and synthetic drugs [1-2]. Numerous compounds carrying this heterocyclic part have showed varied and attractive biological activities, such as antibacterical, antimalarial, anticonvulsant, anti-inflammatory, antihistamic properties, as well as anti-hypertensive activities [3-8].

Multicomponent reactions (MCRs) are placed one of the most significant reaction in the synthetic organic chemistry. They have been known as one of the key means to form highly efficient, atom economic and environmental friendliness. The synthesis of tetrahydropyridine compounds using MCRs is a domain of classical carbonyl condensation chemistry [4-8].

In the recent times, one-pot synthesis of substituted tetrahydropyridines have been reported in the presence of molecular I_2 [2, 9, 10], $LaCl_3$ [11], sulfamic acid [12], p-TsOH.H_2O [13], cerium ammonium nitrate (CAN) [14], oxalic acid dihydrate [15], tetrabutylammonium tribromide (TBATB) [16], $Bi(OTf)_3$ [17], $Ce(OTf)_4$ [3], $B(C_6F_5)_3$ [18], PEG-embedded KBr_3 [19] and $ZrCl_4$ [20] as efficient catalysts. However, the above deliberated processes have some drawbacks, such as the use of pricey and excessive amount of catalysts or long reaction times. Therefore, efficacious new approaches for the preparation of tetrahydropyridines are gaining great significance. Nowadays, triflates M(OTf)x have been employed as efficient catalysts for a wide variety of synthetic organic reactions [3, 17, 21]. During the last two decades, much attention has given to improving rare earth metal triflates particularly $Yb(OTf)_3$ catalyzed organic reactions. The features of these are low toxicity, moisture stability, commercial availability and recyclability [22, 23].

Ultrasonic irradiation is widely used in synthetic organic chemistry as it is associated with a series of key characteristics such as safety, energy savings, waste prevention and the use of ambient conditions. Therefore the usage of ultrasound to accelerate classical organic reactions has been significant. This procedure can be used to various organic reactions to perform better yields, under mild reaction circumstances and shorter reaction times [23]. The particular and interesting characteristics of ultrasound waves in chemical reactions arise from the physical phenomenon known as acoustic cavitation. Cavitation is the production, growth, and collapse of microbubbles in a liquid when a large negative pressure is applied to it. The formation of

cavitation bubbles is initiated during the rarefaction cycle. This phenomenon supplies the main mechanism for sonochemical effects. For the period of cavitation, bubble collapse or implosion releases enormous amounts of energy and produces strong local heating, high pressures, and very short lifetimes. Ultrasonic irradiation decreases reaction times, gets better yields and reduces side product construction by giving the activation energy contrast to classical conventional heating that gives thermal energy to the reaction [24].

Herein we report on the preparation of functionalized tetrahydropyridines under conventional conditions and ultrasonic conditions in the presence of $Yb(OTf)_3$ as a catalyst.

2. EXPERIMENTAL

^1H NMR and ^{13}C NMR spectrums were recorded on "Inova 500" and "Bruker 400" spectrometers, in the presence of TMS as an internal standard in $CDCl_3$ or DMSO solvents. FT-IR spectra were recorded on a "Philips PU 9714 ATR spectrophotometer", and using the "Perkin-Elmer Spectrum One" program. Mass Spectrums were obtained using a "Finnigan Trace DSQ" instrument. GC/MS spectra were recorded on an Agilent 6890N GC system-5973 IMSO instrument. TLC was carried out on silica gel 60 F254 precoated plates. The ultrasonication was performed in an "Intersonik ultrasound cleaner" (model: MIN4) with a frequency of 25 kHz, an US output power of 100 W and, a heating of 200 W. The temperature of the water bath was controlled by an automatic constant temperature cooling circulatory system. All of the chemical reagents were commercially available and were used without any purification.

2.1 General experimental procedures for the preparation of functionalized piperidines

Method A:

A mixture of p-anisidine (aromatic primer amine) **1** (2 mmol), methyl acetoacetate (β-ketoester) **2** (1 mmol), and 5 % mol $Yb(OTf)_3$ in 5 mL MeOH was stirred for 30 min at room temperature. Afterward the aldehyde **3** (2 mmol) was added to the reaction mixture and stirred for the time indicated in Table 2. The progress of the reaction was checked by thin-layer chromatography (TLC) at regular intervals. After the completion of the reaction, the raw product was filtered off and washed with water and then crystallized from EtOH to give pure product **4a-4j**.

