Journal of Chemistry, Vol. 47 (4), P. 518 - 522, 2009

MICROWAVE-ASSISTED DIRECT SYNTHESIS OF SOME 5-ALKYL-2-AMINO-1,3,4-THIADIAZOLES

Received 10 December 2008

NGUYEN DINH THANH[1*], PHAM HONG LAN[2] AND NGUYEN THI MINH HAI[1]

[1]*Faculty of Chemistry, Hanoi University of Science, VNU*

[2]*Institute E17,Head Department VI, Ministry of Public Security*

ABSTRACT

Some 5-alkyl-2-amino-1,3,4-thiadiazoles have been synthesized by the MW-mediated solvent-free method. The reaction mixture is consisted of aliphatic acid, thiosemicarbazide and concentrated sulfuric acid (98%). Molar ratio of thiosemicarbazide and carboxylic acid was 1:2, reaction time was shortened (20 houres vs. 30 minutes). The structures of these aminothiadiazoles were confirmed by spectrospcopic methods (IR and ^{1}H-NMR).

I - INTRODUCTION

The different classes of thiadiazole compounds have drawn attention of many organic chemists during recent years, since many of these compounds known to possess interesting biological properties such as antimicrobial [1], antituberculosis [2], antiinflammatory [3], anticonvulsant [4], antihypertensive [5], local anesthetic [6], anticancer [7] and hypoglycemic activities [8]. The 1,3,4-thiadiazole derivatives, hence, were synthesized with the aim of new antituberculosis drugs development. The most common procedure for synthesis of 5-substituted 2-amino- or 2-alkylamino-1,3,4-thiadiazoles is the acylation of a thiosemicarbazide or alkylthiosemicarbazides followed by dehydration in the presence of some inorganic acids, such as sulfuric acid, polyphosphoric acid or phosphorus halides [9 - 11].

2-Amino-5-alkyl-1,3,4-thiadiazole compounds are also conventionally prepared by cyclization of a 4-alkylthiosemicarbazide and cyclodehydrating the resulting product. The cyclodehydration is customarily carried out in the presence of concentrated sulfuric acid or polyphosphoric acid. Other well documented methods of cyclodehydration involve the use of polyphosphoric acid, phosphorous pentachloride, or acid chlorides as catalytic agents. In this paper, the syntheses of these amino compounds have been performed using microwave-assistant method.

II - EXPERIMENTAL

Melting points of the synthesized compounds were measured on STUART SMP3 (BIBBY STERILIN-UK). The FT/IR-spectra were recorded on Magna 760 FT-IR Spectrometer (NICOLET, USA) in KBr pellets. The ^{1}H-NMR spectra were recorded on an AVANCE AMX500 FT-NMR Spectrometer (BRUKER, Germany) at 500.13 MHz, using DMSO-d_6 as solvent and TMS as internal standard and coupling constants are reported in Hz. Chemical shift are expressed as δ unit. The reactions were carried out using modified TIFANY 750W microwave oven.

Conventional method for synthesis of 5-alkyl-2-amino-1,3,4-thiadiazoles (3a□f).

General Procedure. The synthetic reaction was carried out as the procedure described in the reference [9] with some modifications. A mixture of aliphatic acid (0.2 mol), thiosemicarbazide (0.075 mol) and 15 mL of concentrated sulfuric acid was mixed up in a round bottomed flask and heated for 20 hours under reflux. After the reaction was complete the reaction mixture was allowed to cool and poured into ice water. The mixture was basified using concentrated ammonium hydroxide solution. The aminothiadiazole product precipitated. It was filtered and the crude product obtained, which was recrystallized from aqueous ethanol (10-15%). The pure product was dried over phosphorus pentoxide under vacuum for 24 hours.

