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Diastereoselective Electrophilic Amination of Ketone Enolates in 2-Substituted 2-Acyl-1,3-dithiane 1-Oxides

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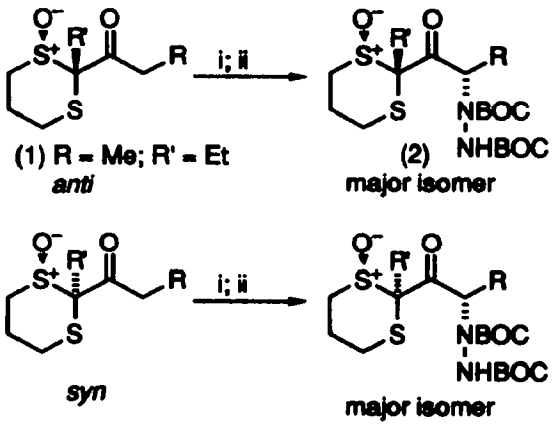
Abstract: Enolate anions derived from 2-substituted 2-acyl-1,3-dithiane 1-oxides react readily with the nitrogen electrophile di-*tert*-butyl azodicarboxylate (DBAD) to give α-aminoketones with good diastereoselectivity and in reasonable yields; in some cases diastereoselectivity appears sufficiently high that the minor isomer cannot be detected by 400 MHz ^{1}H NMR spectroscopy.

We have used simple 1,3-dithiane 1-oxide (DITOX) derivatives, substituted at the C-2 position, as asymmetric building blocks to obtain very high levels of induced diastereoselectivity in several different types of carbonyl group reaction;[1-7] in many cases stereoselectivity is sufficiently high that the minor isomer is not detected by 400 MHz ^{1}H NMR spectroscopy. A simple empirical chelation-control model of the reactivity of these systems allows us to forecast with certainty which product isomer will be the major component in any given transformation. The acyl dithiane oxide systems and the 2-substituted DITOX starting materials may be prepared enantioselectively in up to optical purity; both enantiomers are available in all cases;[8] the DITOX units are inexpensive and of relatively low molecular weight. We have recently shown that the Mannich reaction is successful for the stereoselective introduction of β-aminoketone moieties.[2] The diastereofacially selective electrophilic amination of enolates is attractive as a complementary approach to the asymmetric preparation of α-aminoketones, and is commonly used in the preparation of α-amino acids; the electrophilic amination of diethylmalonate with azodicarboxylates was reported as far back as 1924.[9-16] We now wish to report our progress in this area.

Di-*tert*-butyl azodicarboxylate (DBAD) has a number of advantages over other electrophilic aminating reagents:[12-16] Vederas has established that, of a series of azodicarboxylate esters, the *tert*-butyl derivative gives some of the highest levels of diastereofacial selectivity on reaction with various chiral enolates;[12] methods for the removal of the *tert*-butyloxycarbonyl protecting groups under mild, non-racemizing conditions are well established and are complementary to known methods for N-N bond cleavage;[12-16] DBAD is a stable, crystalline solid; it is available commercially.

In our initial reaction the lithium enolate of *anti* 2-ethyl-2-propanoyl-1,3-dithiane 1-oxide (1) was generated using LHMDS (1.1 equiv.) in dry THF at –78 °C and transferred *via* cannula to a pre-cooled solution of DBAD (1.1 equiv.) in THF solution at –78 °C. The solution was allowed to reach room temperature over 12 hours before quenching with aqueous ammonium chloride and normal work-up. The desired aminated product (2) was isolated as a 2 : 1 mixture of inseparable diastereoisomers in 52% yield.[17] Interestingly, the ^{1}H NMR spectra observed at 20 °C were largely uninterpretable, with significant signal broadening, presumably due to hindered rotation about the BOC groups. In direct analogy to a related study by Evans,[15] the corresponding spectrum obtained at elevated temperatures (47-52 °C) was considerably improved.



Reagents: i) LHMDS (1.1 eq.), –78 °C, THF;
ii) DBAD (1.1 eq.), THF, –78 °C, 15 min; HOAc, –78 °C
Scheme

On repeating the reaction under identical reaction conditions but using a –78 °C acetic acid quench after allowing 10-15 minutes for reaction with DBAD at –78 °C, we observed a similar yield but a much improved diastereoselectivity of ≥99:1, only one product isomer being detectable by 400 MHz ^{1}H NMR spectroscopy (Scheme). As expected, the major isomer proved to have the same stereochemistry for both –78 °C quench and for room temperature quench. The low temperature acetic acid quench may prevent loss of stereochemical integrity at the new asymmetric centre which may

otherwise occur at higher temperature.

We believe the sense of induced stereochemistry to be as shown on the basis of a simple chelation-control model of acyl dithiane oxide reactivity successful for other reactions backed by X-ray crystallographic structure determinations,[8] coupled with analogy of ^{1}H NMR spectroscopic features with those of similar compounds of known absolute configuration.

In common with our earlier work, variation of 2-alkyl substituent was expected to exert a dramatic effect upon diastereoselectivity. A selection of results obtained by variation of the 2-substituent is given in Table I and closely parallels those observed during our investigations of enolate alkylation and other reactions of acyl dithiane oxides,[1,3] optimum diastereoselection being obtained on incorporation of a 2-ethyl substituent. The pattern of diastereoselectivity can be rationalized on the basis of our usual chelation-control models; additional interaction of the metal counter-ion with the reagent is also a possibility. It is also conceivable that some loss of stereochemical integrity by equilibration may still be occurring under the reaction conditions in some cases. Readers are referred to our investigation of Mannich reactions for a full discussion.[2]

Table I. Diastereoselectivity of electrophilic amination of 2-acyl-2-alkyl-1,3-dithiane 1-oxide enolates using DBAD

Substrate	R	R'	Yield/%	Ratio of isomers[a]
anti	H	Et	72	—
syn	H	Et	89	—
anti	Me	Me	69	2 : 1
anti	Me	Et	48	≥99 : 1[b]
anti	Me	Ph	37	2.7 : 1
syn	Me	Me	76	3 : 1
syn	Me	Et	42	12 : 1

a. determined by 400 MHz ^{1}H NMR spectroscopy[17]
b. minor isomer not detected

Electrophilic amination of the lithium enolates derived from *syn* and *anti* 2-acetyl-2-ethyl-1,3-dithiane 1-oxides with DBAD under our standard conditions also proceeded smoothly and in good yields. The products are of interest as potential synthons for chiral α-aminoacid synthesis.

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17. The diastereoselectivity of the reactions were determined by 400 MHz ^{1}H NMR spectroscopy. For example, for the major isomer of (2) the 2-ethyl group triplet appears at δ 0.98 ppm and for the minor isomer at δ 1.04 ppm.

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