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Reductive Fragmentation of Tetrazoles: Mechanistic Insights and Applications toward the Stereocontrolled Synthesis of 2,6-Polysubstituted Morpholines

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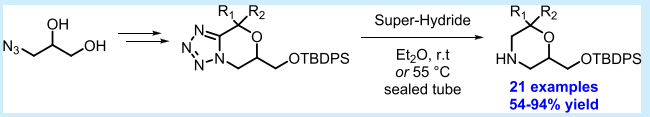
Supporting Information

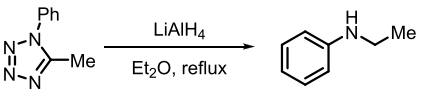
ABSTRACT: A new methodology to synthesize 2,6-di-, and 2,2′,6-trisubstituted morpholines via the reduction of oxabicyclic tetrazoles under mild conditions is described. The reaction proved successful for a wide range of tetrazoles, including sterically encumbered ones harboring *gem*-substituents on tertiary carbon centers. The mechanism for the decades-old reduction of tetrazoles to secondary amines is elucidated.



In spite of its availability for many decades, it is only recently that the incorporation of a tetrazole core unit in drug substances has gained enormous popularity with a number of FDA-approved entities for a variety of medical uses.[1] Its electronic structure, stability under a variety of chemical and physiological conditions, and physical properties appear to confer highly beneficial, pharmacological properties to the parent molecules, resulting in enhanced biological activities across a wide spectrum of biomedical applications.[2] Consequently, there has been a sustained interest in the synthesis of tetrazoles in general.[3] The first synthesis of the tetrazole nucleus was reported by Bladin in 1885 and involved the thermal cyclization of an organic nitrile with sodium azide.[4] The first intermolecular cycloaddition reaction between an organic azide and a nitrile is credited to Hantzch and Vagt in 1901.[5] Over the next century and a half, and following a German patent by von Kereszty and Wolf,[6] the synthesis of 1,5-disubstituted tetrazoles by inter- and intramolecular cycloaddition reactions has been extensively investigated.[7] We recently showed that proximity effects in such intramolecular cycloaddition reactions in the presence of $BF_3{\cdot}OEt_2$ were highly favorable to give bicyclic and polycyclic tetrazoles under remarkably mild conditions at room temperature or below. Extension to acetals and TMSCN led to oxabicyclic tetrazoles.[8] By and large, tetrazoles have been used as whole entities rather than to exploit their synthetic potential in other contexts. For example, *N*-substituted tetrazoles are considered as "neutral" heterocycles that are inert to reductants.[3c,9] However, over six decades ago, LaForge, Cosgrove, and D'Adamo reported the reductive transformation of 1-phenyl-5-methyltetrazole to *N*-ethylaniline in the presence of lithium aluminum hydride in refluxing ether[10] (Scheme 1).

In this remarkable reductive ring-cleavage reaction, the authors noted that the formation of the amine product also resulted in the loss of three nitrogen atoms without specifying the nature of the extruded nitrogenous product. The reaction was extended to pentamethylene tetrazole and other carbobicyclic tetrazoles containing reducible groups such as esters and ketones, which were transformed to the corresponding secondary amines. They studied the stoichiometry of the reaction showing that at least 0.75 equiv of the hydride reagent was required to complete the reaction. Since the resulting secondary amine products could also be accessed by alternative and more conventional synthetic methods (albeit in lower yields in some cases), they made the following statement: "*While this reaction has no general preparative value, it may be a very useful tool in special cases.*" Surprisingly, since the publication of the original paper in 1956, we are aware of only four examples of such reductions.[11] Furthermore, no mechanistic rationales have been proposed for this intriguing extrusion of three nitrogen atoms from the tetrazole nucleus under hydride reductive conditions.

Scheme 1. First Report of the Reduction of Tetrazoles to Amines by Laforge and Co-workers



Herein, we report our studies toward a proposed mechanism of this decades-old reaction, and we show applications toward the synthesis of stereochemically defined 2,6-di- and 2,2′,6-trisubstituted morpholines. Suspecting that the mechanism might involve a fragmentation with the release of azide ion, we conducted a time course study of the reduction of 1-phenyl-5-methyltetrazole (**1**) with lithium aluminum hydride by IR and indeed confirmed our postulate.[12] The characteristic peak for azide ion at 2100 cm^{-1} steadily increased in intensity as the reaction progressed, reaching a maximum after 4−6 h. The white precipitate formed in the reaction mixture and presumed to be LiN_3 (possibly as an $Al(OH)_3$ complex) was isolated after removal of the organic material by washing with ether. Adding benzyl bromide to the solid and heating in a 1:1

