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Synthesis of 6-(4-Chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines: Comparative Evaluation of Dehydrosulfurization Methods of Starting 4-Chloro-*N*-(2,2,2 -trichloro-1-(3-arylthioureido)ethyl)benzamides.

Chaired by DR. JULIO A. SEIJAS

molecules MDPI

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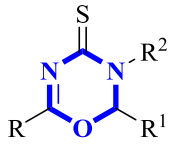
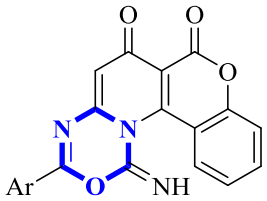
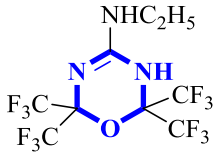
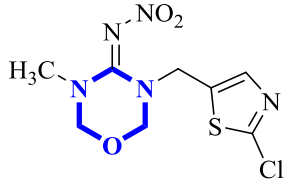
Introduction

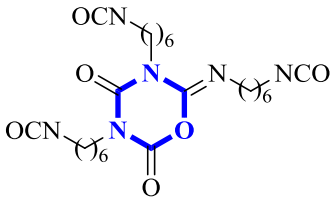
antibacterial and fungicidal activity



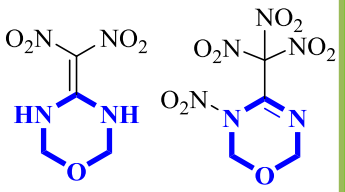
Synthazin
antitumor activity



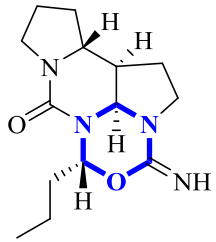
Thiamethoxam and its analogues (pesticides)



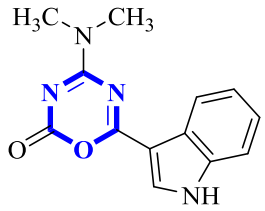
HDIOD
Used in the synthesis of polymers.



explosives



Fissoldhimine



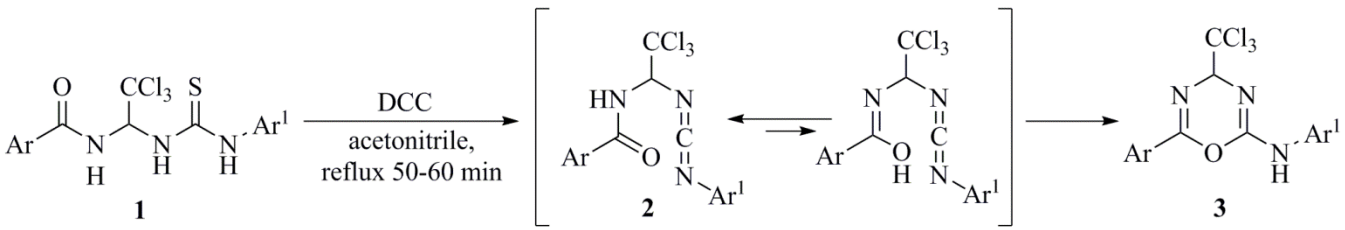
Alboinon

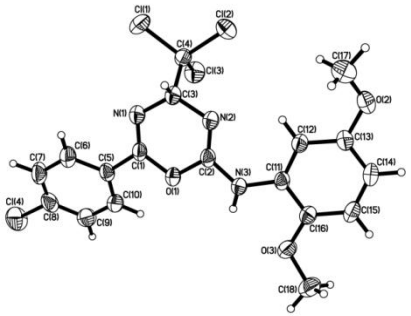
1. Zadorozhnii, P.V.; Kiselev, V.V.; Kharchenko, A.V. 1,3,5-Oxadiazines and 1,3,5-Thiadiazines. In *Comprehensive Heterocyclic Chemistry*, 4th ed.; Black, D.St.C., Cossy, J., Stevens, Ch.V., Eds.; Elsevier: 2022; Volume 9, pp. 456-506. https://doi.org/10.1016/B978-0-12-818655-8.00105-0

