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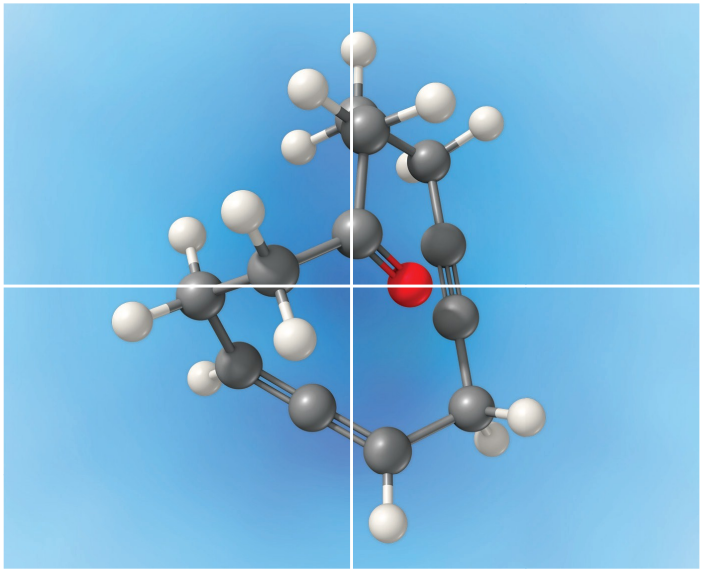

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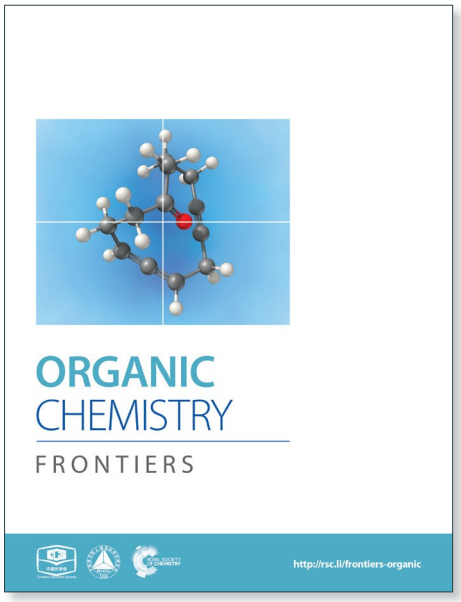

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ARTICLE TYPE

Regio- and Stereoselective Synthesis of α-hydroxy-β-azido tetrazoles

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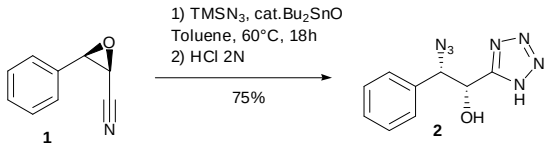
Unreported α-hydroxy-β-azido tetrazoles were prepared in one step from readily available α,β-epoxy nitriles. This reaction involves a dibutyltin oxide-catalysed cycloaddition of the nitrile reacting with $TMSN_3$ leading to the tetrazole moiety, and opening of the epoxide by the azide anion. High levels of regio- and stereoselectivity are obtained in this reaction and are discussed, also by means of quantum mechanical DFT calculations. The azido group in these compounds could be uneventfully reduced to the corresponding amine thus leading to an α-hydroxy-β-amino tetrazole, surrogate of the corresponding carboxylic acid, while reaction with triphenylphosphine led to propargylic amines.

