

SYNTHESIS OF SOME 2-R-5-FORMYL-1,3,4-THIADIAZOLE DERIVATIVES BY SOMMELET REACTION

GEORGETA ȘERBAN^{1*}, STELA CUC², EVA EGRI³,
ANAMARIA SALVAN⁴

¹*University of Oradea, Faculty of Medicine and Pharmacy,
Pharmaceutical Chemistry Department, 29 Nicolae Jiga, 410028
Oradea, România*

²*University of Waterloo, Department of Earth Sciences, Environmental
Isotope Laboratory, Waterloo, Ontario, Canada*

³*Vitalogy Farmacia, Aleșd, Bihor, România*

⁴*Phania Farmacia, Sânmartin, Bihor, România*

*corresponding author: getaserban_2000@yahoo.com

Abstract

Some 2-R-5-formyl-1,3,4-thiadiazole derivatives have been synthesized and characterized by their spectral data. Thus, the present paper describes the formation and hydrolysis, through Sommelet reaction, of some hexamethylenetetramine salts from which some new heterocyclic aldehydes resulted.

Rezumat

Au fost sintetizați și caracterizați prin metode spectrale noi derivați 2-R-5-formil-1,3,4-tiadiazolici. Astfel, lucrarea prezintă sinteza și hidroliza, prin intermediul reacției Sommelet, a unor săruri de urotropiniu din care s-au obținut noi aldehyde heterociclice.

Keywords: 1,3,4-thiadiazoles, hexamethylenetetramine salts, Sommelet reaction

Introduction

In recent years 1,3,4-thiadiazole derivatives have received significant attention and have been increasingly investigated due to their diverse range of biological properties. They exhibit, for example, antimicrobial [5, 6, 7, 11], antimycobacterial [14], anticancer [2, 3, 13], antiinflammatory [9], carbonic anhydrase inhibiting effect [1, 15], antianxiety, antidepressant [4], antioxidant properties [12]. 1,3,4-Thiadiazoles exhibit diverse biological activities, possibly due to the presence of =N–C–S moiety [8].

The Sommelet reaction allows the synthesis of aldehydes from benzylhalides by the reaction with hexamethylenetetramine HMTA (urotropine) and subsequent acidic hydrolysis of the resulting quaternary ammonium salt. Although initial examples indicated that hindered substrates were not proper for the Sommelet reaction, the scientists discovered that

some 2,6-disubstituted benzylamines underwent the amine to aldehyde conversion in 17-68% yields. After that, the Sommelet reaction was applied for obtaining aromatic dialdehydes with moderate to good yields. The Sommelet reaction has been widely extended to heterocycles which are important to chemists. With yields ranging from 50% to 57%, aldehydes of pyridine, isoquinoline and thiazole were prepared from the corresponding heteroarylmethyl bromides [10, 19].

Considering the above facts, the goal of the present study was to synthesize, by Sommelet reaction, some bisheterocyclic aldehydes which combine substituted 1,3,4-thiadiazoles with six-member heterocyclic rings in order to develop hybrid molecules with potential of enhanced biological activity.

Materials and methods

Substrates: thiosemicarbazides **2a-d** and 2-R-5-chloromethyl-1,3,4-thiadiazoles **3a-d** are known compounds presented in a previous paper [17].

General procedure for the synthesis of hexamethylenetetramine salts **4**

Hexamethylenetetramine (0.8 g, 6 mmol) was dissolved in 7 mL of chloroform and the corresponding 1,3,4-thiadiazole **3** (5.5 mmol) solved in chloroform was added as rapidly as possible under stirring. A reflux condenser was attached and the mixture was refluxed over a water bath for 1h. During the heating a white solid appeared. After cooling to room temperature, the precipitate separated was filtered to obtain the desired product **4**. It is usually very difficult to purify the salt.

