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A ring expansion reaction of 1,3-oxathiolanes

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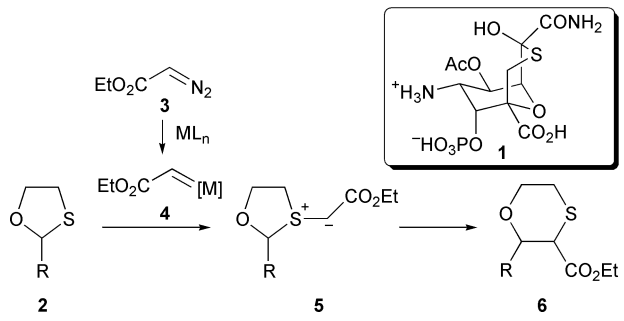
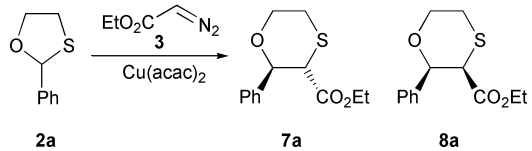
1,3-Oxathiolanes are efficiently converted, *via* sulfur ylide intermediates, to 1,4-oxathianes by ring expansion with a silylated diazoacetate in the presence of a copper catalyst.

As part of a project directed towards the total synthesis of the RNA polymerase inhibitor tagetitoxin (**1**),[1] we wished to develop a synthesis of 1,4-oxathianes. The route we chose to investigate was ring expansion of 1,3-oxathiolanes (Scheme 1). Treatment of a 1,3-oxathiolane **2** with the metal carbene **4** derived from ethyl diazoacetate (**3**) and an appropriate metal catalyst[2] should generate a sulfur ylide **5**, which we anticipated would undergo a 1,2-rearrangement to the ring-expanded product, 1,4-oxathiane **6**. Related rearrangements of sulfur ylides derived from monothioacetals have previously been used for the synthesis of *C*-glycosides.[3]



Scheme 1 Proposed ring expansion (ML_n = $Rh_2(OAc)_4$ or $Cu(acac)_2$).

Initial studies focused on the reaction of 2-phenyl-1,3-oxathiolane (**2a**, Scheme 2) with ethyl diazoacetate (**3**).[4] Under the best conditions found, **2a** was treated with ethyl diazoacetate (1.5 equivalents) in the presence of $Cu(acac)_2$, and formed a *ca.* 2 : 1 mixture of desired 1,4-oxathianes **7a** and **8a**, together with diethyl maleate, diethyl fumarate[5] and significant quantities of recovered starting material. From this mixture, a combined 19% yield of **7a** and **8a** could be isolated.



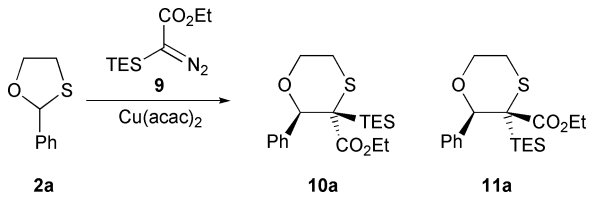
Scheme 2 *Reagents and conditions:* EtO_2CCHN_2 (1.5 equiv.), $Cu(acac)_2$ (10 mol%), benzene, reflux, 16 h, 19% yield.

When a larger amount of ethyl diazoacetate was used, in an attempt to force the reaction to completion, complex mixtures of unidentified compounds were formed. We suspect that this is because the copper carbene **4** does not distinguish strongly between the sulfur atoms of starting material **2a** and products **7a** and **8a**; as a result, when a large excess of the diazo compound is used, **7a** and **8a** react further to give undesired byproducts.

Similar side reactions (formation of maleate and fumarate, and over-reaction of products) have been observed in the [2,3]-sigmatropic rearrangement of allylic sulfur ylides derived from allylic sulfides and ethyl diazoacetate. Van Vranken[6] and Aggarwal[7] have independently reported that these problems can be circumvented by the use of a silylated diazo compound, (trimethylsilyl)diazomethane, in place of ethyl diazoacetate.

As our goal was the synthesis of 1,4-oxathianes bearing an ester substituent in the 3-position, we decided to employ a diazo compound bearing *both* a silyl group and an ester for the ring expansion reaction, in the hope that the presence of a silyl substituent would suppress the undesired side reactions.[8]

Ring expansion of 1,3-oxathiolane **2a** with ethyl (triethylsilyl)diazoacetate (**9**)[9,10] in the presence of $Cu(acac)_2$ proceeded efficiently (Scheme 3). Only a small excess of **9** was necessary to drive the reaction to completion, giving a 67% yield of 1,4-oxathianes **10a** and **11a** in an 8 : 1 ratio.



Scheme 3 *Reagents and conditions:* **9** (1.2 equiv.), $Cu(acac)_2$ (10 mol%), benzene, reflux, 23 h, 67% yield.