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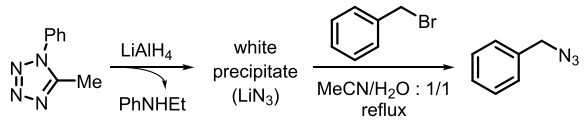
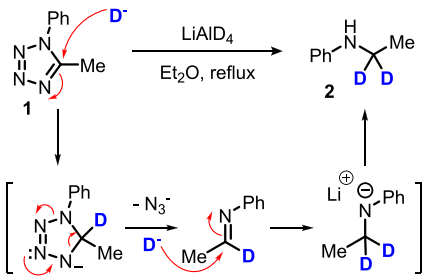
mixture of acetonitrile and water gave benzyl azide (Scheme 2).

Scheme 2. Extrusion of Azide Anion over the Course of the Reductive Cleavage of Tetrazoles



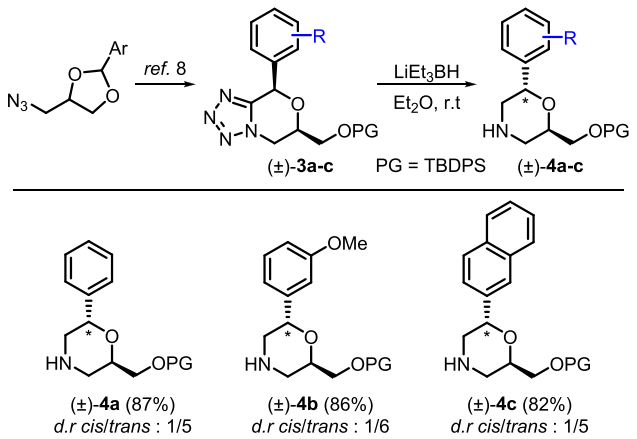
To the best of our knowledge, this represents the first example of azide ion extrusion from a tetrazole and attests to the astute observation made by LaForge and co-workers.[10] A plausible mechanism involving hydride attack at C5 followed by concomitant or stepwise release of azide ion is shown in Scheme 3. Consistent with this proposal, reduction of 1-phenyl-5-methyltetrazole **1** with $LiAlD_4$ afforded the dideuterated *N*-ethylaniline **2**.

Scheme 3. Proposed Mechanism for the Reductive Cleavage



In an effort to extend the reaction to a more complex substrate, we used a model oxabicyclic *cis*-tetrazole **3a**, which in the event of a successful extrusion of azide anion would lead to the corresponding 2,6-disubstituted *cis*-morpholine (Scheme 4). Indeed, treatment with $LiAlH_4$, or more conveniently Super-Hydride ($LiEt_3BH$), in ether at room temperature led to **4a** as the major isomer in excellent yield. Curiously, the product was the *trans*-morpholine. The same results were observed with the *m*-methoxy (**4b**) and naphthyl (**4c**) analogues. When the course of the reaction was monitored by ^1H NMR with increasing ratios of $LiEt_3BH$, we realized that

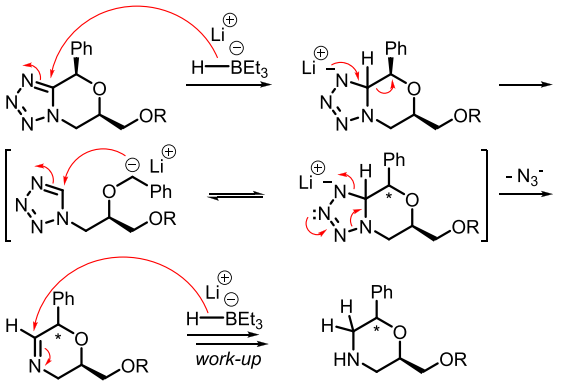
Scheme 4. Reductive Cleavage of Oxabicyclic Tetrazoles to 2,6-Disubstituted Morpholines



the *cis*-tetrazole was being converted into the *trans*-tetrazole **3a** as the reaction was progressing. Suspecting that the hydride was acting as a base and as a nucleophile, we performed the reduction of **3a** containing a deuterium atom at the benzylic position with $LiEt_3BH$, only to recover the deuterated *trans*-morpholine **4a**-d_1 without loss of deuterium. Reduction of **3a** with deuterated Super-Hydride or $LiAlD_4$ led to the 3,3′-dideuterio morpholine **4a**-d_2. Moreover, reduction of **3a** with $LiEt_3BH$ or $LiAlH_4$ followed by addition of D_2O or MeOD revealed no incorporation of deuterium in the resulting *trans*-morpholine. Quenching the reaction mixture with benzyl bromide gave the *trans*-*N*-benzylmorpholine derivative of **4a** in 70% yield.