2. Ke, S.; Cao, X.; Liang, Y.; Wang, K.; Yang, Z. Synthesis and Biological Properties of Dihydro-Oxadiazine-Based Heterocyclic Derivatives. *Mini Rev. Med. Chem.* 2011, *11*, 642-657. https://doi.org/10.2174/138955711796268769

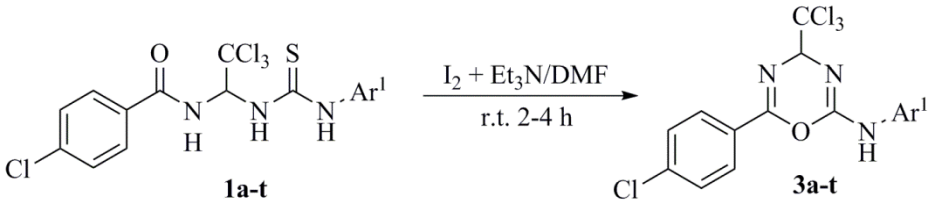
Introduction

Previous works





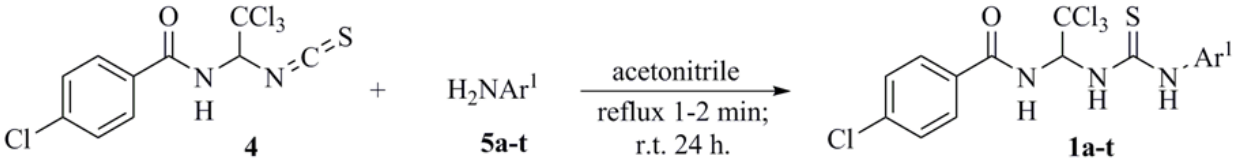
This work



Scheme 1. Synthesis of 4*H*-1,3,5-oxadiazine derivatives (**3**) using dicyclohexylcarbodiimide and I_2 + Et_3N as a dehydrosulfurizing agent.

1. Zadorozhnii, P.V.; Kiselev, V.V.; Pokotylo, I.O.; Kharchenko, A.V. A new method for the synthesis of 4*H*-1,3,5-oxadiazine derivatives. *Heterocycl. Commun*. 2017, *23*, 369-374. https://doi.org/10.1515/hc-2017-0083
2. Zadorozhnii, P.V.; Kiselev, V.V.; Pokotylo, I.O.; Okhtina, O.V.; Kharchenko, A.V. Synthesis and mass spectrometric fragmentation pattern of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines. *Heterocycl. Commun*. 2018, *24*, 273-278. https://doi.org/10.1515/hc-2018-0082
3. Zadorozhnii, P.V.; Pokotylo, I.O.; Kiselev, V.V.; Kharchenko, A.V.; Okhtina, O.V. Synthesis and Spectral Characteristics of Some New 4*H*-1,3,5-Oxadiazine Derivatives. *Res. J. Pharm., Biol. Chem. Sci.* 2019, *10*, 1508-1515.
4. Zadorozhnii, P.V.; Kiselev, V.V.; Hrek, O.O.; Kharchenko, A.V.; Okhtina, O.V. Synthesis, spectral characteristics, and molecular structure of 2-(2,4-dichlorophenyl)-6-(2-methoxybenzyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazine. *Struct. Chem.* 2022 https://doi.org/10.1007/s11224-022-02024-9 (in press).

