DE GRUYTER OPEN

Nova Biotechnol Chim (2017) 16(2): 147-151
DOI: 10.1515/nbec-2017-0020

Nova Biotechnologica *et* Chimica

NMR spectroscopic properties of furo[2',3':4,5]pyrrolo[1,2-d][1,2,4]triazine derivatives

Ivana Zemanová and Renata Gašparová✉

Department of Chemistry, Faculty of Natural Sciences, University of SS. Cyril and Methodius in Trnava, Nám. J. Herdu 2, Trnava, SK-917 01, Slovak Republic

Article info

Article history:
Received: 12th June 2017
Accepted: 4th July 2017

Keywords:
Chemical shift
furo[3,2-b][pyrrole
NMR spectroscopy

Abstract

The ^{1}H and ^{13}C NMR spectroscopic properties of a series of furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-ones and -thiones were investigated. The influence of various electron donating as well as electron withdrawing substituents at C-5 or N-7 on ^{1}H NMR chemical shifts as well as ^{13}C chemical shifts at C8 were observed. The 5-chloromethyl group had a little influence on the chemical shift of H-7 proton and the 8-thione group causes deshielding of H-7 as well as H-5 protons in comparison with the C-8 carbonyl group.

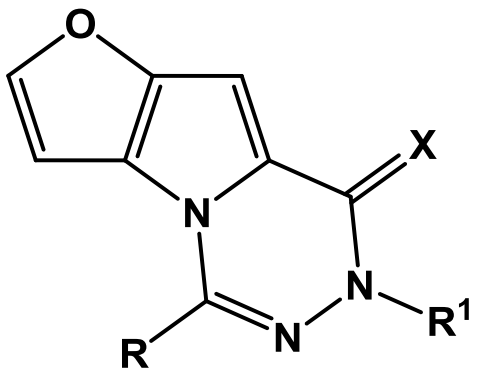
Introduction

Furo[3,2-*b*]pyrroles are isosteres of the indole ring system in which the benzene ring is replaced by the furan ring. Efficient synthetic routes to these heterocycles are of great interest (Krutošíková *et al.* 1992; Beccalli *et al.* 2008; Zhao *et al.* 2014) as the furo[3,2-*b*]pyrrole core has been found in compounds with diverse biological activities (Sparey *et al.* 2008; Fehér *et al.* 2010) or they are used as the fluorescent dyes (Umezawa *et al.* 2008). Heterocyclic compounds containing five- and six-membered nitrogen heterocyclic rings have also attracted the attention due to the fact that they exhibit many biological interactions (Astakhina *et al.* 2016). In addition, 1,2,4-triazin-6-one is structural system found in numerous natural and synthetic biologically active compounds with a wide range of biological activity including anti-inflammatory (George *et al.* 2015) or anticonvulsant (El-Gendy *et al.* 2008). We have recently reported the synthesis of furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-ones with interesting antibacterial activity (Zemanová *et al.* 2017), but more complex spectroscopic studies were realised only on benzothieno[3,2-*d*]-1,2,3-triazines (Lauria *et al.* 2014) or 7-aryl-7H-pyrazolo[3,4-*d*]-[1,2,3]triazin-4-ols (Khutova *et al.* 2012). Therefore we report here on the NMR spectroscopic properties of the full series.

Results and Discussion

The title compounds **1a-1c** (Fig. 1) are well accessible from methyl 4*H*-furo[3,2-*b*]pyrrole-5-carboxylate *via* its hydrazinolysis and subsequent cyclization of hydrazides with orthoesters (triethyl orthoformate, triethyl orthochloroacetate or triethyl orthoacetate) in dimethylformamide. Resulting furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-ones **1** were obtained in 69-75%. The carbonyl group at C-8 of triazine ring of **1a** can be easily thionated by reaction with phosphorus pentasulfide in pyridine to give thione **2a** in 85% yield Alkylation or acylation of triazines **1a** and **2a** with alkylhalides (CH_3I, n-C_6H_9Br, $ClCH_2CO_2Me$)

✉ *Corresponding author:* renata.gasparova@ucm.sk



	X	R	R1
1a	O	H	H
1b	O	CH_2Cl	H
1c	O	CH_3	H
1d	O	H	CH_3
1e	O	H	n-C_4H_9
1f	O	H	CH_2Ph
1g	O	H	$CH_2CO_2CH_3$
1h	O	H	$COCH_3$
2a	S	H	H
2b	S	H	CH_3
2c	S	H	$CH_2CO_2CH_3$

Fig. 1. Structure of furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-ones **1** and thiones **2**.

or acetic anhydride in dimethylformamide in the presence of sodium hydride provided 7-substituted triazinones **1d-1h** or thiones **2b, 2c** (Fig.1) in 45-72 % yields (Zemanová *et al.* 2017).