Introduction

Tetrazoles have found applications in various domains including energetic materials, owing to their high nitrogen content, and medicinal chemistry, due to the fact that 5-subtituted tetrazoles (5-ST) are bioisosteres of carboxylic acids.[1] This last property has been notably popularized with the release of the antihypertensive drug Losartan,[2] which soon became a blockbuster. The synthesis of tetrazoles has been extensively studied, cycloaddition of azides (anion or derivatives) with nitriles being the most popular way to efficiently produce this heterocycle. Many key improvements in this reaction, which can be promoted either by Brönstedt or Lewis acids have appeared, including the use of sodium azide or $TMSN_3$ with NH_4Cl,[3] $ZnBr_2$,[4] Me_3Al,[5] I_2,[6] or $AgNO_3$.[7] Microwave irradiation[8] has also been used with much success, but this reaction still requires elevated temperatures (typically above 100°C) to proceed, thus narrowing its scope to quite robust nitriles. Another possibility lies in the use of dibutyltin oxide as a catalyst, in conjunction with $TMSN_3$.[9] In contrast to the above methods, this reaction involves neutral reaction medium and a weak Lewis acid, thus allowing cycloaddition of nitriles fitted with a Lewis base, such as amino nitriles.[10] We therefore decided to study this cycloaddition with α,β-epoxy nitriles, aiming at the preparation of functionalized tetrazoles suitable for further synthetic transformations. Our findings are exposed in the next section.

Results

We first studied reaction depicted in Scheme 1 with epoxide **1**, readily prepared by a Darzens reaction.[11] Thus, reacting this epoxide (18h) in toluene at 60°C with $TMSN_3$ (5 equiv.) and a substoechiometric amount of Bu_2SnO (0.5 equiv.) led, after acidic hydrolysis, to the α-hydroxy-β-azido tetrazole **2** in good yield. Much to our delight, this reaction, involving both cycloaddition and epoxide opening, occurred with high regioselectivity and complete inversion at the β-carbon.[12] The structure of **2** was verified by X-ray crystallography (see ESI).[13]



Scheme 1: Bu_2SnO-catalysed reaction of epoxynitrile **1** with $TMSN_3$ leads regioselectively to α-hydroxy β-azido tetrazole **2**.

We were surprised by the low temperature required for completion of this reaction and we first screened the amount of catalyst and $TMSN_3$ needed in order to maintain a high yield. Reactions were run in toluene at 60°C for 18h. (Table 1).

Table 1: Screening of the optimal amount of Bu_2SnO and $TMSN_3$.

Entry	$TMSN_3$ (equiv.)	Bu_2SnO (equiv.)	Yield(%)
1	5	0.5	75
2	5	2	92
3	3	0.5	85
4	2.5	0.5	70
5	3	0.2	60
6	1	1	trace[a]

[a] β-chloro-α-azido tetrazole was isolated after acidic hydrolysis in 33% yield.

Increasing the amount of Bu_2SnO (entry 2) gave an excellent yield of **2**, and lowering the amount of $TMSN_3$ to three equiv. (entry 3) maintained a high yield, but decreasing of the amount of catalyst to 20 mol% lowered the yield significantly (entry 5). In order to determine which event first occurred (cycloaddition or epoxide opening), we also used one equivalent of $TMSN_3$ and Bu_2SnO (preheated until dissolution) and isolated after reaction and acidic workup β-chloro-α-hydoxy tetrazole, resulting from the opening of the epoxide by the chloride anion (entry 6), suggesting that cycloaddition first occurs. Thus, we chose to

examine the scope of this reaction with other epoxides (shown in Figure 1) with 3 equiv. of $TMSN_3$, using 50 mol% of Bu_2SnO (conditions of entry 3). Structures of the isolated compounds are shown in Figure 2.

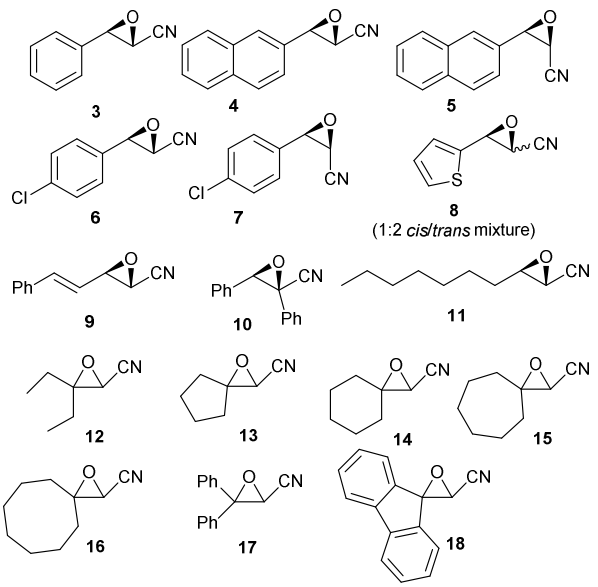


Figure 1: Structures of the cyanoepoxides used to examine the scope of this reaction.

