First Isolation of Thione-Propiolic Acid Adducts − Synthesis of Thiodioxenones

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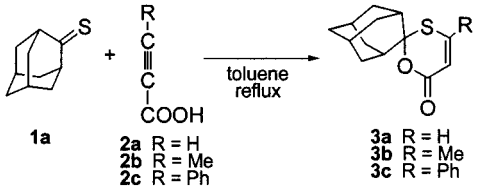
Treatment of adamantane-2-thione (**1a**) with propiolic acid (**2a**) afforded a novel type of cycloadduct, spiro[adamantane-2,2′-[1,3]oxathiin]-6-one (**3a**), in quantitative yield. The reaction proceeds through a concerted process, as was confirmed by kinetic analysis. Treatment of **1a** with butynoic acid or phenylpropiolic acid gave the corresponding adducts regioselectively. Interestingly, only one isomer was obtained by treatment of thiofenchone with propiolic acid, suggesting that the reaction proceeded stereospecifically.

Introduction

Thioketones **1** are well known to react with dienes to give the corresponding Diels−Alder adducts.[1] α,β-Unsaturated thioketones readily dimerize, and these dimers have been employed as sources of the monomers through the retro-Diels−Alder reaction, the monomers reacting with dienophiles to give the corresponding adducts.[2] Dihydrobenzothiopyrans have been synthesized by treatment of thiobenzophenones with dimethyl acetylenedicarboxylate.[3] Recently, we have reported that the reaction between monomeric thiones **1** and benzyne gives the corresponding four-membered benzothietes in good yields.[4] To the best of our knowledge, however, there is no report on reactions between monomeric thiones **1** and acetylenic acids, which would produce new types of heterocycles, thiodioxenones. Here we report the first cycloaddition between thiones and propiolic acid.

Results and Discussion

Treatment of adamantane-2-thione (**1a**) with propiolic acid (**2a**) in refluxing toluene resulted in the formation of new type of cycloadduct, spiro[adamantane-2,2′-[1,3]oxathiin]-6-one (**3a**), in quantitative yield (Scheme 1). The structure of **3a** was determined by spectroscopic analysis. The characteristic feature of its proton NMR spectrum is two doublet signals at δ = 6.11 and 7.36 ppm, which clearly shows the existence of two olefinic protons.



Scheme 1

Similarly, 2-butynoic acid (**2b**) and phenylpropiolic acid (**2c**) reacted with **1a** to give the corresponding 1,3-oxathiin-6-ones (**3b** and **3c**), which are thio analogues of dioxenones (Table 1). Dioxenones, which are produced by cycloaddition of ketones with Meldrum's acid,[5] are well known precursors of many natural products.

Table 1. Reaction between **1a** and acetylenic acids **2**

Acid **2**	Equiv.	Conditions Solvent	Time (h)	Product **3**	Yield (%)
2a	3	toluene	3	**3a**	86
2a	3	toluene	6	**3a**	100
2a	4	benzene	12	**3a**	85
2a	3	chloroform	12	**3a**	100
2a	3	acetone	12	**3a**	0[a]
2b	3	toluene	96	**3b**	68
2c	3	toluene	96	**3c**	65

[a] The reaction did not proceed in polar solvents such as DMSO, acetonitrile, and methanol.

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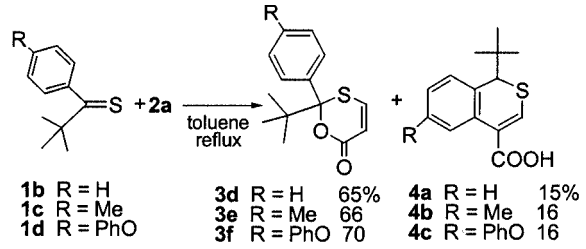


Scheme 2

When thiopivalophenone (**1b**), one of the thiones, was chosen as a substrate, 2-*tert*-butyl-2-phenyl-[1,3]oxathiin-6-one (**3d**) was obtained in 65% yield (Scheme 2). Less than 15% of normal cycloadduct **4a** was also obtained as a side product, suggesting that the rate of formation of **3d** was faster than that of **4a**.

Other monomeric thiones such as thiofenchone (**1e**) afforded the corresponding cycloadduct (**3g**, 83%). Interestingly, only one isomer (*exo* form) was obtained, suggesting that the reaction proceeded diastereospecifically (Scheme 3). The structure of *exo*-**3g** was confirmed by X-ray crystallographic analysis (Figure 1).[6]

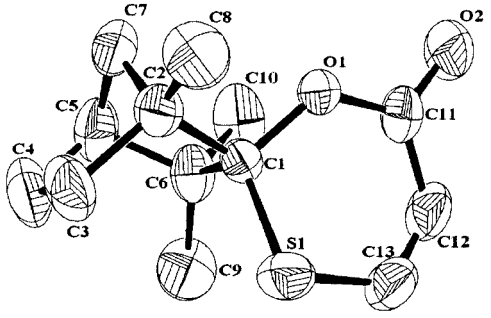
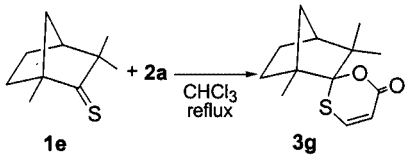
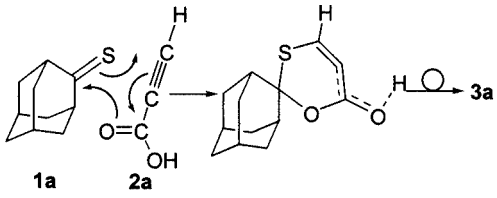


