Synthesis of Highly Functionalized 1,3-Oxathioles via an Unusual [4+1] Annulation of α,α'-Dioxothione with 1,2-Diaza-1,3-dienes

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Received: 15.10.20120; Accepted: 23.10.2012

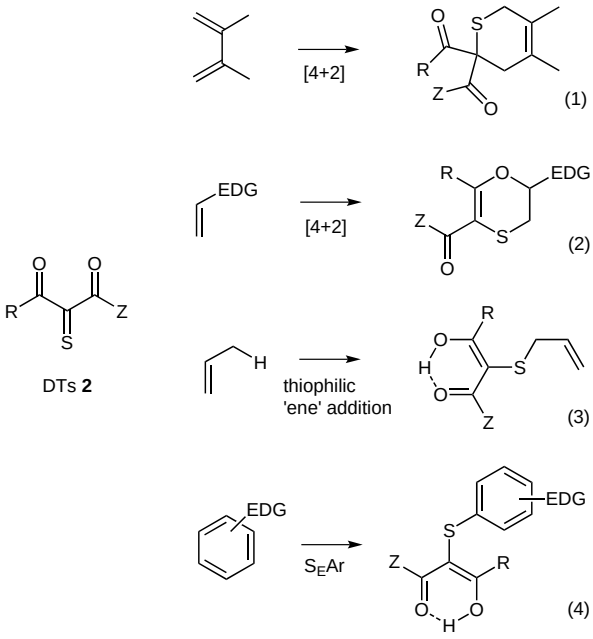
Abstract: The present method provides highly functionalized 1,3-oxathioles through an unusual base-promoted [4+1] annulation between α,α'-dioxothione, generated in situ from a phthalimide precursor, and 1,2-diaza-1,3-dienes. An intriguing scaffold comprised of spiro-fused oxathiole and pyrazolone components was also obtained in moderate yield.

Key words: oxathioles, Michael addition, [4+1] annulation, spiro compounds

Heterocyclic compounds, especially those containing five/six-membered rings, are very important units in organic and pharmaceutical chemistry. Among them, oxathioles remain a relatively unexplored class of *O*,*S*-heterocycles.[1] The limited number of synthetic methods that can be used to access such systems fall into three groups: (i) reactions of α-diazo ketones with thiobenzophenone[2] or azibenzil/diaryldiazomethanes with monothiobenzils,[3,4] (ii) Rh(II)-catalyzed cycloadditions of carbomethoxy iodonium ylides,[5] and (iii) reactions of carbonyl-stabilized sulfonium ylides with elemental sulfur.[6] Surprisingly, only a few of the reported methods are general, and many suffer from limited functional group tolerance, modest regioselectivities, harsh reaction conditions, expensive metal catalysts, or laborious work-up. Consequently, the development of new strategies for the construction of such scaffolds is highly desirable.

The utility of polyfunctional α-acylthiocarbonyl compounds as versatile intermediates in organic synthesis is well documented.[7–10] Detailed studies on the reactivity of α,α'-dioxothiones (DTs) **2** showed that they can act as efficient dienophiles[7] (Scheme 1, equation 1), electron-poor heterodienes[8] (equation 2), as well as enophiles[9] (equation 3) that are able to react with appropriate unsaturated counterparts to give dihydrothiopyrans, 1,4-oxathiins, and thiophilic ene adducts, respectively.

In addition to acting as 1,4-heterodipoles[10] (Scheme 1, equation 4), DTs have been applied in electrophilic aromatic substitution (S_EAr) with a variety of phenols and *N*,*N*-dimethylaniline to afford the corresponding alkyl, aryl, or diaryl sulfides.



Scheme 1 Reactivity of α,α'-dioxothiones **2**

During ongoing studies, we came to appreciate the advantages of diverse 1,2-diaza-1,3-dienes (DDs, **3**; Figure 1).[11–15] In particular, we found that conjugated azoenes with electron-withdrawing substituents (e.g., esters or amides) on the terminal carbon and/or nitrogen (Figure 1), were particularly suitable as versatile synthetic building blocks because of their five-atom (3C + 2N) C4-electrophilic nature, dense substitution patterns, and flexible functionality that was capable of undertaking multiple roles.