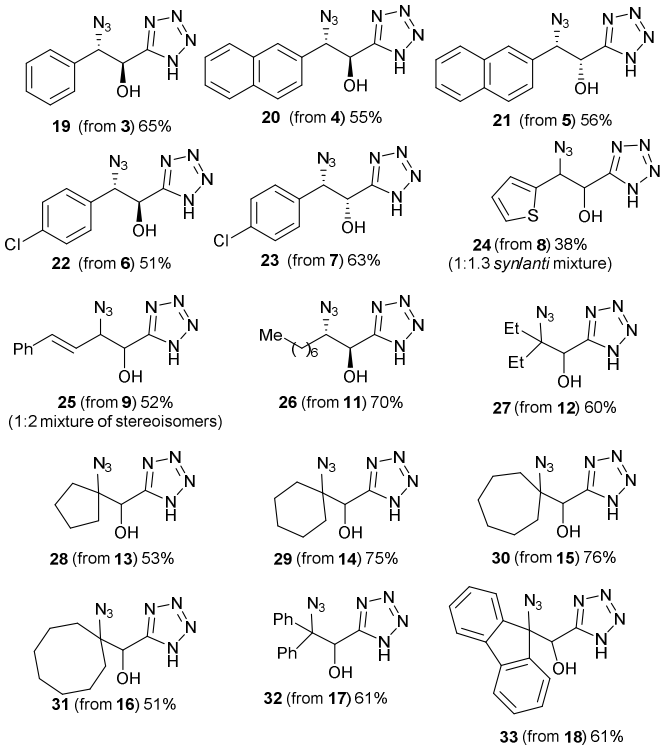
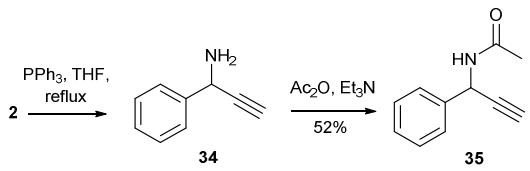


Figure 2: Structures and yields of the produced isolated α-hydroxy-β-azido tetrazoles.

As depicted in these figures, the scope of this reaction was very good, tolerating aryl, alkenyl and alkyl groups at the β-position of the epoxide. Yields are modest to good (38-76%) and these compounds are isolated as crystalline materials. ‡ β-Disubstituted epoxides **12**-**18** also reacted very well and tertiary azides were obtained in good yields. Only α-disubstituted epoxide **10** failed to react in these conditions, leaving unreacted starting material. Regioselectivity was constantly excellent, leading to a unique β-azido regioisomer whatever the degree and the nature of substitution at the β-carbon. The stereoselectivity of this reaction could be evaluated with the *cis* or *trans* epoxides **1**, **3**-**9** and **11**. For **1**, **3**-**7** and **11** the reaction appears to be stereospecific and involves an inversion at the β-carbon as shown from the X-ray structure of **2** and slightly different NMR data for diastereoisomers **2**:**19**, **20**:**21** and **22**:**23** (see ESI). Starting with **8** (1:2 *cis*-*trans* mixture), a 1:1.3 mixture of isomers **24** was obtained, albeit in low yield, which also might reflect the stereospecificity of this reaction. Only the starting *trans* epoxide **9** reacted with epimerization at the β-carbon, leading to **25** as a 1:2 mixture of diastereoisomers.