Method B:

A mixture of p-anisidine (aromatic primer amine) **1** (2 mmol), methyl acetoacetate (β-ketoester) **2** (1 mmol), and 5 % mol $Yb(OTf)_3$ in 5 mL MeOH was sonicated at 60 ºC in an ultrasound cleaner for 30 min. Afterward the aldehyde **3** (2 mmol) was added and the reaction mixture was sonicated for the time indicated in Table 2. The progress of the reaction was checked by thin-layer chromatography (TLC) at regular intervals. After the completion of the reaction, the mixture was cooled to room temperature, the raw product was filtered off and washed with water and then crystallized from EtOH to give pure product **4a-4j**.

2.1.1. Methyl 2,6-bis(phenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-carboxylate (4a)

White solid, mp. 223-225 º C. FTIR (ATR): υ= 3258, 3058, 2949, 1648, 1589, 1509, 1176, 808 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.51-2.65 (dd, J_1= 12.50 Hz, J_2= 2.55 Hz, 1H), 2.72-2.86 (dd, J_1= 15.15 Hz, J_2= 2.50 Hz, 1H), 3.67 (s, 3H), 3.72 (s, 3H), 3.90 (s, 3H), 5.05 (br s, 1H), 6.14-6.19 (d, J= 8.50 Hz, 2H), 6.32 (s,1H), 6.41-6.46 (d, J= 8.50 Hz, 3H), 6.59-6.67 (dd, J_1= 8.80, J_2= 9.01 Hz, 4H), 7.13-7.32 (m, 9H), 10.02 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 33.74, 50.56, 54.72, 55.66, 55.66, 55.75, 55.94, 56.08, 58.21, 96.92, 113.53, 114.12, 114.33, 114.82, 126.03, 126.46, 126.72, 127.68, 127.99, 128.19, 128.19, 128.60, 128.81, 130.60, 141.53, 143.24, 144.23, 150.82, 157.09, 157.79, 168.67 ppm. MS m/z: 520, Anal. Calcd. for $C_{33}H_{32}N_2O_4$: C, 76.13; H, 6.20; N, 5.38. Found: C, 75.93; H, 5.98; N, 5.12.

2.1.2. Methyl 2,6-bis(4-methylphenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine- carboxylate (4b)

White solid, mp. 225-226 º C. FTIR (ATR): υ= 3245, 2948, 2914, 1655, 1595, 1509, 1176, 808 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.20 (s, 3H), 2.35 (s, 3H), 2.59-2.68 (dd, J_1= 12.60 Hz, J_2= 2.50 Hz, 1H), 2.73-2.82 (dd, J_1= 15.20 Hz, J_2= 5.70 Hz, 1H), 3.65 (s, 3H), 3.75 (s, 3H), 3.90 (s, 3H), 5.01 (br s, 1H), 6.14-6.24 (d, J= 8.70 Hz, 2H), 6.35 (s,1H), 6.40-6.46 (d, J= 9.10 Hz, 1H), 6.59-6.67 (dd, J_1= 8.80, J_2= 9.01 Hz, 4H), 6.85-7.35(m, 7H), 7.75 (d, J= 8.00 Hz, 2H), 10.02 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 21.33, 21.55, 33.62, 50.52, 51.29, 55.13, 55.67, 55.76, 56.09, 57.94, 97.04, 113.51, 114.11, 114.82, 121.99, 122.37, 126.21, 126.66, 127.60,

128.19,128.03, 129.03, 129.48, 129.68, 130.74, 133.86, 135.69, 136.54, 140.16, 141.52, 145.11, 150.73, 157.79, 158.57, 168.67 ppm. MS m/z: 548, Anal. Calcd. for $C_{35}H_{36}N_2O_4$: C, 76.62; H, 6.61; N, 5.11. Found: C, 76.53; H, 6.70; N, 5.13.

