# SYNTHESIS AND CHARACTERIZATION OF FLUORINATED 1,3,4-OXADIAZOLE-2-THIONES.

Radhia Ben Châabane, Ahmed Hedhli*

*Laboratoire de Chimie Moleculaire Organique, Ecole Supérieure des Sciences et Techniques de Tunis, 5 avenue Taha Hussein, Montfleury, 1089, Tunis, Tunisia*

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**ABSTRACT:** Oxadiazoles have attracted a wide attention of chemists in search of the new therapeutic compounds. Fluorine atom is often introduced into organic molecules to improve such a therapeutic activity. In this context, a series of perfluoroalkylated 1,3,4-oxadiazole-2-thiones was prepared from the corresponding hydrazides. Characterization of these new compounds indicates a displacement of the tautomeric equilibria in favour of the thione form.

**Keywords:** hydrazide, 1,3,4-oxadiazole-2-thione, fluorine.

**RESUME:** Les oxadiazoles ont attiré l'attention des chimistes à la recherche de nouveaux composés thérapeutiques. L'atome de fluor est souvent introduit dans les molécules organiques pour améliorer une telle activité thérapeutique. Dans ce contexte, une série de perfluoroalkyl 1,3,4-oxadiazoles a été préparée à partir des hydrazides correspondants. La caractérisation de ces nouveaux composés indique un déplacement de l'équilibre tautomérique en faveur de la forme thione.

**Mots clés:** hydrazide, 1,3,4-oxadiazole-2-thione, le fluore.

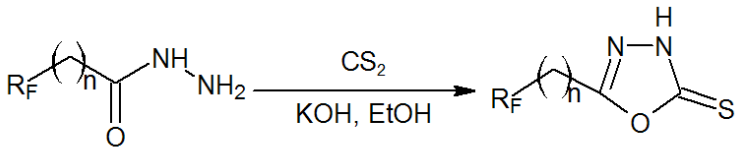
## INTRODUCTION

Oxadiazoles have been the subject of extensive study during the recent past years [1]. Numerous reports have highlighted their chemistry and use [2-4]. Diverse biological activities, such as antiviral [5], anti-tuberculostatic, anti-inflamatory [6], analgesic, antipyretic, anticonvulsant [7,8], antifungal [9-11], antiparasitic and antimicrobial [11-15], have been reported.

A useful method to obtain 1,3,4-oxadiazole-2-thione is the use of the corresponding hydrazide as starting material.

## RESULTS AND DISCUSSION

Reaction of hydrazide **1** with carbon disulphide in the presence of potassium hydroxide leads to the fluorinated 1,3,4-oxadiazole-2(3H)-thione **2** [16] (scheme 1)




**1** **2**

$R_F = C_6F_{13}, C_7F_{15}, C_8F_{17}, C_{11}F_{23}$

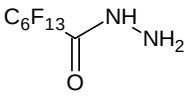
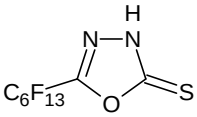
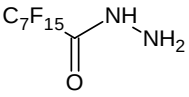
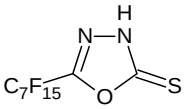
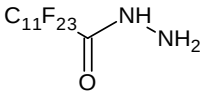
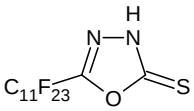
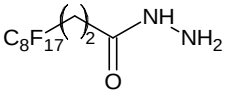
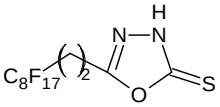
n = 0, 2

**Scheme 1:** Synthesis of 1,3,4-oxadiazole-2-thiones

*Corresponding author, email: ahmed.hedhli@esstt.rnu.tn

The synthesized hydrazides **1** and oxadiazoles **2** are collected in table I.

