

Mounim Lebrini <sup>a</sup>, Fouad Bentiss <sup>a,b</sup> and Michel Lagrenée <sup>a,\*</sup><sup>a</sup>Laboratoire de Cristalchimie et Physicochimie du Solide, CNRS UMR 8012  
ENSCL, B.P. 90108, F-59652 Villeneuve d'Ascq Cedex, France<sup>b</sup>Laboratoire de Chimie de Coordination et d'Analytique, Université Chouaib Doukkali,  
Faculté des Sciences, B.P. 20, El Jadida, Morocco

Received December 6, 2004

The one pot, three-components condensation of aromatic aldehydes, hydrazine and sulfur in ethanol under microwave irradiation provided symmetrically 3,5-disubstituted 1,3,4-thiadiazoles in high yields and good purity. This reaction must be conducted under pressure of hydrogen sulfide produced *in-situ*. The structure of the compounds was confirmed by <sup>1</sup>H, <sup>13</sup>C NMR, MS and elemental analysis.

*J. Heterocyclic Chem.*, **42**, 991 (2005).

## Introduction

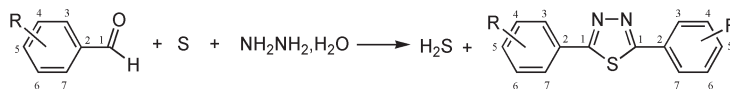
As a part of a program directed to obtain heterocyclic molecules which can be used as corrosion inhibitors [1-4] and which can exhibit antimicrobial and antibacterial activities [5,6], a number of symmetrically 2,5-disubstituted-1,3,4-thiadiazoles are quickly prepared by the reaction of aromatic aldehyde on hydrazine hydrate in presence of sulphur under microwave irradiation. Several publications and patents describe the synthesis of these heterocyclic compounds by treatment of mono or 1,2-dibenzoylhydrazine with phosphorous pentasulfide [7] and by treatment of aromatic aldehydes with sulphur and hydrazine hydrate in a steel autoclave at 150 °C for 12 hours [8]. Microwave assisted organic reaction constitute an emerging technology that make experimentally and industrially important organic syntheses more effective and more eco-friendly than conventional reactions [9,10]. This technique has been applied with success to a number of synthesis of heterocyclic compounds proceeding with or without solvent such as 1,2,4-triazoles [11,12], 1,3,4-oxadiazoles [13] and 1,3,4-thiadiazoles [14].

## Results and Discussion

The reaction of aromatic aldehydes with hydrazine hydrate and sulfur takes place in good yields and rapidly under microwave irradiation (Scheme and Table 1) and

must be conducted under pressure of hydrogen sulfide. For this purpose we have used a microwave equipment designed for extraction, digestion, dissolution, hydrolysis or drying material. The primary purpose of this equipment is the rapid preparation of samples for a variety of analysis procedures, but we report here that it can be very efficient for organic syntheses, which must be carried out under a moderate controlled pressure. In each synthesis of thiadiazoles, the initial product is the yellow colored benzalazine, which can be isolated after 15 mn of reaction. After 1 h of microwave heating under pressure of hydrogen sulfide, the thiadiazoles can be obtained in excellent yields and good purity. Under classical heating, a good completion of this reaction required much longer times (12 h) and if the reaction is stopped after 1 hour of reaction as in microwave experiments, the thiadiazoles can be detected in very low quantities, the major products of the reaction being the corresponding azines. 2-Chlorobenzaldehyde yields 3*H*-1,2-benzodithiole-3-thione under the same experimental conditions, as it was reported by G. Mazzone *et al.* [8]. The elemental analysis (Table 2) and mass spectra are in accordance with the proposed structures. The melting points of the already known thiadiazoles agree with those reported in the literature (Table 2). The <sup>1</sup>H and <sup>13</sup>C nmr data are given in Table 3 and 4. A typical reaction procedure is as follows for the preparation compounds **2a-p**.

