

## Synthesis of 2-Amino-5-Substituted-1,3,4-Thiadiazoles (ATDA) and Their Derivatives Using Conventional and Microwave Techniques\*

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### ABSTRACT

A variety of 2-Amino-5-substituted -1,3,4-thiadiazoles (ATDA) were prepared by the reaction of thiosemicarbazide with different substituted carboxylic acids and phosphorous oxychloride as catalyst using conventional methods in comparison with the advantages of microwave techniques.

The 5-(substituted-1,3,4-thiadiazol-2-yl) carbamates derivatives were prepared by refluxing these (ATDA) with ethyl chloroformates using pyridine as a base to neutralize the acid produced which gave higher yield than sodium carbonate. The structures of the products were supported by IR spectroscopy.

**Keywords:** Thiadiazole, carbamates, microwave techniques.

-1,3,4-                      -5-                      -2

-4 3 1-                      -2

( -2-                      -4 3 1-                      )-5 .

## INTRODUCTION

Several procedures were reported for the synthesis of 2-aminothiadiazoles, in many of these methods a thiosemicarbazide was the starting material. Among the most important procedures described were the acylation of thiosemicarbazide to produce 1-acylthiosemicarbazide which then cyclized with a suitable dehydrating agent (Shmeiss *et al.*, 2002).

Acylation was generally performed with an acid chloride and elimination of water from the intermediate was conveniently affected with cold concentrated sulfuric acid (Chubb, 1959; Ohta and Higashijimia, 2002; Solak and Rollas, 2006), 100% phosphoric acid or phosphorous halides (Foxton *et al.*, 1978 ; Saied, 1983).

The energy profile in a microwave-assisted this cyclization was directly absorbed by the reactant molecules (Ajay *et al.*, 2001), and may be quite different from that in which the reaction mixture was heated conventionally by conduction/convection using concentrated sulfuric acid, phosphorous oxy chloride or phosphoric acid (Saied, 1983).

A number of methods for the synthesis of carbamates have been reported, the reactions of amines with alkyl chloroformates being the most common (Saied, 1983; Olofson, 1988).

As part of continuous program directed toward the studies with polyfunctionally substituted heterocycles (AL-Gwady *et al.*, 2007), it was become of interest to investigate preparative routs to synthesize anticipated insecticidal active carbamate derivatives by the reactions of chloroformate with a variety of some 2-amino-5-substituted -1,3,4-thiadiazoles (ATDA). These (ATDA) were synthesized by the reaction of thiosemicarbazide and substituted carboxylic acids using microwave irradiation with comparison with conventional method in which phosphorous oxychloride was used as catalyst.

## EXPERIMENTAL

All melting points were determined on a Gallen Kamp and Electro thermal 1A9300 Digital-Series (1998) apparatus and were uncorrected. The IR-spectra were recorded on Perkin-Elmer 590B Spectrophotometer.

### **2-Amino-5-substituted-1,3,4 – thiadiazoles (ATDA) (1 a-g) and 2,6-bis (5-amino-1,3,4-thiadiazol-2yl) pyridine 1(h):**

**Conventional method (a):**(Saied, 1983 ; Kidwai *et al.*, 1999)

Phosphorous oxychloride (4.6g,0.034mole) was added drop-wise to an ice cold mixture of (0.9g,0.01mole) thiosemicarbazide powdered and (0.01 mole) of the proper carboxylic acid (0.005 mole for 2,6-pyridine dicarboxylic acid) with stirring, reflux was continued for one hour, cooled to room temperature, added to 250 ml of stirred ice-cold water and neutralized with 10% sodium carbonate solution. The precipitated cyclized product was filtered, washed with water and crystallized from aqueous ethanol. Physical and spectral data were listed in Table (1).

**Microwave irradiation method (b):** (Kidwai, 2001; Aly *et al.*, 2006; AL-Gwady *et al.*, 2007)

The reaction mixture of (0.9 g ,0.01 mole) thiosemicarbazide and (0.01 mole) of the proper carboxylic acid (0.005 mole for 2,6-pyridine dicarboxylic acid) were mixed with a spatula for a few minute, placed in an open conical flask in a domestic microwave oven

(containing crucible of 2 gm magnesium sulfate) and irradiated for 5 min. (the reaction was monitored by TLC to indicate the disappearance of the starting material). The resulting mixture was cooled, added to 250ml of stirred ice-cold water, neutralized with 10% sodium carbonate solution and worked up as in method (a).