Microwave-assisted method for synthesis of 5-alkyl-2-amino-1,3,4-thiadiazoles (3a□f). ***General procedure.*** A mixture of aliphatic acid **1** (0.2 mol), thiosemicarbazide **2** (0.1 mol) was placed in a 50-mL one-necked, round-bottomed flask, equipped with condenser, and mixed up. Concentrated sulfuric acid (15 mL) was added dropwise and the reaction mixture was stirred carefully. The mixture as irradiated in the domestic microwave oven for 30 min. The reaction mixture was poured into ice-water (for compounds **3a-d**) or distilled with steam for separation of unreacted organic acid (for compounds **3e,f**). The obtained solution was basified using sconcentrated ammonium hydroxide solution to pH 8 and filtered precipitated solid by suction, washed carefully with cold water and recrystallized from 96% ethanol. The pure product was dried over phosphorus pentoxide under vacuum for 24 hours.

2-Amino-5-methyl-1,3,4-thiadiazole (3a). Pale yellow solid, 85%, mp 223 - 224□C; ν_{max}(KBr)/cm^{-1} 3247 (NH), 3084 (NH), 2969 (CH), 1636 (NH), 1531, 1511; δ_H (500 MHz; DMSO-d_6; TMS) 6.932 (2H, s, NH_2), 2.434 (3H, s, CH_3).

2-Amino-5-ethyl-1,3,4-thiadiazole (3b). Pale yellow solid, 78%, mp 181 - 182□C; ν_{max}(KBr)/cm^{-1} 3301 (NH), 3101 (NH), 2976, 2771, 2721 (CH), 1640 (NH), 1524, 1494; δ_H (500 MHz; DMSO-d_6; TMS) 6.961 (2H, s, NH_2), 2.799 (2H, q, *J* 7.5 Hz, CH_2CH$_3$), 1.209 (3H, t, *J* 7.5 Hz, CH$_2$CH_3).

2-Amino-5-*n*-propyl-1,3,4-thiadiazole (3c). Pale yellow solid, 78%, mp 194 - 195□C; ν_{max}(KBr)/cm^{-1} 3271 (NH), 3111 (NH), 2958, 2928, 2870, 2799, 1643 (NH), 1531, 1494; δ_H (500 MHz; DMSO-d_6; TMS) 6.973 (2H, s, NH_2), 2.749 (2H, t, *J* 7.0 Hz, CH_2CH$_2$CH$_3$), 1.628 (2H, sextet, *J* 7.0 Hz, CH$_2$CH_2CH$_3$), 0.913 (3H, t, *J* 7.0 Hz, 3H, CH$_2$CH$_2$CH_3).

2-amino-5-isopropyl-1,3,4-thiadiazole (3d). Pale yellow solid, 82%, mp 189 - 190□C; ν_{max}(KBr)/cm^{-1} 3288 (NH), 3122 (NH), 2962, 2871, 2759 1630 (NH), 1524, 1511; δ_H (500 MHz; DMSO-d_6; TMS) 6.967 (2H, s, NH_2), 3.119 [1H, quintet, *J* 7.0 Hz, CH(CH$_3$)$_2$], 1.233 [6H, t, *J* 7.0 Hz, CH(CH_3)$_2$].

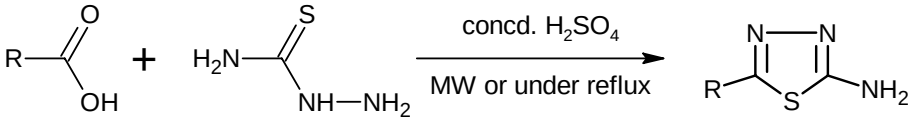
2-amino-5-isobutyl-1,3,4-thiadiazole (3e). Pale yellow solid, 74%, mp 214 - 215□C; ν_{max}(KBr)/cm^{-1} 3288 (NH), 3122 (NH), 2982, 1632 (NH), 1531, 1511; δ_H (500 MHz; DMSO-d_6; TMS) 6.966 (2H, s, NH_2), 2.650 [2H, d, *J* 7.0 Hz, CH_2CH(CH$_3$)$_2$], 1.877 [1H, q, *J* 6.5 and 7.0 Hz, CH$_2$CH(CH$_3$)$_2$], 0.903 (6H, d, *J* 6.5 Hz, CH$_2$CH(CH_3)$_2$]); δ_C (125.76 MHz; DMSO-d_6; TMS) 168.187, 157.253, 38.229, 28.683, 21.910.

