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RESEARCH ARTICLE

An Efficient One Pot Green Synthesis of 5-(Substituted Phenyl)-4*H*-1,2,4, triazol- 3- ols Under Ultrasonic Irradiation

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Abstract: Here we describe the one pot efficient and eco-friendly synthesis of 5-(substituted phenyl)-4*H*-1,2,4 triazol-3-ols from benzaldehyde and semicarbazide hydrochloride using ultrasound irradiation avoiding toxic reagents. The combined use of 20 kHz US probe and 40 kHz US bath reduced the reaction time and improved the yield.

Keywords: 1,2,4 Triazol-3-ols,Semicarbazide hydrochloride, Dual frequency ultrasonic irradiation

Introduction

1,2,4, Triazoles and its derivatives have been widely used as a building blocks for a number of important drugs and exhibit a broad spectrum of pharmacological properties. Some well known examples are anticancer[1], anticonvulsant[2], antifungal[3,4,] antioxidant[5], antitubercular[6], antidepressant[7], antiasthmatic[8] and a potent sedative and hypnotic agents[9].

The 5-(substituted phenyl)-4*H*- 1,2,4,- triazol- 3- ols were synthesized by boiling of aryl semicarbazide with formic acid[10], oxidation[11] of benzaldehyde and azodicarbamide mixture with $FeCl_3$ and by the condensation of aryl aldehyde with semicarbazide hydrochloride to give corresponding semicarbazone[12] which on oxidative cyclization give 1,2,4 triazole -3-ols using $FeCl_3$. $6H_2O$, the shortcoming of these methods includes longer reaction time (28 hours), low yield, use of toxic solvents *etc*.

In present work, we wish to report our efforts toward one pot, green and efficient synthesis of 5-(substituted phenyl)-4*H*-1,2,4-triazol-3-ols from substituted benzaldehyde and semicarbazide hydrochloride using dual frequency ultra sonication. Ultrasound assisted organic synthesis is a greener synthetic approach and a powerful technique that is being used to enhance the so many organic reactions like synthesis of oxime[13], 1,2,4, oxadiazole[14], pyrazoles[15], isoxazoles[16], thiazolidiones[17], pyrimidines[18], imidazolines[19], benzoxazoline[20], polycyclic-4-aryl-3 methyl-4, 7-dihydro-1*H*-pyrazolo [3,4-b] pyridines[21] *etc*.

Simple experimental procedure, high yield, improved selectivity, shorter reaction time and avoidance the use of hazardous chemicals are the main advantages of ultrasound

assisted reactions[22-26]. The effect of ultrasound observed during organic reaction is due to cavitation process that creates enlarged vapors cavities in irradiated liquid. Cavitation induces very high local temperature and pressure inside the cavities, leading to turbulent flow of liquid and enhance mass transfer.

Experimental

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded on Perkin-Elmer FT-IR spectrophotometer. NMR spectra were recorded on Baker advance (400 MHz) instruments using TMS as an internal standard. Sonication were performed using an Oscar make Proble sonicator of 20 kHz and Labsoul make ultrasonic bath of 40 kHz when combined ultrasound experiment were performed the probe was immerged in the tube which was place in ultrasonic bath

General procedure for the synthesis of 5-(phenyl substituted)-4H- 1,2,4 triazol-3-ols (5-phenyl-4H-1,2,4 trazol-3-ol)

A mixture of substituted benzaldehyde (5 mmole) semicarbazide hydrochloride (5 mmole), potassium hydroxide (10 m mole) in an equimolar mixture of C_2H_5OH-H_2O) (1:1) (25 mL) was irradiated with dual frequency ultrasound for 30 min. The completion of the reaction was checked by TLC. The reaction mixture was acidified with conc. hydrochloric acid. The solid that separated out was filtered and recrystallized with dioxane-water to afford 5-phenyl-4*H*-1,2,4 triazol-3ol.

*5-Phenyl-4H-1,2,4 triazol-3-ol (**IIIa**)*

IR (KBr): 3465 cm^{-1} (OH), 3286 cm^{-1} (NH), 1590 cm^{-1} (C=N), ^{1}HNMR ($CDC1_3$): δ7.43-7.76 (m, 5H, C_6H_5), 8.03 (s, 1H, NH) 9.91 (s, 1H, OH)

*5-(4-Chlorophenyl) – 4H-1, 2,4,-triazol-3-ol (**IIIb**)*

IR (KBr): 3460 cm^{-1} (OH), 3278 cm^{-1} (NH), 1589 cm^{-1} (C=N), ^{1}HNMR ($CDC1_3$): δ7.46 (d, 2H, J = 8.41 Hz, H-3′, H-5′), 7.64 (d, 2H, J= 8.42 Hz, H-2′, H-6′), 7.96 (s, 1H, NH), 9.92 (s, 1H, OH).