2.1.3. Methyl 2,6-bis(4-bromophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine- carboxylate (4c)

White solid, mp. 177-179 º C. FTIR (ATR): υ= 3173, 3086, 2961, 1661, 1597, 1253, 838cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.51-2.55 (dd, J_1= 15.00 Hz, J_2= 2.00 Hz, 1H), 2.62-2.66 (dd, J_1= 15.00 Hz, J_2= 5.00 Hz, 1H), 3.68 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 4.88 (br s, 1H), 6.14-6.19 (d, J = 8.75, 1H), 6.58-6.68 (dd, J_1= 8.50 Hz, J_2= 2.00 Hz, 2H), 6.84-6.86 (d, J= 9.00 Hz, 2H), 6.92-7.52 (m, 10 H), 7.67-7.68 (d, J= 8.50 Hz, 2H), 10.02 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 33.60, 51.07, 55.45, 55.53, 55.64, 57.39, 96.42, 114.13, 114.40, 114.44, 114.58, 120.17, 120.86, 122.27, 127.80, 128.32, 128.63, 129.94, 130.38, 131.24, 131.69, 132.00, 135.37, 140.92, 141.94, 143.15, 144.43, 151.39, 156.71, 156.82, 158.00, 158.52, 168.38 ppm. MS m/z: 678, Anal. Calcd. for $C_{33}H_{30}Br_2N_2O_4$: C, 58.42; H, 4.46; N, 4.13. Found: C, 58.64; H, 4.61; N, 4.02.

2.1.4. Methyl 2,6-bis(4-*iso*propylphenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine- carboxylate (4d)

White solid, mp. 230-232 º C. FTIR (ATR): υ= 3249, 3050, 2957, 1651, 1593, 1512, 1176, 805 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.07-1.14 (d, J= 16.50 Hz, 12 H), 2.49 (d, J= 16.50 Hz, 1H), 2.67 -2.71 (dd, J_1= 12.60 Hz, J_2= 2.50 Hz, 1H), 2.77-2.86 (m, 2H), 3.65 (s, 3H), 3.75 (s, 3H), 3.85 (s, 3H), 4.95 (br s, 1H), 5.96 (d, J= 8.56 Hz, 2H), 6.25 (s, 1H), 6.38-6.41 (d, J= 9.10 Hz, 2H), 6.45-6.59 (dd, J_1= 8.80, J_2= 9.01 Hz, 2H), 6.85-7.35, (m, 10H), 10.01 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 24.02, 24.07, 24.13, 24.30, 33.61, 33.84, 50.88, 55.36, 55.64, 58.32, 97.20, 113.67, 113.81, 114.49, 120.11, 123.44, 124.36, 126.21, 126.33, 126.65, 126.68, 127.57, 128.06, 130.73, 132.84, 135.20, 140.89, 141.47, 141.72, 146.55, 147.78, 150.62, 155.94, 157.28, 158.45, 168.70 ppm. MS m/z: 604, Anal. Calcd. for $C_{39}H_{44}N_2O_4$: C, 77.45; H, 7.33; N, 4.63. Found: C, 77.83; H, 7.20; N, 4.51.

2.1.5. Methyl 2,6-bis(4-methoxyphenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine- carboxylate (4e)

White solid, mp. 217-219 º C. FTIR (ATR): υ= 3233, 3033, 2952, 1658, 1580, 1505, 1171, 832 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.60-2.65 (dd, J_1= 19.00 Hz, J_2= 3.50 Hz, 1H), 2.73-2.79 (dd, J_1= 19.00 Hz, J_2= 5.50 Hz, 1H), 3.66 (s, 3H), 3.74 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 3.89 (s, 3H), 4.97-4.98 (d, J= 2.00 Hz, 1H), 6.23 (s, 1H), 6.29-6.31 (d, J= 11.00 Hz, 2H), 6.44-6.46 (d, J= 1.50 Hz, 2H), 6.63-6.67 (m, 3H), 6.79-6.83 (m, 3H), 6.91-6.94 (dd, J_1= 8.00 H, J_2= 2.50 Hz, 1H), 6.96-6.99 (dd, J_1= 8.00 H, J_2= 2.50 Hz, 1H), 7.05-7.08 (d, J= 10.50 Hz, 1H), 7.19-7.22 (m, 2H), 7.82-7.85 (dd, J_1= 8.00 H, J_2= 2.50 Hz, 1H), 10.13 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 33.67, 50.85, 55.19, 55.29, 55.38, 55.47, 55.62, 57.42, 97.04, 113.43, 113.94, 114.14, 114.35, 122.05, 127.57, 127.82, 129.48, 130.23, 130.75, 135.10, 136.17, 141.60, 145.25, 150.89, 157.08, 157.75, 157.87, 157.98, 158.62, 161.98, 168.66 ppm. Ms m/z: 580, Anal.Cal. for $C_{35}H_{36}N_2O_6$: C, 72.39; H, 6.25; N, 4.82, Found: C, 72.01; H, 6.03; N, 4.71.