Scheme 1



|              |                                                       |              |                                                                       |
|--------------|-------------------------------------------------------|--------------|-----------------------------------------------------------------------|
| <b>1, 2a</b> | Ar = 2-HOC <sub>6</sub> H <sub>4</sub>                | <b>1, 2i</b> | Ar = 4-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> |
| <b>b</b>     | Ar = 3-HOC <sub>6</sub> H <sub>4</sub>                | <b>j</b>     | Ar = 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>                  |
| <b>c</b>     | Ar = 4-HOC <sub>6</sub> H <sub>4</sub>                | <b>k</b>     | Ar = 4-ClC <sub>6</sub> H <sub>4</sub>                                |
| <b>d</b>     | Ar = 3,4-HOC <sub>6</sub> H <sub>4</sub>              | <b>l</b>     | Ar = 2-pyridyl                                                        |
| <b>e</b>     | Ar = C <sub>6</sub> H <sub>5</sub>                    | <b>m</b>     | Ar = 3-pyridyl                                                        |
| <b>f</b>     | Ar = 2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> | <b>n</b>     | Ar = 4-pyridyl                                                        |
| <b>g</b>     | Ar = 3-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> | <b>o</b>     | Ar = 2-thienyl                                                        |
| <b>h</b>     | Ar = 4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> | <b>p</b>     | Ar = 3-thienyl                                                        |



Table 3  
<sup>1</sup>H nmr data (δ values, dimethyl-d<sub>6</sub> sulfoxide) for 2,5-Diaryl-1,3,4-thiadiazoles **2a-p**

| Compound No. | Aromatic signals                                                                                              | Substituent                   |
|--------------|---------------------------------------------------------------------------------------------------------------|-------------------------------|
| <b>2a</b>    | 7.02 (t, J = 7.2 Hz, 2H); 7.09 (d, J = 8.06 Hz, 2H),<br>7.39 (t, J = 7.08 Hz, 2H); 8.25 (d, J = 7.33 Hz, 2H)  | 11.31 (s, 2H) OH              |
| <b>2b</b>    | 6.96-7.00 (m, 2H); 7.41-7.42 (m, 6H)                                                                          | 9.97 (s, 2H) OH               |
| <b>2c</b>    | 6.95 (d, J = 8.79 Hz, 4H); 7.81 (d, J = 8.54 Hz, 4H)                                                          | 10.41 (s, 2H) OH              |
| <b>2d</b>    | 6.88 (d, J = 8.06 Hz, 2H); 7.25 (d, J = 8.06 Hz, 2H);<br>7.41 (s, 2H)                                         | 9.60 (s, 4H) OH               |
| <b>2e</b>    | 7.58-7.61 (m, 6H); 8.00-8.05 (m, 4H)                                                                          | —                             |
| <b>2f</b>    | 6.91 (d, J = 7.32 Hz, 2H); 7.00 (t, J = 8.24 Hz, 2H);<br>7.16 (d, J = 7.33 Hz, 2H); 7.29 (t, J = 7.78 Hz, 2H) | 3.78 (s, 6H) OCH <sub>3</sub> |
| <b>2g</b>    | 7.16 (d, J = 7.63 Hz, 2H); 7.45-7.59 (m, 6H)                                                                  | 3.85 (s, 6H) OCH <sub>3</sub> |
| <b>2h</b>    | 7.13 (d, J = 8.54 Hz, 4H); 7.94 (d, J = 8.54 Hz, 4H)                                                          | 3.85 (s, 6H) OCH <sub>3</sub> |
| <b>2i</b>    | 6.82 (d, J = 8.54 Hz, 4H); 7.76 (d, J = 8.54 Hz, 4H)                                                          | 3.01 (s, 12H) CH <sub>3</sub> |
| <b>2j</b>    | 7.32 (d, J = 7.94 Hz, 4H); 7.84 (d, J = 7.94 Hz, 4H)                                                          | 2.37 (s, 6H) CH <sub>3</sub>  |
| <b>2k</b>    | 7.69 (d, J = 7.82 Hz, 4H); 8.05 (d, J = 7.82 Hz, 4H);                                                         | —                             |
| <b>2l</b>    | 7.62 (d, J = 6.1 Hz, 2H); 8.07 (d, J = 7.78 Hz, 2H)<br>8.34 (t, J = 7.92 Hz, 2H); 8.76 (t, J = 3.96 Hz, 2H)   | —                             |
| <b>2m</b>    | 7.65 (t, J = 4.85 Hz, 2H); 8.44 (d, J = 7.82 Hz, 2H);<br>8.79 (d, J = 7.82 Hz, 2H); 9.22 (s, 2H)              | —                             |
| <b>2n</b>    | 8.02 (d, J = 6.4 Hz, 4H); 8.84 (d, J = 6.4 Hz, 4H)                                                            | —                             |
| <b>2o</b>    | 7.27 (t, J = 4.42 Hz, 2H); 7.81 (d, J = 3.67 Hz, 2H);<br>7.88 (d, J = 4.88 Hz, 2H)                            | —                             |
| <b>2p</b>    | 7.68 (d, J = 5.19 Hz, 2H); 7.80 (d, J = 5.19 Hz, 2H);<br>8.33 (s, 2H)                                         | —                             |