2-amino-5-*n*-pentyl-1,3,4-thiadiazole (3f). Pale yellow solid, 73%, mp 193 - 194□C; ν_{max}(KBr)/cm^{-1} 3281 (NH), 3095 (NH), 2955, 2918, 2853, 1637 (NH), 1521, 1498; ^{1}H-NMR (DMSO-d_6): δ=6.949 (2H, s, NH_2), 2.766 (2H, t, *J* 7.5 Hz, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.602 (2H, t, *J* 7.5 Hz, CH$_2$CH_2CH$_2$CH$_2$CH$_3$), 1.289 (4H, quintet, *J* 7.5 Hz, CH$_2$CH$_2$CH_2CH_2CH$_3$), 0.861 (3H, t, *J* 7.5 Hz, CH$_2$CH$_2$CH$_2$CH$_2$CH_3).

III - RESULTS AND DISCUSSION

Some 5-alkyl-2-amino-1,3,4-thiadiazoles have been synthesized by the MW-mediated solvent-free method (scheme 1). The reaction

mixture is consisted of aliphatic acid, thiosemicarbazide and concentrated sulfuric acid (98%). Molar ratio of thiosemicarbazide and carboxylic acid was 1:2.



1a-f **2** **3a-f**

1 and **2:** R=CH_3(**a**), CH_2CH_3 (**b**), $CH_2CH_2CH_3$ (**c**), $CH(CH_3)_2$ (**d**), $CH_2CH(CH_3)_2$ (**e**), $CH_2(CH_2)_3CH_3$ (**f**)

Scheme 1

The comparative results, regarding the conventional preparation [9] (Method A) and MW-assisted syntheses of **3a-3f**, using domestic microwave unit (Method B), are summarized in Table 1. In the last years a growing interest in the use of microwave-assisted reactions in organic synthesis and medicinal chemistry could be observed. Effects noticed with microwave dielectric heating are different from heating: Microwave irradiation produces efficient internal heating (in-core volumeric heating) by direct coupling of microwave energy with the molecules (reagents, solvent,□) that are present in the reaction mixture. These are a shortening of the reaction time, rate enhancement, better selectivity, and reduction of thermally degradative products when compared to conventional syntheses [10].

We indicated that 2-amino-1,3,4-thiadiazole could not be synthesized from formic acid and thiosemicarbazide using MW method, because almost amount of formic acid was evaporated out of the reaction mixture. This compound has been only synthesized by refluxing the mixture of formic acid and thiosemicarbazide in the presence of concentrated sulfuric acid as catalyst. Other aliphatic acids could be obtained by two methods: conventional method and microwave-assisted method.

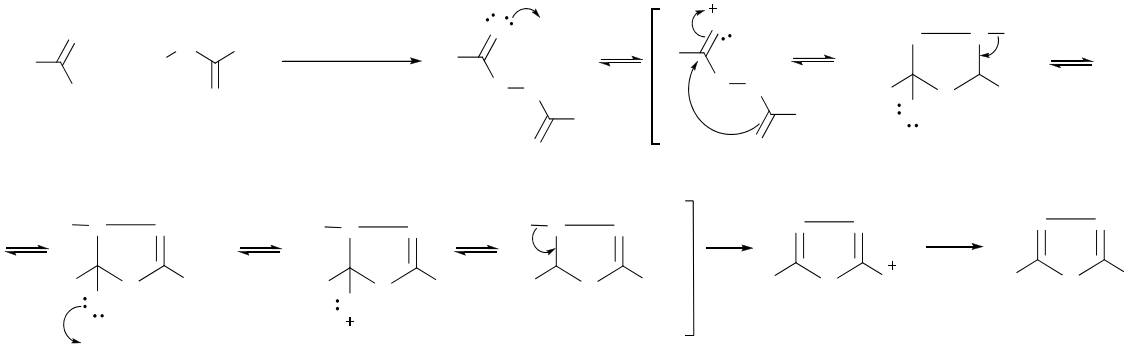
Table 1: Some 5-alkyl-2-amino-1,3,4-thiadiazoles (**3a-f)**

