trans-1,3-Dithiane-1,3-Dioxide, a New Chiral Acyl Anion Equivalent for the Preparation of Masked Activated Acids: Application to the Synthesis of α-Hydroxy Acid Derivatives

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trans-1,3-Dithiane-1,3-dioxide reacts with high diastereoselectivity with aromatic aldehydes and the 1,3-dithiane-1,3-dioxide moiety can be easily converted to a thiolester without racemisation by carrying out a Pummerer reaction; the thiolester is a group that can be readily transformed into acids, esters, amides, ketones and aldehydes.

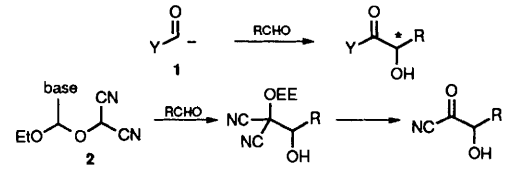
There are now a number of masked, nucleophilic acylation agents of type **1** (Scheme 1, Y = heteroatom) for one-carbon homologation of carbonyl compounds in which high levels of enantiocontrol can be achieved.[1–5] Most notable amongst these in terms of operational simplicity and high enantioselectivity is the asymmetric hydrocyanation of aldehydes.[1–3] A nucleophilic, masked, activated acid anion **2** has also been reported for efficient homologation *and* subsequent coupling.[6] No reagent at present embodies the two desirable features inherent in both reagents **1** and **2**, namely a reagent that shows high levels of enantiocontrol in addition reactions and one that, upon unmasking, liberates an activated acid suitable for direct coupling.

We have addressed this problem and have developed a chiral carbonyl anion equivalent (metallated-**4**) that not only reacts highly selectively with aldehydes but also can be easily converted to a thiolester. Thiolesters are activated acids and can be directly transformed into esters, amides, ketones and aldehydes. This greatly extends the usefulness of this chemistry.

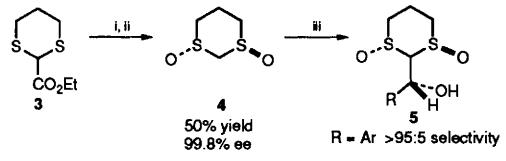
An efficient, two-step, asymmetric synthesis of *trans*-1,3-dithiane-1,3-dioxide **4** has recently been described[7] together with conditions for obtaining high diastereoselectivity in anion reactions with aromatic aldehydes (Scheme 2).[8] We now describe a method for converting the *trans*-1,3-dithiane-1,3-dioxide moiety into the versatile thiolester functional group.

Adduct **5a** was protected as the tetrahydropyranyl (THP) ether and the product **6a** subjected to a Pummerer reaction (Scheme 3).[9] Using trifluoroacetic anhydride (TFAA) in CH_2Cl_2 in the presence of pyridine[10] the starting material was rapidly consumed and workup with NaOMe–MeOH gave protected methyl mandelate **7** in good overall yield (Scheme 3). However, the product obtained was not enantiomerically pure. Since there are several literature references of Pummerer reactions occurring without loss of optical purity on substrates bearing readily epimerisable protons[10,11] we assumed that the basic hydrolysis conditions were responsible for causing the partial epimerisation observed. Indeed, in choosing to prepare α-hydroxy esters/α-hydroxy thiolesters bearing an aromatic ring in the α-position we have set ourselves a test substrate that is most prone to racemisation.

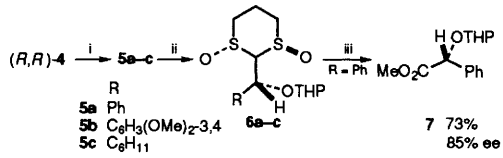
Carrying out a neutral aqueous workup following the Pummerer reaction gave thiolester **9a** in 95% yield. The mechanism for the formation of the thiolester 'dimer' **9a** is depicted in Scheme 4 and follows from the known chemistry of sulfenic acids to self condense and form thiosulfinates.[12] Having formed the thiolester 'dimer' we sought to use the known coupling methods for formation of esters and amides using Ag, Hg or Cu catalysis.[13–17] Since these reactions would be carried out under essentially neutral conditions little epimerisation would be expected to occur, if any. However, all attempted literature reactions with various salts of the above metals failed or gave poor yields due to interference by the thiosulfinate group. The thiolester **9a** was therefore



Scheme 1



Scheme 2 *Reagents*: i, (*R,R*)-diethyl tartrate, $Ti(OPr^i)_4$, $PhCMe_2OOH$, CH_2Cl_2; ii, NaOH, H_2O; iii, NaHMDS, RCHO, THF, py