Figure 1. ORTEP Drawing of Compound **3g**



Scheme 3

Since we felt that the reaction might proceed through a cycloaddition mechanism, we carried out a kinetic analysis. The formation of **3a** from thione **1a** and **2a** could be conveniently and accurately monitored by ^{1}H NMR spectroscopy. A second order reaction was observed by this technique. A rate constant of 2.89×10^{-2} mol^{-1}·dm^3·min^{-1} at 353 K was obtained. This value was essentially independent of solvent (relative rate; toluene/benzene, 1:1.78 at 353 K, chloroform/toluene, 1.23:1 at 333 K). Variable temperature NMR spectroscopy over the 60 to 110 °C range in toluene as solvent was used to obtain activation parameters of $\Delta H^{\ddagger}$ = 44 KJ·mol^{-1} and $\Delta S^{\ddagger}$ = −184J·K^{-1}.



Scheme 4

The observation of second order reaction kinetics and highly stereoselective addition strongly support a cycloaddition mechanism for the thermal addition (Scheme 4). The large, negative entropy of activation is consistent with a rigid, cyclic transition state, which indicates the relative independence of reaction rate on solvent.

Photocycloadditions between thiobenzophenone and olefins have afforded thietanes and 1,4-dithianes through radical intermediates.[7] Cycloaddition and photoreaction of thiobenzophenone with **2a** gave benzothiopyran derivatives.[8,9] To the best of our knowledge, however, there is no report on the formation of **3**, thiodioxenone, through the reaction between thiones and propiolic acid in a [4+2] manner.

Dioxenones are important precursors of many natural products,[10] whereas thiodioxenones **3** were not straightforward to prepare in such a short way. This method requires only two-step reactions from commercially available ketones and propiolic acids and would provide a new type of substrate of carbocyclic ring systems.

Experimental Section

Compound 3a: Propiolic acid (422 mg, 6 mmol) was added in one portion to a solution of adamantane-2-thione (332 mg, 2 mmol) in toluene (15 mL). After the mixture had been heated at reflux for 6 h, the reaction solvents were evaporated to give pale-yellow crystals of [1,3]-oxathiine-6-one **3a**, which was almost pure (568 mg). Recrystallization from hexane gave pure adduct **3a**. M.p. 141−142 °C.^{1}H NMR ($CDCl_3$): δ = 1.65 (d, J = 13 Hz, 2 H, CH_2), 1.75 (s, 2 H, CH_2), 1.83 (d, J = 14 Hz, 2 H, CH), 1.88 (s, 2 H, CH_2), 2.05 (d, J = 14 Hz, 2 H, CH), 2.37 (d, J = 13 Hz, 2 H, CH_2), 2.53 (s, 2 H, CH), 6.12 (d, J = 10 Hz, 1 H, =CH), 7.34 (d, J = 10 Hz, 1 H, =CH) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.51, 26.68, 32.26, 34.75, 36.55, 37.53, 95.53 (S−C−O), 113.57 (=CH), 142.08 (=CH−S), 161.94 (C=O) ppm. MS: Found: 236 [M$^+$], calcd for $C_{13}H_{16}O_2S$: 236. $C_{13}H_{16}O_2S$: calcd. C 66.07, H 6.82; found C 65.96, H 6.78.

4-Phenylspiro[adamantane-2,2′-[1,3]oxathiin]-6-one (3c): M.p. 129−130 °C. ^{1}H NMR ($CDCl_3$): δ = 1.70 (d, J = 12 Hz, 2 H, CH_2), 1.78 (s, 2 H, CH_2), 1.87 (d, J = 12 Hz, 2 H, CH), 1.93 (s, 2 H, CH_2), 2.20 (d, J = 13 Hz, 2 H, CH), 2.41 (d, J = 12 Hz, 2 H, CH_2), 2.58 (s, 2 H, CH), 6.40 (s, 1 H, =CH), 7.42−7.51 (m, 3 H, Ph), 7.64−7.67 (m, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.47, 26.50, 32.28, 34.90, 36.43, 37.53, 94.69 (S−C−O), 109.52 (=CH), 127.33, 128.82, 131.33, 135.68, 155.26 (=C−S), 163.57 (C=O). $C_{19}H_{20}O_2S_2$: calcd. C 73.04, H 6.45; found C 72.97, H 6.41.

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[6] Crystal data for $C_{13}H_{15}O_2S$ **3g**: M = 235.32, a = 13.924(3), b = 14.060(4), c = 6.480(3) Å, V = 1268.5(7) Å^3, T = 298 K , orthorhombic, space group $P2_12_12_1$, Z = 4, μ(Mo-K_α) = 2.38 cm^{-1}. The final R and wR were 0.049 and 0.112 respectively, using 1116 reflections.

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