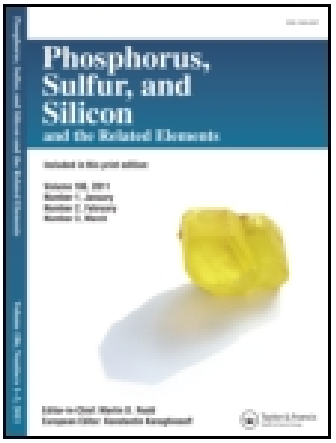

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A Comparative Study of the Effect of Water and Organic Solvents on 1,3-Dipolar Cycloaddition Reactions of Mesitonitrile Oxide with C-Sulfonyl- and Sulfanyl-Dithioformates

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A COMPARATIVE STUDY OF THE EFFECT OF WATER AND ORGANIC SOLVENTS ON 1,3-DIPOLAR CYCLOADDITION REACTIONS OF MESITONITRILE OXIDE WITH *C*-SULFONYL- AND SULFANYL-DITHIOFORMATES

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1,3-Dipolar cycloadditions of the C-sulfonylated- and sulfanylated-dithioformates with mesitonitrile oxide occurred smoothly in organic and aqueous media to afford 1,4,2-oxathiazoles in good yields. The structures of these cycloadducts have been established via the analysis of NMR data and elemental analyses.

Keywords 1,3-Dipolar cycloaddition; mesitonitrile oxide; 1,4,2-oxathiazole derivatives; sulfanyldithioformates; sulfonyl dithioformates

INTRODUCTION

1,3-Dipolar cycloaddition reactions of nitrile oxides have found many useful applications in organic synthesis, particularly with respect to the synthesis of compounds with new chiral centers.[1,2] Such asymmetric syntheses have a growing importance in the pharmaceutical and agricultural industries with respect to the preparation of chiral drugs and natural products.[3] Also, beyond the capability of the 1,3-dipolar cycloadditon reaction to produce heterocycles, the ability of heteroatom-containing cycloadducts to transform into a variety of other functionalized organic molecules, cyclic or acyclic, has been reported.[4] There also has been wide interest in the 1,3-dipolar cycloaddition reactions of thione dipolarophiles.[5] The >C═S double bond displays an unusually high reactivity with a number of 1,3-dipoles, and because of this, thiones have been regarded as super-dipolarophiles. In this context, *C*-sulfonylated- and sulfanylated-dithioformates **5** and **9** are versatile thiocarbonyl reagents, and they have received much of our attention due to their numerous synthetic applications.[5,6] Recently, we have reported the cycloaddition reactions of **5** toward 1,3-dienes and diazoalkanes.[5,b,c] However, to the best of our knowledge, the chemistry of and information on the 1,3-dipolar cycloaddition of **5** and **9** to nitrile oxides are scant and deserve further investigation.[7] Another intriguing point to be addressed in this 1,3-dipolar cycloaddition

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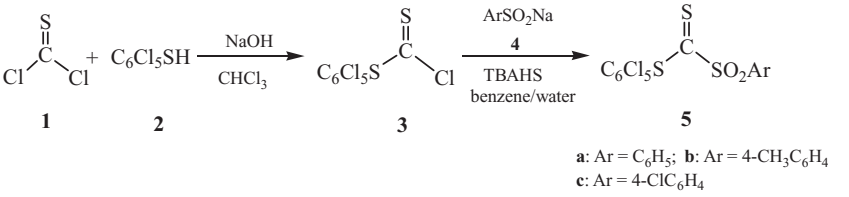
reactions is to investigate the use of water as an environmentally friendly alternative to organic solvents, and efforts in this field are certainly worthwhile. More specifically, we are interested to know how water affects this reaction and whether or not water is generally a favorable reaction medium. Another aim in this work is to compare the dipolarophilicity of the >C=S group of sulfonyldithioformates **5** and sulfanyldithioformates **9** in organic and aqueous media.