**Table I:** Oxadiazoles **2** prepared from hydrazides **1**

| Hydrazide **1** | | Yield (%) | Oxadiazole **2** | | Yield (%) |
|---|---|---|---|---|---|
|  | **1a** | 81 |  | **2a** | 64 |
|  | **1b** | 76 |  | **2b** | 56 |
|  | **1c** | 73 |  | **2c** | 46 |
|  | **1d** | 89 |  | **2d** | 73 |

NMR and IR data of compound **2** indicate the presence of only thione form. Indeed, IR spectra of **2** displays signals at 3192 $cm^{-1}$ (NH) and 1467-1353 $cm^{-1}$ (C=S) but no S-H absorption at 2600-2550 $cm^{-1}$. The absence of SH group is also confirmed by $^{1}H$ NMR spectra which exhibits no signals at 14 ppm.

## EXPERIMENTAL

The $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectra were recorded on a Bruker AC 300 at 300, 75 and 282 MHz, respectively. The TMS was used as standard reference for $^{1}H$ and $^{13}C$ NMR spectra and $CFCl_3$ for $^{19}F$. The IR spectra were recorded on a Brucker IFS 66v/s. Melting points were determined in capillaries and they are uncorrected. Elemental microanalysis was in a Horiba EMIA-220 V.

### Preparation of fluorinated carbohydrazides 1: general procedure

In a 25 mL round bottom flask, were introduced at 0°C and under nitrogen atmosphere, ester (5 mmol), hydrazine hydrate (15 mL) and methanol (10 mL). The mixture was vigorously stirred at room temperature for 4 h. Upon completion of the reaction, methanol and excess of hydrazine hydrate were removed under vacuum. The obtained crude product was purified by recrystallization from Chloroform/Ethanol to afford the desired compound.

***(F-hexyl) carbohydrazide*** (**1a**)

m. p. = 87°C. IR ($cm^{-1}$): $\nu_{C-F}$ = 1010, $\nu_{C=O}$ = 1705, $\nu_{N-H}$= 3450, $\nu_{C-N}$ = 1100. $^{1}H$ NMR ($CDCl_3$) δ (ppm) 3.42 (s, 3H, CONHNH$_2$). $^{13}C$ NMR ($CDCl_3$) δ (ppm) 157.03 (t, 1C, $C_6F_{13}CO$, $^{2}J_{C-F}$ = 29.55 Hz). $^{19}F$ NMR δ (ppm) -120.00 (m, 2F, $CF_{2\alpha}$), -123.42 (m, 2F, $CF_{2\beta}$), -124.26 (m, 4F, $CF_{2\gamma}$, $CF_{2\delta}$), -127.76 (m, 2F, $CF_{2\omega}$), -82.52 (m, 3F, $CF_3$).

***(F-heptyl) carbohydrazide*** (**1b**)

m. p. = 98°C. IR ($cm^{-1}$): $\nu_{C-F}$ = 1012, $\nu_{C=O}$ = 1715, $\nu_{N-H}$= 3465, $\nu_{C-N}$ = 1155. $^{1}H$ NMR ($CDCl_3$) δ (ppm) 4.01 (s, 3H, CONHNH$_2$). $^{13}C$ NMR ($CDCl_3$) δ (ppm) 158.83 (t, 1C, $C_7F_{15}CO$, $^{2}J_{C-F}$ = 29.55 Hz). $^{19}F$ NMR δ (ppm) -114.97 (m, 2F, $CF_{2\alpha}$), -121.99 (m, 2F, $CF_{2\beta}$), -122.44 (m, 2F, $CF_{2\gamma}$), -122.77 (m, 2F, $CF_{2\delta}$), -123.19 (m, 2F, $CF_{2\varepsilon}$), -126.65 (m, 2F, $CF_{2\omega}$), -81.55 (m, 3F, $CF_3$).

***(F-undécyl) carbohydrazide*** (**1c**)

m. p. = 171°C. IR ($cm^{-1}$): $\nu_{C-F}$ = 1015, $\nu_{C=O}$ = 1718, $\nu_{N-H}$= 3475, $\nu_{C-N}$ = 1175. $^{1}H$ NMR ($CDCl_3$) δ (ppm) 3.44 (s, 3H, CONHNH$_2$). $^{13}C$ NMR ($CDCl_3$) δ (ppm) 169.00 (t, 1C, $C_{11}F_{23}CO$, $^{2}J_{C-F}$ = 9.11 Hz). $^{19}F$ NMR δ (ppm)

-119.70 (m, 2F, $CF_{2\alpha}$), -122.80 (m, 12F, $CF_{2Q}$), -123.77 (m, 4F, $CF_{2\beta}$, $CF_{2\gamma}$), -127.25 (m, 2F, $CF_{2\omega}$), -81.97 (m, 3F, $CF_3$).

