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-catalyzed cycloaddition of the nitrile reacting with TMSN3 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-azido 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-substituted tetrazoles (5-ST) are bioisosteres of carboxylic acids. This last property has been notably popularized with the release of the antihypertensive drug Losartan, 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 Brønsted or Lewis acids have appeared, including the use of sodium azide or TMSN3 with NH₄Cl, ZnBr₂, Me₃Al, I₂, or AgNO₃. Microwave irradiation 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 TMSN₃. 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. 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. Thus, reacting this epoxide (18 h) in toluene at 60 °C with TMSN₃ (5 equiv.) and a substoichiometric amount of Bu₂SnO (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.

We were surprised by the low temperature required for completion of this reaction and we first screened the amount of catalyst and TMSN₃ needed in order to maintain a high yield. Reactions were run in toluene at 60 °C for 18 h. (Table 1). Increasing the amount of Bu₂SnO (entry 2) gave an excellent yield of 2, and lowering the amount of TMSN₃ to three equiv. (entry 3) maintained a high yield, but decreasing of the

Scheme 1. Bu₂SnO-catalyzed reaction of epoxyxitrile 1 with TMSN₃ leads regioselectively to α-hydroxy β-azido tetrazole 2.
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 TMSN₃ and Bu₂SnO (preheated until dissolution) and isolated after reaction and acidic workup β-chloro-α-hydroxy 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 Fig. 1) with 3 equiv. of TMSN₃, using 50 mol% of Bu₂SnO (conditions of entry 3). Structures of the isolated compounds are shown in Fig. 2.

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.

‡ 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.

Table 1 Screening of the optimal amount of Bu₂SnO and TMSN₃

| Entry | TMSN₃ (equiv.) | Bu₂SnO (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 β-chloro-α-azido tetrazole was isolated after acidic hydrolysis in 33% yield.
Thus, aiming to reduce the azido through Staudinger conditions, 2 was reacted with triphenylphosphine in refluxing THF for 2 h, 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).

The scope of this reaction, conducted in one pot without isolation of the intermediate amine, was briefly screened (Table 2 and Fig. 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.

Alternatively, Pd/C-catalyzed hydrogenation of 19 led quantitatively to the α-hydroxy-β-aminotetrazole 39 as its chloro-hydrate salt (Scheme 3).

### Table 2

| 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.

The unexpected formation of propargylic amines during the reaction of α-hydroxy-β-aminotetrazoles 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 that collapses to the aziridine 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-5H-tetrazole 43 with release of triphenylphosphine oxide, that could further decompose to vinylic carbene 44.23 This intermediate would ultimately lead to the propargylic amine 45 through a Fritsch–Buttenberg–Wiechell rearrangement (Scheme 4). Recent precedents in the literature have demonstrated the possibility of smoothly generating vinylic carbenes from α-hydroxy tetrazoles upon activation with DCC.24

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 TMSN₃ has been reported to proceed with varying regio- and stereoselectivity (Sₙ₂ or Sₙ₃), depending on the stereochemistry of the epoxide,12 in our case, no reaction occurred in the absence of Bu₂SnO suggesting the crucial role of the tin catalyst for both cycloaddition and epoxide opening. The mechanism of Bu₂SnO-catalyzed cycloaddition of TMSN₃ with alkynes has been studied in details.26 It was demonstrated that the active catalytic species is Bu₂Sn(OTMS)N₃, and that regeneration of this catalyst occurs through a Sₙ₂ displa-
cement at the silicon atom, which was calculated to require only 28 kcal mol$^{-1}$, followed by fast ligand exchange at the tin atom (Scheme 5). 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 $\beta$-position. This concerted reaction would account for the regioselectivity of the opening and the SN2 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$^{-1}$) compared to the O–Sn bond (130 kcal mol$^{-1}$).

In order to evaluate the feasibility of this tin to silicon exchange (47→48), simplified reaction depicted in Scheme 6 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$^{-1}$, together with the structures RC1 and RC2 of pre- and post-reaction complexes are shown in Fig. 4, while Fig. 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.

Conclusions

In conclusion, we have described a straightforward entry to so far unreported $\alpha$-hydroxy-$\beta$-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. Further work is in progress to extend the scope and applications of this reaction.

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