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One-Pot Stereocontrolled Cycloalkanone Synthesis using 1,3-Dithiane 1-Oxides

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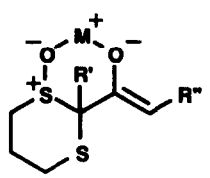
Abstract: Lithium enolates of 2-acyl-1,3-dithiane 1-oxides, generated in one pot from 1,3-dithiane 1-oxide, undergo highly diastereoselective alkylation upon treatment with alkyl iodides; similar *in situ* treatment of these substrates with diiodoalkanes furnishes the corresponding medium-ring cycloalkanones with extremely high diastereoselectivity and in moderate to good yields.

Over recent years we have developed the uses of simple 1,3-dithiane 1-oxide (DITOX) derivatives as chiral auxiliaries and asymmetric building blocks for the enantiocontrol of a range of organic reactions including enolate alkylation,[1] Grignard reagent addition,[2] hydride reduction,[3] conjugate addition,[4] and heterocycloaddition;[5] more recently the Mannich reaction has been studied in an enantioselective approach to amines.[6] In most of these cases, the observed stereoselectivities are sufficiently high that the minor isomers are not detectable by 400 MHz ^{1}H NMR spectroscopy.

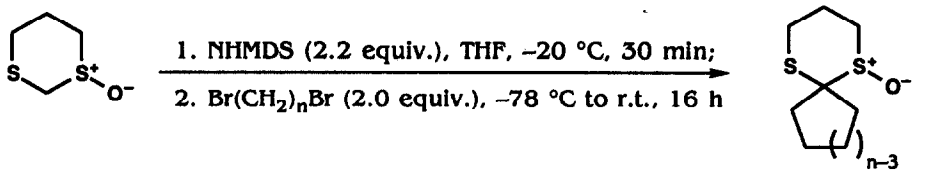
The high degree of stereoselectivity observed in these reactions may be rationalized in terms of an association of both the enolate and the sulphoxide oxygen atoms with a metal counter-ion which forces the system into a conformation in which the acyl moiety is held in a highly asymmetric environment (Figure). This simple chelation-control model allows us easily and successfully to predict the sense of induced stereochemistry in each reaction type. The DITOX unit may be removed from 2-acyl-2-alkyl-1,3-dithiane 1-oxides by treatment with base or through hydrolysis.[7] We have recently become interested in the possible application of these concepts to the use of DITOX building blocks in stereocontrolled cyclization.



Figure

An efficient method for preparation of the 2-acyl-2-alkyl-1,3-dithiane 1-oxide substrates in optically pure form has until recently been lacking. However, lately we have made two considerable advances in the preparation of acyl dithiane oxides: we are able to prepare 1,3-dithiane 1-oxide (DITOX) enantiomerically pure in both enantiomeric forms,[7] and we have solved the unexpectedly difficult problem of acylation of DITOX itself. Acylation is efficiently effected using *N*-acyl imidazoles under mixed base (sodium hexamethyl disilazide/butyl lithium) conditions furnishing 2-acyl-1,3-dithiane 1-oxides in good yields after protic work-up.[8]

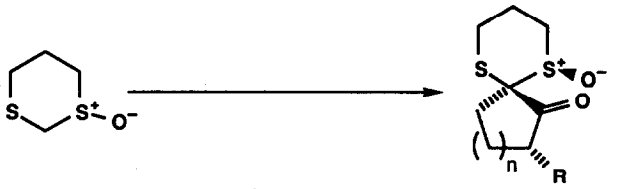
Table I. Perkin Ring Synthesis using 1,3-Dithiane 1-Oxides



n	Yield/%
4	75
5	79
6	81
7	—†

† uncyclized haloalkylated material (62%) isolated

We have found that anions derived from dithiane oxide substrates undergo efficient Perkin ring synthesis upon treatment with dihaloalkanes (Table I) to provide up to seven membered carbocycles, 1,7-dibromoheptane providing the haloalkylated material but not ungergoing cyclization to the eight membered ring. However, this process introduces no new asymmetric centres. We reasoned that suitable deprotonation of our 2-acyl-1,3-dithiane 1-oxides followed by treatment with dihaloalkanes should lead, by tandem inter- and intra- molecular enolate alkylation, to carbocycles, with a strong possibility of stereocontrol during the cyclization process (Scheme 1).