^{1}H NMR Spectroscopy

The influence of various substituents (C5)-R and (N7)-R^1 on ^{1}H NMR chemical shifts of the protons in triazinones **1** and triazinethiones **2** were investigated (Table 1).The influence of C-5 substituent (H, CH_2Cl, CH_3) on chemical shifts of the protons of derivatives **1a-1c** showed the slight increasing of the chemical shift value of H-7 proton in case of electron withdrawing group (CH_2Cl) at C-5 (Fig. 2).

Table 1. ^{1}H NMR chemical shifts of furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-ones **1a-1h** and thiones **2a-2c** in DMSO-d6.

	Chemical shift (ppm)					
	H-2	**H-3**	**H-5**	**H-7**	**H-9**	**other**
1a	8.00	7.11	8.75	11.81	7.14	-
1b	7.97	6.67	-	12.09	6.88	5:09 (CH_2)
1c	7.99	7.15	-	11.65	7.10	2.60 (CH_3)
1d	7.99	7.09	8.81	-	7.14	3.56 (CH_3)
1e	7.99	7.09	8.82	-	7.13	3.99 (t,CH_2), 1.73 (sextet, CH_2), 1.37 (sextet, CH_2), 0.93 (t, CH_3)
1f	8.01	7.09	8.83	-	7.19	5.17 (CH_2)
1g	8.01	7.09	8.83	-	7.20	4.77 (CH_2), 3.67 (CH_3)
1h	8.09	7.11	8.83	-	7.39	2.59 (CH_2)
2a	8.09	7.15	9.16	13.29	7.29	-
2b	8.31	7.34	10.98	-	7:76	4.17 (CH_3)
2c	8.11	7.15	9.24	-	7.36	5.32 (CH_2), 3.67 (CH_3)

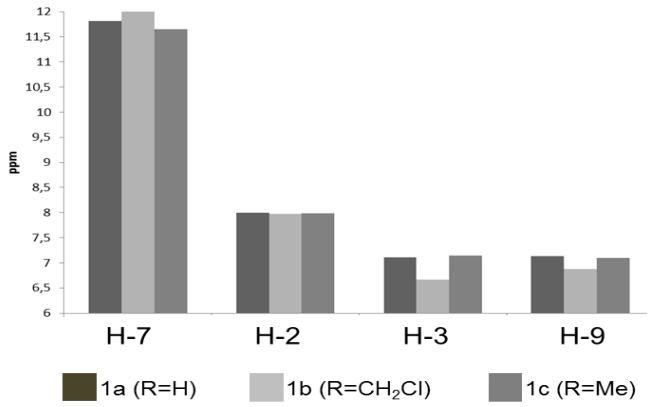


Fig. 2. The influence of substituent on C-5 of **1a-1c** on the chemical shifts of protons in ^{1}H NMR.

As it is shown in Table 1, the presence either electron withdraving either electron donating substituents at N-7 has no significant influence on the chemical shifts of protons in compounds **1d-1h** in comparison with N-7 unsubstituted derivative **1a.** The values of H-2 shifts are in 7.99-8.09 ppm region, H-3 resonate in 7.09-7.11 ppm. In case of H-5 the range is only 8.81-8.83 ppm. The chemical shifts of H-9 are in 7.14 - 7.39 ppm range (Fig. 3).When the carbonyl group at C-8 was replaced by thione, the chemical shifts of H-2 and H-3 were not significantly influenced, but the shifts of H-5 significantly deshielded to 9.16 - 10.98 ppm. Deshielding of H-7 protons is not so remarkable, except **2b** with value 7.76 ppm (Fig. 4).

