High Diastereofacial Selectivity in Asymmetric Mannich Reaction of Acyldithiane Oxide Enolates

Philip C. Bulman Page,* Steven M. Allin, Eric W. Collington,† and Robin A. E. Carr†

Robert Robinson Laboratories, Department of Chemistry, University of Liverpool, Oxford Street, Liverpool L69 3BX, England

Received June 21, 1993

The Mannich reaction is a very common synthetic transformation for the preparation of β-amino ketones. The Mannich reaction can be viewed as an imino analogue of the aldol reaction, and although methods for stereocontrol of the aldol reaction are very well documented, including diastereofacial selectivity in reactions of chiral enolates,[1] stereoselectivity in the Mannich reaction appears to have received relatively little attention.[2,3] Indeed, the first report of a diastereofacially selective asymmetric Mannich reaction involving a chiral enolate is that of Oppolzer in 1986,[4] although the related process involving imines is also known.[5]

β-Keto sulfoxides are well known as stereocontrol elements.[6] We have been able to obtain very high levels of induced diastereoselectivity in several different types of carbonyl group reactivity using acyl-1,3-dithiane 1-oxide (DITOX) derivatives as substrates; the acyldithiane oxide systems and the 2-substituted dithiane oxide starting materials are available using our own chemistry in both chiral senses in up to optical purity.[7] Reactions subject to a high degree of diastereocontrol include inter- and intramolecular enolate alkylation,[8] Grignard reagent addition,[9] carbonyl group reduction,[10] heterocycloaddition,[11] and conjugate addition reactions,[12] in many of which stereoselectivity is sufficiently high that the minor isomer is not detected by 400-MHz ^{1}H NMR spectroscopy. In addition, in most cases we are able to predict with certainty which product isomer will be formed in any given transformation using a simple model.

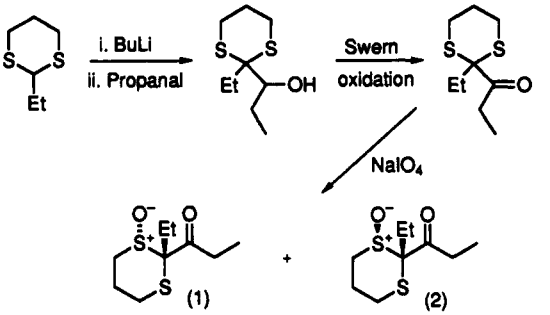
We can now report that enolates derived from racemic 2-acyl-2-alkyl-1,3-dithiane 1-oxides can undergo asymmetric Mannich reaction with very high levels of diastereoselectivity indeed.

The *syn*- and *anti*-2-ethyl-2-propanoyl-1,3-dithiane 1-oxide substrates were prepared by deprotonation of 2-ethyl-1,3-dithiane using butyllithium and subsequent reaction with propanal, followed by Swern oxidation and periodate sulfoxidation (Scheme I); the *syn* (1) and *anti* (2) products were easily separated by flash column chromatography.[13] Initially we have employed the system containing a 2-ethyl substituent as this has provided optimum selectivity in our enolate alkylation reactions.[7]

Mannich reactions were first performed with the commercially available Eschenmoser's salt using enolates derived from *syn*- and *anti*-2-ethyl-2-propanoyl-1,3-dithiane 1-oxide, under a range of reaction conditions and using a variety of metal counterions (Scheme II, Table I).

