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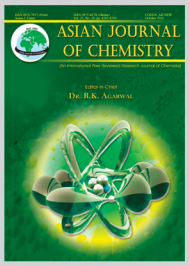

Ultrasound Assisted Syntheses of Some 1,2,4-Triazole Derivatives

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A facile preparation of a series of 1,2,4-triazole derivatives under ultrasound irradiation, that proceeded *via* one-pot reaction of α-nitrophenyl hydrazones with different methylene amines, using sodium nitrite as oxidant and benzyl triethyl ammonium chloride (BTEAC) as phase transfer catalysis, respectively, was described.

Key Words: 1,2,4-Triazole, Ultrasound, One-pot, α-Nitrophenylhydrazone, Benzyl triethyl ammonium chloride.

INTRODUCTION

Ultrasound irradiation has been considered as an important energy source for organic reactions, since that it can produce microbubbles in liquid, the cavitational collapses of which would generate intensively strong shock waves, high temperature (*ca.* 5000 K) and pressure (*ca.* 1000 atm), as well as liquid jet streams (*ca.* 400 km/h)[1]. Many organic reactions can be conducted smoothly by sonication to supply improved yields and increased selectivities[2-4]. Therefore, ultrasound irradiation has been regarded as an significant technique in organic synthesis[5,6].

In the past decade, the derivatives of 1,2,4-triazoles have attracted considerable interest because they exhibit a wide range of biological effects including antiviral[7], anticancer[8], antibacterial[9], antiinflammatory[10] and antihypertensive effects[11]. Thus, a synthesis of this heterocyclic nucleus has been of much importance in current years. Condensation of α-halogenated phenylhydrazones and methylene amines at high temperatures, using different oxidants, are general methods[12-14]. Reaction of acylhydrazine and hydrazine is another method[15]. In addition, solid-phase organic synthesis is also introduced in the synthesis of 1,2,4-triazoles[16,17]. However, most of these routes need complicated operation and work-up or require long reaction time. Thus, preparation of functionalized 1,2,4-triazoles derivatives is still a major challenge in organic synthesis[12-17].

In view of the important application of 1,2,4-triazoles derivatives and interest in ultrasound technique, we provide a new and convenient strategy for the syntheses of 1,2,4-triazole derivatives (**Scheme-I**). To the best of our knowledge, this method has not been described previously in literature and it is very simple but useful compared with previously reported methods.