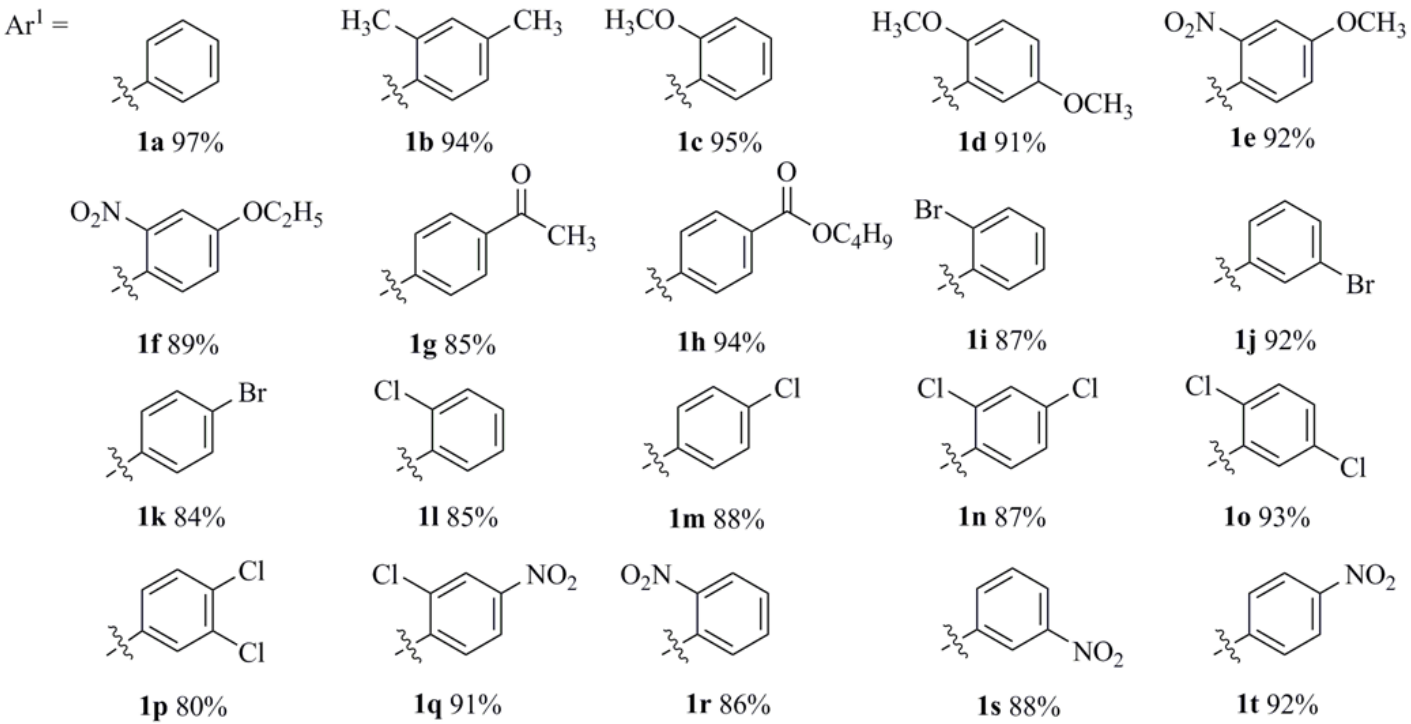
Results and discussion

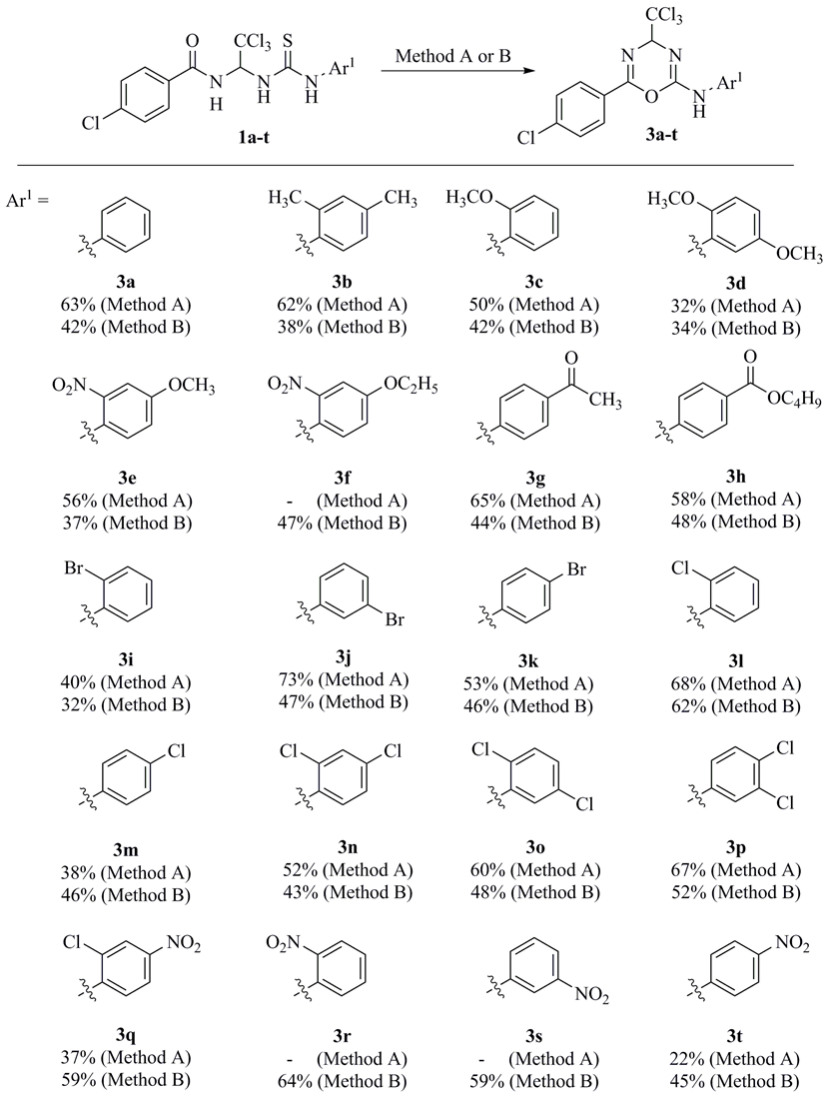


4 + H_2NAr^1 (5a-t) → 1a-t

Scheme 2. Synthesis of 4-chloro-*N*-(2,2,2 -trichloro-1-(3-arylthioureido)ethyl)benzamides (**1a-t**).

Ar^1 =





Scheme 3. Synthesis of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines (**3a-t**). **Method A:** 1.1 DCC, CH_3CN, reflux 50-60 min. **Method B:** 1.1 I_2, 3.0 Et_3N, DMF, r.t. 2-4 h.

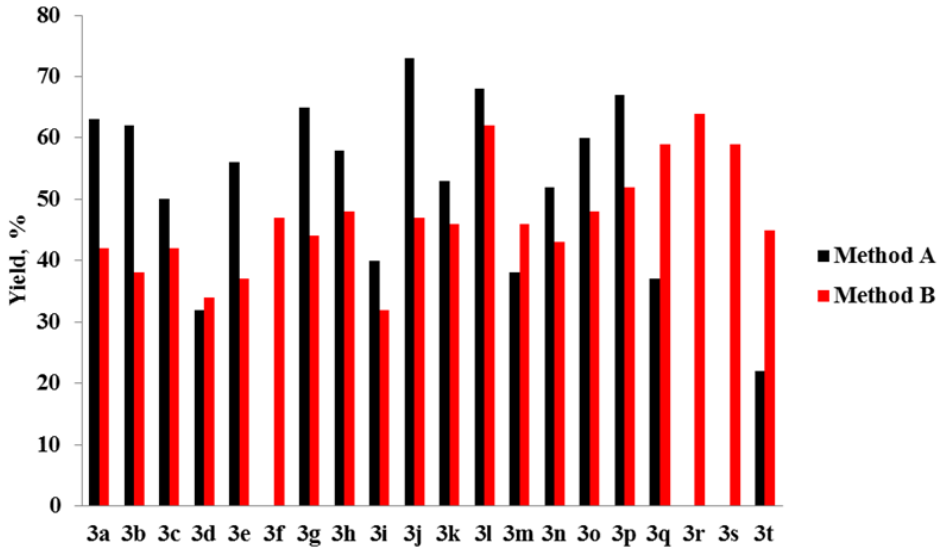


Figure 1. Estimation of the yield ratio of 4*H*-1,3,5-oxadiazines **3** depending on the method used for dehydrosulfurization of starting thioureas **1**.