In the light of these results, it was clear that the reductive fragmentation reaction of the oxabicyclic tetrazole **3a** was under kinetic control favoring the *trans*-isomer and leading to the *trans*-morpholine **4a**. An X-ray crystal structure of the *N*-tosyl amide derivative confirmed the stereochemistry.[12] The conservation of the benzylic hydrogen atom during the reductive fragmentation of the oxabicyclic *cis*-tetrazole **3a** while undergoing an inversion of configuration as evidenced in the product *trans*-morpholine **4a** suggests that a direct attack of hydride on the tetrazole as may have been the case in the LaForge substrate is not likely (Scheme 3). An alternative mechanism, which is consistent with the observed results, is proposed and illustrated in Scheme 5.

Scheme 5. Proposed Mechanism of the Reduction of Disubstituted Oxabicyclic Tetrazoles



Thus, attack of the first hydride leads to a charged tetrazole anion which undergoes β-elimination to the benzylic carbanion in an S_NAr fashion. This transient species cyclizes back from the face opposite to the bulky TBDPS ether group, affording the now epimerized oxabicyclic *trans*-tetrazoline, which undergoes fragmentation to the corresponding *trans*-morpholine with loss of azide. Alternative mechanisms to describe this dynamic process may also involve imidoyl azide intermediates.

Capitalizing on these successful reductive fragmentations as a means to access *trans*-2,6-disubstituted morpholines, we directed our efforts toward the reduction of oxabicyclic tetrazoles containing geminal 2,2′-substituents, which would lead to the corresponding arduously accessible 2,2′,6-branched morpholines as racemates or in enantiomerically enriched forms.

Thus, treatment of oxabicyclic tetrazoles **5a**–**e** derived from symmetrical ketones[8a] with Super-Hydride led to the corresponding novel 2,2′-spirocyclic morpholines **6a**–**e** in good to excellent yields (Scheme 6).

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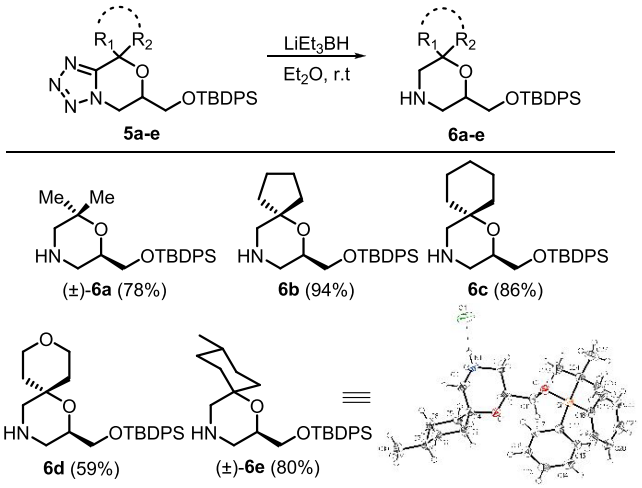
Scheme 6. Reduction of Trisubstituted Oxabicyclic Tetrazoles Derived from Ketones to Spirocyclic Morpholines



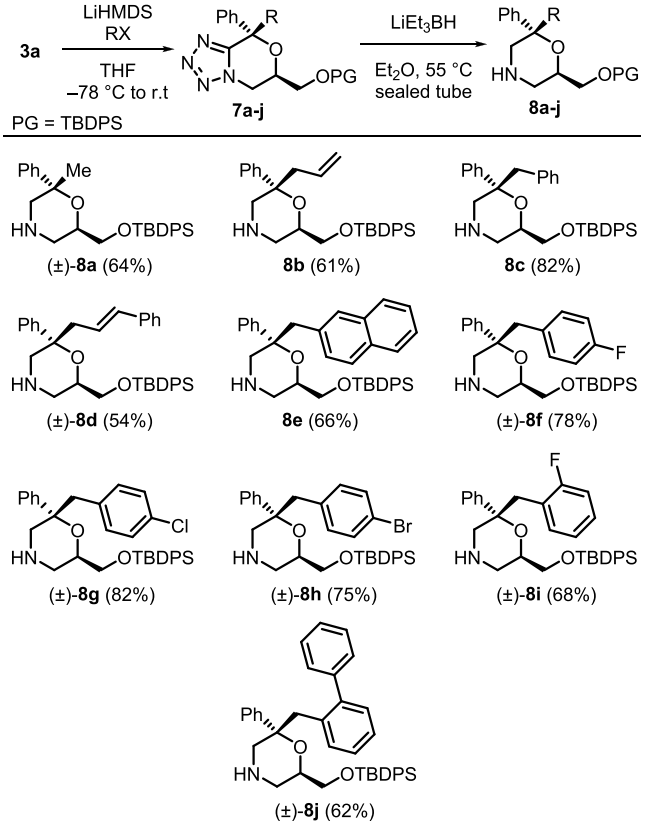
A crystal structure of the 4-methylcyclohexyl HCl salt **6e** showed the equatorial disposition of the $CH_2OTBDPS$ group. The scope of the reductive cleavage reaction toward 2,2′-geminally disubstituted morpholines with different groups could be widened by alkylation of **3a** with suitable electrophiles in the presence of LiHMDS at −78 °C.