Table 1: Physical and spectral data of 2-Amino-5-substituted-1,3,4-thiadiazoles (ATDA) (1 a-g) and 2,6-bis (5-amino-1,3,4-thiadiazol-2yl) pyridine 1(h):

Compd. No.1	Method/ Yield %		mp °C	Color	IR, Nujol, Cm <sup>-1</sup>		
	A	B			NH <sub>2</sub> (medium)	C = N (medium)	C – S (weak)
a	60	91	180-84	Brown	3157	1623	625
b	55	92	199-200	Yellow	3150	1623	625
c	35	94	204-6	Gray	3148	1628	620
d	65	91	240-44	Pale yellow	3148	1622	618
e	60	88	167-69	Brown	3145	1624	618
f	36	60	188-90	Yellow	3144	1624	624
g	30	80	210-12	Brown	3149	1621	625
h	70	91	160 (decomposed)	Brown	3155	1621	625

**Ethyl- N-(5-substituted-1,3,4-thiadiazol-2-yl) carbamates (2a – g) and Pyridine -2,6-bis-ethyl-N-(1,3,4-thiadiazole) carbamate 1(h):**

**Method (a):** (Morren, 1959)

(1.085 gm, 0.01 mole) of ethyl chloroformate was added drop-wise to a solution of 0.01 mole of proper amine in 15 ml pyridine (0.005 mole for amine 1h). The reaction mixture was left at room temperature for one hour with occasional shaking. It was then poured onto 100 ml ice water and the precipitated carbamate was filtered, washed with water, dilute hydrochloric acid, then with water again and crystallized from aqueous ethanol. Physical data were listed in Table (2).

**Method (b):** (Petrow, 1959)

(0.84 gm, 0.01 mole) of anhydrous sodium carbonate was added to a solution of 0.01 mole of the appropriate amine in 20 ml. absolute ethanol (0.005 mole for amine 1h), then (1.085 gm, 0.01 mole) of ethyl chloroformate was added drop wise.

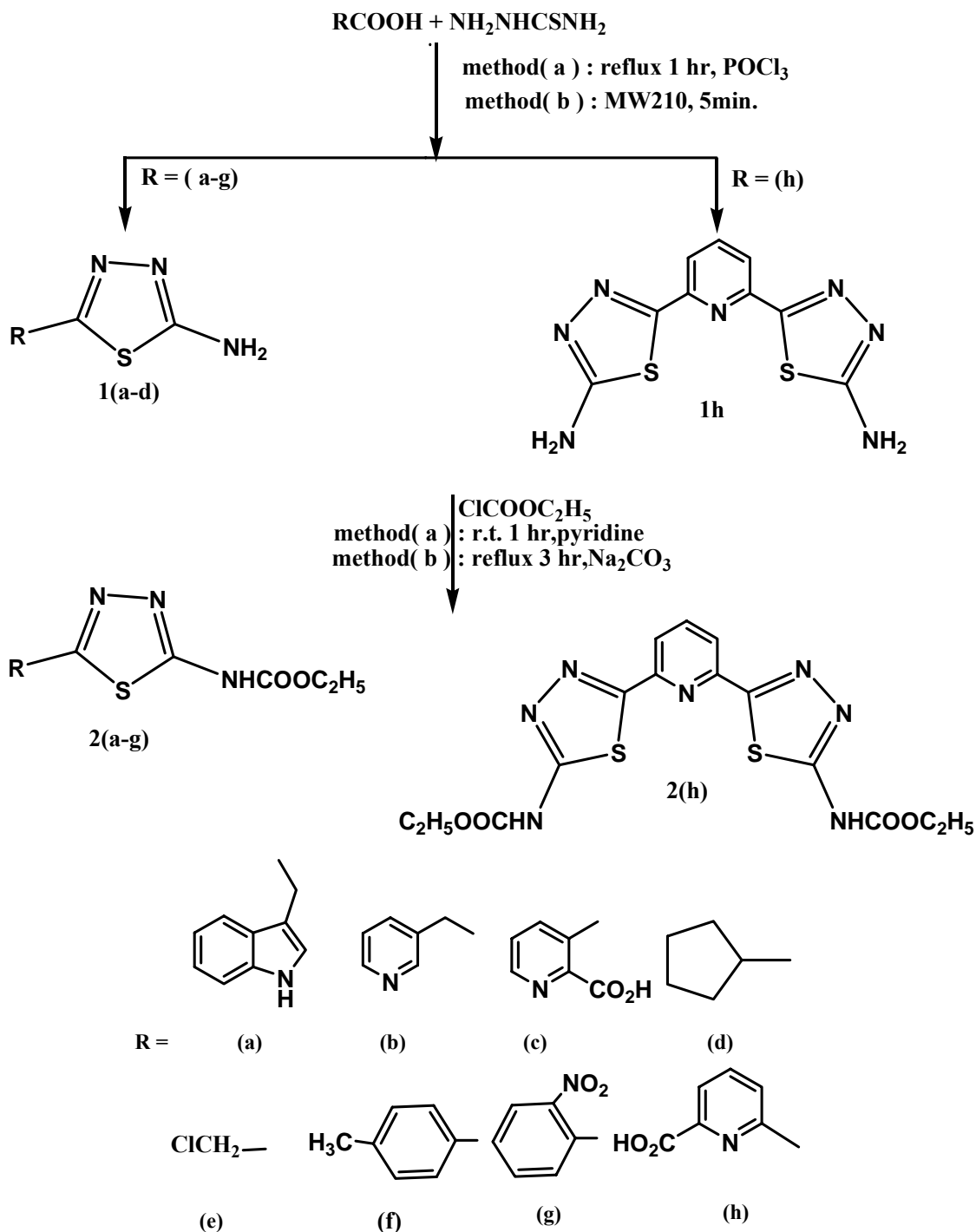
The reaction mixture was refluxed for three hours, cooled to room temperature and poured onto 100 ml ice water. The precipitated product was filtered, and worked up as in method(a).

