JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2005; **18:** 86–89
DOI: 10.1002/poc.857

Review Commentary

Reactions of dimethoxycarbene with carbon–sulfur double bonds[†]

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Received 3 November 2003; revised 1 February 2004; accepted 5 March 2004

ABSTRACT: Unlike electrophilic carbenes, which react at sulfur to produce thiocarbonyl ylide intermediates, dimethoxycarbene (DMC), generated by thermolysis of an oxadiazoline at 110 °C in benzene in a sealed tube, reacts at carbon, possibly to generate a zwitterionic intermediate, or at both carbon and sulfur in a concerted process that generates a thiirane. In case of the strained 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**2**), an assumed zwitterion undergoes ring expansion. In analogous reactions, unstrained thiones afford thiiranes, possibly by ring closure of the postulated intermediates or by concerted addition. Desulfurization of thiiranes, which occurs spontaneously in some instances, results in the formation of ketene acetals, many of which hydrolyze during workup. *O*-Alkyl thioesters and xanthates react to afford products via insertion of the DMC into C_{sp^2}—O or C_{sp^2}—S bonds, respectively. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: dimethoxycarbene; ketene acetals; oxadiazoline; reactive intermediates; thiiranes; thiocarbonyl compounds

INTRODUCTION

Although there are numerous publications concerning reactions of electrophiliic carbenes and carbenoids with thiocarbonyl groups (see, for example, Ref. 1), there are fewer concerning reactions of nucleophilic carbenes with analogous compounds (see, for example, Ref. 2). Electrophilic carbenes add to sulfur of C═S compounds to generate thiocarbonyl ylides,[1] whereas nucleophilic carbenes add to carbon of C═S, either in concert with addition at S or to form a dipolar intermediate. A dipolar intermediate has been demonstrated for the case of diaminocarbenes and CS_2 only[2c] (Scheme 1), and it seems reasonable to postulate an analogous intermediate for reactions of dimethoxycarbene (DMC) with thiocarbonyl compounds, particularly because such a postulate seems to explain many of the observed products (the fact that the postulate is convenient for the explanation of diverse reaction paths does not mean that it is right, of course). On the other hand, thiocarbonyl groups are known to undergo carbophilic and/or thiophilic reactions[3] with other nucleophilic agents and, in the case of DMC, both reaction courses could compete. This mini-review covers our groups's research on the chemistry of DMC with thiocarbonyl compounds and the limited research of some others.

RESULTS AND DISCUSSION

2,2,4,4-Tetramethyl-1,3-cyclobutanedithione

Reaction of dimethoxycarbene (DMC, **1**) with the cyclobutanedithione **2** resulted in two major products, **6** [^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 6H), 1.49 (s, 6H), 3.33 (s, 6H).^{13} C NMR (75 MHz, $CDCl_3$): δ 24.1, 33.6, 50.6, 64.5, 70.3, 198.6, 259.1, 272.0. MS (HR): *m/z* calcd for $C_{11}H_{18}O_2S_2$ 246.0748; found 246.0749] and **7** [^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 6H), 1.48 (s, 3H), 1.54 (s, 3H), 3.35 (s, 3H), 3.40 (s, 3H), 3.55 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 27.9, 29.1, 32.4, 50.6, 52.5, 55.6, 60.2, 66.4, 108.4, 109.4, 278.5. MS (EI): *m/z* 320 (M^+)], formed by primary ring expansion of

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[†]Selected article presented at the Seventh Latin American Conference on Physical Organic Chemistry (CLAFQO-7), 21–26 September 2003, Florianópolis, Brazil.

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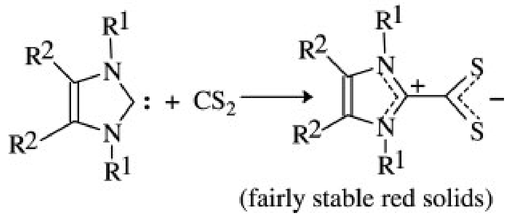
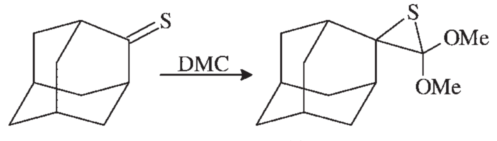
Contract/grant sponsor: Natural Sciences and Engineering Research Council of Canada; *Contract/grant number:* 1110.
Contract/grant sponsor: Polish State Committee for Scientific Research; *Contract/grant number:* 4 T09A 046 25.



