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Some mechanistic observations on the borohydride mediated reductive cyclisation of tosylhydrazones

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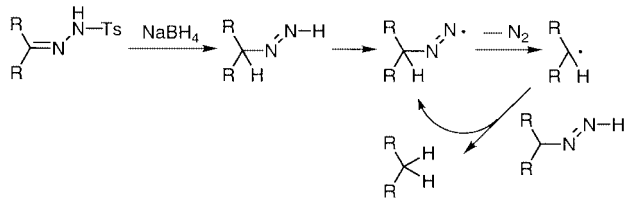
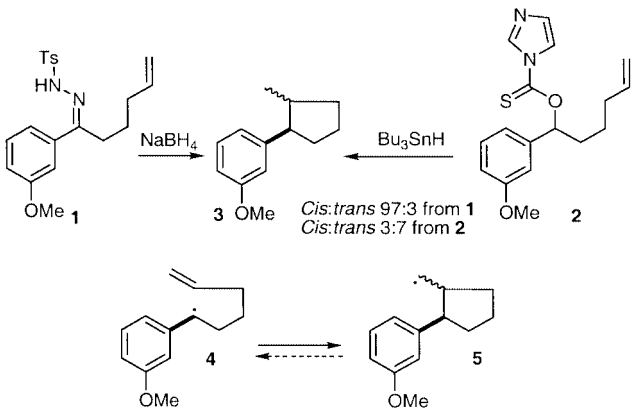
The previously described, highly stereoselective ring-closure of δ-unsaturated tosylhydrazones upon reduction with borohydride may not be a radical process but rather an ene-type concerted transformation of the intermediate mono-substituted diimide.

Reduction with borohydride of tosylhydrazones derived from ketones may lead to the formation of radical species through loss of molecular nitrogen as shown in Scheme 1.[1] Various other related and important transformations such as the reduction of diazonium salts,[2] the Wolff–Kishner reaction,[3] the Wharton rearrangement,[4] sometimes proceed through a similar radical pathway.



Scheme 1

In a pioneering study in this area, Taber and colleagues[5] described a remarkably diastereoselective cyclisation reaction starting with hydrazone **1** (Scheme 2). This transformation was presumed to involve ring closure of a benzyl type radical **4**, and the unusually high diastereoselectivity (97:3) was ascribed to the non-reversibility of the cyclisation step under these specific conditions. The corresponding tributylstannane mediated ring-closure starting from the imidazole thiocarbamate derivative **2** is much less stereoselective, leading to a 3:7 ratio of the same diastereoisomers **3**, and the possible reversibility of the ring-forming step was invoked as the cause of the erosion in selectivity. While reversible 5-*exo* cyclisations involving benzylic and other stabilised carbon centred radicals are known,[6] it seemed to us that the ring-opening, reverse step, must be too slow in this case to compete with hydrogen atom abstraction from the stannane by the primary radical **5**. In the present study, we adduce evidence indicating that the radical cyclisation is indeed irreversible under the stannane reduction conditions and that the cyclopentane formation in the case of the hydrazone precursor may in fact not be a radical process at all.

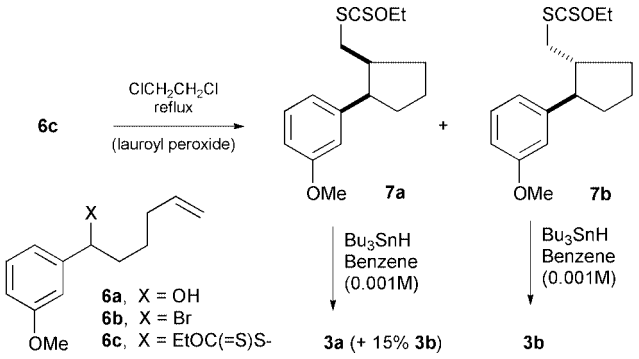


Scheme 2

Our approach hinges on the separate generation of the cyclised radical **5** and showing that this species does *not* undergo ring opening under dilute tributylstannane reduction conditions. This was accomplished by exploiting the properties of the xanthate transfer reaction.[7] In this case, the cyclised product is itself a xanthate and therefore allows the regeneration of the cyclised radical. The requisite starting xanthate **6c** was readily obtained in 66% overall yield by reacting crude bromide **6b**, itself derived from alcohol **6a**, with commercially available potassium *O*-ethyl xanthate. Heating this xanthate with a small amount of lauroyl peroxide in 1,2-dichloroethane (0.1 M) resulted in the smooth formation of cyclopentylmethyl xanthates **7a** and **7b** in a 3:7 ratio and in 78% combined yield (Scheme 3). It is interesting to note that the ratio of the *cis* and *trans* isomers did not change when the reaction was conducted at 1 M concentration. This is a first indication that the cyclisation is not so readily reversible under these conditions.

The two isomers could be separated using preparative thin-layer chromatography, albeit with some difficulty. Reductive dexanthylation of the pure *trans* isomer **7b** using tributylstannane in benzene at 0.001 M concentration gave the corresponding pure *trans* methyl cyclopentanes **3b** in 70% yield. Perhaps more importantly, exposure of an almost pure sample (95:5 *cis*:*trans*) of the thermodynamically less stable *cis* isomer **7a** to the same conditions gave methylcyclopentanes **3a** and **3b** in 85:15 ratio, *i.e. with only a very slight modification of the initial relative stereochemistry*. Clearly, under such highly dilute conditions, a roughly 3:7 mixture of the two diastereoisomers should have been obtained in both cases if the equilibrium between radicals **4** and **5** was fast in comparison to hydrogen atom abstraction from the stannane.

The above findings constitute strong evidence against the operation of a radical mechanism in the transformation of the tosylhydrazone depicted in Scheme 2. The high diastereoselectivity cannot be explained by a kinetically controlled,



Scheme 3

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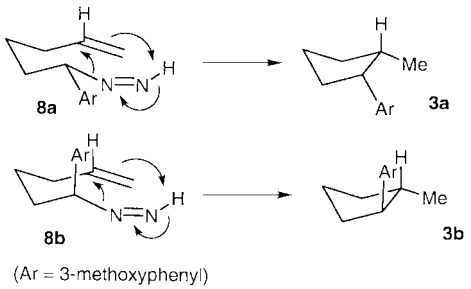

Scheme 4

irreversible radical ring closure. The radical cyclisation in such systems is inherently poorly diastereoselective: a similar 1 : 2.5 *cis* : *trans* ratio was recently reported by Studer,[8] who generated the analogous 1-phenylhex-5-enyl radical by heating the TEMPO derived precursor at 130 °C. Cyclisations involving non-stabilised secondary radicals also take place with a modest preference for the *trans* isomer.[9] The very high *cis*-selectivity observed by Taber and his colleagues in the present case is probably the result of an intramolecular, ene-type pericyclic process, as shown in Scheme 4. Placing the aryl group in the less hindered pseudo-equatorial position leads to the *cis* isomer. Such a concerted mechanism parallels that proposed for reductions with diimide itself,[10] the rigid, highly organised transition state being more consonant with the observed high *cis* selectivity. Thus, depending on the structure, the experimental conditions, and the eventual presence of initiators, monoalkyldimides (monoalkyldiazenes) may react by an ionic, a radical, or a concerted pericyclic-type mechanism. Whatever the exact mechanism operating in the present case, the observations of Taber and co-workers[3,5] will certainly have important consequences for organic synthesis.

Notes and references

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