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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4733–4736

Studies concerning the double reduction of Diels–Alder derived bicylic sulfonamides

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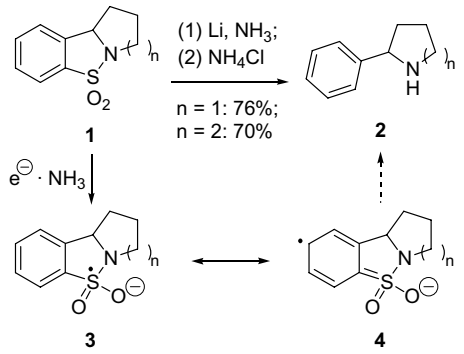
Received 8 March 2007; revised 25 April 2007; accepted 2 May 2007
Available online 10 May 2007

Abstract—A series of bicyclic sulfonamides, **14**–**17**, was prepared by thermal, intramolecular Diels–Alder cycloaddition. The ratio of *exo*:*endo*-diastereoisomers formed following this process was found to be dependent on the substitution pattern of the dienophile. Styryl substituted sulfonamides preferentially formed the corresponding *exo*-adducts, whereas vinyl substituted sulfonamides preferentially gave the *endo*-adducts. These adducts were treated under dissolved metal reduction conditions and it was found that compounds possessing an *N*-benzyl substituent underwent preferential debenzylation and resisted further reduction. The complementary *N*-isobutyl functionalised materials only underwent the double reduction when a phenyl substituent was present.

We have recently reported that a series of bicyclic aromatic sulfonamides undergo a novel reductive process in which both the N–S and the C–S bonds undergo cleavage.[1] This reaction, termed the sulfonamide double reduction, represents a useful method for the synthesis of aryl functionalised pyrrolidines and piperidines in which the sulfonyl group acts both as a protecting group for the amino motif and a 'traceless' tether. For example, as shown in Scheme 1, a mixture of lithium in liquid ammonia converts sulfonamide **1** (where $n = 1$ and 2) to bicyclic amine **2** in good yields.[1a] The mechanism for this process is not entirely clear; however, we have demonstrated that a minimum of 4 equiv of reducing species (lithium) was required for an efficient reaction. The likely initial step involves the formation of the radical anion **3**, stemming from the addition of first electron (Scheme 1).



Scheme 1. Proposed mechanism for the double reduction of bicyclic aromatic sulfonamides.

This study describes our preliminary attempts to determine whether the resonance stabilisation of the putative radical anionic intermediate, that is, **3**↔**4**, is key to the success of this sequence. We envisaged that the preparation of cyclic sulfonamides in which the carbon atom flanking the sulfonyl moiety was sp^3 hybridised, as opposed to sp,[2] would enable us to probe this type of effect. In relation to this question, methane sulfonamide groups, in which no such stabilisation of the analogous radical anion is possible, have been reported to successfully undergo N–S bond cleavage using Na/naphthalenide[2] and Metz and co-workers have employed a similar tactic for the preparation of pamamycin, albeit with a cyclic sulfonate (sultone) rather than a cyclic sulfonamide (sultam).[3] In contrast, during their approach to (+)-aloperine, Overman and co-workers reported the failure of a tetracyclic sultam to undergo this type of double reduction under a variety of reductive conditions.[4] In addition to providing valuable mechanistic understanding, the success of the process in the proposed manifold would serve to increase greatly the scope and utility of this reaction.

Keywords: Cyclic sulfonamide; Sultam; Dissolved metal reduction; Double reduction; Diels–Alder cycloaddition.
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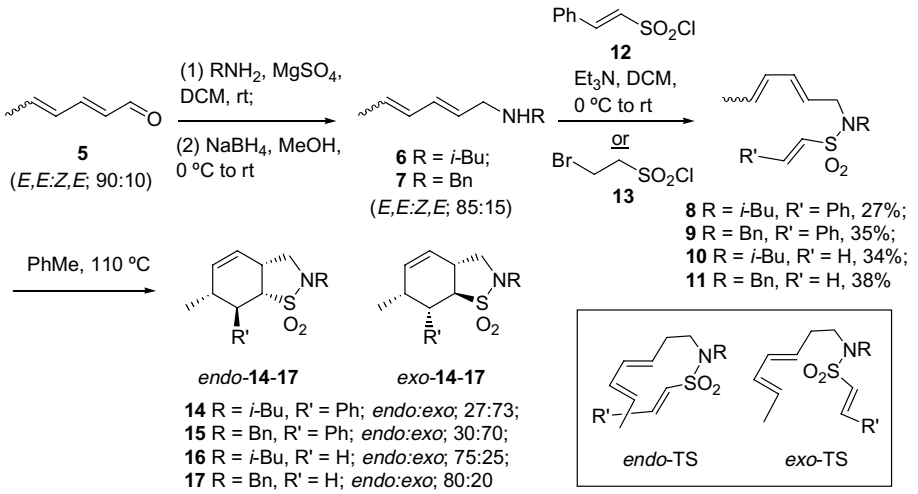
doi:10.1016/j.tetlet.2007.05.015