2.1.6. Methyl 2,6-bis(3,4-dimethoxyphenyl)-1-(3,4-dimethoxyphenyl)-4-(3,4-dimethoxyphenylamino) -1,2,5,6-tetrahydropyridine- carboxylate (4f)

White solid, mp. 221-223 º C. FTIR (ATR): υ= 3242, 3053, 2988, 1652, 1589, 1510, 1189, 795 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.62-2.66 (dd, J_1= 19.00 Hz, J_2= 4.00 Hz, 1H), 2.79-2.84 (dd, J_1= 19.00 Hz, J_2= 7.00 Hz, 1H), 3.65 (s, 3H), 3.73 (s, 6H), 3.77 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.91-4.93 (d, J= 4.00 Hz, 1H), 6.18 (s, 1H), 6.32-6.35 (d, J= 11.00 Hz, 2H), 6.44-6.47 (d, J= 11.50 Hz, 2H), 6.63-6.70 (m, 6H), 6.73-6.77 (m, 3H), 6.87 (s, 1H), 10.12 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 33.82, 50.78, 55.39, 55.58, 55.69, 55.80, 55.91, 55.97, 57.59, 95.55, 109.46, 110.47, 111.10, 113.92, 114.31, 114.72, 118.69, 127.95, 130.70, 135.49, 136.53, 141.56, 147.42, 147.88, 148.65, 149.01, 151.10, 157.31, 157.84, 168.57 ppm. MS m/z: 640. Anal.Calcd. for $C_{37}H_{40}N_2O_8$: C, 69.36; H, 6.29; N, 4.37. Found: C, 68.98, H, 6.46, N, 4.24.

2.1.7. Methyl 2,6-bis(3-nitrophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine- carboxylate (4g)

White solid, mp. 250-251 º C. FTIR (ATR) υ: 3216, 3007, 2916, 1645, 1610, 1584, 1508, 1343,

1185, 810 cm^{-1}. ^{1}H NMR ($CDCI_3$, 500 MHz) δ: 2.74 (dd, J_1= 15.00 Hz, J_2= 2.86 Hz, 1H), 2.82 (dd, J_1=15.53 Hz, J_2= 2.81 Hz, 1H), 3.69 (s, 3H), 3.74 (s, 3H), 3.83 (s, 3H), 5.19 (br s, 1H), 6.31 (s, 1H), 6.38-6.41 (m, 3H), 6.65-6.68 (d, J= 2.50 Hz, 1H), 7.24-8.17 (m, 12H), 10.16 (s, 1H) ppm. ^{13}C NMR ($CDCI_3$, 125MHz) δ: 33.78, 51.28, 55.46, 55.58, 56.26, 56.97, 95.68, 114.27, 114.80, 115.20, 121.64, 121.73, 125.04, 126.36, 127.67, 129.20, 129.63, 130.75, 132.87, 134.93, 140.12, 141.29, 144.86, 146.49, 148.53, 148.54, 152.17, 156.24, 157.61, 158.32, 168.16 ppm. MS m/z: 610. Anal.Calcd. for $C_{33}H_{30}N_4O_8$: C, 64.91; H, 4.95; N, 9.18. Found: C, 65.13; H, 5.01; N, 4.86.

2.1.8. Methyl 2,6-bis(4-benzyloxyphenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino) -1,2,5,6-tetrahydropyridine- carboxylate (4h)