Table 2: Yields, melting points and I.R. data of Ethyl- N-(5-substituted-1,3,4-thiadiazol-2-yl) carbamates (2a – g) and Pyridine -2,6-bis-ethyl-N-(1,3,4-thiadiazole) carbamate 1(h):

Compound no.2	Yield %		mp °C	IR, Nujol, Cm <sup>-1</sup>		
	Method			N-H (medium)	C = O (strong)	C = N (medium)
	a	B				
a	85	80	108-09	3100	1720	1570
b	85	80	170-72	3150	1720	1595
c	90	70	190-91	3120	1728	1565
d	90	73	137-39	3300	1729	1565
e	80	70	180-82	3300	1730	1580
f	62	30	210-12	3200	1720	1585
g	80	69	235-37	3225	1730	1590
h	93	73	155-56	3280	1730	1575

## RESULTS AND DISCUSSION

Scheme (1) summarizes the synthetic route followed for the preparation of the title compounds.

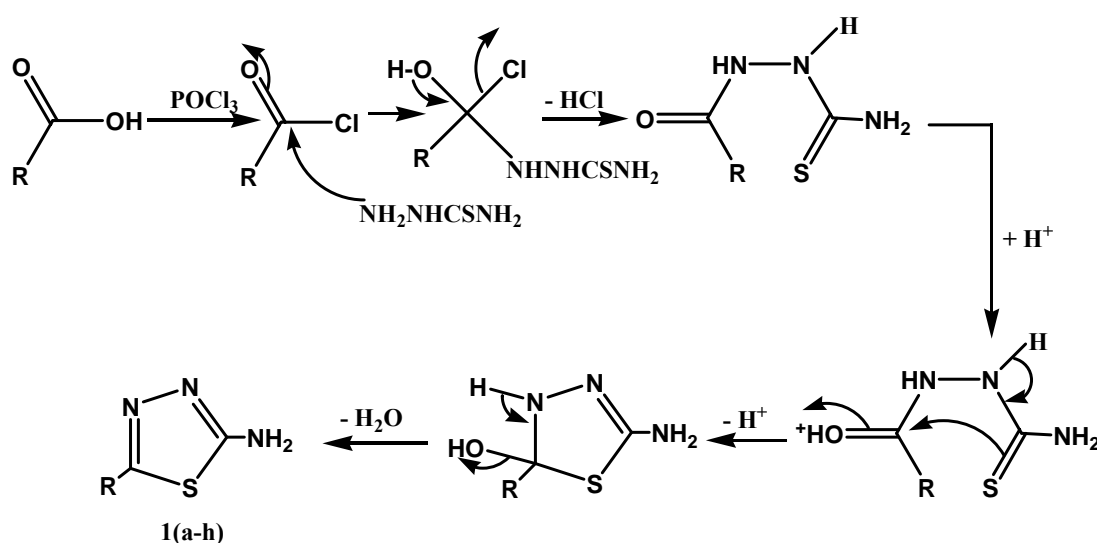


Scheme (1)