The first reaction, using the lithium enolate of the *anti* substrate 2, gave a 72% yield of β-amino ketone as an inseparable mixture of diastereoisomers in a disappointing

Scheme I. Preparation of 2-Ethyl-2-propanoyl-1,3-dithiane 1-Oxides



Scheme II. Mannich Reactions with Eschenmoser's Salt

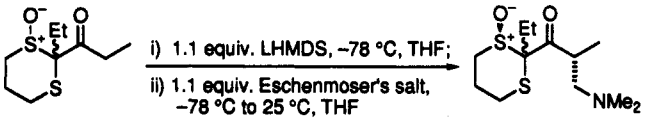


Table I. Mannich Reactions with Eschenmoser's Salt at -78 °C

substrate	metal	selectivity[a]	yield/%
anti-2	lithium	1.6:1[b]	72
anti-2	zinc	1.6:1	68
anti-2	boron	1.4:1	64
syn-1	lithium	6:1	68
syn-1	zinc	6:1	64
syn-1	boron	4:1	56

[a] All ratios determined by integration of signals observed in 250- or 400-MHz ^{1}H NMR spectra; the sense of selectivity observed was judged to be the same in each case and is as shown in Scheme VI.[19] [b] Increased to 3:1 by addition of benzotriazole prior to addition of enolate.

† Glaxo Group Research Ltd., Greenford Road, Greenford, Middlesex UB6 0HE, England.

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(13) Assignment of *syn* and *anti* substrate diastereoisomers was made on the basis of NMR evidence and by correlation with our previous work. The *anti* diastereoisomers characteristically display a discrete signal in their ^{1}H NMR spectra at *ca.* δ 1.7–1.9 ppm, corresponding to a dithiane ring proton. This signal appears at lower field for *syn* isomers and is often masked by other resonances. *Anti* diastereoisomers are normally observed to be more polar than *syn* upon thin-layer chromatography, enabling efficient separation by column chromatography.

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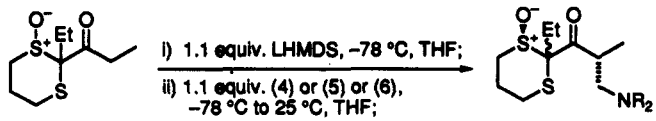
Scheme III. Mannich Reactions with Benzotriazole Derivatives



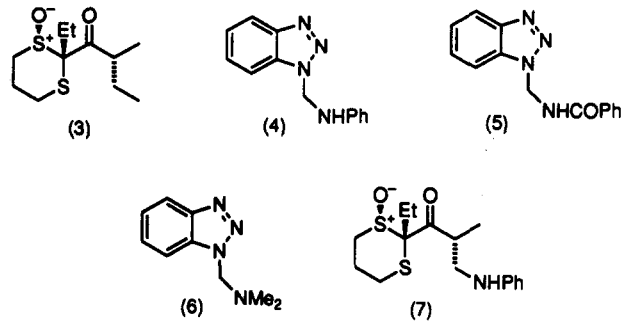
NR_2 = NHPh, NHCOPh, NMe_2

Table II. Mannich Reactions with Benzotriazole Derivatives

substrate	benzotriazole	selectivity[a]	yield/%
1 *anti*-2	4	≥48:1[b]	72
2 *syn*-1	4	≥54:1[b]	61
3 *anti*-2	5	36:1	81
4 *syn*-1	5	≥40:1[b]	72
5 *anti*-2	6		
6 *syn*-1	6	1:1	64

[a] All ratios determined by integration of signals observed in 250- or 400-MHz ^1H NMR spectra; the sense of selectivity observed was judged to be the same in each case and is as shown in Scheme VI.[19] [b] Signals corresponding to minor isomers were not detected in 400-MHz ^1H NMR spectra.

1.6:1 ratio. In contrast, alkylation of the same substrate using iodoethane under similar reaction conditions gave 66% of the alkylated product **3** with sufficiently high diastereoselectivity that the minor isomer could not be detected by 400-MHz ^1H NMR spectroscopy.[14] We therefore decided to examine the effect of variation of metal counterion on product diastereoselectivity, and initially chose zinc and boron as alternatives to lithium as both of these metals have been utilized with considerable success in influencing simple diastereoselectivity in aldol condensations[15] and, in at least one case, in the preparation of Mannich bases.[3] However, no significant increase in diastereoselectivity was observed; in addition, titanium and zirconium enolates failed to give any of the desired products.



