Tetrahedron Letters,Vol.31,No.1,pp 135-138,1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

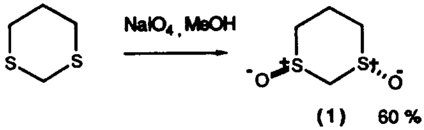
ADDITIONS OF ALDEHYDES TO METALLATED TRANS-1,3-DITHIANE-S,S-DIOXIDE UNDER CONDITIONS OF KINETIC AND THERMODYNAMIC CONTROL

Varinder K. Aggarwal,*[a] Ian W. Davies,[a] John Maddock,[a] Mary F. Mahon,[b]
Kieran C. Molloy[b]
a. School of Chemistry, University of Bath, Bath, BA2 7AY, England
b. X-ray crystallographic unit, University of Bath, Bath, BA2 7AY, England.

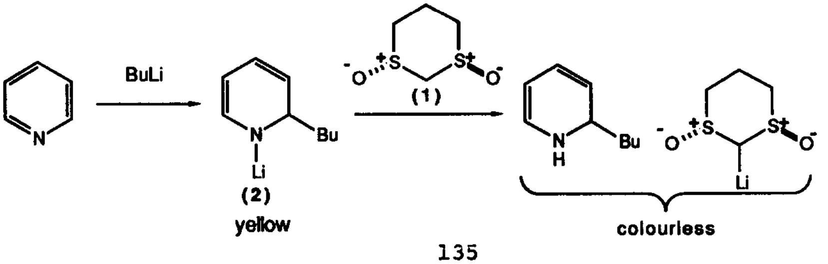
Summary *The chiral acyl anion equivalent (1) can be metallated with n-BuLi/py and reacts with aldehydes to give adducts in high yield. At -78°C the reaction is under kinetic control whereas at 0°C equilibration occurs with PhCHO and t-BuCHO resulting in good yields of single diastereoisomers.*

Chiral acyl anion equivalents are highly sought after moieties since their reactions with aldehydes furnish α-hydroxy carbonyl compounds and this class of compounds is very important in asymmetric synthesis.[1] A number of chiral acyl anion equivalents have been reported[2] and of these Eliel's oxathiane[2a] has been most widely used. Our own studies in this area centre around using the chiral, C_2 symmetric acyl anion equivalent (1) and in this letter we describe its addition reactions with aldehydes.

Trans-1,3-dithiane-S,S-dioxide (1) was prepared by $NaIO_4$ oxidation of dithiane.[3] This compound was found to be soluble only in very polar solvents H_2O, DMF, DMSO and sparingly soluble in MeOH, EtOH, pyridine. Use of polar aprotic solvents limits the temperature range that can be used and often causes equilibration of adducts in aldol type reactions.[4]



It was found that (1) could be dissolved in pyridine and diluted with THF without significant precipitation. Dropwise addition of n-BuLi to this faint suspension caused the appearance of a transient yellow colour which remained when an excess of n-BuLi was present and as a result of these observations, in practice, n-BuLi was simply titrated into the reaction. Evidently, n-BuLi adds to pyridine[5] to give the yellow coloured adduct (2) and this acts as the base to deprotonate (1). To our knowledge the combination of n-BuLi/py has not been used



as a base before. The anion was cooled to -78°C and benzaldehyde was added. The reaction was monitored by removing aliquots at various time intervals and subjecting the crude mixtures to HPLC analysis. The reaction was found to be extremely rapid (complete after 1 minute) and no change in ratios was observed over a 4h period. The pure minor isomer obtained in this reaction was subjected to the reaction conditions and none of the major isomer was observed. The kinetic ratio in this reaction was 66:34. Similar results were obtained in reactions with other aldehydes (**table 1**) and again it was demonstrated that no equilibration occurred at -78°C using the procedure described above.