Scheme 2. Synthesis of bicyclic sulfonamides **14**–**17**, via intramolecular Diels–Alder cycloaddition.

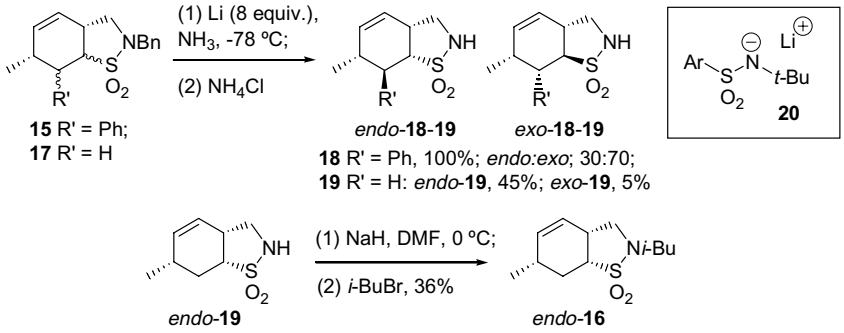
Various methods have been described in the literature for the rapid construction of cyclic sulfonamides (sultams).[5] As Scheme 2 illustrates, we chose to focus our efforts on the intramolecular Diels–Alder reaction between an α,β-unsaturated sulfonamide containing a dienyl motif in order to access compounds in which the group flanking the sulfonyl portion is sp^3 hybridised.[6] The Diels–Alder precursors were assembled following the initial two-step reductive amination of hexadienal **5**. Thus, isobutylamine and benzylamine were used to prepare the secondary amines **6** and **7**. In both cases, a small amount of isomerisation of the distal double bond was observed, as indicated by ^{1}H NMR spectroscopy. Amines **6** and **7** were then converted into sulfonamides **8** and **9** using commercially available styrenesulfonyl chloride **12**. In order to prepare the corresponding compounds **10** and **11** (where R′ = H) we found that conversion of sodium 2-bromoethylsulfonate to 2-bromoethylsulfonyl chloride **13**, with PCl_5, followed by one-pot sulfonamide formation and concomitant bromide elimination was more effective than the prior preparation of vinylsulfonyl chloride.[7] No additional alkenyl-isomerisation was observed during sulfonamide formation. The series of Diels–Alder precursors **8**–**11** underwent efficient cycloaddition in toluene at 110 °C[6] generating the desired adducts **14**–**17** in good yields.

However, inspection of the crude ^{1}H NMR spectra for these adducts indicated that they were formed as mixtures of *exo*- and *endo*-diastereoisomers, that proved to be inseparable by flash column chromatography. It has been appreciated for some time that the *E*,*Z*-dienyl motif participates more sluggishly in [4+2]-cycloaddition reactions than their *E*,*E*-counterparts and it was clear that this was also true in these examples.[8] Evidence supporting this conclusion included the fact that on purification the recovered starting materials **8**–**11** exhibited increased levels of the *Z*,*E*-isomer and following resubmission of these mixtures to the thermal [4+2] process the formation of adducts **14**–**17** with the same ratio of *endo*- and *exo*-diastereoisomers were observed. Assignment of the relative stereochemistries of adducts **14**–**17**, which were viscous oils, was non-trivial but was ultimately achieved using a combination of nuclear Overhauser measurements and X-ray crystallography of a derivative (see above).

