Environmentally Benign Synthesis and Characterization of Some Novel Pyridine anchored Triazole Derivatives

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Abstract

In the present work, we herein report the differently substituted, pyridine incorporated Triazoles from Thiosemicarbazide (2) as a precursor. Thiosemicarbazides (2) were prepared from methyl 5-bromonicotinate. We have used conventional as well as non-conventional methods for the synthesis of title compounds. Ultrasonic and Microwave mediated synthetic methodology has been showed better yield of the synthesized compounds as compared to conventional method. The formation of the Triazoles has been established by spectral tools.

Keywords: Triazole, Thiadiazole, Thiosemicarbazide, Nicotinic Acid, Ultrasonic, Microwave

Introduction

Among the various N-containing heterocycles azoles are synthetically important class of heterocycles because of broad spectrum of biological activities associated with them[1]. 1,2,4-triazole ring have relevance to the properties such as antitumor[2], anti-inflammatory[3], antibacterial[4], antimycobacterial[5], antifungal[6], anticonvulsant[7], antidepressant[8], antihypertensive[9], antioxidant[10], antiviral[11] and analgesic[12] activities. Thiosemicarbazides are important intermediates in the synthesis of azoles. Thiosemicarbazides were reported to possess activities as antibacterial[13], antimalarial[14], antitubercular[15].

The advantages of non-conventional methods for motivating different reactions are sound described in the literature[16]. Ultrasound and microwave assisted synthesis is a green synthetic approach used to accelerate rate of reaction. This approach is pollution free, environment friendly, safe,rapid and with higher chemical yields[17,18]. These properties make nonconventional methods superior to conventional one. With considering various biological activities associated with triazole nucleus and advantages of non-conventional methods in synthesis prompted us to study the synthesis of triazoles and thiadiazole.

