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New carbon–carbon bond forming reactions of cyclic sulfate esters and cyclic sulfamidates

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Abstract—Carbon–carbon bonding forming reactions of two cyclic sulfate esters and a cyclic sulfamidate are reported, the former with lithium dianions to give substituted tetrahydrofuran derivatives with displacement of sulfate, and the latter undergoes ring-opening monosubstitution reactions with stabilised organolithiums and an organocuprate species.

Cyclic sulfate esters of *vic*-diols and cyclic sulfamidates of *vic*-aminoalcohols are of interest as synthetic intermediates since their precursors are available as single enantiomers from alkenes by asymmetric methodologies introduced by Sharpless.[1,2] Cyclic sulfate esters undergo single substitution reactions at a ring carbon with a range of nitrogen, oxygen and sulfur based nucleophilic species to give the substituted alcohol after hydrolysis of the resulting hemi-sulfate.[3,4] They have found applications in the syntheses of natural products,[5] biologically active materials[6] and heterocyclic systems[7] and also in cascade reactions.[8] Several double substitution reactions with bis-nucleophiles leading to the loss of sulfate have also been reported, notably with dithiolates to give fused dihydro(1,4)dithiins of use in the synthesis of chiral organosulfur donors,[9] with sulfide to give episulfides[10] and with amidines to give diamines.[11] Several monosubstitution reactions with a variety of carbon centred nucleophiles have been reported, for example with cyanide,[3] a Grignard reagent with copper catalysis,[3] and lithiated alkynes[12] and 1,3-dithiane derivatives.[13] The disubstitution reaction with malonate and related species has found considerable application in the preparation of cyclopropane derivatives.[3,14]

We now report double substitution reactions of the racemic cyclic sulfate esters **1** and **2** with a range of dianions generated from molecules of general formula $CH_3COCHR\text{-}X$, where X is $CH_3C(O)$-, CH_3O_2C- and $PhSO_2$-, by treatment with LDA.[15] For example, reaction[16] of the lithium dianion of pentane-2,4-dione **3** with cyclic sulfate ester **1** in THF gave after chromatography both the *E*- and *Z*-stereoisomers of the 5-substituted tetrahydrofuran-2-ylideneacetate **6** and **12** in 42 and 30% yields (Table 1). Attack of the terminal carbon of the dianion at the primary carbon of **1** is followed by attack of oxygen at the secondary centre, this latter

Table 1. Yields of products from reaction of dianions with cyclic sulfate esters

Source of dianion	Cyclic sulfate ester	Product yield (%),[17] *E*-isomer	Product, yield (%), *Z*-isomer
3	**1**	**6** (42)	**12** (30)
	2	**8** (40)	**15** (16)
4	**1**	**7** (43)	**13** (7)
	2	**9** (41)	–
5	**1**	–	**14** (25)
	2	**10** (23)	–
16	**1**	**18** (45)	–
17	**1**	**19** (66)	–

Keywords: cyclic sulfate esters; tetrahydrofurans; cyclic sulfamidates.

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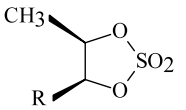
reaction preferring displacement of sulfate by the 'harder' oxygen centre of the enolate. The two compounds were distinguished by their chemical shifts and NOE difference spectra, indicating a NOE effect between the vinyl H atom and the 3-CH_2 group in **12** but not in **6**, and comparison with compounds in the literature. The minor isomer **12** slowly isomerised to the major isomer at room temperature, but this is suppressed below 0°C.