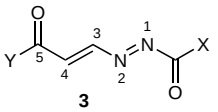


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Figure 1 Structure of 4-alkoxy (or -dialkylamino) carbonyl-1,2-diaza-1,3-dienes (DDs) **3**

SYNLETT 2012, 23, 2947–2950
Advanced online publication: 16.11.2012
DOI: 10.1055/s-0032-1317621; Art ID: ST-2012-D0892-L
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Generally, DDs can afford one to five atoms to construct cyclic molecules. Incorporation of all five atoms of the DD skeleton into pyrazolone structures has been successfully applied in our previous work.[12] As four-atom diene synthons, DDs have found application in both [4+1] and [4+2] strategies for the synthesis of dihydropyrazoles[13] and pyridazines,[14] respectively. In addition, they can participate in formal [3+2]-, [4+2]-, and [5+2]-annulation reactions in which two or three ring atoms (C–C or C–C–N) of the azoene component are incorporated in the final cycloaddition products.[15] Thus, pyrroles, pyrazole *N*-oxides, imidazoles, 2-imino-4-thiazolines, rhodanines, 2,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-ones, 5*H*-1,4-benzodiazepines, and 2-thiohydantoins or 2-iminothiazolidinones can be synthesized.

In the present work, we wish to demonstrate that DT **2a** can behave as a $C_2S_1O_1$ building block in an unusual [4+1] annulation with DDs **3** to afford a series of highly functionalized oxathioles. This observation supports our speculation of a high polarization of the thiocarbonyl moiety in α,α'-dioxothiones **2** (Figure 2).

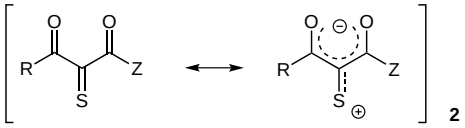

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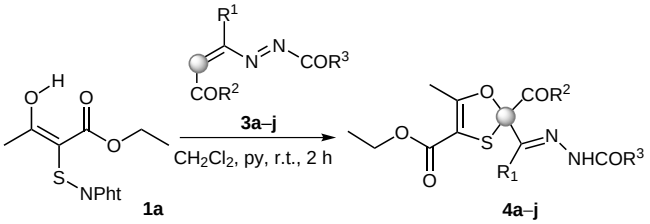
Figure 2 Electrophilic character of thiocarbonyl sulfur in α,α'-dioxothiones **2**

This process represents not only the first example of the use of an α,α'-dioxothione as a four-atom donor partner in the [4+1]-annulation process, but also provides access to α,α'-disubstituted oxathiole molecules, which are underrepresented structures. The incorporation of polarizable heteroatoms within the cyclic framework containing a quaternary center is another important aspect of this approach to this heterocyclic architecture.

To investigate whether DT **2a** could be employed as a partner in heterocyclic ring-forming reactions, upon addition of pyridine, α,α'-dioxothiophthalimide (DTPht) **1a** in dichloromethane at room temperature was transformed into the transient corresponding DT **2a**, which could be directly trapped in situ with azoene **3a** (Table 1). The use of phthalimide precursors for the generation of DTs via base-promoted 1,2-elimination is a well-documented process.[7–10,16]

In the presence of equimolar amounts of reagents (DTPht **1a** and DD **3a**), the reaction proceeded to give the highly functionalized oxathiole **4a**, albeit in low yield (27%). When the amount of DTPht **1a** (and pyridine) was increased to two equivalents, the yield of the reaction also increased to a promising 49%. Surprisingly, the yield diminished when the reaction was performed using three equivalents of DTPht **1a** (38%). In all cases, partial decomposition of reagent **1a** was also observed. The best result (58%) was obtained when the reaction was performed under rigorously anhydrous conditions. With the optimized conditions in hand, we then evaluated the scope of the reaction by using a variety of DDs **3a–j**;[17] the results are summarized in Table 1. Different 4-alkoxy or 4-(dialkylamino)carbonyl-DDs **3** gave the corresponding oxathioles in moderate to good yields. Different substitution on the nitrogen atom of the azo group as well as variations of groups at C3 and C4 of the ene moiety were tolerated.

Table 1 Synthesis of 1,3-Oxathiole Derivatives **3a–j** from DTPht **1a** and DDs **3a–j**[a]



1a **4a–j**

Entry	**3**	R^1	R^2	R^3	**4**	Yield (%)[b]
1	**3a**	Me	OMe	NH_2	**4a**	58
2	**3b**	Me	OAll	NH_2	**4b**	46
3	**3c**	Me	OEt	NHPh	**4c**	51
4	**3d**	Me	NMe_2	NHPh	**4d**	39
5	**3e**	Me	OMe	*t*-BuO	**4e**	52
6	**3f**	Me	OEt	*t*-BuO	**4f**	55
7	**3g**	Et	OMe	*t*-BuO	**4g**	51
8	**3h**	Et	OEt	*t*-BuO	**4h**	47
9	**3i**	*n*-Pr	OMe	*t*-BuO	**4i**	69
10	**3j**	Me	NMe_2	*t*-BuO	**4j**	31

[a] Reaction conditions: CH_2Cl_2 (4 mL), r.t., 2 h, DTPht (**1a**; 2.0 mmol), DD (**3**; 1.0 mmol), pyridine (2.0 mmol) until complete disappearance of **3** (reaction monitored by TLC).
[b] Yield of isolated product.