***(F-octyl) propanohydrazide*** (**1d**)

m. p. = 111°C. IR ($cm^{-1}$): $\nu_{C-F}$ = 1018, $\nu_{C=O}$ = 1725, $\nu_{N-H}$= 3500, $\nu_{C-N}$ = 1200. $^1H$ NMR ($CDCl_3$) δ (ppm) 3.61 (s, 3H, CONHNH$_2$), 2.92 (t, 2H, $C_8F_{17}CH_2CH_2$, $^3J_{H-H}$ = 6.00 Hz), 2.55 (m, 2H, $C_8F_{17}CH_2CH_2$). $^{13}C$ NMR ($CDCl_3$) δ (ppm) 158.83 (s, 1C, $C_8F_{17}CH_2CH_2CO$), 30.57 (t, 1C, $C_8F_{17}CH_2CH_2$, $^2J_{C-F}$ = 21.25 Hz), 27.53 (s, 1C, $C_8F_{17}CH_2CH_2$). $^{19}F$ NMR δ (ppm) -116.14 (m, 2F, $CF_{2\alpha}$), -122.99 (m, 2F, $CF_{2\beta}$), -123.18 (m, 4F, $2CF_{2\gamma}$), -124.02 (m, 2F, $CF_{2\delta}$), -124.76 (m, 2F, $CF_{2\varepsilon}$), -127.47 (m, 2F, $CF_{2\omega}$),-82.93 (m, 3F, $CF_3$).

**Preparation of-oxadiazoles 2: general procedure**

A mixture of hydrazide **1** (10 mmol), potassium hydroxide (10 mmol) in ethanol (10 mL) and carbon disulphide (10 mmol) was refluxed for 6 h. The solvent was evaporated, and then the residue was dissolved in water (30 mL). The solution was acidified with HCl (1N) and the precipitate was filtered off and washed with water. The crude product was recrystallized from ethanol to afford compound **2**.

***5-(F-hexyl) -1,3,4-oxadiazole-2(3H)-thione*** (**2a**)

m. p. = 125°C. IR ($cm^{-1}$): $\nu_{C-F}$ = 1010, $\nu_{C=N}$ = 1640, $\nu_{N-H}$= 2856.92, $\nu_{C=S}$ = 1353. $^1H$ NMR ($CD_3COCD_3$) δ (ppm) 4.33 (b, 1H, NNH). $^{13}C$ NMR ($CD_3COCD_3$) δ (ppm) 174.03 (s, 1C, C=S), 127.06 (t, 1C, $C_6F_{13}C$=N, $^2J_{C-F}$ = 29.55 Hz). $^{19}F$ NMR δ (ppm) -120.00 (m, 2F, $CF_{2\alpha}$), -123.42 (m, 2F, $CF_{2\beta}$), -124.26 (m, 4F, $CF_{2\gamma}$, $CF_{2\delta}$), -127.76 (m, 2F, $CF_{2\omega}$), -82.52 (m, 3F, $CF_3$). Anal. for $C_8HF_{13}N_2OS$ Calcd. : C, 22.87; N, 6.67; S, 7.63, Found: C, 23.86; N, 6.05; S, 6.61.