Next we briefly examined the reactivity of these α-hydroxy-β-azido tetrazoles. We first tried to reduce the azido moiety into an amino group, in order to access α-hydroxy-β-amino tetrazoles,[14] which can be viewed as surrogates of the corresponding α-hydroxy-β-amino acid.[15] The latter compounds occupy a very important place within the family of β-amino acids, being constituents of several drugs and natural molecules such as *inter alia* Taxol,[16] Taxotere,[17] Bestatin,[18] Microginin[19] and the HIV protease inhibitor R-87366.[20] Moreover, α-hydroxy-β-amino tetrazoles have found uses in the design of bioactive peptides with *cis*-conformationally restricted peptide bonds.[21]

Thus, aiming to reduce the azido through Staudinger conditions, **2** was reacted with triphenylphosphine in refluxing THF for 2h, but the crude reaction mixture unexpectedly showed formation of propargylic amine **34**, together with phosphine oxide. This compound was acetylated for easier purification and **35** was isolated with an overall yield of 52% (Scheme 2):



Scheme 2: Reaction of α-hydroxy-β-azido tetrazole **2** with triphenylphosphine leads to the formation of propargylamine **34**.

The scope of this reaction, conducted in one pot without isolation of the intermediate amine, was briefly screened (Table 2 and Figure 3) and it was found to be general, with yields varying from 23 to 71% in the case of secondary azides. However, no trace of acetylenic compound could be detected in the crude reaction mixture starting from tertiary azides **28** or **32**.

Table 2: Reaction of α-hydroxy-β-azido tetrazoles with $P(Ph)_3$ (refluxing THF, 2h, followed by acetylation (Ac_2O and Et_3N, 3 equiv.).

Entry	Starting azide	Product	Yield(%)
1	**2**	**35**	55
2	**19**	**35**	44
3	**23**	**36**	71
4	**26**	**37**	30
5	*anti*-**25**	**38**	23
6	**28**	-	-[a]
7	**32**	-	-[b]

[a]: Starting material was consumed after overnight reflux but no alkyne was detected. [b]. No reaction.

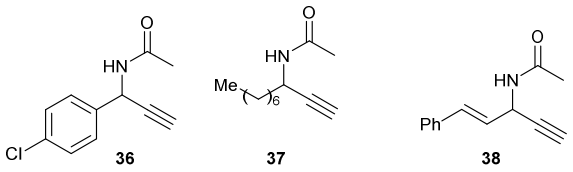
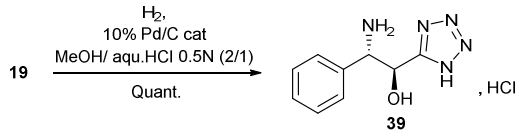


Figure 3: Structure of propargylamines **36**-**38**.

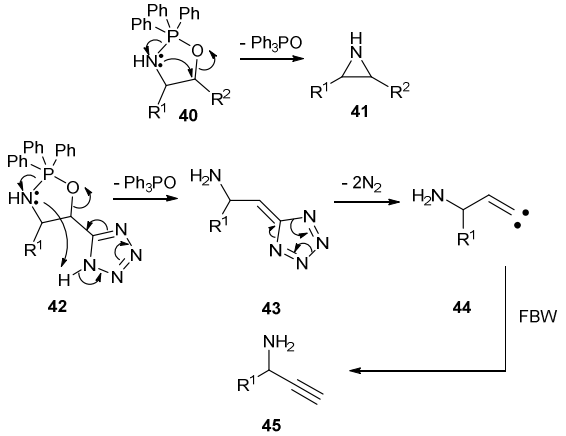
Alternatively, Pd/C-catalyzed hydrogenation of **19** led quantitatively to the α-hydroxy-β-amino tetrazole **39** as its chlorhydrate salt (Scheme 3):



Scheme 3: Reduction of the azide is conveniently achieved by Pd/C-catalyzed hydrogenation.