White solid, mp. 166-168 º C. FTIR (ATR) υ: 3242, 3034, 2913, 1650, 1574, 1247, 840 cm^{-1}. ^{1}H NMR ($CDCI_3$, 500 MHz) δ: 2.51 (dd, J_1= 15.00 Hz, J_2= 2.86 Hz, 1H), 2.69 (dd, J_1= 15.53 Hz, J_2= 2.81 Hz, 1H), 3.56 (s, 3H), 3.65 (s, 3H), 3.80 (s, 3H), 4.98 (d, J= 5.00 Hz, 1H), 5.03 (s, 1H), 6.15-6.22 (m, 4H), 6.38-6.60 (m, 2H), 6.63-6.88 (m, 6H), 6.95 (d, J= 9.20 Hz, 2H), 7.12-7.39 (m, 14H), 7.78 (d, J= 5.02 Hz, 2H), 10.11 (s, 1H) ppm. ^{13}C NMR ($CDCI_3$, 125 MHz) δ: 33.78, 50.91, 55.26, 55.52, 55.67, 57.48, 70.00, 70.04, 70.11, 97.00, 114.00, 114.24, 114.38, 114.49, 114.94, 115.08, 118.31, 122.12, 123.57, 126.26, 127.47, 127.58, 128.17, 128.65, 128.69, 129.74, 130.29, 132.46, 136.53, 138.04, 140.31, 140.87, 141.28, 144.83, 145.27, 152.41, 157.33, 157.86, 158.01, 161.17, 168.70 ppm. MS m/z: 732. Anal. Calcd. for $C_{47}H_{44}N_2O_6$, C, 77.03; H, 6.05; N, 3.82. Found: C, 77.42; H, 6.14; N, 3.90.

2.1.9. Methyl 2,6-bis(2-thiophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino) -1,2,5,6-tetrahydropyridine- carboxylate (4i)

White solid, mp. 190-192 º C. FTIR (ATR) υ: 3258, 3002, 2948, 1655, 1594, 1511, 1189, 696 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.75-2.80 (dd, J_1= 13.00 Hz, J_2= 4.50 Hz, 1H), 2.95-3.00 (dd, J_1= 13.00 Hz, J_2= 6.50 H, 1H), 3.69 (s, 3H), 3.77 (s, 3H), 3.86 (s, 3H), 5.25-5.27 (d, J= 5.50 Hz, 1H), 6.26 (s, 1H), 6.55-6.56 (d, J= 2.50 Hz, 1H), 6.56-6.57 (d, J= 2.50 Hz, 1H), 6.70-6.71 (d, J= 1.00 Hz, 3H), 6.72-6.73 (d, J= 3.00 Hz, 1H), 6.74-6.75 (d, J= 3.00 Hz, 1H), 6.77-6.79 (dt, J_1= 4.00 Hz, J_2= 1.00 Hz, 1H), 6.80-6.82 (dt, J_1= 4.50 Hz, J_2=1.50 Hz, 1H), 6.86-6.89 (m, 2H), 7.11-

7.13 (m, 3H), 10.29 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.19, 37.08, 51.07, 53.66, 55.41, 56.98, 60.81, 96.12, 114.04, 114.16, 115.78, 118.98, 123.37, 124.41, 126.15, 126.32, 126.49, 127.71, 130.79, 131.11, 140.56, 144.57, 147.53, 148.75, 149.59, 151.99, 156.78, 157.84, 168.24 ppm. MS m/z: 532. Anal. Calcd. for $C_{29}H_{28}N_2O_4S_2$, C, 65.39; H, 5.30; N, 5.26. Found: C, 65.58; H, 5.21; N, 5.08.

2.1.10. Methyl 2,6-bis(5-methyl-2-thiophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino) -1,2,5,6-tetrahydropyridine- carboxylate (4j)

