

## Uncharacteristic thione behavior in a Huisgen cycloaddition reaction: a kinetic and theoretical study

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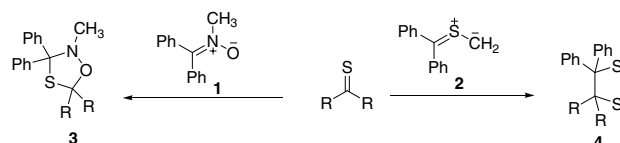
**Abstract**—In the reaction of phthalazinium-2-dicyanomethanide with adamantanethione the rare ring system [1,3]thiazolo[2,3-*a*]phthalazine was obtained. An X-ray crystal structure of the product shows regioselectivity with the thione carbon bonded to the dicyanomethanide terminus of the 1,3-dipole. UV kinetic measurements and DFT calculations showed that the rate of cycloaddition of adamantanethione was significantly slower than that of DMAD and no super-dipolarophile character was exhibited. This arose from exceptional lowering of the HOMO energy of the 1,3-dipole by the cyano substituents.

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There has been wide interest in the 1,3-dipolar cycloaddition reactions of thione dipolarophiles. The C=S double bond displays an unusually high reactivity with a number of 1,3-dipoles and because of this thiones have been classed as super-dipolarophiles.<sup>1,2</sup>

For nitron 1,3-dipoles **1** the nucleophilic oxygen terminus of the dipole invariably bonds to the thione carbon atom as in **3**. With diazomethanes as 1,3-dipoles, mixtures of regioisomers are formed and the balance of these may vary with solvent polarity.<sup>3,4</sup> Adamantanethione also reacts with CH<sub>2</sub>N<sub>2</sub> to give an intermediate 1,3,4-thiadiazoline with the diazomethane CH<sub>2</sub> bonded to the sulfur.<sup>4b</sup>

The most famous reaction of methanide 1,3-dipoles with thiones is the Schönberg reaction between thiobenzophenone and diazomethane. In this reaction, the CH<sub>2</sub><sup>-</sup> terminus of diazomethane bonds to the S atom of thiobenzophenone in a cycloaddition giving a 1,3,4-thiadiazoline intermediate, which eliminates N<sub>2</sub> to give thiobenzophenone-*S*-methanide 1,3-dipole **2**. This in turn undergoes a cycloaddition with thiobenzophenone in which the CH<sub>2</sub><sup>-</sup> terminus again bonds to the S-atom giving the product **4** (Scheme 1).<sup>5,6</sup> Adamantanethione



**Scheme 1.** Regiochemistry of addition for thione dipolarophiles.

also reacts with phenyl azide to give an intermediate 2-phenyl-spiro-adamantyl-1,2,3,4-thiatiazoline, with the phenyl-bearing nitrogen atom bonded to the sulfur.<sup>7</sup>

We have found that the cycloaddition reaction of the short lived phthalazinium-2-methanide 1,3-dipole (**7** H for CN) with a number of thione dipolarophiles including **5** and **6**<sup>8</sup> showed the expected reactivity with high yields of cycloadducts obtained. For sterically unhindered thiones the regiochemistry was similar to the Schönberg reaction and the methanide carbon bonded to the thione sulfur atom. However with adamantanethione as dipolarophile the regiochemistry was reversed and the methanide carbon bonded to the thione carbon atom. The regioselectivity was also reversed for adamantanethione in cycloadditions of thione dipolarophiles with acyclic azomethine ylide 1,3-dipoles.<sup>9</sup> Herein, we report that changing the methanide terminus of the dipole to a dicyanomethanide causes a remarkable change of reactivity. We have recently established<sup>10,11</sup> from an extensive kinetic study that the

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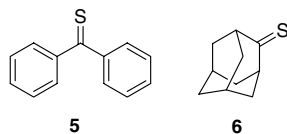


Figure 1. Thione dipolarophiles.

phthalazinium dicyanomethanide 1,3-dipole **7** is a Sustmann Type II species, and it can react through either HOMO<sub>dipole</sub> or LUMO<sub>dipole</sub> mode depending on the electronic nature and frontier orbitals of the dipolarophile.

The only reported reaction of 1,3-dipole **7** with heterodipolarophiles was that of Regitz et al.<sup>12</sup> for the reaction with phosphalkynes. This led us to examine the cycloaddition reaction of this 1,3-dipole with thione heterodipolarophiles. When the phthalazinium-2-dicyanomethanide 1,3-dipole **7**, synthesized according to literature procedures,<sup>8</sup> was treated with thiobenzophenone **5** or adamantanthione **6**<sup>13</sup> (Fig. 1), using equimolar amounts of the dipolarophile in acetonitrile no reaction was observed. The amount of the thione was increased to two equivalents and a number of solvents were screened.<sup>14</sup> The adamantanthione dipolarophile **6** was found to react but the aromatic thione **5** did not react (Table 1).