Scheme 1. Reaction of stable diaminocarbenes with carbon disulfide

2 (Scheme 2).[2b] The expected thiirane **5** was not found in the reaction mixture. Products **6** and **7** can be accounted for in terms of intermediate **3** (or an analogous transition state) that does not have the correct geometry for facile formation of thiirane **5** but does have the correct geometry for ring expansion to **6**.

Ring-expansion product **6** could be formed most rapidly, because of relief of ring strain, either from an intermediate such as **3** or a transition state analogous to it. Compound **6**, with non-equivalent C═S groups, reacts regioselectively with **1**, at the C═S moiety flanked by the methoxy substituents. We attribute the enhanced reactivity of that group (the isomeric thiirane was not found) to the polar effect of those methoxy groups. Two α-methoxy groups (as in 2,2-dimethoxycyclopentanone) raise the carbonyl stretching frequency above that of cyclopentanone, by about $15\,\mathrm{cm}^{-1}$. A through-space interaction of a methoxy group with the incoming carbene unit, that becomes positively charged as it bonds to carbon of C═S, cannot be ruled out.[2a,b] Presumably addition to **6** involves an intermediate (or transition state) similar to **3** but, in the absence of strain, further ring expansion is slowed.



10 (92%)

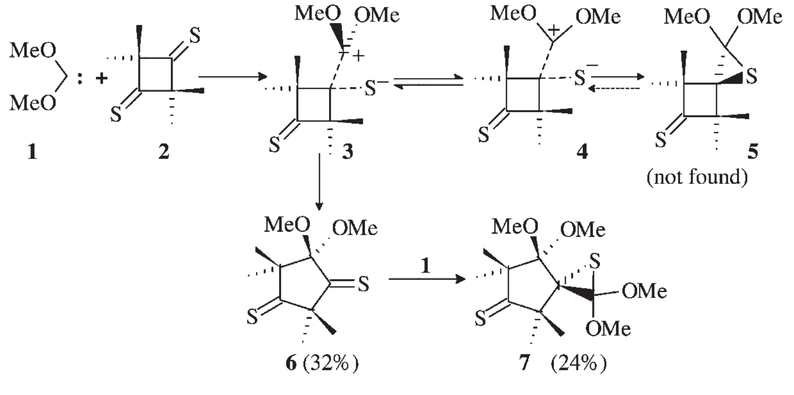
Scheme 4. Thiirane formation from reaction of DMC with adamantanethione

Along with the zwitterionic intermediate from the reaction of a diaminocarbene with carbon disulfide, presented in Scheme 1, there is a report by Hoffmann *et al.*,[4] who postulated a similar structure **8** for an intermediate formed initially from DMC and phenyl isothiocyanate. Hoffmann's group trapped DMC with aryl isocyanates and aryl isothiocyanates to give 5,5-dimethoxyhydantoins and 5,5-dimethoxydithiohydantoins, respectively. The short-lived dipolar intermediate was trapped efficiently with another molecule of phenyl isothiocyanate to yield the imidazolidine-2,5-dithione (**9**) shown in Scheme 3.[4] Nair *et al.* have also invoked a dipolar intermediate, from the reaction of dimethoxycarbene with dimethyl acetylenedicarboxylate, which adds to carbonyl compounds.[5]

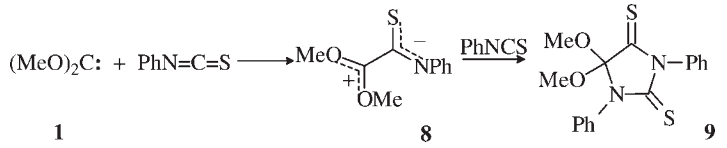
Dimethoxythiiranes have been isolated in a few cases,[2a] most notably from reaction of **1** with adamantanthione[6] to afford **10** (Scheme 4).