N-(2-Piperidyl-1,3,4-thiadiazole-5-yl-methyl)hexamethylene-tetramine hydrochloride (4c). Colorless prisms, mp 185-187°C, 46% yield. IR (KBr) cm^{-1} : 2725 (N^+), 1625 ($\text{C}=\text{N}$), 1010 ($\text{C}-\text{N}$), 683 ($\text{C}-\text{S}-\text{C}$). ^1H -NMR (300 MHz, CDCl_3) δ : 1.61-1.82 (m, 6H, C_{2-4} -H pip), 2.95 (t, 4H, C_1 -H, C_5 -H pip), 3.51 (s, 2H, CH_2), 4.59 (s, 12H, $\text{N}-\text{CH}_2-\text{N}$). *Anal.* Calcd for $\text{C}_{14}\text{H}_{24}\text{ClN}_7\text{S}$: C, 46.98; H, 6.76; N, 27.39. Found: C, 47.12; H, 6.53; N, 27.58. MW 357.91.

N-(2-Morfolinyl-1,3,4-thiadiazole-5-yl-methyl)hexamethylene-tetramine hydrochloride (4d). Colorless prisms, mp 194-196°C, 52% yield. IR (KBr) cm^{-1} : 2700 (N^+), 1620 ($\text{C}=\text{N}$), 1015 ($\text{C}-\text{N}$), 680 ($\text{C}-\text{S}-\text{C}$). ^1H -NMR (300 MHz, CDCl_3) δ : 3.27 (t, 4H, C_1 -H, C_5 -H morph), 3.65 (s, 2H, CH_2), 4.01 (t, 4H, C_2 -H, C_4 -H morph), 4.67 (s, 12H, $\text{N}-\text{CH}_2-\text{N}$). *Anal.* Calcd for $\text{C}_{13}\text{H}_{22}\text{ClN}_7\text{OS}$: C, 43.39; H, 6.16; N, 27.24. Found: C, 43.45; H, 6.07; N, 27.09. MW 359.88.

General procedure for the synthesis of 2-R-5-formyl-1,3,4-thiadiazole derivatives 5

The hexamethylenetetramine salt **4** (3.6 mmol) was heated in 50% acetic acid (15 mL) under reflux for 1h, then water (15 mL) and concentrated hydrochloric acid (3 mL) were added and refluxed for another 5 min. The mixture was cooled, filtered and the filtrate was neutralized with saturated solution of sodium bicarbonate when a solid product separated. The product was removed, washed with cold water and further recrystallised from aqueous ethanol to obtain the desired product **5**.

2-Piperidyl-5-formyl-1,3,4-thiadiazole (5c). Colorless needles, mp 195-197°C (aqueous ethanol), 65% yield. IR (KBr) cm^{-1} : 1712 (C=O), 1665 (C=N), 746 (C-S-C). $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 1.85-1.96 (m, 6H, $\text{C}_{2-4}\text{-H}$ pip), 3.12 (t, 4H, $\text{C}_1\text{-H}$, $\text{C}_5\text{-H}$ pip), 10.07 (s, 1H, CHO). MS (FAB, positive ion mode) m/z 198 $[\text{M}+\text{H}^+]$. *Anal.* Calcd for $\text{C}_8\text{H}_{11}\text{N}_3\text{OS}$: C, 48.71; H, 5.62; N, 21.30. Found: C, 48.79; H, 5.47; N, 21.25. MW 197.26.

2-Morfolinyl-5-formyl-1,3,4-thiadiazole (5d). Colorless needles, mp 211-213°C (aqueous ethanol), 69% yield. IR (KBr) cm^{-1} : 1698 (C=O), 1645 (C=N), 710 (C-S-C). $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 3.46 (t, 4H, $\text{C}_1\text{-H}$, $\text{C}_5\text{-H}$ morph), 4.12 (t, 4H, $\text{C}_2\text{-H}$, $\text{C}_4\text{-H}$ morph), 10.34 (s, 1H, CHO). MS (FAB, positive ion mode) m/z 200 $[\text{M}+\text{H}^+]$. *Anal.* Calcd for $\text{C}_7\text{H}_9\text{N}_3\text{O}_2\text{S}$: C, 42.20; H, 4.55; N, 21.09. Found: C, 42.34; H, 4.57; N, 21.01. MW 199.23.

