Synthesis and Spectral Characteristics of *N*-(1-(((2*E*,4*E*)-6-(2-Bromophenyl)-3-cyclohexyl-2-(cyclohexylimino)-2,3-dihydro-4*H*-1,3,5-oxadiazin-4-ylidene)amino)-2,2,2-trichloroethyl)acetamide

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INTRODUCTION & AIM

In recent decades, 1,3,5-oxadiazine derivatives have attracted increasing attention from researchers across various scientific disciplines. Compounds containing the 1,3,5-oxadiazine ring are considered in pharmacy and medicine as potential chemotherapeutic agents, as well as compounds with antibacterial and antifungal activity. 1,3,5-oxadiazine derivatives are also highly significant in agriculture, especially as insecticides (for instance, thiamethoxam and its analogues, herbicides, and substances with larvicidal activity. It is important to note that compounds in this class are of interest not only as biologically active agents but also as synthons and catalysts in organic synthesis. Notably, 1,3,5-oxadiazines have been used to produce ionic liquids, polymers, and explosives. Of particular interest are cucurbit[n]uryls containing a 1,3,5-oxadiazine ring, employed in supramolecular chemistry for preparing molecular clips [1,2].

Most 1,3,5-oxadiazine compounds are synthetically derived, with only two naturally occurring substances containing this ring known so far. The primary methods of synthesis include [4+2]-cycloaddition reactions and the intramolecular cyclization of diols, bisamidials, and substituted thioureas. Recently, synthesis of 1,3,5-oxadiazines via transformation of other heterocyclic systems has also been explored [2]. This article reports the synthesis of a new member of the 1,3,5-oxadiazine series: *N*-(1-(((2*E*,4*E*)-6-(2-bromophenyl)-3-cyclohexyl-2-(cyclohexylimino)-2,3-dihydro-4*H*-1,3,5-oxadiazin-4-ylidene)amino)-2,2,2-trichloroethyl)-acetamide.

METHOD

Spectral studies, including ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz), were conducted on DMSO-d_6 solutions using a Varian Agilent VNMRS 400 MHz spectrometer. Residual solvent signals served as internal standards. Elemental analysis was performed with a LECO CHNS-900 instrument. The reaction progress and purity of the synthesized compounds were monitored by thin-layer chromatography on Silufol UV-254 plates with a chloroform and acetone (3:1) eluent ratio. Melting points were determined in open capillaries.

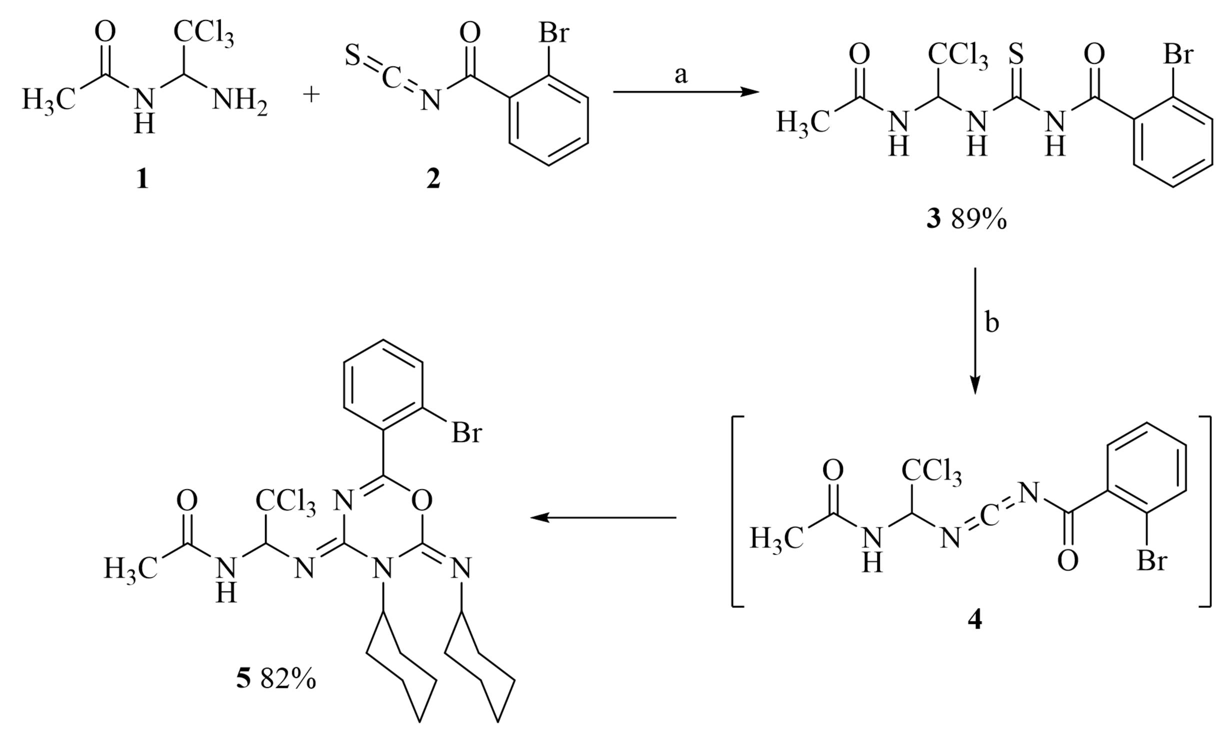
Synthesis of *N*-((1-acetamido-2,2,2-trichloroethyl)carbamothioyl)-2-bromobenzamide (3). A solution of 10 mmol of 2-bromobenzoyl isothiocyanate (2) in 10 mL of acetonitrile was added to 10 mmol (2.05 g) of N-(1-amino-2,2,2-trichloroethyl)acetamide (1) [3] in 15 mL of MeCN. The mixture was brought to a boil and left at room temperature for 12 hours. The resulting precipitate of thiourea (3) was filtered, washed with 10 mL of acetonitrile, and purified by recrystallization from methanol.