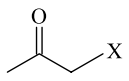
Reaction of the β-ketoester **4** with cyclic sulfate ester **1** under similar conditions gave the corresponding tetrahydrofuran derivative as *E*- and *Z*-isomers **7** and **13** in 43 and 7% yields, respectively, with **13** isomerising to **7** slowly. However, the dianion from β-ketosulfone **5** reacted with **1** to give only the *Z*-isomer of the tetrahydrofuran derivative **14**, identified by comparison of ^1H chemical shifts with the corresponding 5-unsubstituted analogues.[18]

Reactions of the dianions with the disubstituted cyclic sulfate ester **2** were also successful, even though both nucleophilic displacements are at secondary carbon atoms. Dianions of compounds **3**–**5** gave useful yields of the 2,4,5-trisubstituted tetrahydrofuran derivatives **8**–**10**, all of which have *E* stereochemistry at the alkenyl bond. The β-diketone **3** also gave some of the alternative stereoisomer **15**. It was of particular interest to find that the β-ketoester **16** and β-diketone **17**, which are monosubstituted at the methylene position, also reacted in the same way with cyclic sulfate ester **1** to give tetrahydrofurans **18** and **19**, a reaction which could find application in the synthesis of derivatives of methyl nonactate **20** and thus nonactins.

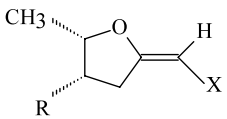
The synthesis of such tetrahydrofuranylidenes has also been effected by reaction of epoxides with dianions[19] or bis(trimethylsilyloxy)-1,3-butadienes.[20] In both these approaches the reactions proceed via inversion of configuration at one site only on the epoxide ring (the position of C,C bond formation at the less hindered site) so cannot be used to give enantiopure 4,5-*trans* disubstituted products. Reactions of epibromohydrins with dianions also yield alkylidenetetrahydrofuran derivatives.[21] Tetrahydrofuran **6** has been prepared from the corresponding tetrahydrofuran-2-thione and methyl bromozincacetate.[22] Hoye and Crawford[23] have reported ring opening of the cyclic sulfate ester of dodecane-1,2-diol by several simple lithium enolates. They found that the lithium enolate of *t*-butyl acetate gave tetrahydrofuran **11** as a by-product, probably because under the conditions the starting material underwent Claisen condensation to a β-ketoester. A related synthesis of (*S*)-coniine via double substitution on a cyclic sulfate ester of a 1,3-diol with the disodium salt of *N*-tosyl tosylacetamide has been reported recently.[24]



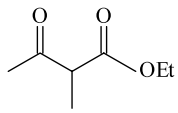
1 R = H
2 R = CH_3



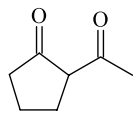
3 X = $COCH_3$
4 X = CO_2Me
5 X = SO_2Ph



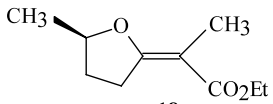
6 R = H; X = $COCH_3$
7 R = H; X = CO_2Me
8 R = CH_3; X = $COCH_3$
9 R = CH_3; X = CO_2Me
10 R = CH_3; X = SO_2Ph
11 R = $C_{10}H_{21}$; X = CO_2tBu