Melting points were measured using the open capillary tube method on Schmelzpunkt Bestimmer Apotec apparatus and are uncorrected. The purity of the synthesized compounds was checked by thin layer chromatography on Silicagel 60 F_{254} Merck plates and visualized by exposure in UV light. The IR spectra were recorded as potassium bromide pellets using a JASCO FTIR-615 spectrophotometer. The $^1\text{H-NMR}$ spectra in deuteriochloroform were recorded by a Varian Mercury-300 spectrometer. The NMR spectral data are reported in parts per million downfield from the internal standard (tetramethylsilane, δ 0.0). The Fast Atom Bombardment tandem Mass Spectroscopy (FAB-MS) spectra were obtained using a VG-70SE spectrometer. The elemental analysis was performed using a Vario El CHNS analyzer. All chemicals and solvents were purchased from Farmachim Ploiești, Reactivul București, Chimprod, Fluka Chemie and Merck.

Results and discussion

In previous papers [16-18] we reported the synthesis of some 2,5-disubstituted 1,3,4-thiadiazoles using aromatic and heterocyclic amines as

starting materials. Considering that thiosemicarbazide structure is a very good skeleton for the synthesis of some heterocyclic rings (e.g. 1,2,4-triazole, 1,3,4-thiadiazole, 1,3,4-oxadiazole, 1,3,4-triazine derivatives, etc.) [5, 14, 16], the cyclization of substituted thiosemicarbazides in acidic media was used for the formation of 1,3,4-thiadiazoles.

The synthesis of 2-R-5-formyl-1,3,4-thiadiazole derivatives was achieved through the synthetic routes outlined in Figure 1 and Figure 2. The aromatic and heterocyclic amines **1a-d**, after treatment with carbon disulfide in ammonium hydroxide followed by refluxing with hydrazine hydrate in ethanol were converted to the thiosemicarbazides **2a-d**. After treatment with monochloroacetyl chloride, the intermediary thiosemicarbazides **2a-d** were cyclized into the 2-R-5-chloromethyl-1,3,4-thiadiazoles **3a-d** as the result of a ring closure reaction. The study revealed a different behavior of the intermediary thiosemicarbazides **2a-d** during the cyclization reaction to form the 1,3,4-thiadiazole ring. Since the yields for the obtained products **3a-d** are very different even if we worked in the same experimental conditions, these results showed that the heterocyclic thiosemicarbazides **2c,d** were more reactive compared to aromatic thiosemicarbazides **2a,b** possibly due to the influence of the heterocyclic ring.

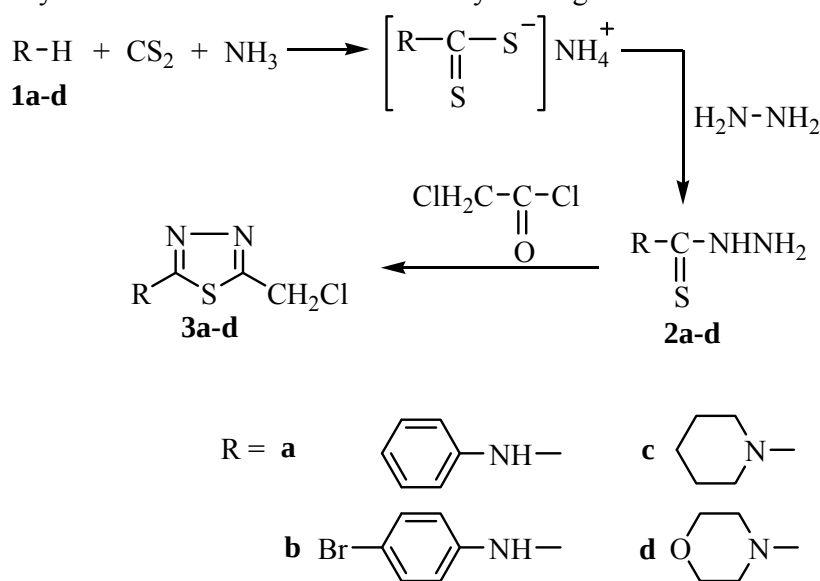


Figure 1

Synthesis of 2-R-5-chloromethyl-1,3,4-thiadiazole derivatives **3a-d**

Taking into account the high reactivity of the chloromethyl group, we decided to study the applicability of the Sommelet reaction to the formation of the desired aldehydes. The key intermediates of the Sommelet reaction, the quaternary hexamethylenetetramine salts were prepared after refluxing the 2-R-5-chloromethyl-1,3,4-thiadiazole derivatives **3c,d** with hexamethylenetetramine in chloroform, when the salt products crystallized out. Hydrolysis of the hexamethylenetetramine salts was performed with 50% acetic acid under reflux. The Sommelet reaction allowed the synthesis of 2-R-5-formyl-1,3,4-thiadiazole derivatives with yields of 65-69%.