Table 1. 1,3-Dipolar cycloaddition reaction of phthalazinium-2-dicyanomethanide **7** with adamantanthione **6** at ambient temperature

Entry	Solvent	$E_T$ (30) kcal mol <sup>-1</sup>	Time (h)	Yield (%)
1	MeCN	46.0 <sup>a</sup>	48	<1
2	H <sub>2</sub> O	63.1	48	<1
3	Acetone	42.2	24	46
4	THF	37.4	24	54
5	1,4-Dioxane	36.0	12	86

<sup>a</sup>  $E_T$  (30) values taken from Ref. 15.

In acetonitrile, the common solvent for this 1,3-dipole, no reaction was observed after 48 h (Table 1, entry 1). We have found that many 1,3-dipolar cycloaddition reactions of 1,3-dipole **7** can be carried out in water<sup>16,17</sup> but no reaction was observed with dipolarophile **6** (Table 1, entry 2). On changing the solvent to acetone a reasonable yield of 46% was obtained (Table 1, entry 3). The cyclic ethers THF and 1,4-dioxane gave the highest yields, and in 1,4-dioxane an 86% yield was achieved after 12 h (Table 1, entry 5) with thione **6** but no reaction was observed with thione **5**.

The structure of the cycloadduct **8** was established by a single crystal X-ray structure.<sup>18–21</sup> The crystals were grown from chloroform to afford the product as off-white crystals (Fig. 2). The X-ray crystal structure shows regiochemistry with the carbon of the thione attached to the methanide C(CN)<sub>2</sub> terminus of the 1,3-dipole. This regiochemistry parallels that observed with nitrene **1** (also a Sustmann Type II 1,3-dipole). The fused thiazolo[2,3-*a*]phthalazine ring system is not well known and we have found just a single report of a derivative of this ring system.<sup>22</sup>

We have examined the kinetics of phthalazinium-2-dicyanomethanide 1,3-dipole **7** with a wide range of dipolarophiles.<sup>11,16,17</sup> These previous kinetic studies measured the rate of the disappearance of the 1,3-dipole **7** over time by UV–vis spectrophotometry using pseudo first-order kinetics in acetonitrile.<sup>23</sup> In order to compare

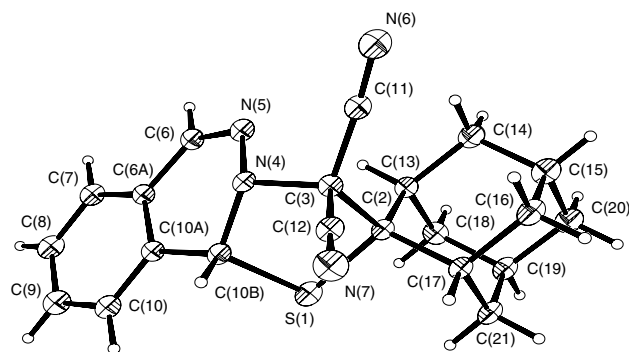


Figure 2. X-ray crystal structure of cycloadduct **8**.

Table 2. Rate constants for reaction of **7** with various dipolarophiles in 1,4-dioxane at 37 °C,  $k_2/10^{-3}$  dm<sup>3</sup> mol<sup>-1</sup> s<sup>-1</sup>

Entry	Dipolarophile	$k_2/10^{-3}$ <sup>a</sup> (dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup> )	IP <sup>b</sup> (eV)	$E_a$ (DFT)	Relative $k_2$ (to DMAD)
1	DMAD	2530	8.762	53.8	1
2	<i>N</i> -Phenylmaleimide	948	8.504	—	0.37
3	<i>N</i> - <i>t</i> -Butylmaleimide	406	8.283	—	0.16
4	Adamantanethione	340	7.647	65.2 <sup>c</sup>	0.13
5	Methyl vinyl ketone	222	7.603	—	0.08
6	Methyl methacrylate	13.8	7.217	60.6	0.005
7	<i>n</i> -Butyl vinyl ether	5.6	5.853	68.2 <sup>d</sup>	0.002
8	2,3-Dihydrofuran	2.06	5.546	69.8	0.0008
9	1-Morpholinocyclohexene	33.0	5.159	—	0.013

<sup>a</sup> For kinetic measurements see Ref. 23.

<sup>b</sup> Ionization potential (IP) calculated for the  $\pi$ -HOMO energies.