Given that a larger and perhaps less reactive electrophile might distinguish between the faces of the enolate to a higher degree than Eschenmoser's salt, and so lead to an increase in diastereoselectivity, we next chose to employ the benzotriazole-based aminoalkylating agents pioneered by Katritzky (Scheme III).[16] Ratios of diastereoisomers obtained in a selection of reactions are given in Table II.

We were pleased to find that reactions of the lithium enolates derived from *syn*- and *anti*-2-ethyl-2-propanoyl-1,3-dithiane 1-oxides as before with benzotriazole **4**, prepared by the method of Katritzky,[16] each smoothly provided the aminoalkylated products in good yields and with extremely high diastereoselectivity at −78 °C (Table II, entries 1 and 2).

As an extension of this work we decided to explore the stereoselective introduction of a primary amine equivalent and chose the amidoalkylating agent **5**, also developed by Katritzky.[17] The β-amido ketones were isolated in good yields and again with excellent diastereoselectivity from reactions carried out at −78 °C (Table II, entries 3 and 4).

From the high diastereoselectivities observed when employing the benzotriazole reagents **4** and **5** we reasoned that addition of 1 molar equiv of benzotriazole to a stirred solution of Eschenmoser's salt at room temperature prior to reaction with a lithium enolate at −78 °C might provide an increase in diastereoselectivities by forming a similar masked iminium ion *in situ*. Under these conditions an increase in diastereoselectivity was indeed observed for the *anti* substrate (up to 3:1), although no improvement was seen with the *syn* isomer.

Subsequently, the benzotriazole-based equivalent to Eschenmoser's salt, [(dimethylamino)methyl]benzotriazole (**6**), which does not appear to have been used previously for Mannich reactions, was prepared in our laboratory using literature procedures.[18] Curiously, we found this substrate not only to be considerably less reactive than **4** or **5**, requiring stirring at room temperature to mediate the reaction, but also less reactive than the Eschenmoser's salt/benzotriazole reaction system, suggesting that **6** is not formed *in situ* by mixing these two reagents under the conditions used. Interestingly, the product of reaction of **6** with the enolate derived from *syn*-2-ethyl-2-propanoyl-1,3-dithiane 1-oxide was isolated with a diastereoisomeric ratio of only 1:1. The corresponding *anti* dithiane substrate produced a complex mixture of inseparable reaction products (Table II, entries 5 and 6). These observations perhaps suggest that the reaction of **6** proceeds through a different reactive intermediate or rate determining step from that of **4** and **5**. A possible explanation for this pattern of reactivity is provided by considering the probable reactive intermediates involved: fragmentation of **6** with effective loss of benzotriazole anion must necessarily give rise to a reactive, and therefore unselective, iminium salt, a likely candidate for any reactive intermediate in this case; while concomitant proton loss from **4** or **5** could give rise to less reactive neutral imine by similar, but more facile, fragmentation.

It is important to note that in both substrate types the sense of selectivity observed was readily judged to be the same in each case from ^1H NMR evidence.[19] Possible transition states for Mannich reactions using a chelation-control model and steric approach control are illustrated in Schemes IV and V. This simple model of acyl dithiane oxide reactivity, while no doubt an oversimplification of the reaction process, has, however, provided a powerful predictive rule of thumb for many of the reaction types studied by us.

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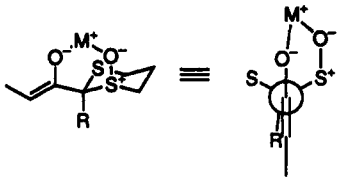
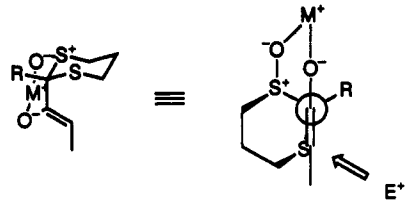
(19) Major diastereoisomers of products in both the *syn* and *anti* series display doublet and triplet signals in their ^1H NMR spectra, corresponding to methyl and ethyl groups, respectively, at higher field than do the minor diastereoisomers, indicating same sense of preferred stereochemistry at the new asymmetric center within each series.