Mechanistically, we propose that the reaction is initiated by nucleophilic addition (Michael addition) of DT **2a**, generated in situ, to the azoene system **3** resulting in a nonisolable zwitterionic intermediate **I**. Subsequently, five-membered cyclic product **4** would be produced by intramolecular azacyclization of **II** through a 1,4-hydrogen shift of **I**, resulting in an overall formal [4+1] cyclization (Scheme 2).

The formation of oxathioles **4a–j** as exclusive compounds indicates that the reaction is regio- and chemoselective. The structure of the products **4a–j** was established by consideration of the spectroscopic properties of **4a**. The ^{1}H NMR spectrum of **4a** in $CDCl_3$ showed one singlet at δ = 8.78 ppm and two broad singlets at δ = 5.98 and 5.00 ppm attributed to the protons of the semicarbazone fragment. The ^{13}C NMR spectrum showed six C-sp^2 signals (δ = 168.5, 162.4, 158.8, 157.3, 142.2 and 101.8 ppm) and one C-sp^3 signal at δ = 96.7 ppm, consistent with the presence of a oxathiole ring,[18,19] and the IR spectrum exhibited a

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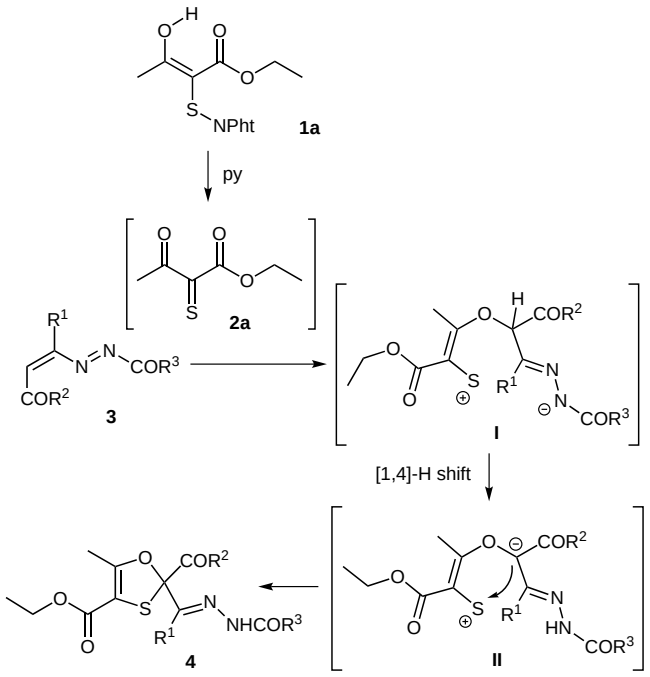
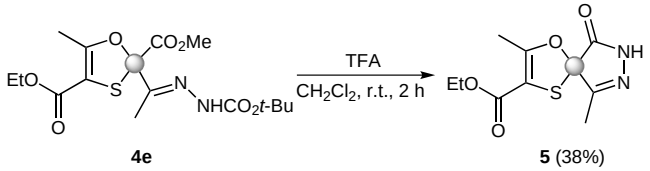
strong band at 1648 cm^{-1} that could be assigned to the C=C double bond of the oxathiole structure;[19] the mass spectrum of **4a** displayed the expected molecular ion peak (*m*/*z* 331 [M^+]).