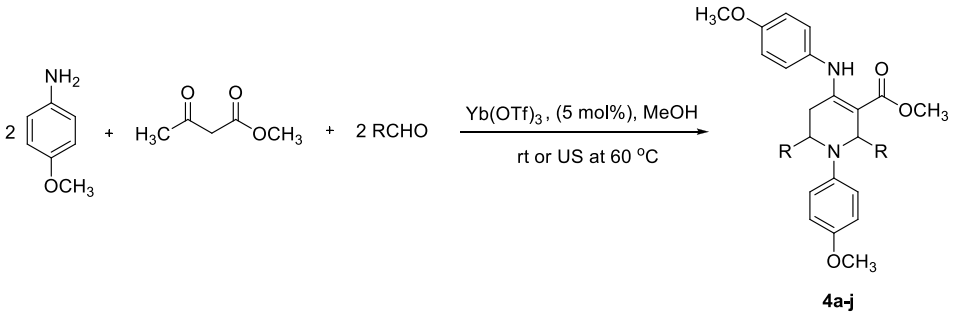
White solid, mp. 196-198 º C. FTIR (ATR) υ: 3244, 3059, 2951, 1659, 1610, 1581, 1508, 1376, 1242, 1179, 807 cm^{-1}. ^{1}H NMR ($CDCI_3$, 500 MHz) δ: 2.38 (s, 3H), 2.41 (s, 3H), 2.75 (dd, J_1= 14.98 Hz, J_2=2,01 Hz, 1H), 2.96 (dd, J_1= 15.03 Hz, J_2= 2.20 Hz, 1H), 3.70 (s, 3H), 3.76 (s, 3H), 3.85 (s, 3H), 5.14 (br s, 1H), 6.12 (br s, 1H), 6.47-7.22 (m, 12H), 10.28 (s, 1H) ppm. ^{13}C NMR ($CDCI_3$, 125 MHz) δ: 15.41, 15.46, 33.90, 50.81, 53.57, 55.44, 55.54, 96.10, 114.13, 114.26, 114.32, 114.46, 115.54, 122.21, 123.84, 124.02, 124.31, 124.46, 126.15, 127.73, 130.96, 132.13, 137.79, 138.49, 140.75, 144.99, 146.91, 151.78, 156.87, 157.77, 168.33 ppm. MS m/z: 560, Anal. Calcd. $C_{31}H_{32}N_2O_4S_2$, C, 67.86; H, 5.88; N, 6.81. Found: C, 67.69; H, 5.97; N, 6.70.

3. RESULTS AND DISCUSSION

In this study, we investigated the three component one-pot reaction of aromatic aldehydes and aromatic amine (p-anisidine) with methyl acetoacetate (2:2:1 ratio) using $Yb(OTf)_3$ as catalyst under stirring at room temperature and ultrasonic irradiation methods (Scheme 1).

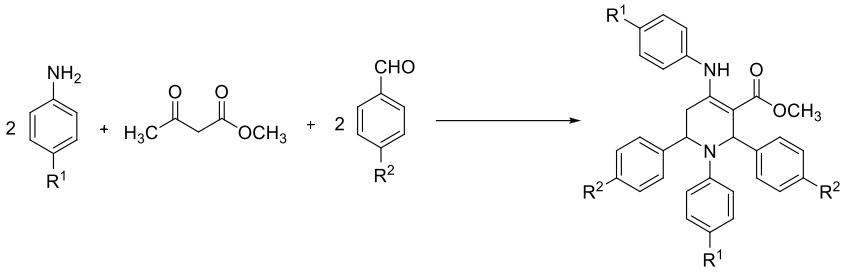
For the initial the identification of the suitable solvent and the appropriate concentration of catalyst, $Yb(OTf)_3$, were examined with the reaction of methyl acetoacetate (1 mmol), benzaldehyde (2 mmol), p-anisidine (2 mmol) to obtained the **4a**.

We have observed that 5 mol % of the catalyst gives the satisfactory results for the reactions. Selections of solvents also play an important role in one-pot reactions. For this reason, we also examined the effect of solvents in the reaction. A variety of solvents, such as EtOH, MeOH, AcOH and ILs (IL 1: 8-ethyl-1,8-diazobicyclo[5.4.0]-7-undecenium trifluoromethane sulfonate, and IL 2: 1-Ethyl-2,3-dimethylimidazoliumtetrafluoroborate) have been investigated. Among the selected solvents MeOH was the best of them in the synthesis of tetrahydropyridines showed in Table 1.



Scheme 1. Multicomponent synthesis of substituted piperidines.

Table 1. Effect of different catalysts, solvents, and conditions on construction of **4a**



Entry	R^1	R^2	Product	Catalyst/ Conditions	Yield (%)
1	$-OCH_3$	-H	**4a**	$Yb(OTf)_3$ (5%)/MeOH, rt, stirring, 20h	83
2	$-OCH_3$	-H	**4a**	$Yb(OTf)_3$ (5%)/ AcOH, rt, stirring, 20h	74
3	$-OCH_3$	-H	**4a**	$Yb(OTf)_3$ (5%)/MeOH, US, 3h	70
4	$-OCH_3$	-H	**4a**	$Yb(OTf)_3$ (5%)/EtOH, US, 60^0C, 3h	76
5	$-OCH_3$	-H	**4a**	$Yb(OTf)_3$ (5%)/MeOH, US, 60^0C, 3h	80
6	$-OCH_3$	-H	**4a**	$Yb(OTf)_3$ (5%)/ CH_3CN, US, 60^0C, 3h	72
7	$-OCH_3$	-H	**4a**	$Yb(OTf)_3$ (5%)/IL 1 , US, 60^0C, 3h	30
8	$-OCH_3$	-H	**4a**	$Yb(OTf)_3$ (5%)/IL 2, US, 60^0C, 3h	63