Synthesis of *N*-(1-(((2E,4E)-6-(2-bromophenyl)-3-cyclohexyl-2-(cyclohexylimino)-2,3-dihydro-4H-1,3,5-oxadiazin-4-ylidene)amino)-2,2,2-trichloroethyl)acetamide (5). A mixture of 10 mmol of thiourea 3 and 20 mmol (4.13 g) of dicyclohexylcarbodiimide was added to 40 mL of dry acetonitrile and refluxed for 40–50 minutes. The reaction mixture was cooled, and the precipitated crystals were filtered and washed with 10 mL of MeCN. The final product was purified by recrystallization from methanol.

RESULTS & DISCUSSION

The initial compound, *N*-(1-amino-2,2,2-trichloroethyl)acetamide (**1**), was prepared following a previously described method [3]. This compound reacted readily with 2-bromobenzoyl isothiocyanate (**2**) to produce N-((1-acetamido-2,2,2-trichloroethyl)carbamothioyl)-2-bromobenzamide (**3**) (Scheme 1). The compound was isolated almost quantitatively, with an overall yield of about 89% after recrystallization. Subsequently, thiourea **3** was reacted with dicyclohexylcarbodiimide (DCC). Under DCC action, hydrogen sulfide was eliminated from thiourea **3**, likely forming carbodiimide **4**. This intermediate then underwent a [4+2] cycloaddition reaction with another DCC molecule, resulting in the formation of the corresponding oxadiazine **5**.

The structure of the synthesized compounds was confirmed through spectral methods. In the ^1H NMR spectrum of compound **3**, signals from three NH protons and a doublet-doublet signal from the CH proton of the alkylamide group were observed. The spectrum of oxadiazine 5 showed only one NH proton signal and a doublet signal of the CH group. Moreover, the ^1H NMR spectrum of compound **5** displayed signals of 22 protons from two cyclohexyl rings, confirming the [4+2] cycloaddition process. The ^{13}C NMR data further supported the formation of oxadiazine 5, showing no C=S signal and only one C=O signal at 168.7 ppm, along with signals of three C=N groups in the 157.4-135.1 ppm range.



Scheme 1. Synthesis of *N*-((1-acetamido-2,2,2-trichloroethyl)carbamothioyl)-2-bromobenzamide (**3**) and its cyclisation into 1,3,5-oxadiazine (**5**). Reagents and conditions: a) MeCN, reflux 1-2 min, r.t. 12h; b) 2 DCC, MeCN, reflux 40-50 min, r.t. 1-2h.

