Novel Synthetic Approach to New Thiadiazolo-Aminotetrazoles

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Abstract

A series of novel 5-amino-1-thiadiazolo-tetrazole derivatives have been synthesized by the condensation of thiadiazolo-thioureas and sodium azide under solid supported microwave irradiations (MWI) efficiently with excellent yield.

Introduction

It has been reported that tetrazoles cover a wider spectrum of bioactive heterocycles with azapyrrole system.[1-3] These compounds have been used for both biological and non-biological applications.[4-6] Among several types of tetrazoles, 5-amino-1-substituted derivatives have been reported as antibacterial, antiviral, anti-inflammatory and antiallergic agents.[7-9] Furthermore, thiadiazole moiety is substituted to N(1) in the 5-aminotetrazole ring, which is well known for its antibacterial, antifungal and antiviral activities.[10-13]

Solid supported microwave methodology has been adopted for the synthesis of title compounds as it is proved to be a rapid, safer and environmentally benign synthetic procedure.[14] Furthermore, the use of inorganic solid supports has reduced the consumption of organic solvents in synthetic works. The reactions were also carried out under conventional heating for comparative studies of reaction methodologies.

The main aim of this research work is to synthesize some new thiadiazolo-aminotetrazoles **(5a-h)** by the condensation of thiadiazolo-thioureas **(4a-h)** and sodium azide under solid supported microwave irradiations considering the biological and non-biological importance of the 5-aminotetrazole and thiadiazole moieties.

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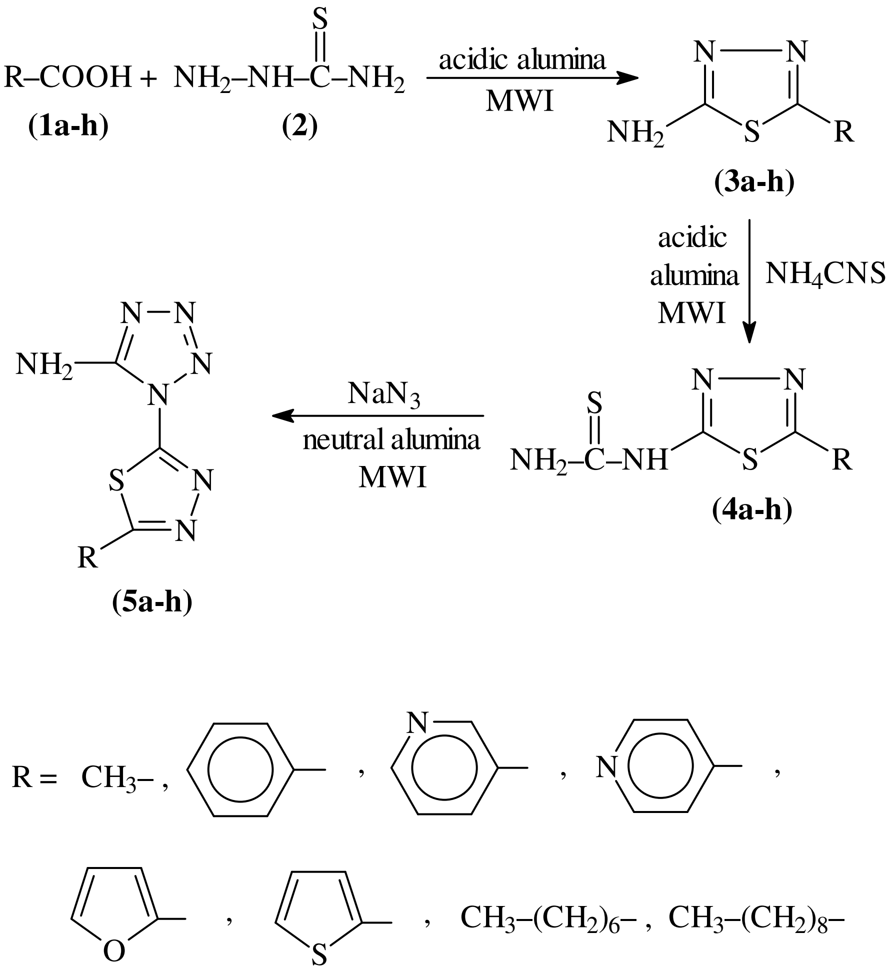
Scheme



Scheme 1: Synthesis pathway of thiadiazolo-aminotetrazoles.