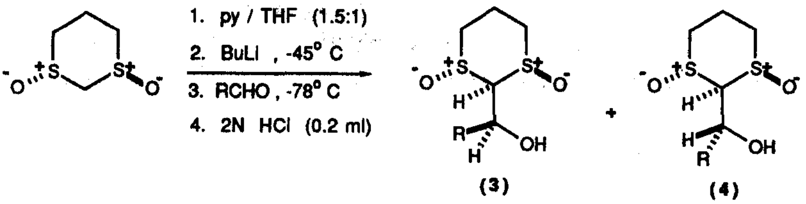


Table 1: **Ratios of diastereoisomers obtained at -78°C**

Entry	Aldehyde	Product distribution (3)	:	(4)
a	n BuCHO	63	:	37
b	i PrCHO	50	:	50
c	t BnCHO	64	:	36
d	PhCHO	66	:	34

The reactions were repeated at 0°C, monitored as before and the results are given in **table 2**. These show that the valeraldehyde adduct does not equilibrate under the reaction conditions but pivalaldehyde and benzaldehyde adducts do equilibrate. Isobutyraldehyde adducts also equilibrate but in addition they undergo elimination at a comparable rate and this complicates the results. In all reactions, elimination to give the ketene thioacetal bisoxide (5) was observed (at different times depending on the aldehyde) and this complication meant that true equilibrium ratios could not be obtained. Further evidence that the valeraldehyde adduct did not equilibrate at 0°C whilst the benzaldehyde and pivalaldehyde adducts did equilibrate was obtained by subjecting major and minor diastereoisomers to the reaction conditions and observing no change for the valeraldehyde adduct but interconversion of diastereoisomers for the benzaldehyde and pivalaldehyde adducts.

In contrast to reactions of methyl p-tolyl sulphoxide anions with imines,[6] higher diastereoselectivity was obtained under thermodynamic conditions compared to kinetic conditions.

From the kinetic and thermodynamic studies, ideal conditions for the preparation of individual diastereoisomers were determined and the reactions were carried out on preparative scale giving isolated yields as shown in **table 3**. The diastereoisomers were easily separated by flash chromatography ($\Delta R_F > 0.1$) and all were crystalline solids.

The relative stereochemistry of the adducts (3d) and (4c) was determined by X-ray crystallography[7] (see below) and it was assumed that the major diastereomer from the valeraldehyde reaction at -78°C was the same as the other aldehydes.

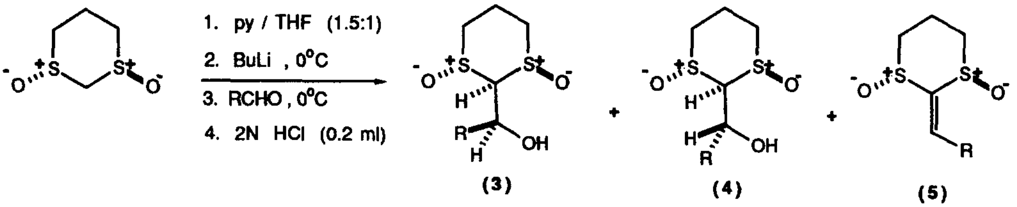
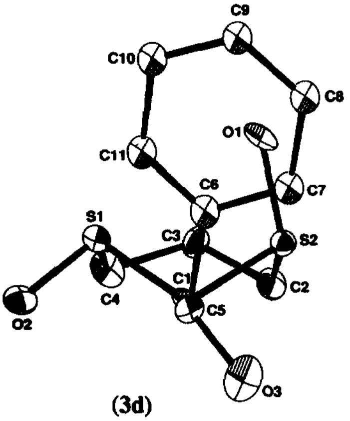


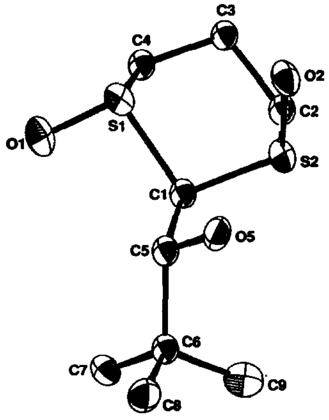
Table 2 Ratios of diastereoisomers obtained at 0°C

Entry	Aldehyde	Time	Product distribution				
			(3)	:	(4)	:	(5)
a	n-BuCHO	5 min	50	:	50	:	-
		30 min	48	;	52	:	-
		60 min	49	:	51	:	trace
		3h	36	:	52	:	12
		6h	15	:	56	:	29
		10h	1	:	26	:	73
b	i-PrCHO	2 min	48	:	44	:	6
		10 min	55	:	38	:	7
		20 min	49	:	37	:	14
		60 min	50	:	34	:	16
		7h	38	:	26	:	36*
c	t-BuCHO	1 min	43	:	57	:	-
		10 min	31	:	69	:	-
		30 min	25	:	75	:	-
		60 min	14	:	86	:	-
		6h	31	:	38	:	31
d	PhCHO	1 min	62	:	38	:	-
		10 min	59	:	41	:	-
		30 min	45	:	55	:	-
		60 min	36	:	64	:	-
		3.5h	13	:	77	:	10