IL 1: 8-ethyl-1,8-diazobicyclo[5.4.0]-7-undecenium trifluoromethane sulfonate (DBU)
IL 2: 1-Ethyl-2,3-dimethylimidazoliumtetrafluoroborate (EDIMIM BF_4)

All stirring at the room temperature reactions were performed in the presence of 5 mol amount of the catalyst for 20 h (method A). We decided to perform this reaction under ultrasonic irradiation to get a shorter reaction time, and higher yield (method B). First the model reaction was examined under US with different solvents and temperature. The reaction was completed in 3 h with a yield of 70 %. When the temperature was increased from room temperature to 60^0C, the yield of the products was better, as indicated in Table 2.

A number of aromatic aldehydes were checked to study the majority and range of this synthetic procedure. Quite a lot of aromatic aldehydes with different substituents for instance Me, Br, NO_2, $OCH_2C_6H_5$ and $CH(CH_3)_2$ were reacted with p-anisidine and methyl acetoacetate in the same reaction conditions. The functionalized piperidines were formed in moderate yields at all these reactions.

Table 2. Synthesis of 2,6-bis(substitutedphenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino) -1,2,5,6-tetrahydropyridine- carboxylate

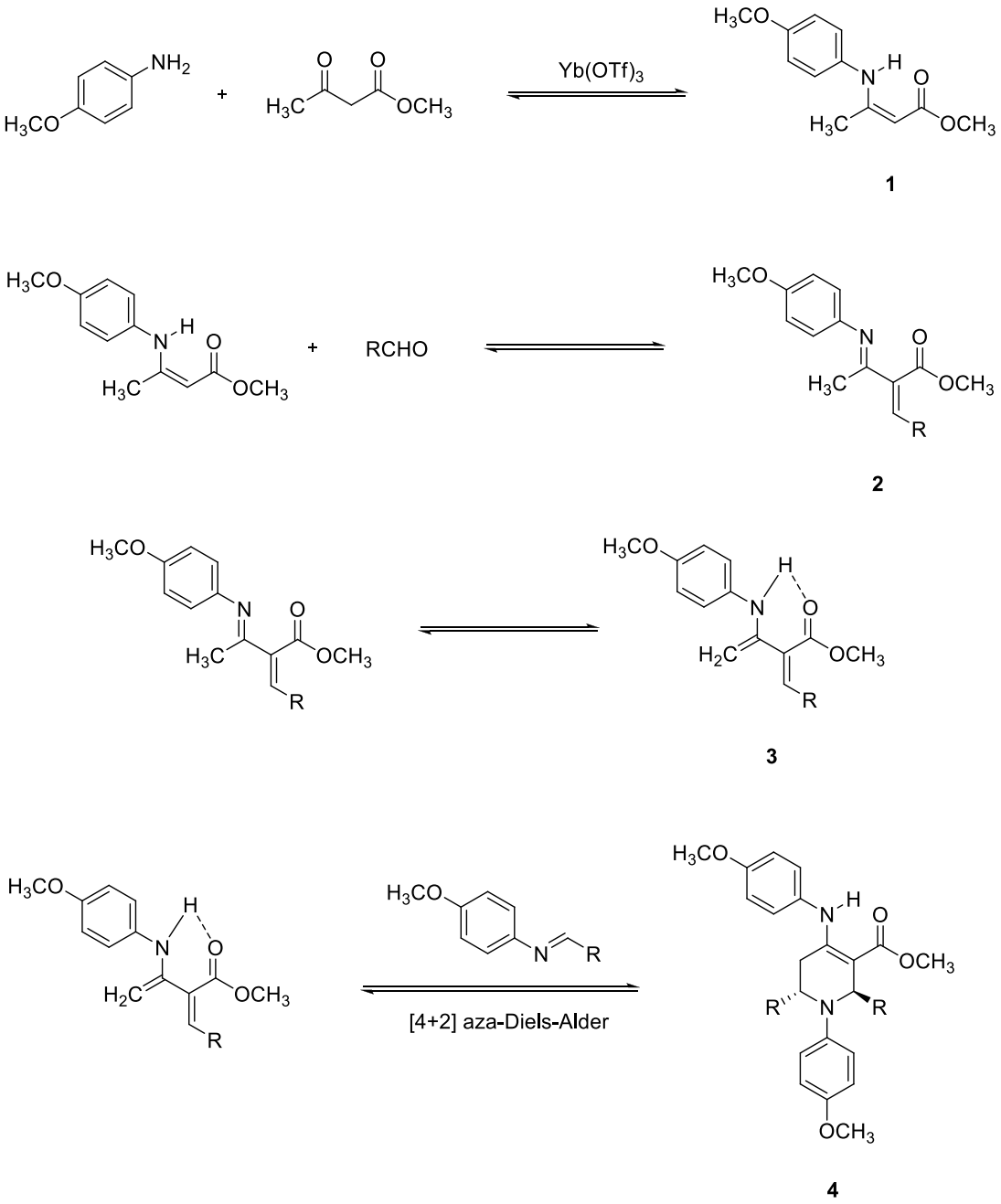
Entry	R	Product	Method A Yield (%)/Time (h)	Method B Yield (%)/Time (h)
1	C_6H_5	**4a**	83/20	80/3
2	4-Me-C_6H_5	**4b**	78/20	76/3
3	4-Br- C_6H_5	**4c**	83/20	82/3
4	4-$CH(CH_3)_2$-C_6H_5	**4d**	90/20	86/3
5	4-OMe-C_6H_5	**4e**	81/20	78/3
6	3,4-diOMe-C_6H_4	**4f**	76/20	72/3
7	3-NO_2- C_6H_5	**4g**	87/20	83/3
8	4-benzyloxy-C_6H_5	**4h**	88/20	85/3
9	2-thiophenyl	**4i**	90/20	87/3
10	5-Me-thiophen-2-yl	**4j**	86/20	83/3