**2-Amino-5-substituted-1,3,4-thiadiazoles (ATDA) (1 a-g) and 2,6-bis-(5-amino-1,3,4-thiadiazol-2yl) pyridine 1 (h):**

Several procedures were reported for the synthesis of 2-amino-1,3,4-thiadiazoles, in many of these methods the thiosemicarbazide was the starting material. Among the most important procedures was the one step acylation and cyclization reaction which was achieved by heating the carboxylic acid with thiosemicarbazide in the presence of phosphorus halide (Foxton *et al.*, 1978; Saied, 1983). In this work two methods were carried out, in method (a), the required 2-amino-5-substituted -1,3,4-thiadiazoles (1a-h) was synthesized by refluxing the proper carboxylic acids with a thiosemicarbazide in the presence of phosphorous oxychloride for one hour (Holan, 1960).

Scheme (2) summarizes the reaction mechanism probably proceeds in this method (Saied, 1983).



Scheme (2)

The disappearance of C=O stretching in IR spectra was good indication of conversion of acid to heterocyclic ring, in addition to the following frequencies: 3144-3157  $\text{cm}^{-1}$  due to NH stretching, 1621-1628  $\text{cm}^{-1}$  for C=N stretching and this came in agreement to the published data (Hipler, 2002), and 618-625  $\text{cm}^{-1}$  for C-S ring stretching, Table (1).

In method (b) and to avoid the difficulty in processing (handling pollutant phosphorous oxychloride), to shorten the reaction time and to increase the yield (Kidwai, 2001; Aly *et al.*, 2006), equimolar amounts of thiosemicarbazide and the appropriate acid were mixed together with 1% magnesium sulfate (as an additional microwave energy absorbant, the level of microwave energy required was reduced—presumably because of the attainment of higher efficiency of microwave energy absorption by the reaction mixture.), and the reaction mixture was irradiated in an open vessel in a domestic microwave oven for 5 minutes (Wilson, 1971; Chaaban, 1984; Kidwai, 2001). The yield of these experiments ranged between 60% and 94%, Table (1).

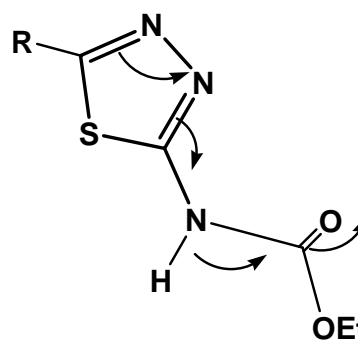
It was worthy to mention that a double cyclization occurred in case of 2,6-pyridine dicarboxylic acid to give compound 1h, while steric effect prevent that to occur in 2,3-pyridine dicarboxylic acid.

### Ethyl- N-(5-substituted-1,3,4-thiadiazol-2-yl)carbamates (2a–g) and Pyridine -2,6-bis-ethyl-N-(1,3,4-thiadiazole) carbamate 1(h):

Many routes in the literatures described the synthesis of carbamates (Metcalf *et al.*, 1962; Armstrong *et al.*, 1969), but the most suitable one which was adopted in this work is the reaction of amines with chloroformic ester (Iradj *et al.*, 1971). The reactivity of chloroformic ester was comparable to that of acid chlorides and not ester due to the strong electron withdrawing inductive effect of adjacent chloride which increase the electrophilicity of carbonyl carbon (Izura *et al.*, 1976; Tóth and Almásy, 2005).

Structures of these products were confirmed by their I.R. spectra which were identical to those published for similar compounds (Saied, 1983), and they were 3100-3300  $\text{cm}^{-1}$ , medium for NH stretching, 1720-1730  $\text{cm}^{-1}$  strong for C=O stretching and 1565-1595, medium, for C = N stretching, this decrease in the frequency (in comparison with that of compounds 1a-h) was due to the decrease of the force constant result from the resonance (produced by the conjugation effects of carbamates groups) (Yukhnovskii, 1967) Scheme (3).

In method (a) Pyridine was used as a base to trap the acid produced at room temperature (Bender, 1960) which gave higher yields (62%-93%) while in method (b) in which the base was sodium carbonate with three-hour refluxed gave yields (30%-80%), Table(2).



Scheme (3)

### CONCLUSION

Microwave irradiation in comparison with conventional methods resolved the important problems in cyclization of thiadiazoles 1(a-h) (the use of the pollutant dehydrating agent phosphorous oxychloride in addition to decrease the work time, increase the products yields, with simplicity in workup). The excellent crystal formation was due to magnesium sulfate. Finally, the new carbamates 2(a-h) were prepared with higher yields, short reaction time using pyridine as a base to trap the acid produced.

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