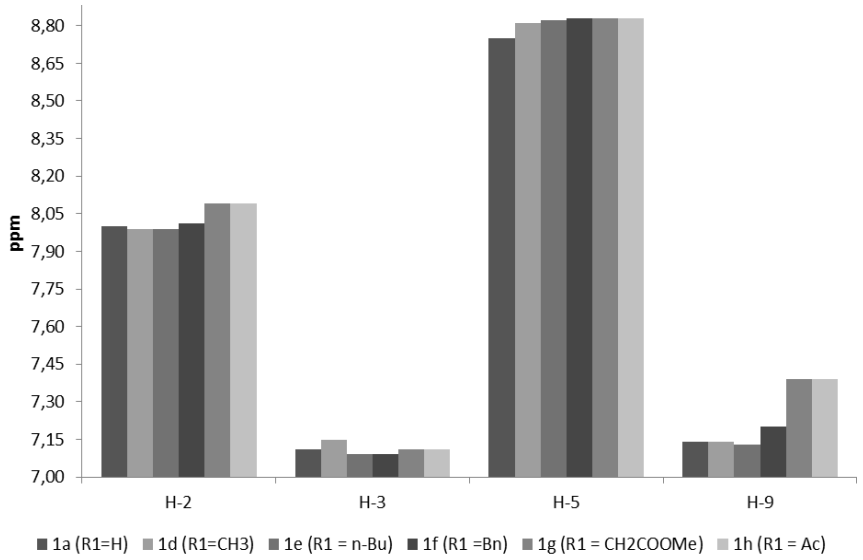


Fig. 3. The influence of substituent on N-7 of **1a, 1d-1h** on the chemical shifts of protons in ^{1}H NMR.

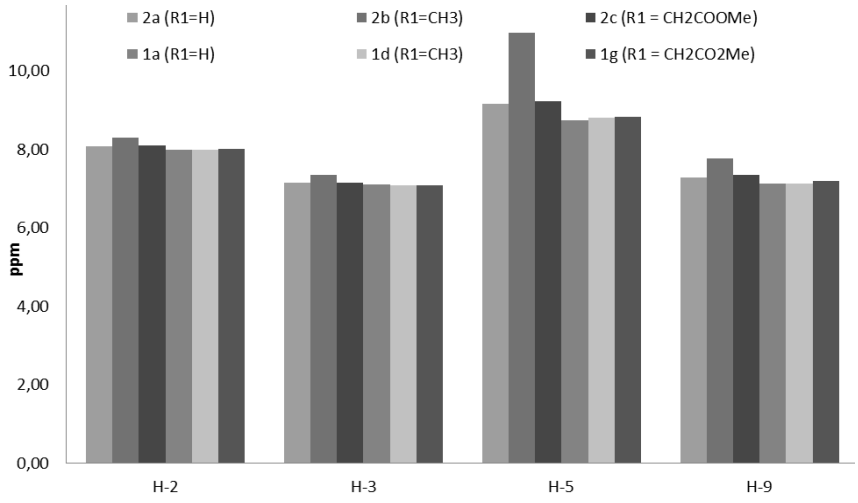


Fig. 4. The influence of C-8 thione group of **2a-2c** on the chemical shifts of protons in ^{1}H NMR in comparison with C-8 carbonyl compounds **1a**, **1d** and **1g**.

^{13}C NMR Spectroscopy

There was very little variation in the C-8 (C=O) signal of triazinones **1a-1h** (Table 1). The range was only 153.7-154.6 ppm. C-8a carbons resonate at 123.6-125.7 ppm and C-5 carbons resonate at 127.7-35.7 ppm, respectively. When the carbonyl group is replaced by thione, the value of C-8 signal of **2a-2c** has deshielded and appear at 173.1-162.3 ppm region, signals of C-8a appear at 130.5-130.9 ppm and C-5 at 131.6-144.8 ppm region, respectively (Table 2).

Table 2. ^{13}C NMR chemical shifts of furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-ones **1a-1h** and thiones **2a-2c** in DMSO-d6.

	Chemical shift (ppm)							
	C-2	**C-3**	**C-3a**	**C-5**	**C-8**	**C-8a**	**C-9**	**C-9a**
1a	149.5	100.0	123.5	127.7	155.2	124.8	92.4	148.4
1b	-	-	-	-	-	-	-	-
1c	149.8	101.7	123.9	135.7	155.3	125.6	92.9	148.9
1d	149.9	100.6	123.8	127.8	154.6	124.9	93.0	149.2
1e	150.0	100.6	123.8	128.0	154.3	124.9	93.3	149.3
1f	149.7	100.1	123.5	128.3	153.9	124.2	93.2	148.7
1g	149.7	99.8	123.5	127.5	153.7	123.6	93.2	148.3
1h	151.6	100.7	124.3	128.6	154.4	125.7	97.6	149.2
2a	150.5	100.2	123.9	131.7	173.1	130.5	95.3	149.4
2b	157.7	106.1	125.9	144.8	162.3	130.9	99.7	156.5
2c	150.9	100.4	127.9	131.6	167.4	130.6	96.8	150.9

The ^{13}C NMR spectrum was unmeasurable because of the low solubility of **1b**.