Method A: $Yb(OTf)_3$ (5%), 5 mL MeOH, rt, stirring.

Method B: $Yb(OTf)_3$ (5%), 5 mL MeOH, 60 ^{o}C, US.

Furthermore, the structure of all products was approved by spectrophotometric methods (FTIR, ^{1}H NMR, ^{13}C NMR, EA and MS). **4a**, **4b**, **4c**, **4e** and **4i** have been synthesized before with the other methods [5, 7, 14, 19, 27].

A possible mechanism for the generation of these functionalized piperidines is outlined in Scheme 2. A similar mechanism was postulated in some literatures [25, 26, and 3] before. In the first step, $Yb(OTf)_3$ be able to act as a Lewis acid catalyst for the reaction of the p-anisidine (4-methoxyaniline) and methyl acetoacetate (1,3-dione) to give the β-enamine **1**. After the addition of aromatic or hetaryl-aldehyde, this enamine **1**, gives the Knoevenagel-type product **2**. The intermediate **2** undergoes catalyzed imine-enamine tautomerization to form **3**, which becomes stable by intramolecular hydrogen bonding. $Yb(OTf)_3$ facilitates the constitution of imine besides that enamine **1** in the multicomponent reaction. This imine form and the intermediate **3** undergo a [4+2] Aza-Diels-Alder reaction to give the polysubstituted piperidine derivatives [10, 17] (Scheme 2).



Scheme 2. A plausible mechanism for the synthesis of piperidines

4. CONCLUSIONS

We have demostrated a remarkable and practical one-pot procedure for synthesis of Methyl 2,6-bis (substitutedaryl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino) -1,2,5,6-tetrahydropyridine- carboxylate compounds via various aldehydes, p-anisidine and metyl acetoacetate. This reaction has been carried out under ultrasound irradiation is the first report of synthesis of tetrahydropyridine compounds catalyzed by $Yb(OTf)_3$ under ultrasonic irradiation. This method has approached several advantages such as short reaction times and good yields.

ACKNOWLEDGMENT

This study financially supported by Yildiz Technical University with the Project Number BAPK2012-01-02-KAP05.

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