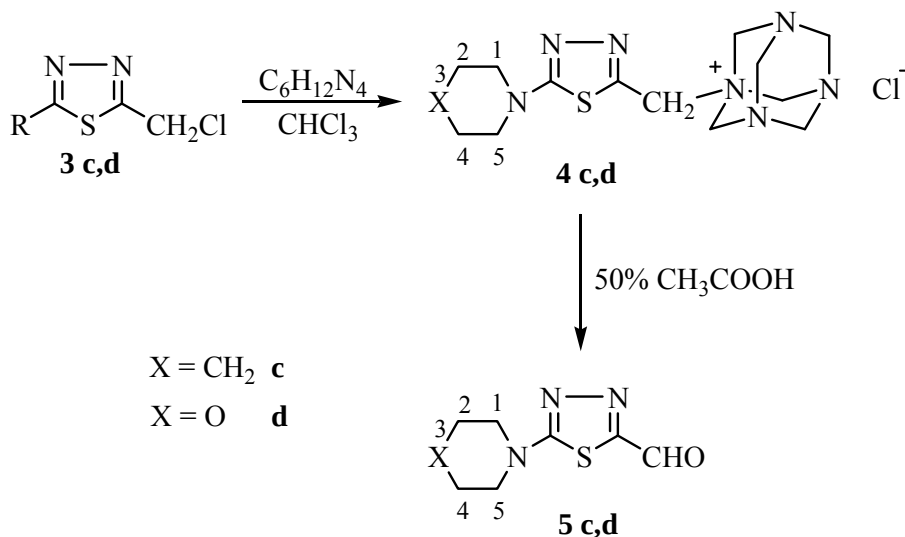


Figure 2

Synthesis of 2-R-5-formyl-1,3,4-thiadiazole derivatives **5c,d**

Conclusions

A series of 2,5-disubstituted-1,3,4-thiadiazole derivatives were synthesized and their structures were elucidated by elemental and spectral data. The synthesis of 2-R-5-formyl-1,3,4-thiadiazoles was achieved through Sommelet reaction using aromatic and heterocyclic amines as starting materials. During the cyclization reaction to form the 1,3,4-thiadiazole ring, the intermediary heterocyclic thiosemicarbazides **2c,d** were more reactive compared to aromatic thiosemicarbazides **2a,b**. The key intermediates, hexamethylenetetramine (HMTA) salts **4c,d**, after treatment under the Sommelet reaction conditions resulting the desired 2-R-5-formyl-1,3,4-thiadiazole compounds **5c,d** with good yields.