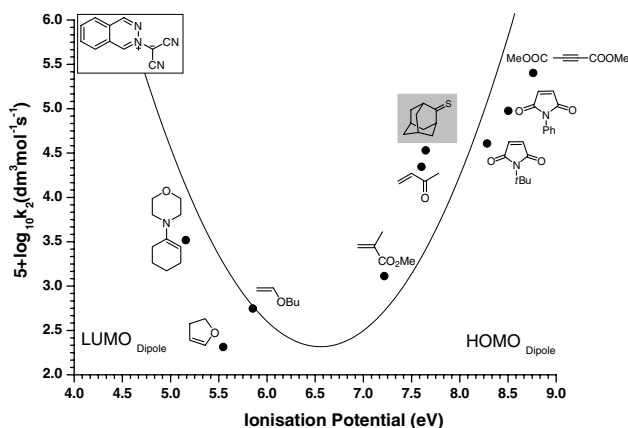
<sup>c</sup> With the methanide dipole (**7**, H for CN)  $E_a$  = 8.43 (Ref. 28).

<sup>d</sup> Me for Bu in calculations.

the rate of adamantanethione **6** to other alkene and alkyne dipolarophiles, the rates were measured in 1,4-dioxane, Table 2.

The most striking result from the kinetic experiments is that the rate of reaction of adamantanethione **6** was slower than DMAD by about a factor of seven unlike its super-reactivity with other 1,3-dipoles where the rates are much faster. Thus for reactions of 1,3-dipole **1**, in toluene at 25 °C, the ratio  $k_{\text{adamantanethione}}/k_{\text{DMAD}}$  was 1500<sup>3</sup> and the rate ratio for dipole **2** with thiobenzophenone and DMAD, in THF at –45 °C, was 3500.<sup>24</sup> In the reaction with dipole **7**, adamantanethione **6** as a dipolarophile is similar to the electron poor *N*-*t*-butylmaleimide dipolarophile (Table 2, entry 3). Hence the special characteristics of the C=S bond, such as low  $\pi$  bond energy,<sup>25</sup> high polarizability,<sup>26</sup> and low HOMO–LUMO distance<sup>27</sup> does not always guarantee superdipolarophile behavior. Steric effects which might disrupt the pre-transition state orientation complexes,<sup>27</sup> would not explain the curtailment of reactivity with 1,3-dipole **7** since the best reactions were obtained with the most sterically hindered thione **6**. The results also run counter to solvent polarity  $E_T$  values (Table 1) and the change from a concerted to a stepwise process is unlikely. For nitrones a strong HOMO<sub>nitron</sub>–LUMO<sub>thione</sub> interaction was the principal reason for high thione reactivity.<sup>27</sup>

A plot of experimental rates versus DFT<sup>28</sup> calculated ionization potentials (Table 2, Fig. 3) representing the HOMO energies clearly places adamantanethione **6** on the right-hand limb of the Sustmann curve and the reaction is still under HOMO<sub>dipole</sub> control. Hence a change of mechanism to orbital inverse electron demand is not the reason for the loss of super-reactive character in the reactions of thiones with substrate **7**. DFT calculated transition states confirm this and display  $E_a$  values lower by 15 kJ mol<sup>–1</sup> for HOMO<sub>dipole</sub> transition states leading to product **8** rather than the reversed regiochemistry. However the calculated activation energy for the formation of **8** ( $E_a$ , 65.2 kJ mol<sup>–1</sup>) is particularly high and significantly higher than for DMAD ( $E_a$ , 53.8 kJ mol<sup>–1</sup>). The calculated  $E_a$  values agree well with the experimental rate ratio  $k_{\text{adamantanethione}}/k_{\text{DMAD}}$ , 0.13.



**Figure 3.** Experimental rates for various dipolarophiles in 1,4-dioxane at 37 °C versus DFT calculated ionization potentials.

The calculated  $E_a$  value for the comparable cycloaddition of phthalazinium methanide (**7**, H for CN) with thione **6** was particularly low at 8.43 kJ mol<sup>–1</sup> in agreement with the superdipolarophile character of compound **6** in that reaction. The DFT calculations further confirm the unexpected loss of superdipolarophile behavior for thiones in cycloaddition reactions with the 1,3-dipole **7**. This arises particularly because the HOMO of 1,3-dipole **7** is extensively delocalised through the CN groups so that its energy is now the second highest MO below the cyano orbitals thereby increasing  $E_a$  for the cycloaddition.

In conclusion, changing the terminus of an azinium unsubstituted methanide 1,3-dipole to a dicyanomethanide dramatically reduced the reactivity of thione dipolarophiles.