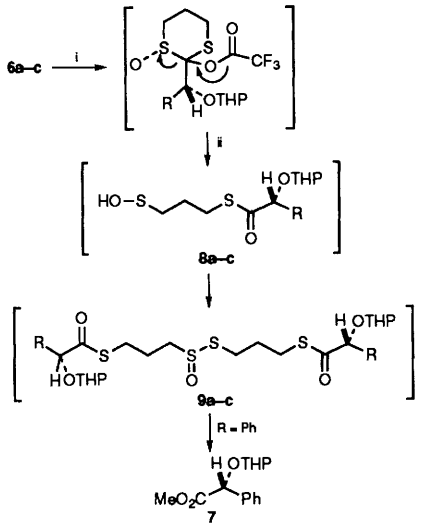


Scheme 3 *Reagents and conditions*: i, NaHMDS, RCHO, THF, py; ii, DHP, CH_2Cl_2, TsOH (cat); iii, (*a*) TFAA, py, CH_2Cl_2, 0 °C, 15 min (*b*) NaOMe, MeOH, 0 °C, 15 min

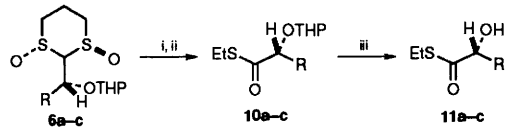
Table 1 Yields and enantioselectivities of products **5**, **6**, **10** and **11**

		5		6	10	11
Entry	R	Diastereoselectivity[a]	Yield[b] (%)	Yield (%)	Yield (%)	ee[c] (%)
1	Ph	>97:3	84	94	86	97 (*R*)[d]
2	$C_6H_3(OMe)_2$-3,4	>97:3	76	93	89	95 (*R*)[e]
3	C_6H_{11}	47:53	40	96	77	>98 (*R*)[d]

[a] Diastereoselectivity observed (by NMR) in the addition reactions of (*R,R*)-**4** with aldehydes. Pure diastereoisomers were obtained by chromatography. [b] Isolated yields of pure diastereoisomer **5**. [c] Enantioselectivities were determined by chiral HPLC using a Chiralcel OD column. To ensure that separation of enantiomers occurred by chiral HPLC, racemates were prepared and tested initially. [d] The absolute configuration was determined by conversion of the thiolester to the known acids and optical rotations compared. [e] Since the same enantiomer of **4** was used and similar diastereoselectivity was obtained in the addition reaction as with benzaldehyde the same absolute configuration is expected.



Scheme 4 *Reagents and conditions*: i, TFAA, py, CH_2Cl_2, 0 °C, 15 min; ii, NaOMe, MeOH, 0 °C, 15 min

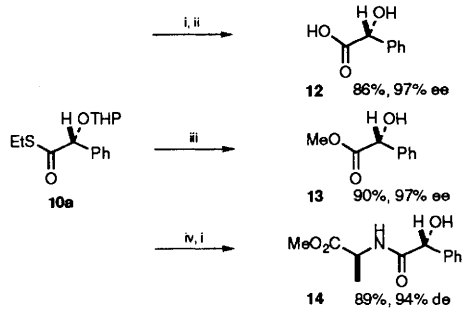


Scheme 5 *Reagents and conditions*: i, TFAA, py, CH_2Cl_2, 0 °C, 15 min; ii, LiOH, EtSH, THF, H_2O, 0 °C–room temp.; iii, PPTS, EtOH

transthiolesterified using LiSEt[18] and this gave the much simpler thiolester **10a** (Scheme 5). Using this reagent, which is very much less basic than NaOMe, little epimerisation occurred (entry 1, Table 1). This is the first example of a transthiolesterification reaction and we presume that the driving force for the reaction is the large excess of ethanethiol used. Other aromatic and non-aromatic aldehydes were investigated and the results are summarised in Table 1.

The ethyl thiolester **10a** was then readily coupled with nucleophiles using either Ag or Hg catalysis (Scheme 6). For example treatment with an alcohol in the presence of both $Hg(OCOCF_3)_2$ and $BF_3{\cdot}OEt_2$ resulted in clean conversion to ester **13**.[13–15,17] Treatment with amines in the presence of $AgOCOCF_3$ gave an amide.[16] Even relatively non-nucleophilic amines derived from amino acids coupled smoothly without any significant epimerisation occurring. Hydrolysis of the thiolester was readily achieved by treatment with LiOOH[19] and again no further epimerisation occurred in this step.

In summary we have shown that the dithiane dioxide moiety is a versatile functional group as it not only reacts with high diastereoselectivity with aromatic aldehydes but can also be easily converted into a thiolester without racemisation. We have improved methods for the conversion of thiolesters into acids and esters, have converted them into amides and there are further literature methods for their conversion to ketones[20] and aldehydes.[21] We are currently applying this



Scheme 6 *Reagents*: i, PPTS, EtOH; ii, LiOH, H_2O_2, THF, H_2O; iii, $Hg(OCOCF_3)_2$, $BF_3{\cdot}OEt_2$, MeOH; iv, L-methyl alaninate, $AgOCOCF_3$, MeCN

methodology to the synthesis of biologically important targets.

We thank the SERC and Zeneca Agrochemicals for a CASE award (R. J. F.), Dr Martin Rice for valuable discussions and Glaxo Group research for further support.

Received, 6th May 1994; Com. 4/02698E

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