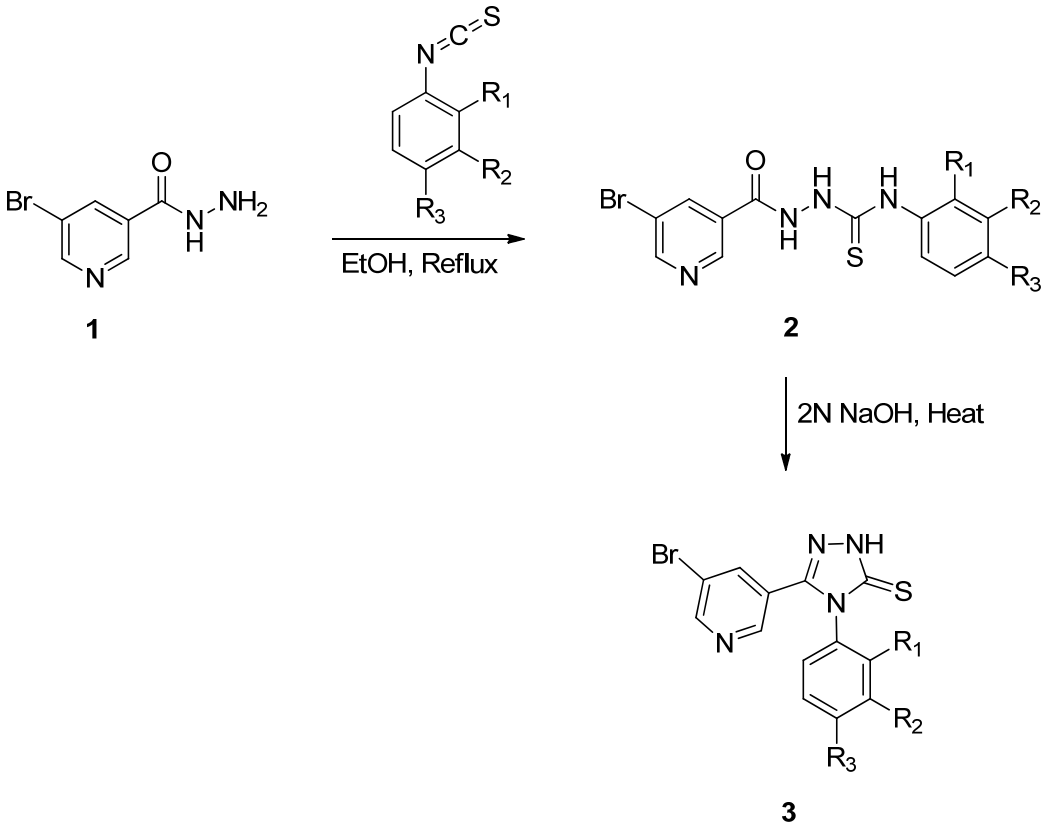
Experimental Work

All melting points were recorded in an open capillary tube in liquid paraffin bath and are uncorrected (Table-1). The purity and the progress of the reaction were routinely monitored by TLC. The product was purified by recrystallization technique. IR spectra were recorded on Perkin-Elmer FTIR spectrum-2 with ATR-single Refl. ZnSe technology. ^{1}HNMR spectra were recorded on BRUKER-ADVANCE II 400 MHz spectrometer in $CDCl_3$ and DMSO-d_6 as solvent and TMS as internal standard. Peak values are shown in δ ppm. Mass spectra were obtained by Finnegan mass spectrometer. TLC was

performed on pre-coated aluminum plate (Kieselgel 60, 254, E. Merck, Germany) and was observed under UV light. Experiment under ultrasonication was performed in ultrasonic cleaner model EN-20US manufactured by Enertech Electronics Pvt. Ltd, Mumbai, India and having determined control output of 100W and 33 KHz operational frequency. Experiment under microwave irradiation was run in RAGA'S Scientific Microwave System's with maximum power output 700W.

Material & Methods

In the present study, 5-bromonicotinic acid was converted into corresponding acid hydrazide (**1**) by treatment with thionyl chloride in methanol followed by hydrazine hydrate. The reaction of acid hydrazide (**1**) with aryl isothiocyanates afford 1-(5-bromonicotinoyl)-4- phenylthiosemicarbazide (**2**) followed by treatment with 2N NaOH yielded triazoles (**3**). 1-(5-bromonicotinoyl)-4-phenylthiosemicarbazide (**2**) and triazoles (**3**) were produced by both conventional and non-conventional (microwave and ultrasound irradiation) methods. The structure of synthesized compound was confirmed by spectral analysis. Outline of synthesis of 3-(5-bromopyridin-3-yl)-4-(R)-1H-1,2,4-triazole-5(4H)-thione is summarized in Scheme-1.



Scheme-1

Synthesis of Thiosemicarbazides (2):

Method (A) - By Conventional Method:

A 100 mL RBF was charged with 5-bromonicotinohydrazide (**1**) (0.01mol) and aryl isothiocyanates (0.01 mol) in an ethanol (15 mL) and the contain were reflux for one hour. Progress of the

reaction was monitored by TLC. After completion of the reaction, the content was cooled and white solid obtained was filtered off and washed with alcohol to afford (**2**).

Method (B) - By Ultrasound Method:

A 100 mL RBF was charged with 5-bromonicotinohydrazide (**1**) (0.01mol) and aryl isothiocyanates (0.01 mol) in an ethanol (15 mL) and the reaction mixture was subjected to ultrasonic irradiation for 25-30 minutes at room temperature. TLC was used for monitoring the reaction. After completion of the reaction, the contents were cooled to room temperature. The separated white solid was filtered to obtain the product (**2**).

Method (C) - By Microwave Method:

A 100 mL RBF was charged with 5-bromonicotinohydrazide (**1**) (0.01mol) and aryl isothiocyanates (0.01 mol) in an ethanol (15 mL) and the contents was subjected to microwave irradiation for 5-10 minutes at 300 watt. TLC was used for monitoring the reaction. After completion of the reaction, the contents were cooled to room temperature. Filtration process was used to obtain the white solid product (**2**).

2a: FT-IR (ν/cm^{-1}): 3330 (N-H stretching), 1686 (-C=O stretching), 1537 (aromatic C=C stretching), 1234 (-C=S stretching), 775 (C-Br bond stretching). ^{1}H NMR (400MHz, DMSO-d_6, δ, ppm): 2.4 (s, 3H, CH_3), 6.54-7.18 (m, 4H, Ar-H), 8.12-9.01 (m, 3H, Hetero Ar-H), 9.72 (s, 2H, N-H), 10.29 (s, 1H, N-H). MS (m/z): 349.2 (M^+), 351.2 (M+2).

Synthesis of Triazoles (3):

By Conventional Method:

A50mL RBF was charged with 1-(5-bromonicotinoyl)-4- phenylthiosemicarbazide (**2**) (0.005 mol) and 10 mL 2N NaOH solution and reflux for 1.5 hours. Thin layer chromatography tool was used for checking the progress of the reaction. After conclusion, the reaction quenched by pouring into ice cold water and dilute HCl was used for acidification. Filtration process was used for isolation of the solid product and purification was done by recrystallization (DMF:Water) to afford the trizoles(**3**).