The relative stereochemistry of **10a** and **11a** was determined by NOE studies (Fig. 1). In **10a**, an enhancement between the *ortho*-protons of the phenyl ring and the axial proton at C-6 indicates that the phenyl group is situated axially; the enhancement between the phenyl and triethylsilyl groups shows that these two are *cis*. In **11a**, an enhancement is seen between the benzylic proton and the axial proton at C-6. The relative stereochemistry and configuration of **10a** and **11a** are thus as shown in Fig. 1.

A series of 1,3-oxathiolanes was subjected to ring expansion using **9** (Table 1).† 2-Aryl-1,3-oxathiolanes **2a–c** reacted with **9** to give the desired products in good yield and moderate to high diastereomeric ratio.[11] 2-Isobutyl-1,3-oxathiolane (**2d**) gave less satisfactory results; the highest yield obtained was 7%, but this was not readily reproducible.[12]

We also investigated the use of a copper (I) salt, $Cu(MeCN)_4PF_6$, in place of $Cu(acac)_2$.[13] Although this did not improve yields in the ring expansion of compounds **2a–c**, a higher and more reproducible yield was obtained with the isobutyl substrate **2d**. *tert*-Butyl oxathiolane **2e** and the parent 1,3-oxathiolane **2f** could also be converted to the corresponding 1,4-oxathianes using this catalyst, although **10f** decomposed on attempted chromatography.

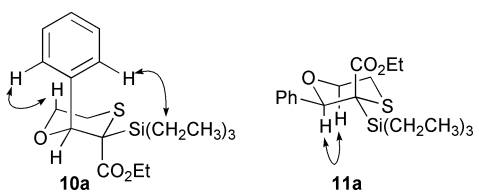


Fig. 1 Selected Nuclear Overhauser Enhancements in **10a** and **11a**.

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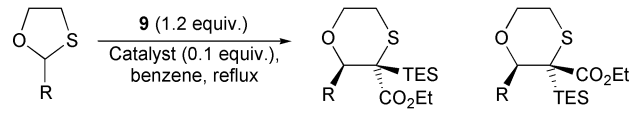
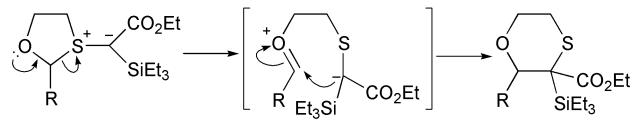
Table 1 Ring expansion of 1,3-oxathiolanes using **9**



2 **10** **11**

Substrate	R	Catalyst[a]	Time/h	Ratio **10**:**11**[b]	Yield[c]/%
2a	Ph	Cu^{II}	24	4:1	67[d]
2b	*p*-$NO_2C_6H_4$	Cu^{II}	22	4:1	62[e]
2c	*p*-$MeOC_6H_4$	Cu^{II}	24	20:1	62
2d	*i*-Bu	Cu^{II}	2	—[f]	7
		Cu^{I}	2.5	—[f]	30
2e	*t*-Bu	Cu^{I}	4	—[f]	12
2f	H	Cu^{I}	2.5	n/a	0[g]

[a] Catalysts: Cu^{II} = $Cu(acac)_2$, Cu^{I} = $Cu(MeCN)_4PF_6$. [b] Determined by integration of ^1H NMR signals in crude reaction mixture. [c] Isolated yields after chromatography on Florisil®. Unless otherwise stated, yields are of pure **10**. [d] 8:1 mixture of diastereomers. [e] 3:1 mixture of diastereomers. [f] Minor isomer not observed. [g] Compound decomposed on attempted purification.

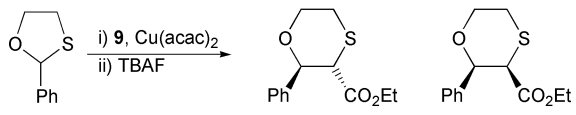


12 **13** **10/11**

Scheme 4 Possible mechanism for ring expansion.

A possible mechanism for the ring expansion reaction is depicted in Scheme 4. Reaction of **2** with the copper carbene formed from **9** gives ylide **12**. The presence of a neighbouring oxygen atom and the positive charge on the sulfur atom of **12** should induce C–S bond heterolysis, giving oxonium ion **13**. Reclosure to the six-membered ring **10/11** can then occur. Our results do not rule out homolysis of the C–S bond of **12** to give a diradical, which on recombination would yield the same ring-expanded products **10** and **11**.

The mixture of silylated 1,4-oxathianes **10a/11a** could be desilylated by treatment with tetra-*n*-butylammonium fluoride in THF, yielding **7a** and **8a** as a 2:1 mixture in quantitative yield. Alternatively, desilylation could be performed without prior purification of the ring-expansion product (Scheme 5), resulting in the generation of **7a** and **8a** as a 2:1 mixture of isomers, in a yield of 87% from **2a**.‡



2a **7a** **8a**

Scheme 5 *Reagents and conditions:* (i) **9** (1.7 equiv.), $Cu(acac)_2$ (10 mol%), benzene, reflux, 24 h; (ii) TBAF (1.3 equiv.), THF–benzene, 0 °C, 1 h, 87% yield (2 steps).