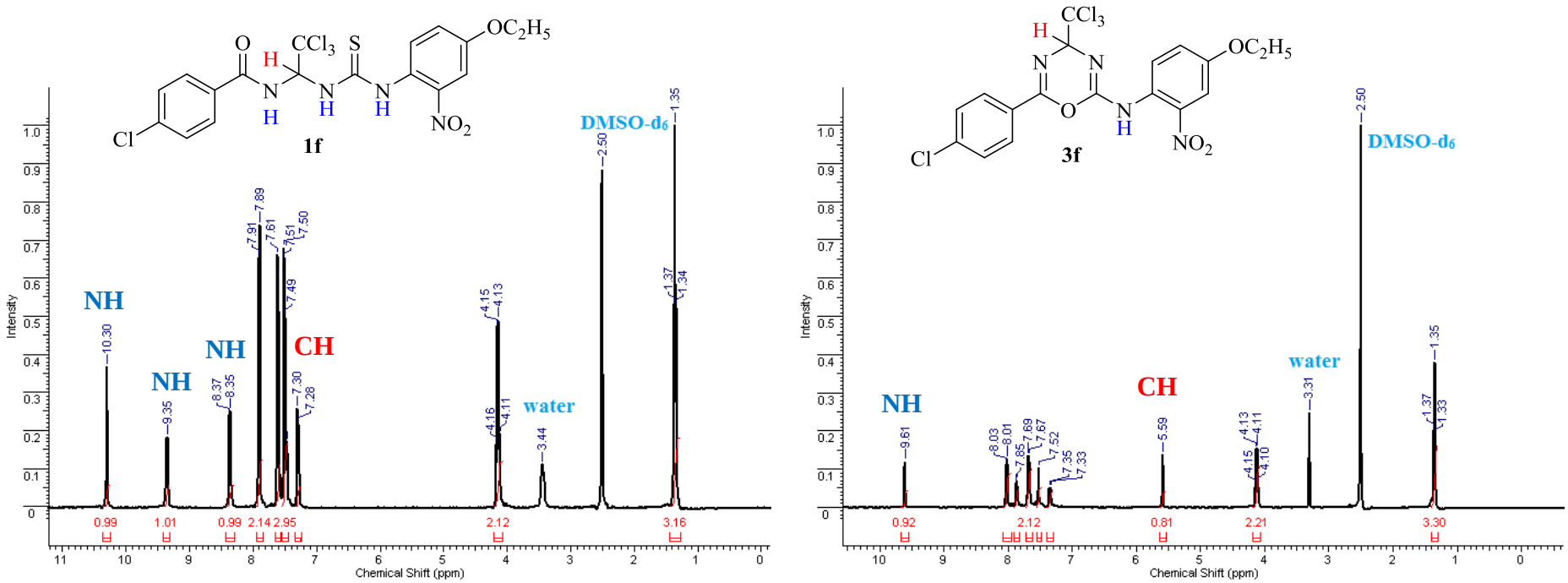


Figure 2. ^{1}H NMR spectra of 4-chloro-*N*-(2,2,2-trichloro-1-(3-(4-ethoxy-2-nitrophenyl)thioureido)ethyl)benzamide (**1f**) (left) and 6-(4-chlorophenyl)-*N*-(4-ethoxy-2-nitrophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (**3f**) (right).