Scheme IV. Transition States for *Syn* Substrates

syn substrate; axial sulphoxide

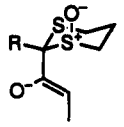


syn substrate; equatorial sulphoxide

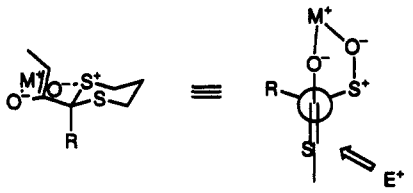


Scheme V. Transition States for *Anti* Substrates

anti substrate; axial sulphoxide



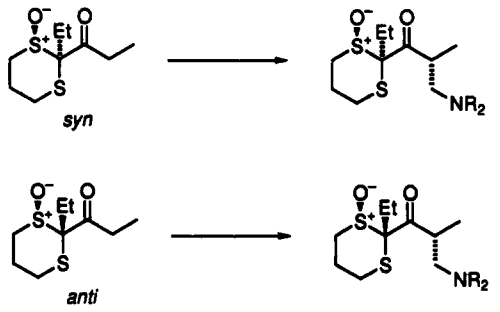
anti substrate; equatorial sulphoxide



For *syn* substrates (Scheme IV), chelated conformations containing axial sulfoxides also contain axial 2-substituents and, while unselective, would be expected to be important only for small 2-alkyl substituents. Further, 1,3-dithiane 1-oxide itself is known to exhibit a preference for the equatorial sulfoxide conformation. In the more general equatorial sulfoxide conformation shown, one face of the enolate is effectively shielded by the bulk of the dithiane ring, the other face being exposed unless a very large 2-alkyl substituent is present. Stereoselectivity is therefore expected to become poorer as the relative size of the (equatorial) 2-alkyl substituent is increased, an effect indeed observed in our studies of enolate alkylation in these systems.

For *anti* substrates (Scheme V), the sulfoxide can only adopt a chelated conformation if the 2-substituent is axial, reasonable except for very large groups. Conversely to

Scheme VI. Induced Stereochemistry in Mannich Reactions



NR_2 = NHPh, NHCOPh, NMe_2

syn substrates however, although one face of the enolate is again partially shielded by the 2-alkyl substituent, the bulk of the dithiane ring is distant from the reacting center, and stereoselectivity is expected to be governed solely by the size of the 2-alkyl substituent. Stereoselectivity is therefore expected to improve as the relative size of the 2-alkyl substituent is increased, again an effect observed in our enolate alkylation studies. In the axial sulfoxide conformation, which also requires the acyl group to be axial, no chelation is possible.

The sense of induced stereoselectivity expected from these models, illustrated in Scheme VI, was borne out by a single crystal X-ray structure determination of the product 7 derived from reaction of *anti*-2-ethyl-2-propanoyl-1,3-dithiane 1-oxide 2 with benzotriazole 4 (Table II, entry 1).[20] It is interesting to note that the same sense of induced stereoselectivity is expected at the new asymmetric center in both the *syn* and *anti* series for a given sulfoxide configuration.

In conclusion, we report excellent diastereofacial selectivity in the synthesis of both β-amino ketones and β-amido ketones using the 1,3-dithiane 1-oxide moiety as stereocontrolling element in asymmetric Mannich reactions. The stereoselective introduction of nitrogen into acyl systems is a significant addition to the arsenal of synthetic transformations controlled by the DITOX asymmetric building block.

Acknowledgment. These investigations have enjoyed the support of Glaxo Group Research Ltd. (studentship to S.M.A.). We are also indebted to the National Service for X-Ray Crystallography at Queen Mary and Westfield College and to the SERC Service for Very High Field NMR Spectroscopy at the University of Warwick for their help and patience.

Supplementary Material Available: Crystal data details for 7 and ^1H NMR spectra of products (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(20) Full details and crystallographic data appear in the supplementary material.