Table 4  
<sup>13</sup>C nmr data (δ values, dimethyl-d<sub>6</sub> sulfoxide) for 2,5-Diaryl-1,3,4-thiadiazoles **2a-p**  
 (Numerotation of C is given in Scheme 1)

| Compound No. | C <sub>1</sub> | C <sub>2</sub> | C <sub>3</sub> | C <sub>4</sub> | C <sub>5</sub> | C <sub>6</sub> | C <sub>7</sub> | Substituent |
|--------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|-------------|
| <b>2a</b>    | 163.12         | 116.49         | 154.74         | 116.80         | 131.87         | 119.66         | 127.65         | —           |
| <b>2b</b>    | 167.64         | 130.67         | 118.67         | 157.99         | 113.72         | 130.56         | 118.56         | —           |
| <b>2c</b>    | 166.55         | 120.63         | 129.20         | 116.18         | 160.28         | 116.18         | 129.20         | —           |
| <b>2d</b>    | 166.58         | 119.79         | 114.10         | 148.64         | 145.83         | 116.19         | 120.95         | —           |
| <b>2e</b>    | 167.72         | 131.45         | 127.64         | 129.46         | 129.51         | 129.46         | 127.64         | —           |
| <b>2f</b>    | 169.56         | 124.91         | 156.95         | 111.12         | 130.79         | 120.03         | 128.96         | 55.43       |
| <b>2g</b>    | 167.63         | 130.64         | 130.73         | 159.73         | 117.35         | 112.28         | 120.15         | 55.40       |
| <b>2h</b>    | 166.58         | 122.15         | 129.16         | 114.85         | 161.56         | 114.85         | 129.16         | 55.46       |
| <b>2i</b>    | 168.52         | 127.54         | 126.09         | 114.15         | 151.85         | 114.15         | 126.09         | 39.68       |
| <b>2j</b>    | 161.12         | 130.96         | 128.69         | 130.69         | 140.5          | 130.69         | 128.69         | 21.25       |
| <b>2k</b>    | 166.91         | 129.59         | 128.20         | 129.35         | 136.15         | 129.35         | 128.20         | —           |
| <b>2l</b>    | 171.14         | 148.17         | —              | 150.30         | 126.22         | 138.02         | 120.56         | —           |
| <b>2m</b>    | 171.12         | 126.20         | 148.16         | —              | 150.29         | 120.54         | 137.99         | —           |
| <b>2n</b>    | 170.23         | 137.27         | 122.76         | 152.22         | —              | 152.22         | 122.76         | —           |
| <b>2o</b>    | 160.89         | 131.10         | —              | 130.69         | 128.67         | 130.94         | —              | —           |
| <b>2p</b>    | 161.76         | 128.62         | 130.75         | —              | 127.95         | 126.21         | —              | —           |

by the reaction of hydrazine with sulfur, leads to the formation of the tetrahydrothiadiazole ring, which is rapidly dehydrogenated by the sulfur (Scheme 2).

The first step, the azine formation, is expected to be faster than the second one, the addition of hydrogen sulfide, which must be present in excess as it can be seen on the figure. When the reaction is stopped just after the

stabilization of the pressure (15 min), the yield in thiadiazoles is very poor and the azine can be isolated in good quantity.