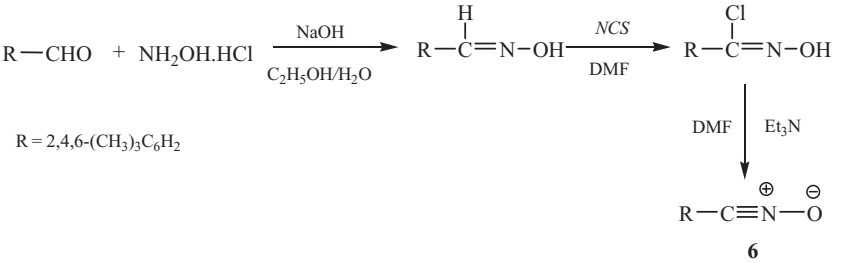
RESULTS AND DISCUSSION

We have chosen the *C*-sulfonylated- and *C*-sulfanylated-dithioformates **5** and **9**, respectively, as thiocarbonyl-based dipolarophiles for the present study because the dipolarophilicity of thiocarbonyl group strongly depends on the nature of the substituents at the thiocarbonyl carbon atom. Thus, the starting *S*-pentachlorophenyl *C*-arylsulfonyldithioformates **5** were prepared in good yields in a two-step procedure as described by us, starting from thiophosgene and pentachlorothiophenol **2**, and subsequent reaction of chlorodithioformates **3** with sodium sulfinates **4** in water/benzene in the presence of tetrabutylammonium hydrogen sulfate afforded 5 in 60–80% yields[8] as depicted in Scheme 1.



Scheme 1

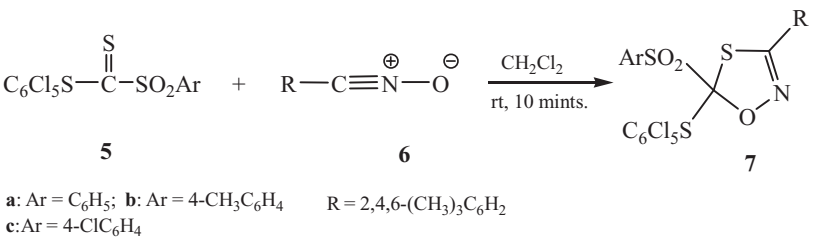
The mesitonitrile oxide **6** was chosen for the aforementioned cycloadditions as one of the most stable nitrile oxides with minimum side reactions.[9] It was generated from the corresponding mesitaldehyde via sequential oxime formation, *N*-chlorosuccinimide (NCS) chlorination, and dehydrochlorination of the corresponding hydroximoyl chloride in the presence of triethylamine as a base according to Scheme 2.



Scheme 2

At room temperature, a methylene chloride solution of **5** reacts with mesitonitrile oxide **6** immediately within **10** min as judged by both TLC analysis and the discharge of the red color of **5**. NMR analysis of the crude products revealed that the cycloadducts

1,4,2-oxathiazoles **7** had been formed in good yields as a stable, white, crystalline product as depicted in Scheme 3.

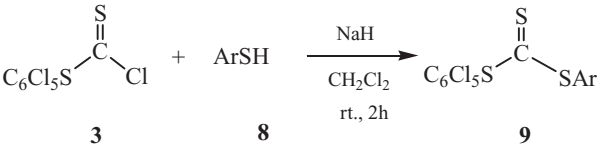


5 **6** **7**

a: Ar = C_6H_5; **b**: Ar = 4-$CH_3C_6H_4$ R = 2,4,6-$(CH_3)_3C_6H_2$
c:Ar = 4-ClC_6H_4

Scheme 3

As expected for 1,3-dipolar reactions, the sulfonyl group at the thiocarbonyl carbon atom of **5** enhanced the dipolarophilic reactivity towards cycloaddition considerably. In the structure proof of the cycloadducts **7**, the ^{13}C NMR analysis showed a signal at around 156 ppm, which is consistent with the assignment to the imine carbon of the oxathiazole ring. In order to compare the influence of the electron-withdrawing substituent on the dipolarophilic reactivity of the thiocarbonyl group of **5**, we have further examined the same reaction with sulfanylated dithioformates **9**. The starting thiocarbonyl compounds **9a** and **9b** needed for this study were prepared in good yields (see the Experimental section) by the reaction of chlorodithioformates **3** with thiolates **8** as depicted in Scheme 4. This synthesis included an optimization of a previously reported method.[10] Employing sodium hydride as a base instead of NaOH, greatly facilitates the reaction by drastically reducing the time for completion from one week to a few hours and at the same time improves the yield greatly.