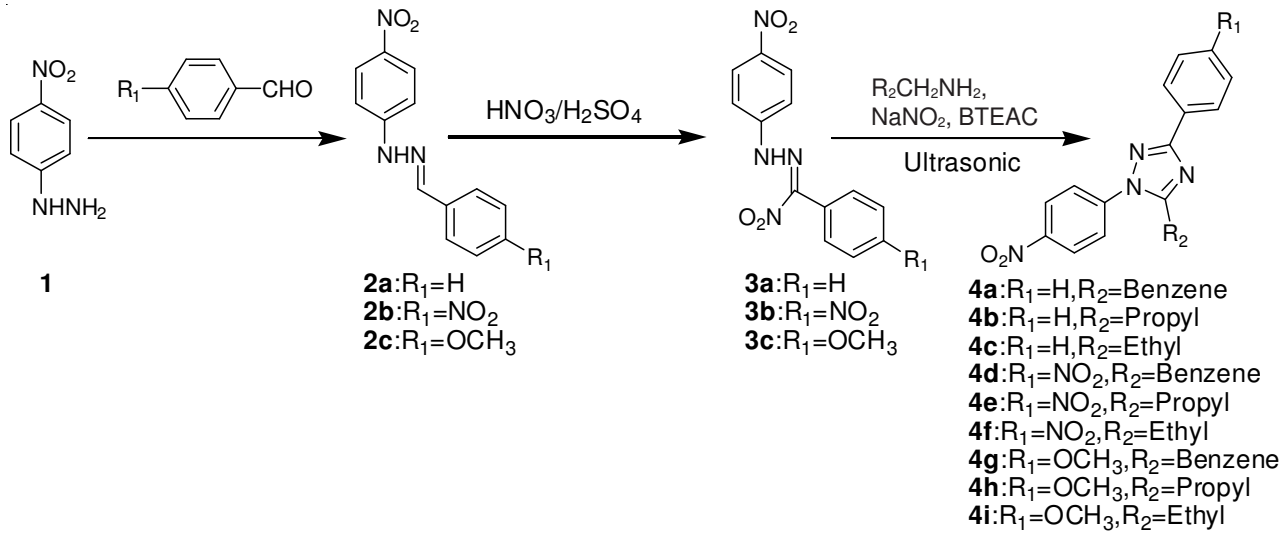
EXPERIMENTAL

All reagents for synthesis were commercially available and employed as received or purified by standard methods prior to use. The ^{1}H and ^{13}C NMR studies were carried out by the BRUKER AVANCE 500 instrument and the mass spectral studies were done using BRUKER ESQUIRE HCT instrument. Elemental analyses were determined in the Carlo Erba model 1106 instrument. Melting points were recorded using an electrothermal-WRS-1A melting point apparatus and were uncorrected. Synthesi of 1,2,4-triazoles derivatives was done in XO-500F ultrasound reactor.

General procedure

Synthesis of compounds (2a-2c): Under the room temperature, the mixture of benzaldehyde (100 mmol), benzene (100 mL) and *p*-nitrophenyl hydrazine (100 mmol) was reacted with stiring for 14 h. The product **2a** was afforded by vacuum distillation of the solvent. The synthetic procedure of compounds **2b-2c** was the same as that of **2a**. Then compounds **2a-2c** was used in the synthesis of product **3a-3c**, without any purification.

Synthesis of compounds (3a-3c): Under the condition of salt-ice, the mixture of compounds **2** (100 mmol) and ether (200 mL) was stired for 10 min and then 100 mL HNO_3-H_2SO_4 mixture (mass ratio = 1:1) was added and reacted for 1.5 h. The pH of the reaction was maintained at 7-8 by adding 0.5 mol/L Na_2CO_3 aqueous solution and the mixture was filtered



Scheme-I

to give powder of **3**. Upon recrystallization in ethanol, crystals of **3** was got.

Synthesis of compounds (4a-4i): The mixture of **3** (1 mmol), methylene amines (1.2 mmol), toluene (10.0 mL), sodium nitrite (5.0 mmol) and benzyl triethyl ammonium chloride (BTEAC) (2.0 mmol) was refluxed for 1 h at 100 ºC under ultrasound irradiation. The reaction was filtered and purified by column chromatography to give compounds **4**, with petroleum ether-ethyl acetate solution ($V_{petroleum\ ether}$:$V_{ethyl\ acetate}$ = 5:1) as eluent.

Characterization data of representative compounds: Compound **4a**: Anal. calcd. (%) for $C_{20}H_{14}N_4O_2$: C, 70.17; H, 4.12; N, 16.37. Found (%): C, 70.31; H, 4.24; N, 16.21. MS (ESI) m/z: 343 $[M + 1]^+$; ^{1}H NMR ($CDCl_3$, 500 MHz, δ, ppm): 8.32 (d, *J* = 9.0 Hz, 2H, Ph-H), 8.25 (d, *J* = 8.0 Hz, 2H, Ph-H), 7.66 (d, *J* = 9.0 Hz, 2H, Ph-H), 7.57 (d, *J* = 8.0 Hz, 2H, Ph-H), 7.47-7.52 (m, 6H, Ph-H); ^{13}C NMR ($CDCl_3$, 500 MHz, δ, ppm): 124.9, 125.2, 126.7, 127.7, 128.7, 129.0, 129.1, 129.9, 130.1, 130.8, 143.0, 146.9, 155.4, 162.8.

Compound 4b: Anal. calcd. (%) for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found (%): C, 66.41; H, 5.36; N, 18.36. MS (ESI) m/z: 309 $[M + 1]^+$; ^{1}H NMR ($CDCl_3$, 500 MHz, δ, ppm): 8.46 (d, *J* = 9.0 Hz, 2H, Ph-H), 8.18 (d, *J* = 9.0 Hz, 2H, Ph-H), 7.78 (d, *J* = 9.0 Hz, 2H, Ph-H), 7.47-7.51 (m, 3H, Ph-H), 2.92 (t, *J* = 7.6 Hz, 2H, CH_2), 1.89-1.97 (m, 2H, CH_2), 1.05 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 500 MHz, δ, ppm): 13.8, 21.3, 29.1, 124.9, 125.0, 126.6, 128.6, 129.7, 130.4, 142.6, 147.1, 157.3, 162.3.