Several new 1,3,4-thiadiazoles have been tested as corrosion inhibitors for steel in acidic media. These studies have shown that the thiadiazole derivatives are very efficient even at low concentration (10<sup>-4</sup> M) [3,15].

## EXPERIMENTAL

A mixture of aromatic aldehyde **1a-r** (0.02 moles), sulfur (0.03 g-atom) and hydrazine hydrate (0.08 moles) in ethanol (20 ml) was introduced into a fluoropolymere cylindrical flask placed in a MARS5 XP-1500 PLUS CEM multimode microwave reactor and irradiated for 1 h (300 W) at 150 °C under pressure (Figure). After cooling, the solvent was evaporated under reduced pressure.

2,5-Diaryl-1,3,4-thiadiazoles **2a-d**.

The residue was treated with ethanol and filtered to remove the sulfur. The ethanolic solution was evaporated under reduced pressure and the residue was treated with 50 ml of an aqueous solution of sodium hydroxide (20 %) and filtered. Treatment of the filtrate with an aqueous hydrochloric acid solution (37 %) gives a yellowish precipitate, which is collected by filtration and washed with water and dried. Products were crystallized from ethanol.

2,5-Diaryl-1,3,4-thiadiazoles **2e-p**.

The residue was dissolved in chloroform. The chloroform solution was shaken with a concentrated sodium sulfide solution (to remove most of the sulfur), with water, dried (magnesium sulfate), filtered and then evaporated by rotary evaporation. The resulting residue was crystallized from ethanol.

Products **2a-p** was identified by <sup>1</sup>H and <sup>13</sup>C nmr and MS: data are in accordance with the proposed structures.

## REFERENCES AND NOTES

\* Corresponding author: Tel.: +33-320-337-746; fax: +33-

320-436-814; E-mail address: michel.lagrenée@ensc-lille.fr (Michel Lagrenée).

- [1] F. Bentiss, M. Traisnel and M. Lagrenée, *J. Appl. Electrochem.*, **31**, 41 (2001).
- [2] M. Lagrenée, B. Mernari, M. Bouanis, M. Traisnel and F. Bentiss, *Corros. Sci.*, **44**, 573 (2002).
- [3] M. El Azhar, B. Mernari, M. Traisnel, F. Bentiss and M. Lagrenée, *Corros. Sci.*, **43**, 2229 (2001).
- [4] F. Bentiss, M. Lebrini, H. Vezin and M. Lagrenée, *Mater. Chem. Phys.*, **87**, 18 (2004).
- [5] G. Mazzone, F. Bonina, G. Puglisi, R. Arrigo-Reina, C. Cosentino and G. Blandino, *Il Farmaco Ed Sci.*, **37**, 685 (1982).
- [6] P. R. Naik, S. N. Pandeya and P. N. Singh, *Pharmaceutike*, **4**, 44 (1991).
- [7] A. E. Siegrist, E. Maeder, M. Duennenberger and P. Liechti, Swiss Patent, 426, 848, (1967); *Chem. Abstr.*, **68**, 69002 (1968).
- [8] G. Mazzone, G. Puglisi, F. Bonina and A. Corsaro, *J. Heterocyclic Chem.*, **20**, 1399 (1983).
- [9] C. O. Kappe, *Angew. Chem. Int. Ed.*, **43**, 6250, 2004.
- [10] A. Loupy, *Microwaves in Organic Synthesis*, Wiley-VCH, Germany, 2002.
- [11] F. Bentiss, M. Lagrenée and D. Barbry, *Tetrahedron Lett.*, **41**, 1539 (2000).
- [12] S. Rostamizadch, H. Tajik and S. Yazdanfarahi, *Synth. Commun.*, **33** (1), 113 (2003).
- [13] F. Bentiss, M. Lagrenée and D. Barbry, *Synth. Commun.*, **31** (6), 935 (2001).
- [14] H.-M. Huang, H.-T. Yu, P.-L. Chen, J. Han and J.-B. Meng, *Youji Huaxue*, **24** (5), 502 (2004).
- [15] M. Lebrini, M. Lagrenée, H. Vezin, L. Gengembre and F. Bentiss, *Corros. Sci.*, **47** (2) (2005) 485.