Experimental Method

Microwave irradiations (MWI) were carried out in Kenstar Microwave Oven, Model No. 0M9925E (2450 MHz, 800 W). IR spectra were recorded on a Perkin Elmer FTIR-1710 spectrophotometer using KBr pellets. The intensities of IR bands are denoted with the symbols m, w and v for medium, weak and variable, respectively. ^{1}H NMR spectra were recorded on Bruker Advance (300 MHz) spectrometer using tetramethylsilane (TMS) as internal reference. The multiplicities of the signals are denoted with the symbols s, t and m for singlet, triplet and multiplet, respectively. Elemental analyses were performed by means of Heraeus CHN-Rapid Analyzer. Temperature of reaction mixture was measured on AZ, Mini Gun Type, Non-Contact IR thermometer, Model No. 8868. Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. The purity of synthesized compounds was checked on aluminum plates coated with silica gel (Merck).

5-Substituted-2-amino-1,3,4-thiadiazoles (**3a-h**) and N-(5-substituted-1,3,4-thiadiazolo)-thioureas (**4a-h**), used for the synthesis of title compounds, were synthesized as mentioned eleswhere.[15,16]

Synthesis of 5-amino-1-(1',3',4'-thiadiazolo)-1,2,3,4-tetrazoles (5a-h)

(a) Microwave irradiation method

15 mL of an ethanolic solution of equimolar amounts (0.01 mole) of thioureas (**4a-h**) and sodium azide was adsorbed on the surface of 20 gm of neutral alumina or montmorillonite K10 clay in a 100 ml beaker and dried in air. Then, the beaker containing reaction mixture was kept in an alumina bath in the microwave oven and irradiated for specified time (Table 1) intermittently. After the completion of the reaction as monitored by TLC, the product (**5a-h**) was eluted with EtOH (3 x 15 ml). The solvent was then recovered by distillation under reduced pressure. The crude product was recrystallized with MeOH.

(b) Conventional method

Equimolar amounts (0.01 mole) of thioureas (**4a-h**) and sodium azide were dissolved in 30 mL of EtOH and the resulted solution was heated under reflux for specified time (Table 1) with constant stirring. On completion of the reaction, the solvent was removed by distillation under reduced pressure. The solid obtained was recrystallized with MeOH to give product (**5a-h**).

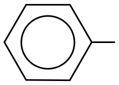
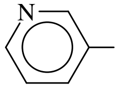
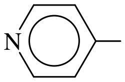
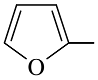
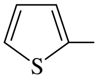
Results and Discussion

Thiadiazolo-aminotetrazoles (**5a-h**) were synthesized from thiadiazolo-thioureas (**4a-h**) and sodium azide under solid supported microwave irradiations. The reactions took 7.00-8.30 minutes for completion with an excellent yield of 70-92%. Conventional reactions took 18.00-19.30 hours for completion with 50-62% yield, which is quite less than in microwave irradiation reactions (Table 1). Reaction time has been reduced from hours to minutes by adopting solid supported microwave reactions.

The structures of synthesized thiadiazolo-aminotetrazoles (**5a-h**) are justified by spectral and analytical data. IR band at 3155-3142 cm^{-1} is due to the presence of primary amino group in the compounds. Cyclic imino group is indicated by the IR band at 1630-1619 cm^{-1} and the adsorption band at 625-615 cm^{-1} is accounted for carbon-sulphur linkage in the compounds. Presence of azide linkage (–N=N–N=) is confirmed by the appearance of the IR band at 2182-2170 cm^{-1} (Table 2).

Chemical shifts are observed for aminohydrogens and hydrogen atoms in aliphatic or aromatic substitutions at C(5') in thiadiazole moiety. ^{1}H NMR at δ 4.3-4.7 is due to aminohydrogens and the signals at δ 0.8-1.9 are due to alkyl hydrogens (**5a, 5g** and **5h**). Various aryl hydrogens have shown the signals at δ 7.2-8.6 in the compounds (**5b-5f**, Table2).