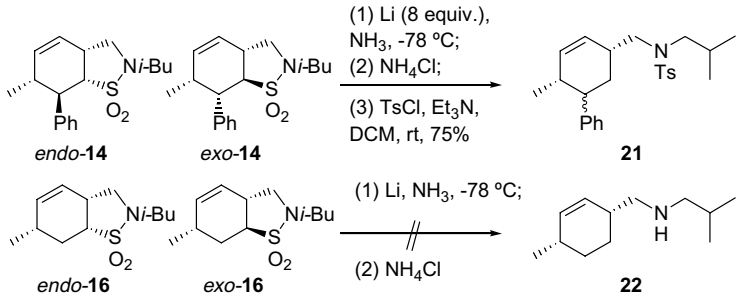
Notably, changing the R′ substituent resulted in drastically different diastereofacial selectivities for this process. Thus, compounds **8** and **9**, where R′ = Ph, predominantly afford the, formally, *exo*-diastereoisomers **14** and **15**. An initial clue for this preference was gleaned by the shielding of the methyl protons proximal to the aromatic ring, for example, *exo*-**15**: 0.64 ppm; *endo*-**15**: 0.77 ppm (*exo*-**17**: 1.02 ppm; *endo*-**17**: 0.98 ppm), and was further corroborated by NOE experiments. In contrast, where R′ = H the *endo*-diastereomers **16** and **17** were preferentially formed. In both series, it was found that the N-substituent did not significantly alter the stereochemical outcome.

With the bicyclic sulfonamides **14** to **17** in hand, their double reduction was investigated (Scheme 3). Initially the reaction of the *N*-benzyl sulfonamides **15** and **17** was performed under the standard dissolved metal conditions used in the previous study[1] (Scheme 1). In both instances only cleavage of the *N*-benzyl substituent was observed. In the case of **14** the resultant compounds *exo*- and *endo*-**18** again proved to be inseparable by column chromatography, however, in the case of **17**, the diastereoisomeric forms of product **19** were separable. The major compound proved crystalline and X-ray crystallography (see Supplementary data)[9] demonstrated its relative stereochemistry, thereby facilitating assignment of the Diels–Alder reaction mixtures (see above). Alkylation of *endo*-**19**, afforded *endo*-**16** in 36% yield as a single diastereomer.

These results are of interest since, in this example, benzylic bond scission is clearly a more rapid process than sulfonamide double reduction. This differs from the reaction in Scheme 1 in which cleavage of the benzylic C–N bond occurs only in the presence of excess reducing agent after full cleavage of the sulfonamide group.[1a] In



Scheme 3. Synthesis of compound **18** and the synthesis and alkylation of *endo*-**19**.



Scheme 4. Investigation into the double reduction of compounds **14** and **16**.

this new case, the resistance of the product to further reaction under the dissolved metal conditions may be due to the intermediate anionic species that serves to inhibit further reaction.

In relation to this last point, it has been reported that the Birch-type reduction–alkylation of aromatic sulfonamides was only successful if the NH group was first converted into the corresponding lithium salt **20** with *n*-butyllithium. Following this operation the aryl sulfonamides were found to undergo reduction of the aromatic ring without competitive reductive cleavage of the sulfonamide bond.[10]

As a consequence of this rapid debenzylation process the analogous reduction was investigated with the *N*-isobutyl substituted compounds **14** and **16**, since it was reasoned that this group would not interfere in the same manner as the *N*-benzyl compounds (Scheme 4). Thus, when compound **14** was subjected to identically dissolved metal conditions, pleasingly, the desired double reductive process was observed and the products **21** were isolated in good overall yield as their toluene sulfonamide derivatives (for ease of purification and characterisation).

Notably using this substrate, the reaction proceeded in comparable yield to those observed for the previously studied aromatic bicyclic sulfonamides.[1] Frustratingly, however, these diastereomers **21** proved again to be inseparable using standard flash column chromatography. We therefore turned our attention to the analogous compound **16** (where $R' = H$) since the chiral centre, leading to the diastereoisomers, would be destroyed following the proposed reduction process. However, submission of **16** to the same conditions resulted only in recovery of starting materials and none of the hoped for secondary amine **22**.

The precise explanation for the different behaviour of **14** and **16** under the identical reductive conditions is not clear; however, it is intriguing to invoke assistance, or delivery of an electron from the phenyl ring, in the β-position, to the sulfonyl functional group. Further studies in this area are underway aiming to probe and uncover the reasons for these reactivity patterns.

Acknowledgement

We thank UCD for the provision of a postgraduate studentship to S.K.

Supplementary data

Experimental details and the X-ray crystal structure of *endo*-**19** are provided in Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.015.

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