Diarylthiones

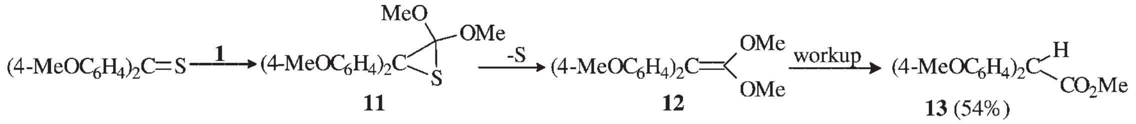
Reactions of aromatic thiones with DMC did not lead to isolable dimethoxythiiranes. Thus 4,4′-dimethoxythiobenzophenone (M. Dawid, G. Mloston and J. Warkentin, unpublished observation) gave the known[7] methyl ester



Scheme 2. Reaction of dimethoxycarbene with a cyclobutanedithione



Scheme 3. Dipolar intermediate from reaction of DMC with phenyl isothiocyanate



Scheme 5. Reaction of DMC with 4,4′-dimethoxythiobenzophenone

of 2,2-bis(4,4′-dimethoxyphenyl)ethanoic acid (**13**) in 54% yield. Scheme 5 illustrates a possible sequence, involving desulfurization of thiirane **11** and subsequent hydrolysis of ketene acetal **12**. Those intermediates might be isolable under some conditions.

O-Methyl thiobenzoate

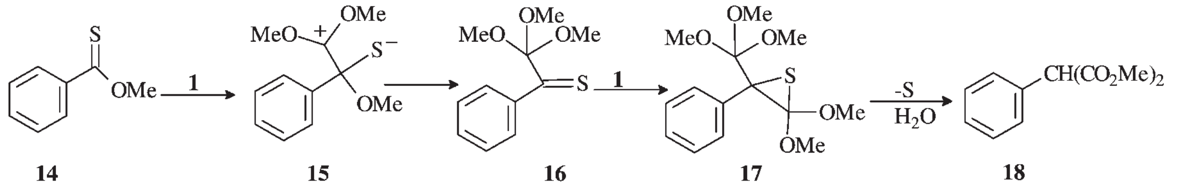
O-Methyl thiobenzoate (**14**) reacted with 2 equiv. of **1** to afford the known[8] **18** in 84% yield (Scheme 6), and we propose **15**–**17** as intermediates in this cascade conversion.[2a]

Compound **17** could not be isolated in completely pure form but its structure was unambigously confirmed by means of spectroscopic data [^{1}H NMR (300 MHz, $CDCl_3$): δ 3.23 (s, 3H); 3.34 (s, 9H), 3.68 (s, 3H), 7.26–7.32 (m, 3H), 7.53–7.57 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 51.4, 56.0, 57.9, 108.1, 113.1, 127.1, 127.4, 130.6, 137.0]. Attempts to purify it by further chromatography led to partial or complete hydrolysis to **18**.

Methyl dithiobenzoate

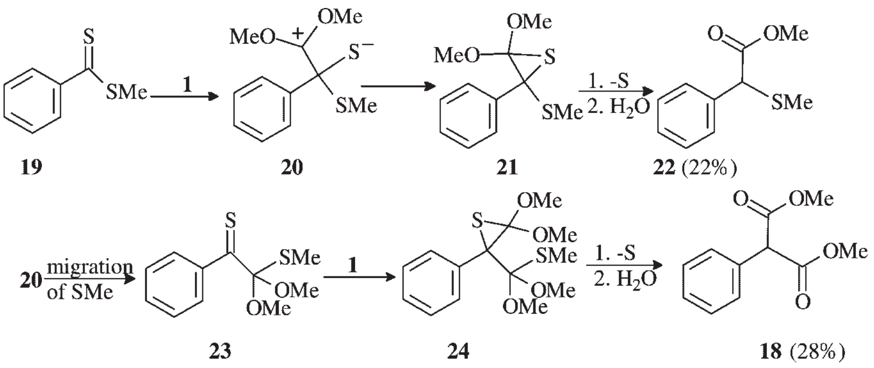
Methyl dithiobenzoate (**19**) gave **22** [^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08 (s, 3H), 3.74 (s, 3H), 4.52 (s, 1H), 7.26–7.46 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.9, 52.6, 53.4, 128.1, 128.4, 128.6, 135.7, 171.1, MS (HR): *m/z* calcd for $C_{10}H_{12}O_2S$ 196.0558; found 196.0545] in 22% yield and **18** in 28% yield (Scheme 7).[2b] Again, it is plausible to think of **22** as a final product arising via **20** and **21**. Some support for the proposed mechanism came from the isolation of an impure sample of a material thought to be **21** {^{1}H NMR (200 MHz, $CDCl_3$): δ 1.98 (s, 3H), 3.52 (s, 3H), 3.77 (s, 3H), 7.18–7.47 (m, 5H). ^{13}C NMR (75 MHz, CD_3Cl): δ 17.0, 57.5, 97.5, 126.4, 128.1, 129.7, 136.9, 159.2. MS (EI): *m/z* (%) 210 ([M – S]$^+$, 70), 195 (100), 167 (32), 135 (15), 121 (85), 105 (58), 91 (12), 77 (55)}, which after chromatographic workup was transformed into **22**. The precursor of **18** is pictured as structure **24**. Neither **23** nor **24** was found.