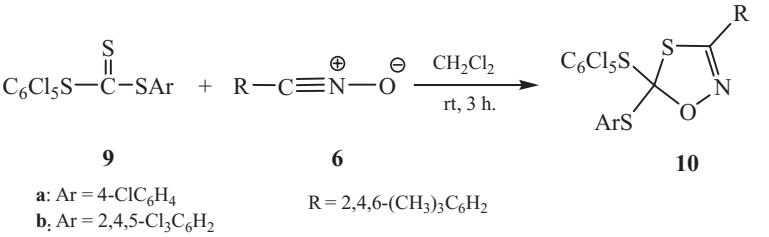
3 **8** **9**

a: Ar = 4-ClC_6H_4
b: Ar =2,4,5-$Cl_3C_6H_2$

Scheme 4

The ^{13}C NMR signal of the >C=S group of **9a** and **9b** resonates at 212.2 and 216.5 ppm, respectively, and a downfield shift of 23 to 27 ppm from the starting chlorodithioformates **3** (189 ppm)[8] occurred. With sulfanylated dithioformates in hand, 1,3-dipolar cycloaddition reactions of **9** with mesitonitrile oxide **6** were then conducted. Treatment of **9** with mesitonitrile oxide **6** at room temperature in dichloromethane for 3 h afforded the corresponding cycloadducts 1,4,2-oxathiazoles **10** in good yields after purification (see Scheme 5).

The adducts **10** are stable to the reaction conditions, and they are characterized as 1,4,2-oxathiazoles on the basis of their NMR spectra and elemental analysis (see the Experimental section). Thus, the imine carbons (identified by their ^{13}C NMR) led to carbon resonances correctly predicted to be 156.31 and 157.34 ppm for **10a** and **10b**, respectively,



9 **6** **10**

a: Ar = 4-ClC_6H_4
b: Ar = 2,4,5-$Cl_3C_6H_2$

R = 2,4,6-$(CH_3)_3C_6H_2$

Scheme 5

and within the normal range of the quaternary imine carbon. This result clearly shows the activating effect of the sulfonyl group on the dipolarophilic character of the thiocarbonyl function of **5**. In an attempt to replace potentially hazardous dichloromethane with environmentally benign solvents such as water or other eco-friendly alternatives, we have performed the cycloaddition in water. Primarily we wanted to know how water affects this reaction and whether or not water is generally a favorable reaction medium. After 3 h of stirring a suspension of solids **5** and **6** in water at ambient temperature, the reaction was completed as monitored by the TLC and the discharge of the red color of **5**. After completion of the reaction, the product settles to the bottom and can then be obtained simply by pouring the water off. The NMR and TLC analysis of the product proved the formation of the cycloadducts **7**. However, when we performed the same reaction with **9**, only 50% conversion of the starting materials into the corresponding cycloadducts **10** was observed after 2 h. Interestingly, using water mixed with ethanol as cosolvent led to the complete conversion of **9** to **10**.

CONCLUSION

In conclusion, we showed that our main goal, which was to replace harmful solvents by water as an environmentally benign alternative, could be achieved. In addition, aqueous media also offer advantages in terms of easy isolation of products. However, there are some drawbacks such as modest yields and low reaction rates. This maybe due to the lower water solubility of the reactants. Understanding the modes of interaction of water with the reactants and enhancing the solubility of the starting materials are currently underway in our laboratory.

EXPERIMENTAL

All ^1H and ^{13}CNMR experiments (solvent $CDCl_3$) were carried out with a 400 MHz Bruker Avance DRX-400 spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C) at University of Antwerp, Belgium. Chemical shifts are reported in part per million (ppm) relative to the respective solvent or tetramethylsilane (TMS). Melting points were recorded on Stuart scientific melting point apparatus and are uncorrected. The microanalysis was performed in the Microanalysis Laboratory at Cairo University. All reactions were followed by thin layer chromatography (TLC) on Kiesel gel F_{254} precoated plates (Merck). Solvents were dried/purified according to procedures in ths literature. Pentachlorophenyldithioformate **3**, *C*-sulfonylated dithioformates **5**, and mesitonitrile oxide **6** were prepared according to procedures in the literature.[8,9]