Product	R	Yield (%)[a]		m.p. (□C)
		Conventional method[b]	MW method[c]	
3a	CH_3	72	85	223-224
3b	CH_3CH_2	70	78	181-182
3c	$CH_3CH_2CH_2$	64	78	194-195
3d	$(CH_3)_2CH$	65	82	189-190
3e	$(CH_3)_2CHCH_2$	64	74	214-215
3f	$CH_3(CH_2)_3CH_2$	65	73	193-194

[a] Products purified by recrystallization; the spectroscopic data of compounds **3a-f** were identical with those of the authentic samples prepared previously by conventional method.[b] Method **A**: Rxn. time: 20 h; molar ratio **1/2**=2.7/1; catalyst: concentrated H_2SO_4; [c]Method **B**: molar ratio **1/2**=2/1; MW irradiation applying 50-75% of the maximum power (750 W), for 30 minutes; in some cases sequential irradiations (5-10 min. each) were applied for the total time (30 min.).

The separation of products out of the reaction mixture depended on carbon chain of aliphatic acid: in case of acetic acid and propionic acid, the reaction mixture was poured into ice-water and the obtained solution was neutralized by ammonia solution to pH 8; in remained cases, firsts, the reaction mixture was distilled by steam to remove unreacted organic acids, and residue was neutralized by ammonia solution to pH 8. Using our MW method for in these syntheses we can reduce amount of aliphatic acids added in reaction.

The mechanism of this reaction. The reaction may proceed via acylthiosemicarbazide **4** formed from carboxylic acid and thiosemicarbazide in the presence of concentrated acid at high temperature, acylthiosemicarbazide **4** then undergoes cyclozation at elevated temperatures to provide the 1,3,4-thiadiazole moiety **5**. The dehydration of **5** is completed by heating the reaction mixture at temperatures between about 100□C and 120□C. Product **6**, salt of 5-alkyl-2-amino-1,3,4-thiadiazole, was formed. The preferred cyclodehydration temperature is about 105□ to 110□C at which thiadiazole formation occurs in about 3-4 hours. The heating time varies inversely with the temperature. After cyclodehydration is completed, preferably at 105□C, the reaction mixture is diluted with water and the acid is neutralized to provide the aminothiadiazole free base (*see scheme 2*).

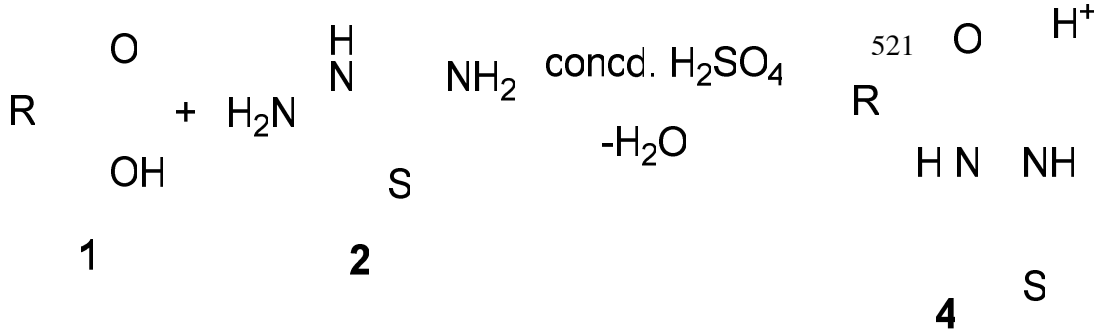


Scheme 2

CONCLUSIONS

We have synthesized a series of 5-alkyl-2-amino-1,3,4-thiadiazoles derivatives by one-pot method under microwave irradiation, thus providing a facile, rapid, efficient and environmentally friendly method. Reaction time was shortened (20 houres *vs*. 30 minutes). The sctructures of these aminothiadiazoles were confirmed by IR- and ^{1}H-NMR spectral data.

Acknowledgements: *This publication is completed with financial support from the Grant QGTĐ.08.03, Vietnam National University, Hanoi*.