### Acknowledgments

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14. *Synthesis of spiro-(2,2'-adamantyl)-3,3-dicyano-[1,3]thiazolo[2,3-a]phthalazine 8*. A solution of phthalazinium-2-

- dicyanomethanide **7** (0.20 g, 1.03 mmol) and adamantane-thione **6** (0.34 g, 2.06 mmol) in 1,4-dioxane (20 ml) was stirred at room temperature for 12 h. The solvent was then removed in vacuo and the residue placed onto a flash column of silica gel (230–400 mesh ASTM) packed with petroleum spirit (bp 40–60 °C). The product was eluted with 1:1 petroleum spirit: dichloromethane to afford the title compound as an off-white solid. 0.319 g, 86%; mp 229–231 °C,  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 1.98–3.05 (m, 14H, adamantane ring), 6.00 (s, 1H, H-10b), 7.23–7.53 (m, 4H, H-7 to H-10), 7.73 (s, 1H, H-6),  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 25.5, 26.1, 27.4, 36.2, 38.6 (CH adamantane), 34.2, 37.3, 37.7, 39.4, 41.1 ( $\text{CH}_2$  adamantane), 57.6 (C-10b), 68.8 (C-2), 111.3, 113.4 ( $\text{C}\equiv\text{N}$ ), 122.9 (C-10a), 126.0, 126.6, 129.7, 132.1, (C-7 to C-10), 130.6 (C-6a), 142.9 (C-6). Anal. Calcd for  $\text{C}_{21}\text{H}_{20}\text{N}_4\text{S}$ : C, 69.79; H, 5.73; N, 15.50. Found C, 69.97; H, 5.59; N, 15.54.
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  - Good quality colorless crystals of compound **8** were grown from chloroform at ambient temperature. The crystal used for data collection had the approximate dimensions 0.40 times 0.32 times 0.25 mm. The crystal was monoclinic with the space group  $P2_1/c$  and had unit cell parameters  $a = 7.9180(8)$  Å,  $b = 16.697(8)$  Å,  $c = 13.538(6)$  Å,  $\beta = 99.59(1)^\circ$ . Reflections were collected on an Enraf-Nonius CAD4F four circle diffractometer, using graphite monochromated Mo-K $\alpha$  radiation,  $\lambda = 0.71069$  Å. The criterion, which qualified a reflection for observation was  $I > 2\sigma(I)$  and 2444 reflections satisfied this condition. The calculated density was  $1.357 \text{ Mg m}^{-3}$  and  $Z = 4$ . The absorption coefficient was  $0.196 \text{ mm}^{-1}$  and the theta range for data collection was  $2.44^\circ$  to  $21.97^\circ$ . The total number of independent reflections was 2164 [ $R(\text{int}) = 0.0282$ ]. The structure was solved by direct methods SHELXS-97,<sup>19</sup> and refined by full matrix least squares using SHELXL-97.<sup>20</sup> SHELX operations were automated using ORTEX, which was also used to obtain the drawings.<sup>21</sup> Data were corrected for Lorentz and polarization effects but not for absorption. Hydrogen atoms were included in calculated positions with thermal parameters 30% larger than the atom to which they were attached. The non-hydrogen atoms were refined anisotropically. All calculations were performed on a Pentium PC. CCDC-633537 (**8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
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  - Kinetic measurements.* The rate constants were measured by recording the disappearance of phthalazinium-2-dicyanomethanide dipole **7** at the maximum wavelength ( $\lambda_{\text{max}}$ , 428 nm in 1,4-dioxane). Spectra were measured using a Hewlett-Packard Agilent Technologies 8453 UV–vis spectrophotometer featuring an automatic changer for up to eight glass cuvettes of path length 1 cm. The temperature of  $37^\circ\text{C}$  ( $\pm 0.2^\circ\text{C}$ ) was maintained by means of a thermostat (Haake DC10)-controlled water bath, with a separate calibrated thermometer check. The reaction was monitored using pseudo-first order conditions. The initial concentration of 1,3-dipole **7** was  $3.2 \times 10^{-5}$  M, and the dipolarophile concentrations were in excesses ranging from 600 to 30,000-fold depending upon the dipolarophile. Kinetic runs were performed at three different concentrations of dipolarophiles and repeated a minimum of three times. The length of time for the reaction ranged from 1 to 30 h, depending on the dipolarophile and conditions. The solution changed from yellow to colorless as the reaction progressed.
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  - DFT calculations were carried out as previously described in Ref. 11. The computer output can be obtained at <http://camchem.rutgers.edu/~burke>.