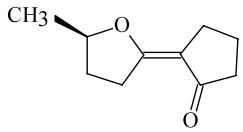
16



17

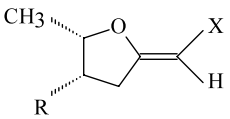


18

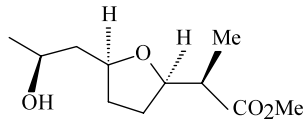


19

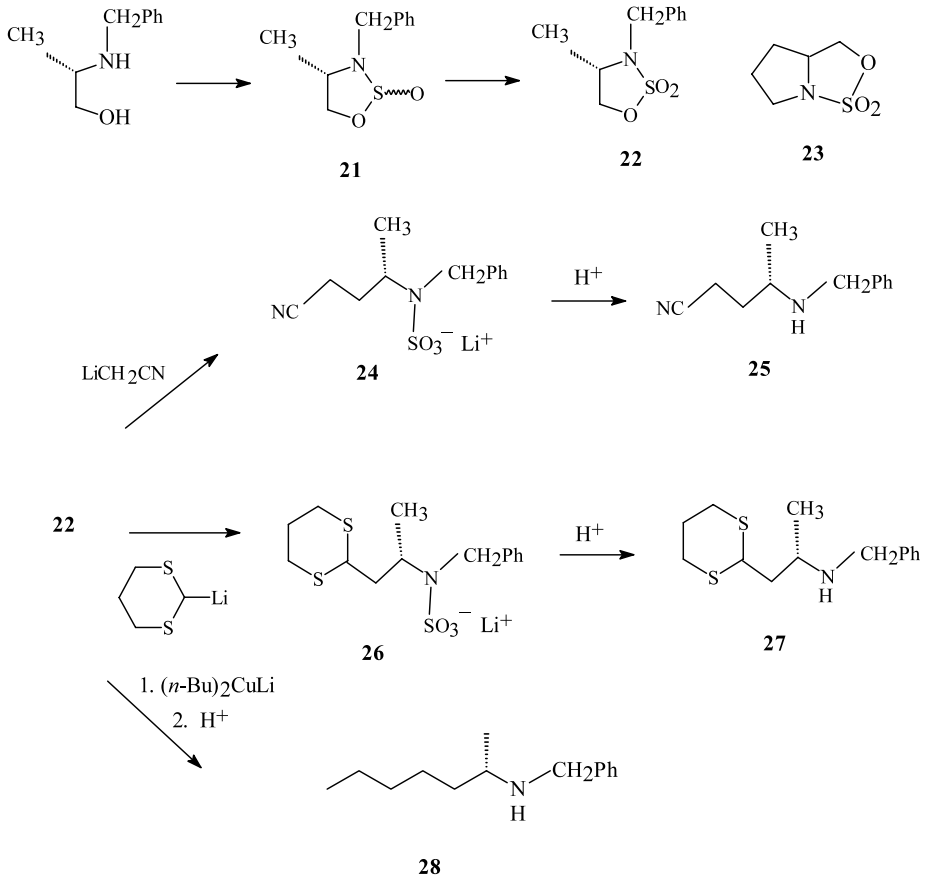
All products are racemic.



12 R = H; X = COMe
13 R = H; X = CO_2Me
14 R = H; X = SO_2Ph
15 R = CH_3; X = $COCH_3$



20



The chemistry of cyclic sulfamidates has not received as much attention as that of cyclic sulfate esters, however, nucleophilic ring opening of cyclic sulfamidates of *vic*-aminoalcohols by attack at the 5-C atom followed by acidic hydrolysis of the sulfamate salt have been investigated in a number of groups.[25–28] We report here several substitution reactions by carbon centred nucleophilic species. The cyclic sulfamidate **22** was prepared in two steps from *N*-benzylalaninol by treatment with thionyl chloride and pyridine in THF to give the cyclic sulfamidite **21** as a mixture of two diastereoisomers and subsequent oxidation with sodium periodate and catalytic ruthenium trichloride in 37% overall yield.

Lithiated acetonitrile was treated with cyclic sulfamidate **22** at −78°C and left to warm to room temperature overnight to give the lithium sulfamate **24** in 90% yield. Hydrolysis of this product with aqueous sulfuric acid (pH 2) gave 4-benzylaminopentanenitrile **25** in 73% yield. Reaction of the cyclic sulfamidite **21** or the bicyclic sulfamidate of prolinol,[25] **23**, with lithiated acetonitrile under similar conditions led to a mixture of products. Lithiated 1,3-dithiane was reacted with cyclic sulfamidate **22** at −25°C and left to warm to room temperature for 24 h to give the lithium sulfamate **26** in 80% yield. Hydrolysis with aqueous sulfuric acid (pH 1) gave the amine **27** in 64% yield. In contrast, reaction of cyclic sulfamidate **22** with the more reactive species *n*-butyllithium and phenyllithium gave mixtures of products, probably due to attack at the sulfur atom as well as at the 5-C atom. Finally, cyclic sulfamidate **22** was found to go undergo a substitution reaction when treated with lithium di(*n*-butyl)cuprate at −20°C, and subsequently hydrolysed with 20% sulfuric acid to give the amine **28** in 23% yield. The cyclic sulfamidate of *N*-benzylthreonine methyl ester yielded a 3:1 mixture of diastereoisomers in 40% yield from the corresponding reaction. Further carbon, carbon bond forming reactions of cyclic sulfate esters and sulfamidates are under investigation.

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