Compound 4c: Anal. calcd. (%) for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found (%): C, 66.53; H, 5.02; N, 18.94. MS (ESI) m/z: 295 $[M + 1]^+$; ^{1}H NMR ($CDCl_3$, 500 MHz, δ, ppm): 8.46 (d, *J* = 9.0 Hz, 2H, Ph-H), 8.19 (d, *J* = 9.0 Hz, 2H, Ph-H), 7.76 (d, *J* = 9.0 Hz, 2H, Ph-H), 7.46-7.49 (m, 3H, Ph-H), 2.21-2.24 (m, 2H, CH_2), 1.07 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 500 MHz, δ, ppm): 13.9, 21.5, 124.9, 125.1, 126.6, 128.7, 129.7, 130.4, 142.6, 147.0, 157.3, 162.4.

Compound 4d: Anal. calcd. (%) for $C_{20}H_{13}N_5O_4$: C, 62.01; H, 3.38; N, 18.08. Found (%): C, 62.22; H, 3.27; N, 18.02. MS (ESI) m/z: 388 $[M + 1]^+$; ^{1}H NMR ($CDCl_3$, 500 MHz, δ, ppm): 8.43 (d, *J* = 7.4 Hz, 2H, Ph-H), 8.33-8.41 (m, 4H, Ph-H), 7.66 (d, *J* = 7.8 Hz, 2H, Ph-H), 7.41-7.61 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$, 500 MHz, δ, ppm): 124.1, 124.9, 125.3, 127.1, 127.5, 129.1, 129.2, 131.1, 136.2, 142.6, 147.3, 148.7, 156.0, 160.8.

Compound 4e: Anal. calcd. (%) for $C_{17}H_{15}N_5O_4$: C, 57.79; H, 4.28; N, 19.82. Found (%): C, 58.04; H, 4.48; N, 19.66. MS (ESI) m/z: 354 $[M + 1]^+$; ^{1}H NMR ($CDCl_3$, 500 MHz, δ, ppm): 8.48 (d, *J* = 8.7 Hz, 2H, Ph-H), 8.33-8.39 (m, 4H, Ph-H), 7.80 (d, *J* = 8.7 Hz, 2H, Ph-H), 2.94 (t, *J* = 7.4 Hz, 2H, CH_2), 1.91-1.97 (m, 2H, CH_2), 1.06 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 500 MHz, δ, ppm): 13.8, 21.2, 29.0, 124.0, 125.1, 125.1, 127.3, 136.4, 142.2, 147.4, 148.6, 158.0, 160.4.

Compound 4f: Anal. calcd. (%) for $C_{16}H_{13}N_5O_4$ (339.1): C, 56.64; H, 3.86; N, 20.64. Found (%): C, 56.86; H, 3.74; N, 20.75. MS (ESI) m/z: 340 $[M + 1]^+$; ^{1}H NMR ($CDCl_3$, 500 MHz, δ, ppm): 8.49 (d, *J* = 8.7 Hz, 2H, Ph-H), 8.33-8.39 (m, 4H, Ph-H), 7.79 (d, *J* = 8.7 Hz, 2H, Ph-H), 2.04-2.08 (m, 2H, CH_2), 1.06 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 500 MHz, δ, ppm): 14.1, 21.3, 124.0, 125.0, 125.1, 127.3, 136.4, 142.2, 147.4, 148.5, 157.9, 160.3.

Compound 4g: Anal. calcd. (%) for $C_{21}H_{16}N_4O_3$: C, 67.73; H, 4.33; N, 15.05. Found (%): C, 67.82; H, 4.20; N, 15.27. MS (ESI) m/z: 373 $[M + 1]^+$; ^{1}H NMR ($CDCl_3$, 500 MHz, δ, ppm): 8.31 (d, *J* = 8.9 Hz, 2H, Ph-H), 8.19 (d, *J* = 8.6 Hz, 2H, Ph-H), 7.65 (d, *J* = 8.8 Hz, 2H, Ph-H), 7.57 (d, *J* = 7.7 Hz, 2H, Ph-H), 7.45-7.54 (m, 3H, Ph-H), 7.03 (d, *J* = 8.7 Hz, 2H, Ph-H), 3.91 (s, 3H, CH_3O); ^{13}C NMR ($CDCl_3$, 500 MHz, δ, ppm): 55.4, 114.1, 122.8, 124.8, 125.1, 127.8, 128.2, 129.0, 129.1, 130.7, 143.0, 146.8, 155.2, 161.1, 162.6.