References

1. Almăjan G.L., Innocenti A., Puccetti L., Manole G., Barbuceanu S., Șaramet I., Scozzafava A., and Supuran C.T., *Bioorg. Med. Chem. Lett.*, 2005, 15, 2347-2352.
2. Azam M.A., Kumar B., Shalini S., Suresh B., Reddy T.K., Reddy C.D., Synthesis and biological screening of 5-[(4,6-disubstituted pyrimidine-2-yl)thio]methyl-N-phenyl-1,3,4-thiadiazol-2-amines, *Indian J. Pharm. Sci.*, 2008, 70, 672-677.
3. Chou J.Y., Lai S.Y., Pan S.L., Jow G.M., Chern J.W., and Guh J.H., Investigation of anticancer mechanism of thiadiazole-based compound in human nonsmall cell lung cancer A549 cells, *Biochem. Pharmacol.*, 2003, 66, 115-124.
4. Clerici F., Pocar D., Guido M., Loche A., Perlini V., Brufani M., Synthesis of 2-amino-5-sulfany-1,3,4-thiadiazole derivatives and evaluation of their antidepressant and anxiolytic activity, *J. Med. Chem.*, 2001, 44(6), 931-936.
5. Demirbas N., Karaoglu S.A., Demirbas A., Sancak K., Synthesis and antimicrobial activities of some new 1-(5-phenylamino-[1,3,4]thiadiazol-2-yl)methyl-5-oxo-[1,2,4]triazole and 1-(4-phenyl-5-thioxo-[1,2,4]triazol-3-yl)methyl-5-oxo-[1,2,4]triazole derivatives, *Eur. J. Med. Chem.*, 2004, 39, 793-804.
6. Desai K., Baxi A.J., Studies on 2-azetidinone: Part VI Synthesis and antimicrobial activity of 5-(2',4'-dichlorophenoxymethyl)-2-(4"-aryl-3"-chloro-2"-azetidinone-1"-yl)-1,3,4-thiadiazole, *Indian J. Pharm. Sci.*, 1992, 54, 183-188.
7. Foroumadi A., Emani S., Hassanzadeh A., Rajaei M., Sokhanvar K., Moshafi M.H., et al., Synthesis and antibacterial activity of N-(5-benzylthio-1,3,4-thiadiazol-2-yl)piperazinylquinolone, *Bioorg. Med. Chem. Lett.*, 2005, 15, 4488-4492.
8. Holla B.S., Poorjary K.N., Rao B.S., Shivananda M.K., *Eur. J. Med. Chem.*, 2002, 37, 511-517.
9. Labanauskas L., Kalcas V., Udrenaitė E., Gaidelis P., Brukstus A., Dauksas A., Synthesis of 3-(3,4-dimethoxyphenyl)-1H-1,2,4-triazole-5-thiol and 2-amino-5-(3,4-dimethoxy phenyl)-1,3,4-thiadiazole derivatives exhibiting antiinflammatory activity, *Pharmazie*, 2001, 56, 617-619.
10. Li J.J., Corey J., Name reaction for functional group transformations, Wiley-Interscience, a John Wiley and Sons, Inc. Publ., New York, 2007, 690.
11. Mamolo M.G., Vio L., Banfi E., Synthesis and antimicrobial activity of some 2,5-disubstituted 1,3,4-thiadiazole derivatives, *Farmaco*, 1996, 51, 71-74.
12. Martinez A., Alonso D., Castro A., Aran V.J., Cardelus I., Banos J.E., et al., Synthesis and potential muscarinic receptor binding and antioxidant properties of 3-(thiadiazolyl)pyridine 1-oxide compounds, *Arch. Pharm. (Weinheim)*, 1999, 332, 191-194.
13. Matysiak J., Nasulewicz A., Pelczynska M., Switalska M., Jaroszewicz I., Opolski A., Synthesis and antiproliferative activity of some 5-substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles, *Eur. J. Med. Chem.*, 2006, 41, 475-482.
14. Oruc E.E., Rollas S., Kandemirli F., Shvets N., and Dimoglo A., 1,3,4-Thiadiazole derivatives. Synthesis, structure elucidation and structure-antituberculosis activity relationship investigation, *J. Med. Chem.*, 2004, 47, 6760-6767.
15. Smaïne F.Z., Pacchiano F., Rami M., Barragan-Montero V., Vullo D., Scozzafava A., Winum J.Y., Supuran C.T., Carbonic anhydrase inhibitors: 2-substituted-1,3,4-thiadiazole-5-sulfamides act as powerful and selective inhibitors of the mitochondrial isozymes VA and VB over the cytosolic and membrane-associated

- carbonic anhydrases I, II and IV, *Bioorg. Med. Chem. Lett.*, 2008, 18(24), 6332-6335.
16. Șerban G., Coman M., Curea E., Proinov L., Obținerea și caracterizarea unor cumarine heterociclice, *Farmacia*, 2001, 49(2), 45-52.
 17. Șerban G., Salvan A., Horvath T., Synthesis of some 2-R-5-aminomethyl-1,3,4-thiadiazole derivatives by Delepine reaction, *Analele Universității din Oradea, Seria Chimie*, 2009, in press.
 18. Șerban G., Suciș A., Coman M., Curea E., Sinteza și studiul fizico-chimic al unor 3-(5-amilamino-1,3,4-tiadiazol-2-il)-cumarine, *Farmacia*, 2002, 50(6), 50-54.
 19. Wood J.H., Tung C.C., Perry M.A., Gibson R.E., The Sommelet Reaction in the synthesis of aromatic dialdehydes, *J. Am. Chem. Soc.* 1950, 72(7), 2992-2993.

Manuscript received: January 28th 2010