In summary, we have developed an efficient method for the conversion of 2-aryl-1,3-oxathiolanes into 2-aryl-1,4-oxathiane-3-carboxylates using a silylated diazoester in the presence of a copper catalyst.

We thank Jorge Gonzalez Outeiriño for performing the NOE experiments, ULIRS for mass spectral determinations, and UCL and EPSRC (studentship to F. S.) for financial support.

Notes and references

† Typical procedure for ring expansion: A mixture of 2-phenyl-1,3-oxathiolane (**2a**) (0.2 g, 1.5 mmol) and copper(II) acetylacetonate (40 mg. 0.15 mmol) in dry benzene (2 ml) was heated to reflux under a nitrogen atmosphere. A solution of ethyl (triethylsilyl)diazoacetate (**9**) (0.41 g, 1.8 mmol) in benzene (1 mL) was added dropwise over 5 minutes. Reflux was continued for a further 22 h, then the mixture was allowed to cool to rt. The solvent was removed under reduced pressure and the residue purified by flash chromatography (Florisil®; petroleum ether–diethyl ether 9:1) to afford ethyl 2-phenyl-3-(triethylsilyl)-1,4-oxathiane-3-carboxylate (**10a** and **11a**, 0.37 g, 67%) as an 8:1 mixture of isomers. Selected data for major isomer **10a**: δ_H (500 MHz, $CDCl_3$) 0.42–0.55 (6H, m, $Si(CH_2CH_3)_3$), 0.82 (9H, t, *J* 7.9, $Si(CH_2CH_3)_3$), 1.37 (3H, t, *J* 7.2, OCH_2CH_3), 2.29 (1H, br d, *J* 13.4, $SCH_{eq}H$), 3.28 (1H, ddd, *J* 13.3, 12.3, 4.0, $SCH_{ax}H$), 3.63 (1H, ddd, *J* 12.3, 4.0, 2.2, $OCH_{eq}H$), 4.07 (1H, td, *J* 12.2, 2.7, $OCH_{ax}H$), 4.29 (1H, dq, *J* 10.8, 7.2) and 4.35 (1H, dq, *J* 10.8, 7.2, OCH_2CH_3), 5.55 (1H, s, PhC*H*), 7.35–7.37 (3H, m) and 8.12–8.14 (2H, m, Ar-*H*); *m*/*z* (FAB): 366 (M^+, 92%), 175 (100), 159 (91).

‡ Procedure for ring expansion–desilylation: 2-Phenyl-1,3-oxathiolane (**2a**) (0.25 g, 1.5 mmol) was subjected to ring expansion with **9** (0.58 g, 2.5 mmol) under the conditions outlined above. After 24 h, the reaction was cooled to 0 °C, and tetra-*n*-butylammonium fluoride (1M in THF, 2.0 mL, 2.0 mmol) was added dropwise over 5 minutes. The mixture was stirred at 0 °C for 1 h then poured into an ice–water mixture (5 mL) overlaid with diethyl ether (5 mL). The aqueous phase was extracted with diethyl ether (4 × 5 mL), then the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (SiO_2; petroleum ether–diethyl ether 8:2) afforded ethyl 2-phenyl-1,4-oxathiane-3-carboxylate (**7a** and **8a**, 0.33 g, 87%) as a 2:1 mixture of isomers. A pure sample of **7a** could be obtained by recrystallisation from methanol.Selected data for **7a**: δ_H (300 MHz, $CDCl_3$) 0.98 (3H, t, *J* 7.1, OCH_2CH_3), 2.55 (1H, dt, *J* 13.7, 2.1, $SCH_{eq}H$), 3.16 (1H, ddd, *J* 13.7, 11.8, 3.3, $SCH_{ax}H$), 3.83 (1H, d, *J* 9.4, $CHCO_2Et$), 3.93 (2H, q, *J* 7.1, OCH_2CH_3), 4.00 (1H, td, *J*11.9, 2.1, $OCH_{ax}H$), 4.39 (1H, ddd, *J* 11.9, 3.1, 2.3, $OCH_{eq}H$), 4.76 (1H, d, *J* 9.4, PhC*H*), 7.31–7.36 (5H, m, Ar-*H*).

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10 The trimethylsilyl derivative was initially employed, but the resulting ring-expanded products showed a tendency to desilylate *in situ*.

11 The relative stereochemistry of **10d** was assigned by NOE spectroscopy; that of **10b/11b**, **10c/11c** and **10e** was inferred from the similarity of their ^1H NMR spectra to those of **10a/11a**.

12 Some attempts to perform ring-expansion on compound **2d** led to ring-opened enol ethers as the major products.

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