***5-(F-heptyl) -1,3,4-oxadiazole-2(3H)-thion*** (**2b**)

m. p. = 143°C. IR ($cm^{-1}$): $\nu_{C-F}$ = 1012, $\nu_{C=N}$ = 1658, $\nu_{N-H}$= 2876, $\nu_{C=S}$ = 1373. $^1H$ NMR ($CD_3COCD_3$) δ (ppm) 4.25 (s, 1H, NNH). $^{13}C$ NMR ($CD_3COCD_3$) δ (ppm) 173.89 (s, 1C, C=S), 128.71 (t, 1C, $C_7F_{15}C$=N, $^2J_{C-F}$ = 29.55 Hz). $^{19}F$ NMR δ (ppm), -114.97 (m, 2F, $CF_{2\alpha}$), -121.99 (m, 2F, $CF_{2\beta}$), -122.44 (m, 2F, $CF_{2\gamma}$), -122.77 (m, 2F, $CF_{2\delta}$), -123.19 (m, 2F, $CF_{2\varepsilon}$), -126.65 (m, 2F, $CF_{2\omega}$), -81.55 (m, 3F, $CF_3$). Anal. for $C_9HF_{15}N_2OS$ Calcd. : C, 22.99; N, 5.96; S, 6.82, Found: C, 23.48; N, 4.89; S, 5.76.

**5-(F-undécyl) -1,3,4-oxadiazole-2(3H)-thione** (**2c**)

m. p. = 185°C. IR ($cm^{-1}$): $\nu_{C-F}$ = 1015, $\nu_{C=N}$ = 1695, $\nu_{N-H}$= 2899, $\nu_{C=S}$ = 1407. $^1H$ NMR ($CD_3COCD_3$) δ (ppm) 5.25 (s, 1H, NNH). $^{13}C$ NMR ($CD_3COCD_3$) δ (ppm) 174.59 (s, 1C, C=S), 127.33 (t, 1C, $C_{11}F_{23}CN$, $^2J_{C-F}$ = 29.55 Hz). $^{19}F$ NMR δ (ppm) -119.70 (m, 2F, $CF_{2\alpha}$), -122.80 (m, 12F, $CF_{2Q}$), -123.77 (m, 4F, $CF_{2\beta}$, $CF_{2\gamma}$), -127.25 (m, 2F, $CF_{2\omega}$), -81.97 (m, 3F, $CF_3$). Anal. for $C_{13}HF_{23}N_2OS$ Calcd. : C, 23.30; N, 4.18; S, 4.78, Found: C, 23.06; N, 4.88; S, 5.06.

***5-(F-octyl) -1,3,4-oxadiazole-2(3H)-thione*** (***2d***)

m. p. = 208°C. IR ($cm^{-1}$): $\nu_{C-F}$ = 1018, $\nu_{C=N}$ = 1705, $\nu_{N-H}$= 2923, $\nu_{C=S}$ = 1467. $^1H$ NMR ($CD_3COCD_3$) δ (ppm) 4.61 (s, 1H, NNH), 3.18 (t, 2H, $C_8F_{17}CH_2CH_2$, $^3J_{H-H}$ = 6.00 Hz), 2.82 (m, 2H, $C_8F_{17}CH_2CH_2$). $^{13}C$ NMR ($CD_3COCD_3$) δ (ppm) 179.74 (s, 1C, C=S), 162.75 (s, 1C, $C_8F_{17}CH_2CH_2C$=N), 30.57 (t, 1C, $C_8F_{17}CH_2CH_2$, $^2J_{C-F}$ = 21.25 Hz), 27.53 (s, 1C, $C_8F_{17}CH_2CH_2$). $^{19}F$ NMR δ (ppm) -116.14 (m, 2F, $CF_{2\alpha}$), -122.99 (m, 2F, $CF_{2\beta}$); -123.18 (m, 4F, $2CF_{2\gamma}$), -124.02 (m, 2F, $CF_{2\delta}$), -124.76 (m, 2F, $CF_{2\varepsilon}$), -127.47 (m, 2F, $CF_{2\omega}$), -82.93 (m, 3F, $CF_3$). Anal. for $C_{12}H_5F_{17}N_2OS$ Calcd. : C, 26.29; N, 5.11; S, 5.85, Found: C, 25.46; N, 4.85; S, 5.16.

## CONCLUSION

In this work, synthesis of a series of fluorinated 1,3,4-oxadiazole-2-thiones was described. The obtained heterocycles were characterized by conventional spectroscopic methods and identified as thione tautomer.

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