It is of interest that alkylation of the generated carbanion took place to give the corresponding *trans*-tetrazole as the major product depending on the bulkiness of the electrophile (Scheme 7).[12] Reduction in the presence of Super-Hydride in Et_2O in a pressure vial at 55 °C afforded the *trans*-2,2′,6-trisubstituted morpholines **8a**−**j**. The stereochemistry was assigned by NMR and NOE experiments. We suggest that in these cases hydride attack occurs with concomitant expulsion of azide ion as shown in Scheme 3, rather than generating the corresponding benzylic disubstituted carbanion, which would have led to partial epimerization upon ring closure.[13]

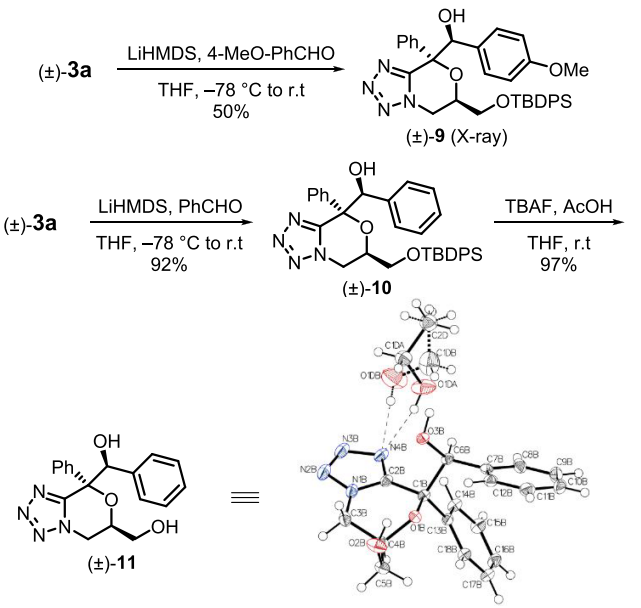
The acidity of the benzylic hydrogen in **3a**[8b] allows facile reactions via the corresponding lithium anion with aldehydes. Thus, treatment of **3a** with *p*-anisaldehyde in the presence of LiHMDS in THF at −78 °C afforded the *syn-trans* product **9** in crystalline form (Scheme 8). Reaction with benzaldehyde led to a mixture of diastereoisomeric alcohols **10** in a ratio of 1/3 in favor of the *syn-trans* product in 92% yield. In view of the ability of the σ lone pairs of the tetrazole moiety to engage in *H*-bonding with biological receptors,[2a−c,14] there is an opportunity to generate a diverse set of functionalized oxabicyclic tetrazoles (formally viewed as fused triazinomorpholines) with stereochemically defined tertiary centers from a variety of aldehydes for biological screening. Indeed, the crystal structure of adduct **11** revealed two *H*-bonded molecules of ethanol attached to *N*4 of the tetrazole unit.

In conclusion, we have elucidated the mechanism of the original LaForge reductive fragmentation of 1,5-disubstituted tetrazoles after 60 years since it was first reported. The extrusion of an intact azide moiety as the Li salt is unprecedented and lends itself to further computational studies in simple and more complex systems. We have extended the reductive fragmentation to oxabicyclic tetrazoles affording hitherto diastereomerically enriched 2,6-disubstituted[15] and 2,2′,6-trisubstituted morpholines.[16] In view of

Scheme 7. Reductive Cleavage of Trisubstituted Oxabicyclic Tetrazoles



Scheme 8. Stereoselective Additions of Oxabicyclic Tetrazole 3a to Benzylic Aldehydes



the importance of morpholines in medicinal chemistry[1,2,17] and their natural occurrence as alkaloid metabolites,[18] we hope that the three-step synthesis of such 2,6- and 2,2′,6-substituted morpholines starting from commercially available enantioenriched 3-chloro- and 3-azidopropane-1,2-diols via readily accessible oxabicyclic precursors[8] will expand their scope of applications toward medicinally relevant compounds.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01842.

Experimental procedures, compound characterizations, NMR spectra and X-ray structures (PDF)

Accession Codes

CCDC 1917618−1917622 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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