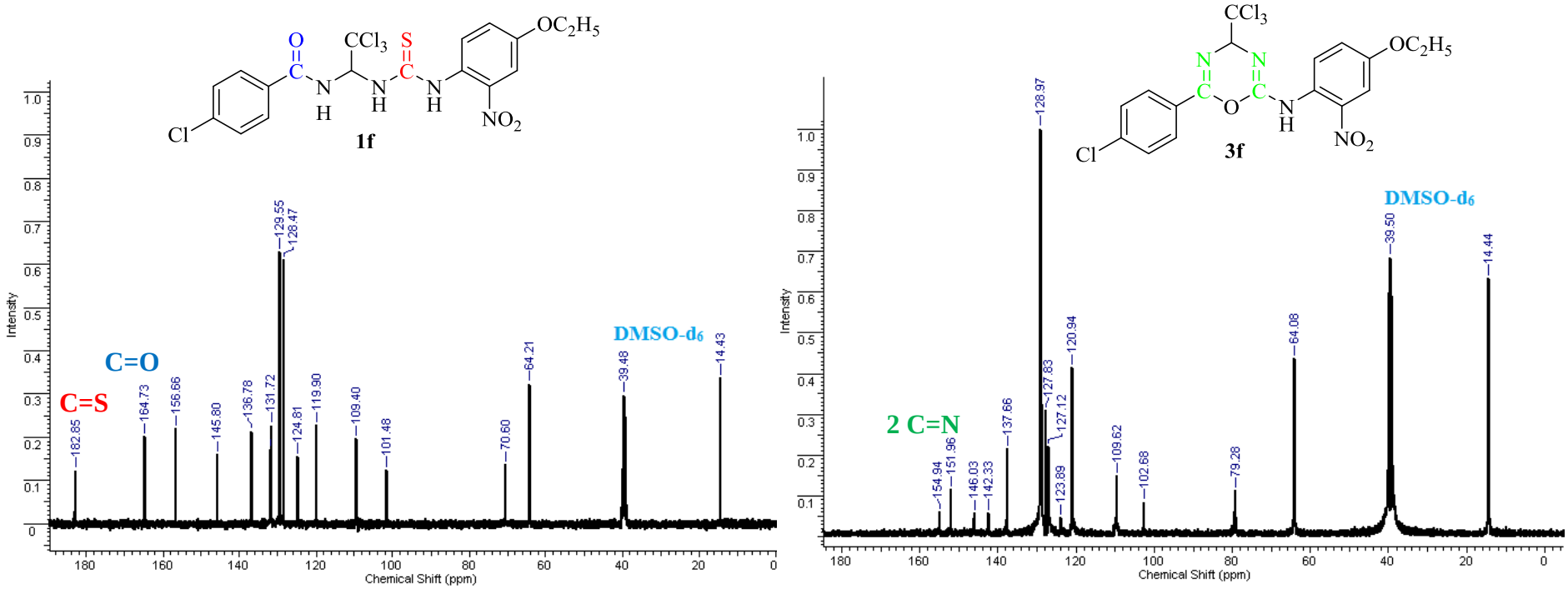


Figure 3. ^{13}C NMR spectra of 4-chloro-*N*-(2,2,2-trichloro-1-(3-(4-ethoxy-2-nitrophenyl)thioureido)ethyl)benzamide (**1f**) (left) and 6-(4-chlorophenyl)-*N*-(4-ethoxy-2-nitrophenyl)-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amine (**3f**) (right).

Conclusions

In this work, we have proposed a new method for the dehydrosulfurization of 4-chloro-*N*-(2,2,2-trichloro-1-(3-arylthioureido)ethyl)benzamides (**1**) leading to the formation of 6-(4-chlorophenyl)-*N*-aryl-4-(trichloromethyl)-4*H*-1,3,5-oxadiazin-2-amines (**3**). As a dehydrosulfurizing agent, we have proposed to use a mixture of iodine with triethylamine. The efficiency of using DCC and I_2+Et_3N for the dehydrosulfurization of thioureas **1** has been compared. It has been shown that the target products are predominantly formed in high yields when using DCC. However, the use of a mixture of I_2 and Et_3N makes it possible to obtain several new compounds of this class, which cannot be obtained under the action of DCC.

Thank you for your attention!