It is not clear what the features are that lead to desulfurization, or what species remove the thiirane

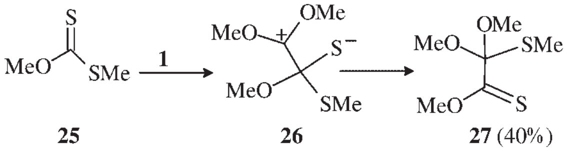


(84%, presumably *via* hydrolysis of the ketene acetal)

Scheme 6. Reaction of DMC with *O*-methyl thiobenzoate



Scheme 7. Reaction of DMC with dimethyl dithiobenzoate



Scheme 8. Reaction of DMC with dimethyl xanthate

sulfur. Moreover, there are additional minor products that might have mechanistic significance.

Dimethyl xanthate

Initial attack of **1** on dimethyl xanthate (**25**) is pictured in terms of **26**, in which the choice for migration is between a methoxy and a methylthio group (Scheme 8). One would expect the latter to migrate to afford the product that was isolated (**27**) [^{1}H NMR (200 MHz, C_6D_6): δ 1.87 (s, 3H), 3.15 (s, 6H), 3.69 (s, 3H). ^{13}C NMR (50.3 MHz, C_6D_6): δ 13.4, 50.9, 58.8, 111.5, 211.6], given the weaker C—S bond and the greater polarizability of sulfur compared with oxygen.[2a]

CONCLUSION

The reactions of thiocarbonyl compounds with nucleophilic carbenes are in their infancy, as indicated by the above early review. However, there is no doubt that their interesting diversity leaves much scope for investigation of mechanisms, by both experimental and computational approaches. It will be particularly important to try, further, to isolate and characterize some of the postulated intermediates.

Acknowledgments

M. D., D. L. R. and J. W. thank the Natural Sciences and Engineering Research Council of Canada for financial support (Grant No. 1110). G. M. acknowledges support by the Polish State Committee for Scientific Research (Grant No. 4 T09A 046 25).

REFERENCES

1. (a) Mloston G, Heimgartner H. *Speciality Chem. Mag.* 2003; **23**: 38; (b) Mloston G, Romanski J, Swiatek A, Heimgartner H. *Helv. Chim. Acta.* 1999; **82**: 946; (c) Mloston G, Heimgartner H. *Pol. J. Chem.* 2000; **74**: 1503; (d) Ibata T, Fukushima K. In *Nitrogen, Oxygen and Sulfur Ylide Chemistry*, Clark JS (ed). Oxford University Press: Oxford, 2002; 265.
2. (a) Dawid M, Reid DL, Mloston G, Warkentin J. *Can. J. Chem.* 2003; **81**: 1025; (b) Dawid M, Mloston G, Warkentin J. *Chem. Eur. J.* 2002; **8**: 2184; (c) Kuhn N, Bohnen H, Henkel G. *Z. Naturforsch., Teil B* 1994; **49**: 1473.
3. Molina MT, Yanez M, Mo O, Notario R, Abboud J-L, M. In *The Chemistry of Double-bonded Functional Groups*, Patai S (ed). Wiley: Chichester, 1997; Chapt. 23, 1355.
4. Hoffmann RW, Steinbach K, Dittrich B. *Chem. Ber.* 1973; **106**: 2174.
5. Nair V, Bindu S, Sreekumar V, Balagopal L. *Synthesis* 2003; 1446.
6. Dawid M, Mloston G, Warkentin J. *Org. Lett.* 2001; **3**: 2455.
7. Earle MJ, Fairhurst RA, Heaney H. *Tetrahedron Lett.* 1991; **32**: 6171.
8. Yang M, Webb PR, Livant P. *J. Org. Chem.* 2001; **66**: 4945.