Scheme 2 Tentative mechanism for the formation of 1,3-oxathioles **4**

The presence of one sp^3-hybridized carbon atom on the heterocyclic skeleton together with both an electrophilic ester group and a nucleophilic hydrazone residue at the C2-position make these compounds attractive for subsequent modification. Therefore, the possibility of derivatization to other α-oxathiolo-related structures was explored. We envisaged that the α-oxathiolo hydrazone **4e** derived from *tert*-butoxycarbonyl-1,2-diaza-1,3-diene (**3e**) might be hydrolyzed and cyclized to oxathiole-pyrazolone spiro compound **5** upon exposure to acidic conditions. Thus, on treatment of oxathiole **4e** with trifluoroacetic acid in CH_2Cl_2, a novel spiro scaffold 1-oxa-4-thia-7,8-diazaspiro[4.4]nona-2,8-dien-6-one (**5**) was formed (Scheme 3).[20] Although the isolated yield was rather moderate (38%), we were pleased to observe that a unique scaffold comprised of spiro-fused oxathiole and pyrazolone components could be readily obtained. To the best of our knowledge, the only previous example of oxathiole-pyrazolone spiro-derivatives was reported by El-Saraf and co-workers.[21]



Scheme 3 Synthesis of oxathiole-pyrazolone spiro-derivative **5**

In conclusion, we report herein a facile base-promoted regioselective synthesis of highly functionalized 1,3-oxathioles **4** starting from α,α'-dioxothione (DT) **2a** and 1,2-diaza-1,3-dienes (DDs) **3**. The mechanism of this reaction is proposed to be an unusual [4+1] annulation undergone by the highly polarized carbon–sulfur double bond. A unique scaffold **5**, comprised of spiro-fused oxathiole and pyrazolone components, was also obtained in moderate yield. Further investigations of other applications, including the use of other α-oxothione/activated alkene reagents, as well as studies on the mechanism of this synthetic transformation are in progress.

Acknowledgment

This work was supported by financial assistance from the Ministero dell'Università, dell'Istruzione e della Ricerca (MIUR) – Rome, Università degli Studi di Urbino 'Carlo Bo' and Università di Firenze, Italy.

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(17) **Typical Procedure:** To a solution of DD **3a** (0.171 g, 1.0 mmol) in CH_2Cl_2 (4 mL) were added DTPht **1a** (0.614 g, 2.0 mmol) and anhydrous pyridine (0.158 g, 2 mmol) at 25 °C. The solution was stirred for 2 h at room temperature (reaction monitored by TLC analysis). The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel; cyclohexane–EtOAc, 20:80) to give the corresponding oxathiole derivative **4a** as a pale-yellow waxy solid (0.191 g, 58%).
4-Ethyl 2-Methyl 2-[1-(2-Carbamoylhydrazono)ethyl]-5-methyl-1,3-oxathiole-2,4-dicarboxylate (4a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3 H), 2.02 (s, 3 H), 2.32 (s, 3 H), 3.84 (s, 3 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 5.00 and 5.98 (br s, 2 H), 8.78 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8 (q), 14.2 (q), 14.4 (q), 53.5 (q), 61.2 (t), 96.7 (s), 101.8 (s), 142.2 (s), 157.3 (s), 158.8 (s), 162.4 (s), 168.5 (s). IR (Nujol): 3466, 1746, 1716, 1648, 1592, 1290, 1253, 1087, 1062 cm^{-1}. MS: *m*/*z* (%) = 331 (10), 314 (48), 288 (18), 271 (100), 243 (38), 229 (30), 199 (45), 157 (50). Anal. Calcd for $C_{12}H_{17}N_3O_6S$ (331.34): C, 43.50; H, 5.17; N, 12.68. Found: C, 43.64; H, 5.08; N, 12.59.

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(20) To a solution of oxathiole **4e** (0.194 g, 0.5 mmol) in CH_2Cl_2 (4 mL) was added TFA (0.057 g, 0.5 mmol) at 25 °C. The solution was stirred for 2 h at r.t., the solvent was removed in vacuo and the residue was purified by column chromatography (silica gel; cyclohexane–EtOAc, 80:20) to give **5** as a pale-yellow waxy solid (0.048 g, 38%).
Ethyl 2,6-Dimethyl-9-oxo-1-oxa-4-thia-7,8-diazaspiro-[4.4]nona-2,6-diene-3-carboxylate (5): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3 H), 2.20 (s, 3 H), 2.31 (s, 3 H), 4.22 and 4.23 (q, *J* = 7.2 Hz, 2 H), 8.57 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7 (q), 14.2 (q), 14.3 (q), 61.4 (t), 87.8 (s), 101.7 (s), 156.9 (s), 159.0 (s), 161.8 (s), 171.7 (s). IR (Nujol): 3349, 3200, 1736, 1712, 1641, 1284, 1087 cm^{-1}. MS: *m*/*z* (%) = 256 (35) $[M]^+$, 213 (100), 185 (66), 141 (36). Anal. Calcd for $C_{10}H_{12}N_2O_4S$ (256.28): C, 46.87; H, 4.72; N, 10.93. Found: C, 46.74; H, 4.77; N, 11.01.

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