By Ultrasound Method:

A 50 mL RBF was charged with 1-(5-bromonicotinoyl)-4- phenylthiosemicarbazide (**2**) (0.005 mol) and 10 mL 2N NaOH solution and the reaction mixture was subjected to ultrasonic irradiation for 25-30 minutes at room temperature. Thin layer chromatography tool was used for checking the progress of the reaction. After conclusion, the reaction quenched by pouring into ice cold water and dilute HCl was used for acidification. Filtration process was used for isolation of the solid product and purification was done by recrystallization (DMF:Water) to afford the trizoles (**3**).

By Microwave Method:

A 50mL RBF was charged with 1-(5-bromonicotinoyl)-4- phenylthiosemicarbazide (**2**) (0.005 mol) and 10 mL 2N NaOH solution and the reaction mixture was subjected to microwave irradiation for 5-10 minutes at 300watt. Thin layer chromatography tool was used for checking the progress of the reaction. After conclusion, the reaction quenched by poured into ice cold water and dilute HCl was used

for acidification. Filtration process was used for isolation of the solid product and purification was done by recrystallization (DMF:Water) to afford the trizoles (3).

3a: FT-IR (ν/cm^{-1}): 3103 (N-H stretching), 2883 (C-H stretching), 1605(C=N stretching), 1332 (C=S stretching), 1537 (aromatic ring), 775 (C-Br bond stretching). ^{1}H NMR (400MHz, DMSO-d_6,δ, ppm): 2.34 (s, 3H, CH_3), 7.82-8.66 (m, 3H, Hetero Ar-H), 7.14-7.41 (m, 4H, Ar-H), 14.26 (s, 1H, N-H), MS (m/z): 347.2 (M^+), 349.2 (M+2).

Results and discussion

The objective of this investigation was to synthesize pyridine anchored triazoles by conservative and environmentally benign methods. Characterization statistics of thiosemicarbazides and trizoles is reported in Table-1.

Compound	Substituent			M. P.(°C)	Conventional Method		Non-conventional Method			
							Ultrasound		Microwave	
	R_1	R_2	R_3		Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
2a	H	-CH_3	H	166	60	72	25	85	6	76
2b	H	H	-CH_3	182	60	74	28	86	5	78
2c	-CH_3	H	H	160	60	68	26	84	7	73
2d	-OCH_3	H	H	168	60	72	30	82	8	74
2e	H	H	-Cl	170	60	74	26	87	6	77
2f	H	-Cl	H	162	60	71	28	83	5	75
3a	H	-CH_3	H	258	90	61	28	81	5	69
3b	H	H	-CH_3	252	90	63	25	84	6	70
3c	-CH_3	H	H	208	90	57	26	75	8	66
3d	-OCH_3	H	H	246	90	60	29	78	9	64
3e	H	H	-Cl	248	90	63	24	77	7	68
3f	H	-Cl	H	230	90	61	26	79	6	67

The IR spectra of the thiosemicarbazides (2a) shows the presence of C=O stretching bands at 1686 cm^{-1}. The disappearance of the C=O stretching bands and the appearance of strong C=N stretching bands at 1605 cm^{-1} is evidence for the ring closure to form the 1,2,4-triazoles. The formation of the thione tautomer was supported by the presence of absorption maxima at 1322 cm^{-1} belonging to the C=S group. The ^{1}H-NMR spectra of compounds showed that the signal of NHC=O and NHC=S appears at 9.29 ppm whereas the NH-Ph peaks appear at 10.29 ppm. The disappearance of the NHC=O and NH-Ph peaks from the ^{1}H-NMR spectra and the appearance of a new peak at 14.26 ppm (N-NHC=S) confirmed the formation of the 1,2,4-triazole-3-thione derivatives.

Compounds (2) and (3) showed moderate yields by conventional methods while yields are found to be improved by non-conventional methods like microwave and ultrasound irradiation. Consistency of the outcomes was confirmed by frequent three times experiments. The effectiveness of nonconventional methods was assessed by comparison between similar reaction carried out by conventional method and it was found that the later process requires ninety min. for achievement and yields are moderately less while nonconventional methods requires shorter reaction times and yields are improved.

Conclusion

This study reveals the successful synthesis of the Pyridine anchored Triazoles using ultrasonic and microwave irradiation methods in better yields. It can be concluded that the nonconventional means of synthesis are clean and required minimum time for completion

Acknowledgement

The authors are highly indebted to the Principal, Annasaheb Awate Arts, Commerce & Hutatma Babu Genu Science College, Manchar for providing necessary laboratory facilities. Authors are also thankful to SAIF, Punjab University for spectral analysis.

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