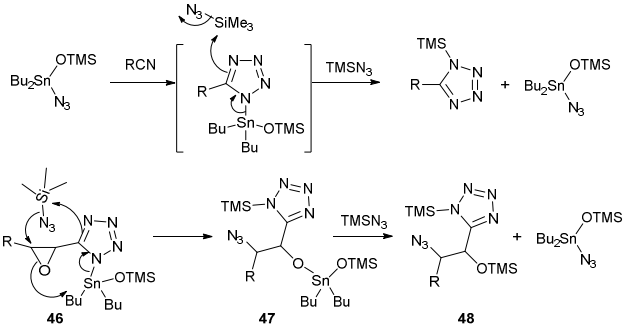
Discussion

The unexpected formation of propargylic amines during the reaction of α-hydroxy-β-amino tetrazoles with triphenylphosphine deserves comment. The Blum-Ittah aziridine synthesis is an established procedure to convert 1,2-azido alcohols into aziridines by treatment with a tertiary phosphine.[22] It is accepted that it goes through an oxazaphospholidine **40** that collapses to the aziridine **41** with release of phosphine oxide. A possible mechanism that would explain our results is the following. In our starting compounds, proton transfer from the acidic tetrazole to the nitrogen of the intermediate oxazaphospholidine **42** would produce 5-methylene-5*H*-tetrazole **43** with release of triphenylphosphine oxide, that could further decompose to vinylic carbene **44**.[23] This intermediate would ultimatively lead to the propargylic amine **45** through a Fritsch–Buttenberg–Wiechell rearrangement (Scheme 5). Recent precedents in the literature have demonstrated the possibility of smoothly generating vinylic carbenes from α-hydroxy tetrazoles upon activation with DCC.[24]



Scheme 5: A plausible mechanism accounting for the formation of propargylic amine upon the reaction of α-hydroxy-β-azido tetrazoles with triphenylphosphine.

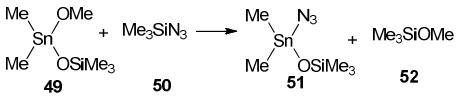
The second point which is worth discussing is the high regio- and stereoselectivity observed during ring-opening of the epoxide. All substrates, except allylic azide **25**, were obtained as single compounds, and the erosion of stereoselectivity in that particular case might be due to a dynamic [3,3] equilibration process of the allylic azide which reflects thermodynamic control.[25] Though uncatalyzed ring opening of glycidates with $TMSN_3$ has been reported to proceed with varying regio- and stereoselectivity (S_N2 or S_Ni), depending on the stereochemistry of the epoxide,[12] in our case, no reaction occurred in the absence of Bu_2SnO suggesting the crucial role of the tin catalyst for both cycloaddition and epoxide opening. The mechanism of Bu_2SnO-catalyzed cycloaddition of $TMSN_3$ with alkynes has been studied in details.[26] It was demonstrated that the active catalytic species is $Bu_2Sn(OTMS)N_3$, and that regeneration of this catalyst occurs through a S_N2 displacement at the silicon atom, which was calculated to require only 28 kcal/mol, followed by fast ligand exchange at the tin atom (Scheme 6). In our case, the tin atom in the produced tetrazole **46** is ideally located to assist in the opening of the epoxide by the azide anion at the β-position. This concerted reaction would account for the regioselectivity of the opening and the S_N2 process. In this case, regeneration of the catalyst would then imply reaction of the produced tin alkoxide **47** with $TMSN_3$, to produce OTMS derivative **48**, an exchange that can be promoted from a thermodynamic viewpoint considering the much stronger O-Si bond (190 kcal/mol) compared to the O-Sn bond (130 kcal/).



Scheme 6: A plausible mechanism accounting for the regio- and stereoselectivity of the ring opening process.

In order to evaluate the feasibility of this tin to silicon exchange (**47**→**48**), simplified reaction depicted in Scheme 7 was considered. Quantum mechanical calculations at the B3LYP level of theory [with LANL2DZ ECP for tin atom[27] and 6-31G ** basis set[28] for other atoms] were performed with the Firefly 8.0.1 package of programs.[29] The structure of the optimized transition state (TS) of this concerted reaction, located at only 17.9 kcal/mol, together with the structures **RC1** and **RC2** of pre- and post-reaction complexes are shown in Figure 4, while Figure 5 outlines the energetic profile of this reaction.

Indeed, calculations demonstrate that this exchange is favored both from kinetic and thermodynamic viewpoints, thus reinforcing our hypothesis.



Scheme 6: Simplified computed reaction for the evaluation of the tin to silicon exchange leading to **48**.