Compound 4h: Anal. calcd. (%) for $C_{18}H_{17}N_4O_3$: C, 63.89; H, 5.36; N, 16.58. Found (%): C, 63.74; H, 5.58; N, 16.37. MS (ESI) m/z: 339 $[M + 1]^+$; ^{1}H NMR ($CDCl_3$, 500 MHz, δ, ppm): 8.44 (d, *J* = 9.0 Hz, 2H, Ph-H), 8.12 (d, *J* = 8.6 Hz, 2H, Ph-H), 7.78 (d, *J* = 9.0 Hz, 2H, Ph-H), 7.01 (d, *J* = 8.6 Hz, 2H, Ph-H), 3.89 (s, 3H, CH_3O), 2.92 (t, *J* = 7.8 Hz, 2H, CH_2), 1.89-1.93 (m, 2H, CH_2), 1.04 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 500 MHz, δ, ppm): 13.8, 21.4, 29.1, 55.4, 114.0, 123.0, 124.8, 125.0, 128.1, 142.7, 146.9, 157.1, 160.9, 162.1.

Compound 4i: Anal. calcd. (%) for $C_{18}H_{18}N_4O_3$ (324.33): C, 62.95; H, 4.97; N, 17.27. Found (%): C, 62.75; H, 5.09; N, 17.09. MS (ESI) m/z: 325 $[M + 1]^+$; ^{1}H NMR ($CDCl_3$, 500

TABLE-1
MELTING POINTS AND YIELDS OF COMPOUNDS **2-4**

Compound	m.p. (ºC)	Yield (%)	Compound	m.p. (ºC)	Yield (%)	Compound	m.p. (ºC)	Yield (%)
2a	150-142	97.6	**3c**	130-132	81.1	**4e**	169-171	58.3
2b	188-190	95.4	**4a**	167-169	85.3	**4f**	148-150	44.7
2c	165-167	98.2	**4b**	133-135	57.2	**4g**	179-181	82.6
3a	120-122	82.3	**4c**	104-106	45.8	**4h**	125-127	49.8
3b	163-165	94.5	**4d**	164-166	86.2	**4i**	106-108	38.6

MHz, δ, ppm): 8.45 (d, J = 9.0 Hz, 2H, Ph-H), 8.11 (d, J = 8.6 Hz, 2H, Ph-H), 7.77 (d, J = 9.0 Hz, 2H, Ph-H), 7.00 (d, J = 8.6 Hz, 2H, Ph-H), 3.90 (s, 3H, CH_3O), 2.03-2.07 (m, 2H, CH_2), 1.04 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 500 MHz, δ, ppm): 13.7, 21.4, 55.4, 114.0, 123.0, 124.9, 125.1, 128.1, 142.7, 146.9, 157.1, 160.9, 162.1.

RESULTS AND DISCUSSION

Firstly, phenylhydrazone **2** were synthesized in 95.4-98.2 % yields (Table-1), through the condensation of *p*-nitrophenyl hydrazine with benzaldehyde and its derivatives, respectively. Then α-nitrophenyl hydrazones **3** were obtained in 81.1.4-94.5 % yields, by nitration of **2**, using the HNO_3-H_2SO_4 mixture as nitrating reagent. Finally, 1,2,4-triazoles **4** were afforded in 38.6-86.2 % yields, by the cyclization between α-nitrophenyl hydrazones **3** and methylene amines under ultrasound irradiation, using sodium nitrite as oxidant and benzyl triethyl ammonium chloride as phase transfer catalysis, respectively.

The structural elucidation of the synthesized compounds **4** was primarily assigned on the basis of their ^{1}H and ^{13}C NMR spectral studies. In the ^{1}H NMR spectra of compounds **4**, the chemical shifts in/around 8.45, 8.11, 7.77 and 7.00 ppm were assigned to the resonance of the hydrogen in benzene of the based 1,2,4-triazoles skeleton (Fig. 1) and all of them were accordingly divided in two peaks, respectively. In ^{13}C NMR, the chemical shifts in/around 114.0, 123.0, 124.9, 125.1, 128.1, 142.7, 146.9, 157.1, 160.9, 162.1 ppm were assigned to the resonance of the carbon in the based 1,2,4-triazoles skeleton. In addition, the resonance of all other protons and carbons was appeared in the expected region.

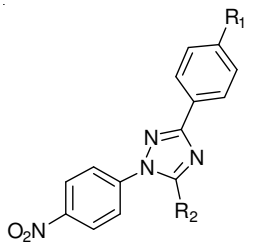


Fig. 1. Structure of the based 1,2,4-triazoles skeleton

The mass spectra and elemental analyses were also coincided with the formula weight and compositions of compounds **4**, respectively. And that provided a good proof to the confirmation of their structures. So the structures of all synthesized 1,2,4-triazoles derivatives **4** were well confirmed by the NMR, mass spectra and elemental analyses data.

ACKNOWLEDGEMENTS

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