General Procedure for the Synthesis of Arylsulfanyldithioformates 9

The thiol **8** was dissolved in a small portion of dry dichloromethane (5 mL), and sodium hydride (166 mg, 3.93 mmol) was added portionwise at 0°C. After 10 min, pentachlorophenyl chlorodithioformates **3** (500 mg, 180.50 mmol) dissolved in 5 mL dry dichloromethane was added dropwise to the above mentioned mixture at room temperature over a period of 10 min. The resulting solution was stirred overnight at room temperature. The dichloromethane solution was washed with water (three times). The organic layer was dried over anhydrous $CaCl_2$, filtered, and then concentrated under reduced pressure to leave an oily residue, which was precipitated with n-hexane. This was then recrystallized from *n*-hexane to yield pure **9**.

Pentachlorophenyl *C*-(4-chlorophenylsulfanyl)dithioformate 9a. Yield: 82%, yellow crystals, melting point, as well ^1H and ^{13}C MNR data are in agreement with those reported in the literature.[6]

Pentachlorophenyl *C*-(2,4,5-trichlorophenylsulfanyl)dithioformate 9b. Yield: 80%, yellow crystal, mp 72–75°C. IR (KBr): 3075($\upsilon_{C-H,Ar}$), 1560 ($\upsilon_{C=C,Ar}$), 1093($\upsilon_{C=S}$); 781 (υ_{C-Cl}). ^1H NMR ($CDCl_3$): $\delta = 7.50$ (s, 1H, Ar); 7.68 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$); δ 128.88; 131.10; 131.94; 132.72; 132.95; 133.14; 137.06; 138.25; 138.74; 139.10; 212.22 (>C=S).

3-Mesityl-5-*(*phenylsulfonyl)-*5*-pentachlorophenylthio (1,4,2-oxathiazole) 7a

The pentachlorophenyl *C*-(phenylsulfonyl)dithioformate **5a** (50 mg, 0.107 mmol) was dissolved in a small portion of dichloromethane (5mL), and mesitonitrile oxide **6** (17.25 mg, 0.107 mmol) was added. The violet color of **5a** disappeared after 10 min, and the solvent was evaporated under reduced pressure to leave a semisolid residue, which was precipitated by washing with diethyl ether to give white crystals. Yield: 73%, mp: 130–132°C. ^1H NMR ($CDCl_3$): δ 1.90 (s, 3H, CH_3); 2.27 (s, 6H, $2CH_3$); 6.81 (s, 2H); 7.65 (d, 2H, $J = 8.4$ Hz); 7.83 (m, 1H); 8.15 (d, 2H, $J = 8.8$ Hz). ^{13}C NMR ($CDCl_3$): δ 22.8; 24.9; 120.13; 128.0; 129.50; 129.60; 132.50; 133; 133.20; 135.30; 136.10; 137.40; 138.60; 140.50; 142.10; 156.15 Calcd: C, 41.76; H, 2.21; N, 2.03 for $C_{12}H_{15}C1_6NO_3S_3$. found: C, 41.71; H, 2.28; N, 2.11.

3-Mesityl-5-tolysulfonyl-5-pentachlorophenylthio(1,4,2-oxathiazole) 7b

The procedure as given for **7a** was followed. Yield 69%, mp 76–78°C, ^1H NMR ($CDCl_{3)}$: δ 1.92 (s, 3H, $CH_{3)}$; 2.25 (s, 6H, $2CH_{3)}$; 2.51 (s, 3H, $CH_{3)}$; 6.81 (s, 2H); 7.44 (d, 2H, $J = 9.3$ *Hz*); 8.07 (d, 2H. $J = 8.1$ Hz). ^{13}C NMR ($CDCl_3$): δ 22.8; 24.30; 24.9; 120.78; 128.0; 128.20; 129.60; 130; 132.50; 133; 133.20; 135.9; 136.10; 138.60; 140.50; 143.40; 156.13. Calcd.: C, 44.91; H, 2.83; N, 2.18. for $C_{24}H_{18}C1_5NO_3S_3$: found: C, 44.40; H, 2.60; N, 2.08.