*5-(4-Methylphenyl) – 4H-1, 2,4- triazol-3-ol (**IIIc**)*

IR (KBr): 3465 cm^{-1} (OH), 3282 cm^{-1} (NH), 1598 cm^{-1} (C=N), ^{1}HNMR ($CDC1_3$): δ 2.31 (s, 3H, CH3), 7.12 (d, 2H,J= 7.82 Hz, H-3′, H-5′), 7.52 (d, 2H, J= 7.84 Hz, H-2′, H-6′), 7.78 (s, 1H, NH), 9.73 (s, 1H, OH)

*5-(4-Methoxyphenyl) – 4H-1, 2,4- triazol-3-ol (**IIId**)*

IR (KBr): 3456 cm^{-1} (OH), 3281 cm^{-1} (NH), 1608 cm^{-1} (C=N), ^{1}HNMR ($CDC1_3$): δ 3.96 (s, 3H, OCH_3), 7.42 (d, 2H, J= 8.42 Hz, H-3′, H-5′), 7.64 (d, 2H, J= 8.42 Hz, H-2′, H-6′), 7.96 (s, 1H, NH), 9.92 (s, 1H, OH)

*5-(4-Hydroxyphenyl) – 4H-1, 2,4- triazol-3-ol (**IIIe**)*

IR (KBr): 3502 cm^{-1}, 3436 cm^{-1} (OH), 3290 cm^{-1} (NH), 1609 cm^{-1} (C=N), ^{1}HNMR ($CDC1_3$): δ 7.02 (d, 2H, J= 8.34 Hz, H-3′, H-5′), 7.71 (d, 2H, J= 8.36 Hz, H-2′, H-6′), 7.75 (s, 1H, NH), 8.14 (s, 1H, Ar-OH), 9.73 (s, 1H, OH)

*5-(4-N,N-Dimethylamino phenyl) – 4H-1, 2,4- triazol-3-ol (**IIIf**)*

IR (KBr): 3460 cm^{-1} (OH), 3290 cm^{-1} (NH), 1607 cm^{-1} (C=N), ^{1}HNMR ($CDC1_3$): δ 3.37(s, 6H, 2xCH_3), 7.56 (d, 2H,J= 8.54 Hz, H-3′, H-5′), 7.92 (d, 2H, J= 8.52 Hz, H-2′, H-6′), 8.02 (s, 1H, NH), 9.98(s, 1H, OH)

*5-(2-Nitrophenyl) – 4H-1, 2,4- triazol-3-ol (**IIIg**)*

IR (KBr): 3460 cm^{-1} (OH), 3287 cm^{-1} (NH), 1605 cm^{-1} (C=N), 1525, 1357 cm^{-1} (NO_2), ^{1}HNMR ($CDC1_3$): δ 7.65-8.02 (m, 4H, H-3′, H-4′ H-5′ H-6′), 8.14 (s, 1H, NH), 9.80 (s, 1H, OH)

*5-(3-Nitrophenyl) – 4H-1, 2,4- triazol-3-ol (**IIIh**)*

IR (KBr): 3467 cm^{-1} (OH), 3290 cm^{-1} (NH), 1582 cm^{-1} (C=N), 1534, 1350 cm^{-1} (NO_2), ^{1}HNMR ($CDC1_3$): δ 7.65-8.01 (m, 4H, H-2′, H-4′ H-5′ H-6′), 8.14 (s, 1H, NH), 9.79 (s, 1H, OH)

