Highly Stereoselective Addition Reactions Of Metallated Trans-1,3-Dithiane-1,3-Dioxide To Aldehydes

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Abstract: The sodium anion of trans-1,3-dithiane-1,3-dioxide reacts with unhindered aromatic and heteroaromatic aldehydes to give adducts with 95:5 to 97:3 diastereoselectivity.

Acyl anions are useful synthons in contemporary organic synthesis since they allow great versatility in the disconnection of molecular structures.^{1,2} Numerous synthons have been developed for the preparation of α -hydroxy carbonyl compounds and this area has been the subject of several recent reviews.^{2,3} However, the growing demands for the synthesis of enantiomerically pure compounds⁴ has fuelled interest in the development of chiral acyl anions equivalents.⁵ Of the acyl anions developed to date, none are ideal in that some require several extra steps to control stereochemistry^{5a,b,c} or only give poor diastereoselectivity^{5d,e} or require extremely low temperatures to obtain reasonable yields^{5f,g} or require high molecular weight auxiliaries.^{5h} In this communication we report a new, low molecular weight, chiral acyl anion equivalent that reacts with aromatic aldehydes with very high stereocontrol at 0°C.

Our rationally designed chiral acyl anion equivalent is trans-1,3-dithiane-1,3-dioxide (1). This molecule possesses C_2 symmetry and this not only reduces the number of competing diastereomeric transition states⁶ but also results in the creation of only one new stereocentre in addition reactions with trigonal electrophiles. Furthermore, the greater acidity of (1) [pK_a 25.0⁷] as compared to dithiane itself [pK_a 31⁸] allows metallation with a greater variety of bases.

Trans-1,3-dithiane-1,3-dioxide (1) was prepared by NaIO₄ oxidation of 1,3-dithiane.⁹ The dioxide (1) was totally insoluble in ether solvents but showed sufficient solubility in pyridine/THF¹⁰ to allow metallation. Metallation with LiHMDS¹¹ and reaction with a variety of aldehydes at -78°C led to a 1:2 ratio of adducts (2):(3). The reactions were



essentially instantaneous and the reactions were under kinetic control. In contrast, metallation with NaHMDS and reaction with benzaldehyde at 0°C gave an initial 1:1 ratio of adducts that improved to a 96:4 ratio [(2):(3)] over 30 minutes. A variety of electron rich and deficient aromatic aldehydes were tried under these conditions together with hindered aromatic and heteroaromatic aldehydes and the results are summarised in table 1. In all aromatic cases, except the 2,6 disubstituted aldehydes high ratios of diastereomers were observed resulting in good isolated yields of recrystallised material. It was pleasing to observe high yields and high selectivity for reactions with aromatic aldehydes bearing two electron donating groups (entry c). Analogous reactions recently reported by Solladie¹² with the sterically more hindered C₂ symmetric variant - (S,S)-bis p-tolysulphinylmethanefailed even to react with such aldehydes. The above reactions were also carried out in pure pyridine or DMF and similar results were obtained. The stereochemistry of the major benzaldehyde isomer was determined by X-ray crystallography.¹³

The results of reactions with aliphatic aldehydes under the same equilibrating conditions are shown in table 1. In contrast to the results with aromatic aldehydes only poor selectivity was observed with aliphatic aldehydes. It is difficult to rationalise why diastereomer A, is favoured over B by over 7 kJ mol⁻¹. Molecular mechanics calculations on the hydroxy adducts gave results contrary to the experimental observations¹⁴ and this suggests that factors other than the direct interaction between the aromatic ring and dithiane moiety are controlling the outcome of the reaction. Instead, association of solvent to the metal or aggregation of the metal alkoxides may contribute important non-bonded or electronic interactions that favour A over B.

In general, the addition of sulphoxide anions to carbonyl compounds often proceeds with high stereoselectivity at the α site (stereochemistry usually destroyed upon removal of sulphoxide) but only poor selectivity at the β site (stereochemistry usually retained).¹⁵ However, there are examples of highly selective addition reactions of aryl sulphoxides with benzaldehyde^{5h,15d,16} and such selectivity has been attributed to favourable π - π stacking interactions.¹⁶ No such interactions are possible in our work and whatever the factors are that contribute to high selectivity for aromatic aldehydes in our work may also operate in the other cases cited above.

In conclusion, 1,3-dithiane-1,3-dioxide can be readily prepared and shows very high selectivity in addition reactions with aromatic aldehydes under equilibrating conditions.







Entry	Aldehyde	Ratio (2):(3)	Isolated yield of isomer (2).
a	С	96:4	87%
b	СНО	95:5	64%
с	RO RO R = SiMe2t-Bu	96:4	74%
d		95:5	76%
e	O₂N CCHO	95:5	42%
f	ГГ _{сно}	70:30	4 7% a
g	Ссно	97:3 b	71% b
h	~~сно	77:23 50:50 d	с 44% d
i	Үсно	60:40 38:62 ^d	с 24% d
j	\mathcal{A}_{cHo}	40:60 87:13 d	c 71% d

a Yield based on recovered starting material. Actual yield 26%.

b Ratio and yield determined after derivatisation of alcohol to TMS ether.

c Pure samples of isomer 2 not isolated under these conditions.

d Ratios and yields obtained using LHMDS at 0° C as detailed in reference 5i.