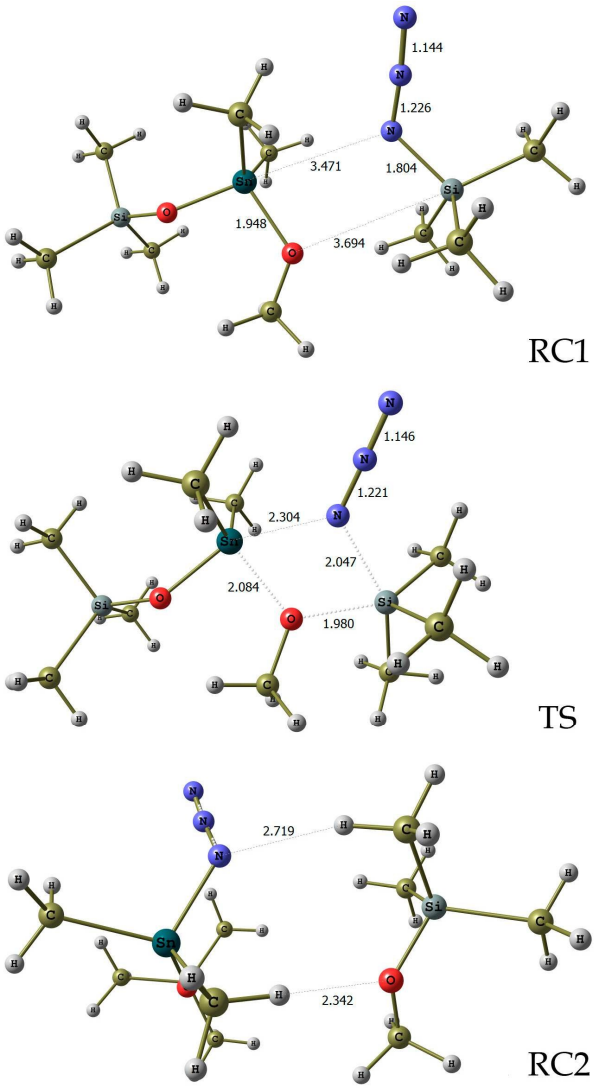


Figure 4: Geometrical details of reaction complexes **RC1**, **RC2** and transition state **TS**. Bond lengths are in angstroms. Imaginary vibration frequency for **TS** is 92.0 cm^{-1}

Conclusions

In conclusion, we have described a straightforward entry to so far unreported α-hydroxy-β-azido tetrazoles, together with a brief examination of their reactivity. Considering the stereospecificity of the opening of the epoxide, this process should allow the preparation of non-racemic molecules starting from readily available enantiopure epoxy nitriles.[30] Further work is in progress to extend the scope and applications of this reaction.

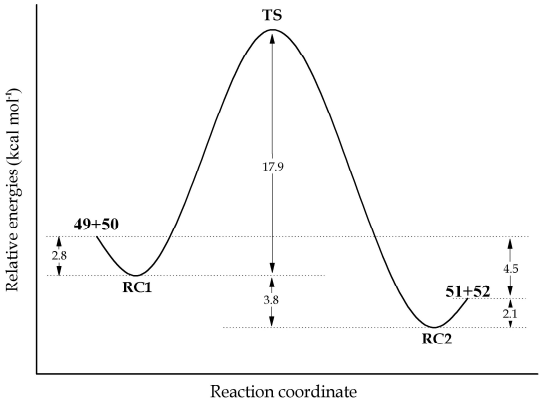


Figure 5: Minimum energy path for the concerted exchange process hold in reaction complex with the modified structure (**RC1** and **RC2**). All values were obtained with zero point energies corrections.

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Notes and references

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† Electronic Supplementary Information (ESI) available: experimental procedures for all compounds, copies of ^{1}H and ^{13}C NMR data for all compounds, X-ray data for **2**. See DOI: 10.1039/b000000x/

‡ Due to the high nitrogen content of these compounds, hazards resulting from violent decomposition must be anticipated, though we have never observed such behaviour with these compounds.

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