*5-(4-Nitrophenyl) – 4H-1,2,4- triazol-3-ol (**IIIi**)*

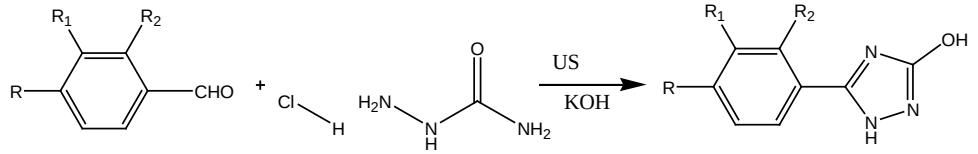
IR (KBr): 3451 cm^{-1} (OH), 3290 cm^{-1} (NH), 1609 cm^{-1} (C=N), 1530, 1349 cm^{-1} (NO_2), ^{1}HNMR ($CDC1_3$): δ 7.85 (d, 2H J=8.20 Hz, H-2′, H-6′), 8.15 (d, 2H J=8.20 Hz, H-3′, H-5′), 8.19 (s, 1H, NH), 9.89 (s, 1H, OH)

*5-(2-Chlorophenyl) – 4H-1, 2,4- triazol-3-ol (**IIIj**)*

IR (KBr): 3470 cm^{-1} (OH), 3278 cm^{-1} (NH), 1609 cm^{-1} (C=N), ^{1}HNMR ($CDC1_3$): δ 7.67-8.13 (m, 4H, H-3′, H-4′ H-5′ H-6′), 8.14 (s, 1H, NH), 9.98 (s, 1H, OH)

Results and Discussion

A mixture of benzaldehyde, semicarbazide hydrochloride and potassium hydroxide in equimolar mixture of C_2H_5OH-H_2O (1:1) was irradiated with dual frequency ultrasound for 30 min using a bath cleaner (40 kHz) and a probe (20 kHz). The progress of the reaction was checked with the help of TLC. After working up the colorless solid which separates out was recrystallized from a mixture of dioxane-water (Scheme 1). The compound thus obtained has m.pt 203-204 ^{0}C and in IR it showed absorption at 3465 cm^{-1}, 3286 cm^{-1}, 1590 cm^{-1} which were assigned to- OH, -NH, -C=N, stretching. In ^{1}H NMR it showed two singlet for proton each at δ8.03 and δ9.91 which were assigned to –NH and -OH and a multiplet at δ 7.43-7.76 for fine proton (-C_6H_5). Based upon the data it was revealed that the compound was 5-phenyl -4H-1,2,4 triazol- 3-ol .Using the above protocol following compounds were synthesized (Table 1).



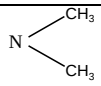
Substituted benzaldehyde **I** | semicarbazide hydrochloride **II** | 5 -(substituted phenyl) -4*H*-1,2,4 triazol -3-ols **III(a-j)**

Scheme 1

Table 1. Synthesis of 5-(substituted phenyl)-4H-1,2,4 triazol -3-ols

Entry	**R**	R_1	R_2	U.S. Bath		U.S. Probe		U.S. Bath and Probe		m.pt.	Lit.
				Time min	Yield, %	Time min	Yield, %	Time min	Yield, %	^{o}C	m.pt. ^{o}C
IIIa	H	H	H	90	50	60	65	30	90	202-203	204[12]
IIIb	Cl	H	H	90	65	60	70	30	87	184-185	187[12]
IIIc	CH_3	H	H	100	45	70	60	40	90	205	207[12]
IIId	OCH_3	H	H	90	50	70	55	40	85	193	195[12]
IIIe	OH	H	H	90	50	60	64	30	85	204	207[12]

Contd…

IIIf		H	H	120	45	90	55	45	80	206-207	209[12]
IIIg	H	H	NO_2	90	65	60	70	30	95	193	195[12]
IIIh	H	NO_2	H	90	64	60	72	30	94	198-199	201[12]
IIIi	NO_2	H	H	90	65	90	75	45	90	187	189[12]
IIIj	H	H	Cl	90	60	90	70	30	95	160-161	162[12]

Multifrequency sonication increases the reaction rate and yield of product. Multifrequency irradiation can disturb and break the surface continuity of a solution in a stronger way as compared to single frequency ultrasound which results in enhancement of mass transfer and cavitation in solution.

Conclusion

In summary we have developed a one pot, mild and highly efficient procedure for the synthesis of 5-(substituted phenyl)-4*H*-1,2,4, triazol- 3-ols avoiding the use of toxic solvent and reagents.

The synergistic effect of the combination of 40 kHz US bath and 20 kHz US probe reduces the reaction time and improves the yield. Our sonochemical method have several advantages over existing method including improved yield cleaner reaction, simple work up and short reaction time which make it an efficient and environmentally, benign strategy for the synthesis of 5-(substituted phenyl)-4H- 1,2,4 triazol-3-ols.

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