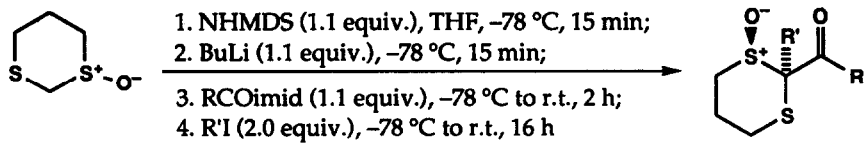
Scheme 1

Unfortunately, we have since discovered that exposure of some isolated acyl derivatives of DITOX to silica gel for a short period of time (< *ca.* 2 hours) at room temperature results in transformation, perhaps through a Pummerer rearrangement process, into thiolester derivatives. Furthermore, in attempted alkylation reactions following deprotonation acyl dithiane oxide substrates were similarly transformed in the presence of stoicheiometric quantities of Lewis acid.[9]

As indicated above, acylation of DITOX using *N*-acyl imidazoles requires the use of base mixtures; the optimum procedure involves generation of the metallated species

from 1,3-dithiane 1-oxide by deprotonation with a solution of sodium hexamethyl disilazide (NHMDS) (1.1 equiv.) followed by addition of a solution of butyl lithium (1.1 equiv.) at –78 °C to prevent yields being compromised by reprotonation of the dithiane oxide anion by the more acidic acyl dithiane oxide product. Consequently, upon acylation, the lithium hexamethyl disilazide generated *in situ* by the butyl lithium deprotonates the highly acidic proton at C-2 of the acyl dithiane oxide, furnishing a lithium enolate. Our judgement was therefore that a work-up procedure involving initial treatment with a carbon electrophile would lead to a one-pot formation of 2-alkyl-2-acyl-1,3-dithiane 1-oxides, normally our starting materials for stereocontrolled reactions in this series, potentially in optically pure form. Indeed, treatment of DITOX acylation reaction mixtures with simple alkyl halides at –78 °C enabled us to isolate 2-alkyl-2-acyl-1,3-dithiane 1-oxides in moderate to good yields and with excellent diastereoselectivity (Table II). Interestingly, the isomer formed predominantly has the *syn* configuration; this route is therefore complementary to our earlier route involving sulphur oxidation as the final stage, which provides predominantly *anti* material. In addition we have discovered that the *syn* isomers are cleanly converted into *anti* by low temperature treatment with trifluoroacetic anhydride.[9]

Table II. One Pot Generation of 2-Acyl-2-alkyl-1,3-dithiane 1-Oxides



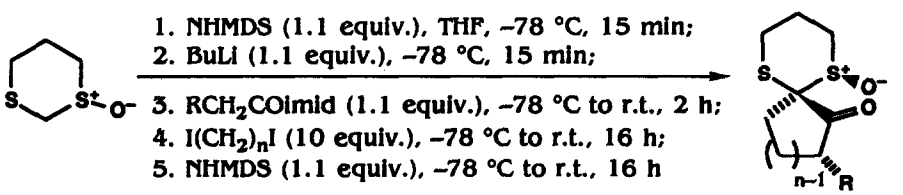
R	R'	Yield/%	Selectivity (Syn/Anti)
Me	Me	65	7 : 1
Me	Et	54	exclusive †
Me	CH_2=$CHCH_2$	73	exclusive †
Et	Me	73	exclusive †
Et	CH_2=$CHCH_2$	75	15 : 1
Bu	Me	71	exclusive †
Bu	CH_2=$CHCH_2$	66	4 : 1
4-tBuPh	Me	67	exclusive †

† minor isomer not detectable by 400 MHz ^{1}H NMR spectroscopy

Particularly exciting to us was the potential application of this chemistry to a stereocontrolled cyclization reaction, as originally envisaged (Scheme 1), but taking place in one pot. We were therefore especially pleased to find that sequential treatment of 1,3-dithiane 1-oxide with NHMDS, butyl lithium, propionyl or butyryl imidazole, and diiodoalkane led to the corresponding haloalkylated materials, which could be isolated in *ca.* 70% yields and which are formed with exclusively *syn* stereochemistry; alternatively, further treatment with NHMDS gave in two cases cyclization to carbocyclic products with sufficiently high diastereoselectivity that the minor isomer at the new asymmetric centre in the ring could not be detected by 400 MHz ^{1}H NMR spectroscopy (Table III). Two new asymmetric centres and two new carbon-carbon bonds are therefore each formed in these one pot cyclization reactions with extremely high stereoselectivity. Curiously it is the seven and eight membered ring compounds which are readily formed; reaction with 1,3-diiodopropane gave preferential elimination of HI to provide only *syn*-2-allyl-2-propanoyl-1,3-dithiane 1-oxide, while 1,6-diiodohexane gave the haloalkylated material

but did not undergo cyclization to the nine-membered ring. 1,2-Diidoethane was not a successful substrate.

Table III. One Pot Stereocontrolled Cyclization Reactions using DITOX



R	n	Yield/%	Selectivity
Me	3	—†	—
Me	4	72	exclusive ‡
Me	5	74	exclusive ‡
Me	6	—§	—
Et	4	60	≥4 : 1
Et	5	63	exclusive ‡

† *syn*-2-allyl-2-propanoyl-1,3-dithiane 1-oxide (78%) isolated
‡ minor isomer not detectable by 250/400 MHz ^{1}H NMR spectroscopy
§ uncyclized haloalkylated material (64%) isolated

Inspection of molecular models suggests that the *syn* intermediate haloalkylated species, expected to be predominant as described above, will lead to a stereochemistry in the cyclized product as shown, in accordance with our acyclic enolate alkylation work.[1] Presumably the conformations adopted by the intermediate are such that cyclization is favoured only for a limited range of ring sizes where the alkyl iodide chain is of an ideal length.

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