* mixture of vinyl and allyl sulphoxides (20:16 respectively)



(3d)



(4c)

It has been demonstrated that lithiated trans-1,3-dithiane-1,3-dioxide adds to aldehydes to give good yields of adducts and for those aldehydes that equilibrate at 0°C, good diastereoselectivity can also be obtained. The crystallinity of the adducts and the large R_F difference between the diastereomers ensures that pure isomers can be readily obtained. The homochiral acyl anion equivalent (**1**) can be readily prepared by literature methods[8] and application of this anion to the chemistry described above would furnish adducts (3) and (4) in homochiral form. We are currently investigating more direct methods for the asymmetric synthesis of this chiral acyl anion equivalent.

Table 3 Isolated yields of diastereoisomers obtained

Entry	Aldehyde	Temperature (°C)	Reaction Time(minutes)	Crude Ratio (3)	:	Crude Ratio (4)	Isolated Yield (%) (3)	Isolated Yield (%) (4)
a	n-BuCHO	-78	10	57	:	43	49	34
		0	10	50	:	50	48	44
b	i-PrCHO	-78	2	50	:	50	34	34
		0	20	62	:	38	40	24
c	t-BuCHO	-78	40	60	:	40	42	29
		0	60	13	:	87	6	71
d	PhCHO	-78	60	66	:	34	58	10
		0	60	36	:	64	24	52

Acknowledgements. We thank Glaxo Group Research for partial support of this work.

References

1. S. Hanessian, 'Total Synthesis of Natural Products: the Chiron Approach', Pergamon Press, 1983, Oxford.
2. (a) E.L. Eliel in 'Asymmetric Synthesis Vol 2', J.D. Morrison (Ed), Academic Press, London, p. 125 (b) L. Colombo, C. Gennari, C. Scolastico, G. Guanti, E. Narisano, *J. Chem. Soc. Perkin Trans I,* 1981, 1278 (c) H. Mahler, M. Braun, *Tetrahedron Lett.,* 1987, 5145 (d) G. Delogu, O. de Lucchi, G. Licini, *J. Chem. Soc. Chem. Commun.*, 1989, 411.
3. The selectivity in this reaction was found to be >95:5 in favour of the trans isomer. This stereoselective oxidation has been studied in detail and will be published elsewhere.
4. C. Reichardt, 'Solvent Effects in Organic Chemistry', Verlag Chemie, 1978, New York.
5. K. Ziegler, H. Zeiser, *Chem. Ber.*, 1930, 63, 1847.
6. S.G. Pyne, B. Dikic, *J. Chem. Soc. Chem. Commun.*, 1989, 826.
7. Both data sets were collected at room temperature on a Hilger and Watts Y290 automatic diffractometer. (3d) Crystallised (CH_2Cl_2) in space group $P2_12_12_1$ with a = 10.547(4), b = 10.637(3), c = 20.329(4)Å, and Dcalcd = 1.29 gcm^{-3} for Z = 4. The structure was solved by direct methods using 1597 unique reflections with $I \geq 3\sigma(I)$ and refined by full matrix least squares, to a final residual of R = 7.25% for unit weights.

   (4c) Crystallised (toluene) in space group $P2_1/c$ with a = 9.866(2), b = 10.215(3), c = 12.399(4)Å, β = 105.30(2)°, and Dcalcd = 1.31 gcm^{-3} for Z = 4. The structure was solved by direct methods using 1238 unique reflections with $I \geq 3\sigma(I)$ and refined by full matrix least squares, to a final residual of R = 5.38% for unit weights.
8. 1,3-Dithiane-S-oxide has been resolved : R.F. Bryan, F.A. Carey, O.D. Dailey, Jr., R.J. Maher, R.W. Miller, *J. Org. Chem.*, 1978, 43, 90. It is known that $NaIO_4$ oxidation of this compound gives the trans dioxide (1) [see ref. 3].

(Received in UK 16 November 1989)