*Table 1: Characterization and analytical data of the compounds (**5a-h**)*

Compd.	R	m. p. (°C)	Reaction time*		% Yield		% CHN, Found (Calcd.)		
			A (min)	B (hrs)	A	B	C	H	N
5a	CH_3–	221	7.00	18.00	72	51	26.24 (26.22)	2.74 (2.73)	53.57 (53.55)
5b		257	7.25	18.30	81	56	44.11 (44.08)	2.85 (2.85)	40.01 (40.00)
5c		249	8.00	18.50	86	62	39.03 (39.02)	2.44 (2.43)	45.53 (45.52)
5d		265	8.15	19.15	92	67	39.03 (3.02)	2.44 (2.43)	45.53 (45.52)
5e		254	7.45	18.45	83	58	35.76 (35.74)	2.13 (2.12)	41.72 (41.70)
5f		241	8.30	19.25	79	57	33.48 (33.46)	2.00 (1.99)	39.05 (39.04)
5g	$CH_3(CH_2)_6$–	232	7.20	18.15	75	54	44.95 (44.94)	6.37 (6.36)	36.71 (36.70)
5h	$CH_3(CH_2)_8$–	238	7.50	18.30	70	50	48.83 (48.81)	7.12 (7.11)	33.22 (33.22)

**A = Microwave irradiation method*
B = Conventional method

*Table 2: Spectral data of the compounds (**5a-h**)*

Compd.	IR, ν/cm^{-1}, (KBr)	^{1}H NMR, δ/ppm, DMSO-d_6

5a	3150 (m, NH_2) 1620 (m, C=N) 625 (w, C–S) 2175 (v, –N=N–N=)	1.9 (s, 3H, $-CH_3$) 4.5 (s, 2H, $-NH_2$)
5b	3145 (m, NH_2) 1619 (m, C=N) 620 (w, C–S) 2172 (v, –N=N–N=)	4.6 (s, 2H, $-NH_2$) 7.3-7.6 (m, 5H, Ar–H)
5c	3143 (m, NH_2) 1620 (m, C=N) 617 (w, C–S) 2170 (v, –N=N–N=)	4.7 (s, 2H, $-NH_2$) 7.5-8.5 (m, 4H, Ar–H)
5d	3147 (m, NH_2) 1621 (m, C=N) 618 (w, C–S) 2174 (v, –N=N–N=)	4.6 (s, 2H, $-NH_2$) 6.9-8.6 (m, 4H, Ar–H)
5e	3142 (m, NH_2) 1622 (m, C=N) 615 (w, C–S) 2170 (v, –N=N–N=)	4.7 (s, 2H, $-NH_2$) 6.5-7.8 (m, 3H, furan)
5f	3148 (m, NH_2) 1623 (m, C=N) 622 (w, C–S) 2177 (v, –N=N–N=)	4.6 (s, 2H, $-NH_2$) 7.2-7.9 (m, 3H, thiophene)
5g	3152 (m, NH_2) 1626 (m, C=N) 624 (w, C–S) 2180 (v, –N=N–N=)	0.8 (t, 3H, $-CH_3$) 1.2-1.6 (m, 10H, 5 x $-CH_2-$) 1.8 (t, 2H, $-CH_2-$ ring) 4.5 (s, 2H, $-NH_2$)
5h	3155 (m, NH_2) 1630 (m, C=N) 625 (w, C–S) 2182 (v, –N=N–N=)	0.9 (t, 3H, $-CH_3$) 1.3-1.7 (m, 14H, 7 x $-CH_2-$) 1.9 (t, 2H, $-CH_2-$ ring) 4.3 (s, 2H, $-NH_2$)

Conclusion

Some novel thiadiazolo-aminotetrazoles (**5a-h**) have been synthesized efficiently by reacting thiadiazolo-thioureas (**4a-h**) with sodium azide under solid supported microwave irradiations. The synthetic methodology has been proved to be facile, rapid and environmentally benign technology accompanied by excellent yield within a few minutes of reaction time.

Acknowledgement

One of the authors (ADM) is thankful to University Grants Commission of Government of Nepal for financial support.

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