3-Mesityl-5-(4-chlorophenylsulfonyl)-5-pentachlorophenylthio (1,4,2-oxathiazole) 7c

The procedure as given for **7a** was followed. Yield: 82%, mp 140–142°C, ^1H NMR ($CDCl_3$): δ 1.91 (s, 3H, CH_3); 2.24 (s, 6H, $2CH_3$); 6.80 (s, 2H); 7.63–8.21 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 22.8; 24.9; 120.20; 128.0; 128.30; 129.60; 129.80; 132.60; 133; 133.20;

133.80; 136.10; 138.60; 138.90; 140.50; 142.10; 156.03. Calcd.: C, 41.71; H, 2.28; N, 2.11. for $C_{23}H_{15}C1_6NO_3S_3$: found: C, 41.76; H, 2.21; N, 2.03.

3-Mesityl-5-p-chlorophenylthio-5-pentachlorophenylthio (1,4,2-oxathiazole) 10a

The pentachlorophenyl *C*-(4-chlorophenylsulfanyl)dithioformate **9a** (50 mg, 0.106 mmol) was dissolved in dichloromethane (5 mL), and mesitonitrile oxide (17.10 mg, 0.106 mmol) was added. The reaction mixture was stirred for 3 h and concentrated under reduced pressure to leave a semisolid residue, which was precipitated by washing with ether to give white crystals, Yield: 59%, mp 138–140°C, ^{1}H NMR ($CDCl_3$): δ 1.85 (s, 3H, CH_3); 2.20 (s, 6H, $2CH_3$); 6.70 (s, 2H); 7.40 (d, 2H); 7.60 (d, 2H).^{13}C NMR ($CDCl_3$): δ 18.8; 21.11; 119.45; 121.74; 128.44; 128.54; 128.69; 128.96; 129.21; 129.66; 136.32; 136.83; 137.52; 138.34; 140.31; 156.31. Calcd: C, 43.83; H, 2.40; N, 2.22 for $C_{23}H_{15}Cl_6NOS_3$. found: C, 43.51; H, 2.27; N, 2.07.

3-Mesityl-5-(2,4,5-trichlorophenylthio-5-pentachlorophenylthio (1,4,2-oxathiazole) 10b

The procedure as given for **9a** was followed. Yield: 57%, mp 152–154°C. ^{1}H NMR ($CDCl_3$): δ 2.00 (s, 3H, CH_3); 2.25 (s, 6H, $2CH_3$); 6.83 (s, 2H); 7.62 (s, 1H); 8.01 (s, 1H.). ^{13}C NMR ($CDCl_3$): δ 18.94; δ 21.17; 120.18; 121.15; 128.21; 128.65;129.88; 129.96; 130.08, 131.11; 131.46; 132.61; 135.43; 137.07; 137.46; 138.39; 141.39; 157.34. Calcd: C, 38.23; H, 1.69; N, 1.71 for $C_{23}H_{13}C1_8NOS_3$. found: C, 39.51; H,1.87; N, 2.00.

General Procedure for 1,3-Dipolar Cycloadditions of *C*-Sulfonylated-dithioformates 5 in Water

A mixture of **5** (0.10 mmol), mesitonitrile oxide **6** (0.12 mmol), and water (2 mL) was left stirring at room temperature. After 3 h, the red color of **5** had vanished, and a white product precipitated. The solid was filtered, washed with cold water, and dried to afford the cycloadducts **7**, in 70–80% yields. The NMR data are consistent with the structure of cycloadducts **7**.

General Procedure for 1,3-Dipolar Cycloadditions of *C*-Sulfanyl-dithioformates 9 in Ethanol/Water Mixture

In a mixture of 1.6 mL of 1:1 (v/v) ethanol/water, 0.10 mmol of **9** and 0.12 mmol of **6** were suspended, and the mixture was left stirring at room temperature. After 2 h, the yellow color of **9** had disappeared and a white solid had precipitated. The solid was filtered, washed with cold water, and dried to yield the cycloadducts **10** in 65–70% yields. The NMR data of **10** are consistent with the structure of cycloadducts obtained in organic solvent.

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