1 2 4

REFERENCES

1. (a) K. Desai, A. J. Baxi. Indian J. Pharm. Sci., **54**, 183 (1992). (b) N. G. Gawande, M. S. Shingare. Indian J. Chem., **26B**, 387 (1987). (c) M. G. Mamolo, L. Vio, E. Banfi. Farmaco, **51**, 71 (1996).
2. H. K. Shucla, N. C. Desai, R. R.. Astik, K. A. Thaker. J. Indian Chem. Soc., **61**, 168 (1984).
3. (a) M. D. Mullican, M. W. Wilson, D. T. Connor, C. R. Kostlan, D. J. Schrier, R. D. Dyer. J. Med. Chem., **36**, 1090 (1993). (b) Y. Song, D. T. Connor, A. D. Sercel, R. J. Sorenson, R. Doubleday, P. C. Unangst, B. D. Roth, V. G. Beylin, R. B. Gilbertsen, K. Chan, D. J. Schrier, A. Guglietta, D. A. Bornemeier, R. D. Dyer. J. Med. Chem., **42**, 1161 (1999). (c) L. Labanauskas, V. Kalcas, E. Udrenaite, P. Gaidelis, A. Brukstus, A. Dauksas. Pharmazie, **56**, 617 (2001).
4. (a) C. B. Chapleo, M. Myers, P. L. Myers, J. F. Saville, A. C. Smith, M. R. Stillings, I. F. Tulloch, D. S. Walter, A. P. Welbourn. J. Med. Chem., **29**, 2273 (1986). (b) C. B. Chapleo, P. L. Myers, A. C. Smith, M. R. Stillings, I. F. Tulloch, D. S. Walter, J. Med. Chem., **31**, 7 (1988).
5. (a) S. Turner, M. Myers, B. Gadie, A. J. Nelson, R. Pape, J. F. Saville, J. C. Doxey, T. L. Berridge. J. Med. Chem., **31**, 902 (1988). (b) S. Turner, M. Myers, B. Gadie, S. A. Hale, A. Horsley, A. J. Nelson, R. Pape, J. F. Saville, J. C. Doxey, T. L. Berridge. J. Med. Chem., **31**, 907 (1988).
6. G. Mazzone, R. Pignatello, S. Mazzone, A. Panico, G. Penisi, R. Castana, P. Mazzone. Farmaco, **48**, 1207 (1993).
7. (a) K. Miyamoto, R. Koshiura, M. Mori, H. Yokoi, C. Mori, T. Hasegawa, K. Takatori. Chem. Pharm. Bull., **33**, 5126 (1985). (b) J. Y. Chou, S. Y. Lai, S. L. Pan, G. M. Jow, J. W. Chern, J. H. Guh. Biochem. Pharmacol., **66**, 115 (2003).
8. M. A. Hanna, M. M. Girges, D. Rasala, R. Gawinecki. Arzneim.-Forsch./Drug Res., **45**, 1074 (1995).
9. (a) G. Kornig. In Comprehensive Heterocyclic Chemistry; A. R. Katritzky, C. W. Rees. Eds.; Elsevier: Oxfor, Vol.6, p. 568 (1997). (b) F. L. Chubb, Nissenbaum. J. Can. J. Chem., **37**, 1121 (1959).
10. (a) H. M. Kingston, S. J. Haswell. Microwave-Enhanced Chemistry: Fundamentals, Sample Preparation and Applications; American Chemical Society: Washington, D.C., 1997. b) Loupy, A. (Ed) Microwaves in organic synthesis; Wiley-VCH: Weinheim, 1997. (c) C. O. Kappe Stadtler. A. Microwaves in organic and medicinal chemistry; Wiley-VCH: Weinheim, 2005; (d) C. O. Kappe. Angew. Chem. Int. Ed., **43**, pp. 6250-6284 (2004).
11. Brooks, J. D.; Charlton, P. T.; Macey, P. E.; Peak D. X.; Short, W. F., J. Chem. Soc., 542 (1950).

Corresponding author: **Nguyen Dinh Thanh**
Faculty of Chemistry,
College of Sciences, Vietnam National University, Hanoi.