Conclusions

The chemical shifts in ^{1}H and ^{13}C NMR spectra of series of furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazin-8(7*H*)-ones were investigated. Among the C-5 substituted compounds the little influence of electron withdraving chloromethyl group on the chemical shift of H-7 proton was observed, while the substitution on N-7 has no significant influence on the chemical shifts of protons. Thione group at C-8 causes deshielding of H-7 as well as H-5 protons in comparison with the C-8 carbonyl group. ^{13}C NMR spectra of **1a-1h** showed only little variation of signals, the significant influence of thione group of **2a-2c** on C-8, C-8a and C-5 chemical shifts deshielding in comparison with C-8 carbonyl was observed.

Acknowledgement

This work was supported by the Slovak Research Agency under the contract No. VEGA 1/0534/16.

References

Astakhina V, Voievudskyi M, Kharchenko O, Novikov V, Komarovska-Porohnyavets E, Petukhova O (2016) Synthesis and biological activity of novel ethyl esthers of 4-R-6,8-dimethyl-1-oxo-1,2-dihydropyrrolo[1,2-d]triazine-7-carboxylic acids. J. Heterocycl. Chem. 53: 421-428.

Beccalli EM, Broggini G, Martinelli M, Sottocornola S (2008) Microwave-assisted intramolecular cyclistion of electron-rich heterocycle derivatives *by* a palladium-catalyzed coupling reaction. Synthesis 2008: 136-140.

El-Gendy AA, Said MM, Ghareb N, Mostafa YM, El-Ashry ESH (2008) Synthesis and biological activity of functionalized indole -2-carboxylates, triazino- and pyridazino-indoles. Arch. Pharm. 341: 294-300.

George DM, Breinlinger EC, Friedman M, Zhang Y, Wang J, Argiriadi M, Bansal-Pakala P, Barth M, Duignan DB, Honore P, Lang Q, Mittelstadt S, Potin D, Rundell L, Edmunds JJ (2015) Discovery of selective and orally bioavailable protein kinase Cθ (PKCθ) inhibitors from a fragment hit. J. Med. Chem. 58: 222-236.

Lauria A, Alfio A, Bonsignore R, Gentile C, Martorana A, Gennaro G, Barone G, Terenzi A, Almerico AM (2014) New benzothieno[3,2-d]-1,2,3-triazines with antiproliferative activity: Synthesis, spectroscopic studies, and biological activity. Bioorg. Med. Chem. Lett. 24: 3291–3297.

Khutova BM, Klyuchko SV, Gurenko AO, Vasilenko AN, Balya AG, Rusanov EB, Brovarets VS (2012) Conversions of 7-aryl-7H-pyrazolo[3,4-d]-[1,2,3]triazin-4-ols by the action of phosphorus pentoxide, pentasulfide, and oxychloride. Chem. Heterocycl. Comp. 48: 1251-1262.

Krutošíková A, Dandárová M, Chylová J, Vegh D (1992) Condensed O-, N-heterocycles by the transformation of azidoacrylates. Monatsh. Chem. 123: 807-815.

Fehér D, Barlow R, McAtee J, Hemscheidt TK (2010) Highly Brominated Antimicrobial Metabolites from a Marine *Pseudoalteromonas* sp. J. Nat. Prod. 73: 1963–1966.

Sparey T, Abeywickrema P, Almond S, Brandon N, Byrne N, Campbell A, Hutson PH, Jacobson M, Jones B, Munshi S, Pascarella D, Pike A, Prasad G S, Sachs N, Sakatis M, Sardana V, Venkatraman S, Young MB (2008) The discovery of fused pyrrole carboxylic acid as novel, potent D-aminoacid oxidase (DAO) inhibitors. Bioorg. Med. Chem. Lett. 18: 3386-3391.

Umezawa K, Nakamura Y, Makino H, Citterio D, Suzuki K (2008) Fluorescent dyes in the visible-near-infrar region. J. Am. Chem. Soc. 130: 1550-1551.

Zemanová I, Gašparová R, Kraic F, Kružlicová D, Maliar T, Boháč A, Addová G (2017) Synthesis of furo[2',3':4,5]pyrrolo[1,2-*d*][1,2,4]triazine derivatives and their antibacterial activity. Arkivoc part iv: 184-193.

Zhao H, Koenig SG, Dankwardt JW, Singh SP (2014) Practical nonazide synthesis of D-amino acid oxidase inhibitor via sequential Erlenmeyer-Plochl reaction and ligand-free copper (I) amination protocol. Org. Process Res. Dev. 18: 198-204.