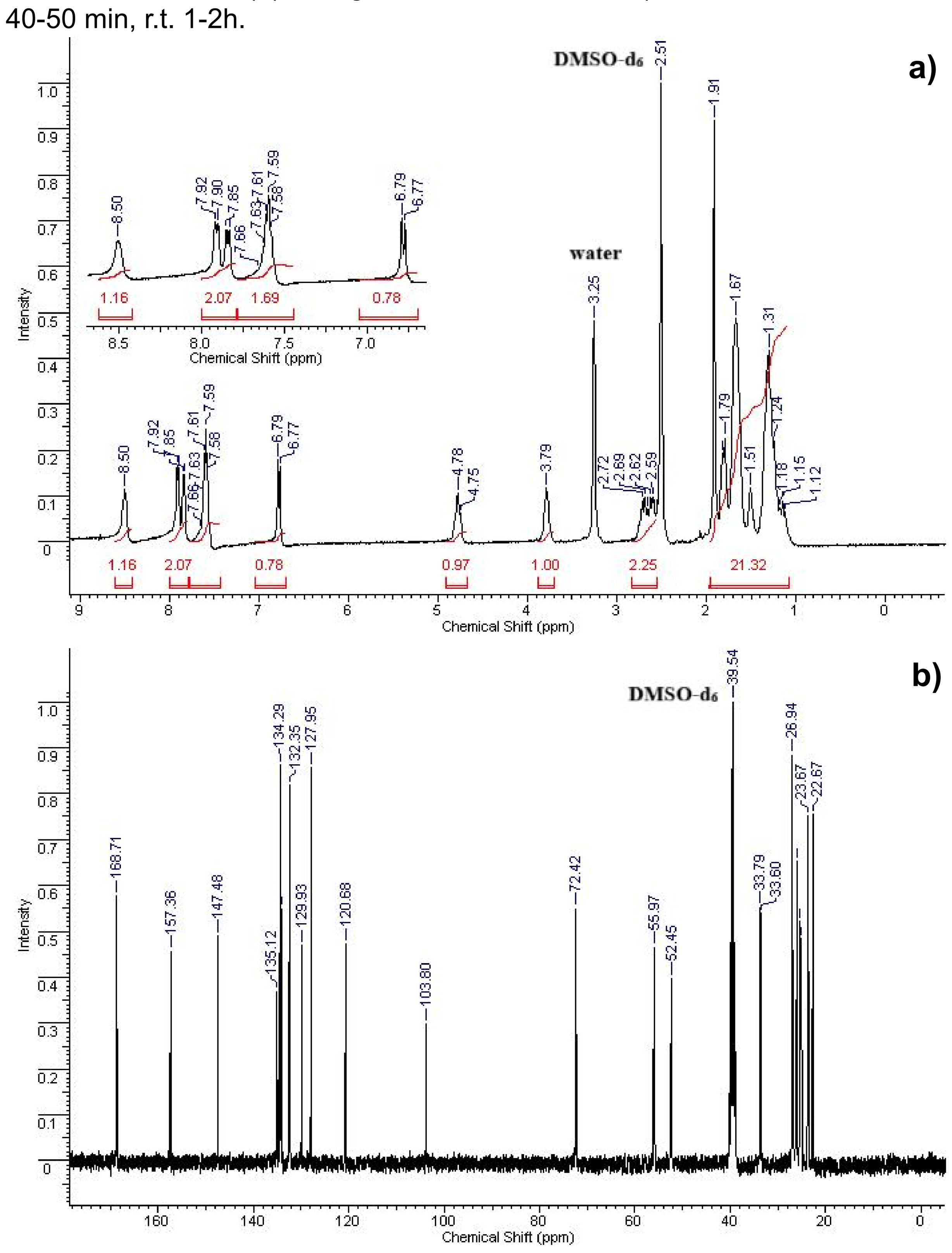


Figure 1. NMR ^1H (**a**) and NMR ^{13}C (**b**) spectra of *N*-(1-(((2*E*,4*E*)-6-(2-bromophenyl)-3-cyclohexyl-2-(cyclohexylimino)-2,3-dihydro-4*H*-1,3,5-oxadiazin-4-ylidene)amino)-2,2,2-trichloroethyl)acetamide (**5**).

CONCLUSION

In this work, we have synthesized *N*-((1-acetamido-2,2,2-trichloroethyl)carbamothioyl)-2-bromobenzamide and carried out its cyclization to *N*-(1-(((2*E*,4*E*)-6-(2-bromophenyl)-3-cyclohexyl-2-(cyclohexylimino)-2,3-dihydro-4*H*-1,3,5-oxadiazin-4-ylidene)amino)-2,2,2-trichloroethyl)acetamide. The structure of the synthesized compounds has been proven by NMR spectroscopy.

FUTURE WORK / REFERENCES

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