TABLE 1

<u>Acknowledgement</u> We thank the SERC and ICI Agrochemicals for a CASE award (to RJF) and the Nuffield Foundation for support.

References

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- 1. Corey, E.J.; Cheng, X. 'The Logic of Chemical Synthesis' J. Wiley & Sons, 1989, New York.
- 2. Ager, D.J. in 'Umpoled Synthons', Hase, T.A. (Ed) John Wiley & Sons, 1987, 19-72. Kolb, M. *ibid*, 73-101.
- 3. Page, P.C.B.; Niel, B.M.; Prodger, J.C. Tetrahedron, 1989, 7643.
- 4. Ariens, E.J. in 'Chirality in Drug Design and Synthesis', Brown, C. (Ed) Academic Press, 1990, 29-43.
- (a) Utimoto, K.; Nakamura, A.; Matsubara, S. J. Am. Chem. Soc., 1990, 112, 8189. (b) Eliel, E.L.; Morris-Natschke, S. J. Am. Chem. Soc. 1984, 106, 2937. (c) Lynch, J.E.; Eliel, E.L. J. Am. Chem. Soc. 1984, 106, 2943. (d) Colombo, L.; Gennanari, C.; Scolastico, C.; Guanti, B.; Narisano, E.; J. Chem. Soc. Chem. Commun. 1979, 591; J. Chem. Soc. Perkin Trans. 1, 1981, 1278; (e) Satoh, T.; Onda, K.; Yamakawa, K.; Tetrahedron Lett. 1990, 3567. (f) Braun, M.; Mahler, H. Synlett, 1990, 587. (g) Mahler, H.; Braun, M.; Tetrahedron Lett. 1987, 5145. (h) Delogu, G.; DeLucchi, O.; Licini, G. J. Chem. Soc. Chem. Commun. 1989, 411; Synlett, 1989, 28. (i) Aggarwal, V.K.; Davies, I.W.; Maddock, J.; Mahon, M.F.; Molloy, K.C. Tetrahedron Lett. 1990, 135. For an alternative strategy based on the addition of organometallics or metal hydrides to 2-keto-1,3-dithiane-1-oxide see (j) Page, P.C.B.; Prodger, J.C. Synlett, 1990, 460 (and references therein).
- (a) Najdi, S.; Kurth, M.J.; Tetrahedron Lett. 1990, 3279. (b) Whitesell, J.K. Chem. Rev. 1989, 89, 1581.
- 7. We are indebted to Professor F.G. Bordwell and Dr X. Zhang for the measurement of the pK_a of (1).
- 8. Streitweiser, A., Jr.; Ewing, S.P. J. Chem. Soc. 1975, 97, 190.
- 9. Aggarwal, V.K.; Davies, I.W.; Franklin, R.J.; Maddock, J.; Mahon, M.F.; Molloy, K.C. J. Chem. Soc. Perkin Commun. 1991, 662.
- 10. Because pyridine freezes at -42°C, pyridine/THF mixtures were used so that selectivities at low temperatures could be determined.
- 11. Similar results were obtained with BuLi at -78°C (ref 5i).
- 12. Solladie, G.; Colobert, F.; Ruiz, P.; Hamdouchi, C.; Carreno, M.C.; Ruano, J.L.G. Tetrahedron Lett., 1991, 30, 3695.
- Details of the crystallographic analysis will be published in the full paper.
 Twelve molecules were built for conformational analysis: these were both
- 14. Twelve molecules were built for conformational analysis: these were both diastereomers of the aliphatic aldehyde adducts and both diastereomers from entry a, d and f. The molecules were systematically analysed using the SYBYL conformational search software. In all cases the hydrogen bonded conformers occupied the low energy minima thereby simulating the proposed metal chelates (A and B). However in all cases diastereomer (3) was found to be thermodynamically more stable than diastereomer (2). We thank R. Viner at ICI Agrochemicals for performing these calculations.
- (a) Satoh, T.; Onda, K.; Yamakawa, K. J. Org. Chem., 1991, 56, 4129. (b) Pyne, S.G.; Boche, G. *ibid*, 1989, 54, 2663. (c) Fang, J.M.; Chou, W-C.; Lee, G-H.; Peng, S-H. *ibid*, 1990, 55, 5515(d) For further examples and exceptions see Solladie, G. in 'Asymmetric Synthesis', Morrison, J.D. (Ed) Academic Press, 1983, volume 2, chapter 6, p. 184.
- 16. Sakuraba, H; Ushiki, S. Tetrahedron Lett., 1990, 37, 5349.