EDGE ARTICLE

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Convergent synthesis of thiodiazole dioxides from simple ketones and amines through an unusual nitrogen-migration mechanism†

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We report the modular preparation of dihydro-1,2,5-thiodiazole dioxide heterocycles starting from methyl ketones and primary amines. This one-pot, three-component coupling employs 2,3-dimethylimidazole-1-sulfonyl azide triflate as a coupling reagent and oxidant. The transformation is scalable and various ketones and amines can be used, yielding thiodiazole dioxide products in up to 89% yield. In addition, [15]N- and ^{13}C-labeling studies suggest a mechanism involving a 1,2-nitrogen migration. Together with the mechanistic studies, DFT calculations provide insight into the reaction pathway and set the stage for further exploration of the mechanistic nuances of reactions that use sulfamoyl azides. In combination with the demonstrated modularity of the approach reported herein, the derivatization of the thiodiazole dioxide products highlights the potential of this methodology to rapidly access diverse chemical structures.

Introduction

Sulfamides and their derivatives, including the tetrahydro-1,2,5-thiodiazole dioxide heterocycle, are well represented structural motifs in pharmaceutical and other bioactive compounds (see Fig. 1A).[1,2] These heterocycles are typically installed either by reaction of the corresponding diamine (**II**) with sulfamide (**III**)[3] or by intramolecular C–H amination from the corresponding sulfamoyl azide (**IV**)[4] (Fig. 1B). While useful, these strategies do not allow for late-stage diversification and in some cases rely on starting materials with limited availability (*e.g.*, diamines, **II**)—two factors which are often important in medicinal chemistry campaigns. To address these limitations, an alternate synthetic entry to tetrahydro-1,2,5-thiodiazole dioxides through functionalization of the closely related dihydro-1,2,5-thiodiazole dioxide (**V**) would be beneficial. In general, the discovery of direct, yet versatile, synthetic methods for the construction of the dihydro-1,2,5-thiodiazole dioxide structural motif is of value to synthetic and medicinal chemists. One of the most direct approaches to **V** is the condensation of sulfamides onto

carbonyl compounds. The key challenge with this approach is the need for α-oxidation of readily available ketones in order to install the C–N bond at the α-carbon. Historically, the requisite oxidation pattern has been obtained by starting from α-oxygenated ketones such as α-hydroxy ketones (**VI**)[5] or 1,2-diketones (**VII**).[6] However, there is limited commercial availability of these highly oxidized starting materials. A simple method for the synthesis of the thiodiazole dioxide motif from readily available commercial materials (*e.g.*, methyl ketones and aliphatic amines) could accelerate medicinal chemistry efforts to explore the function of diverse thiodiazole dioxides.

In the course of a recent collaborative study between the Sarpong group and Janssen Research and Development to prepare aza-bicyclohexanes and bicyclopentanes,[7] we identified **3** as an unexpected product of the reaction between an imine and 2,3-dimethylimidazole-1-sulfonyl azide triflate (**A**, Fig. 1C). We recognized that this transformation seemingly overcomes the key challenge described above by obviating the need for pre-oxidation of the α-carbon of the ketone coupling partner en route to the thiodiazole dioxide structural motif. This transformation represents a modular, three-component coupling that allows for the rapid diversification of methyl ketones and primary amines, two functional groups that are well-represented in pharmaceutical libraries.

In addition to the practical value of this discovery, we also recognized an opportunity to explore the reactivity of 2,3-dimethylimidazole-1-sulfonyl azide triflate (**A**).[8] Sulfamoyl azides have been used in sulfonyl[8] and diazo[9] transfer reactions, cycloadditions,[10] and even nitrogen deletion reactions.[11]

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A: Examples of thiodiazole dioxides in bioactive compounds

γ-secretase inhibitor

HIV protease inhibitor

B: Thiodiazole dioxide synthesis

Previous Work

This Work

= alkyl, allylic, benzylic, etc.

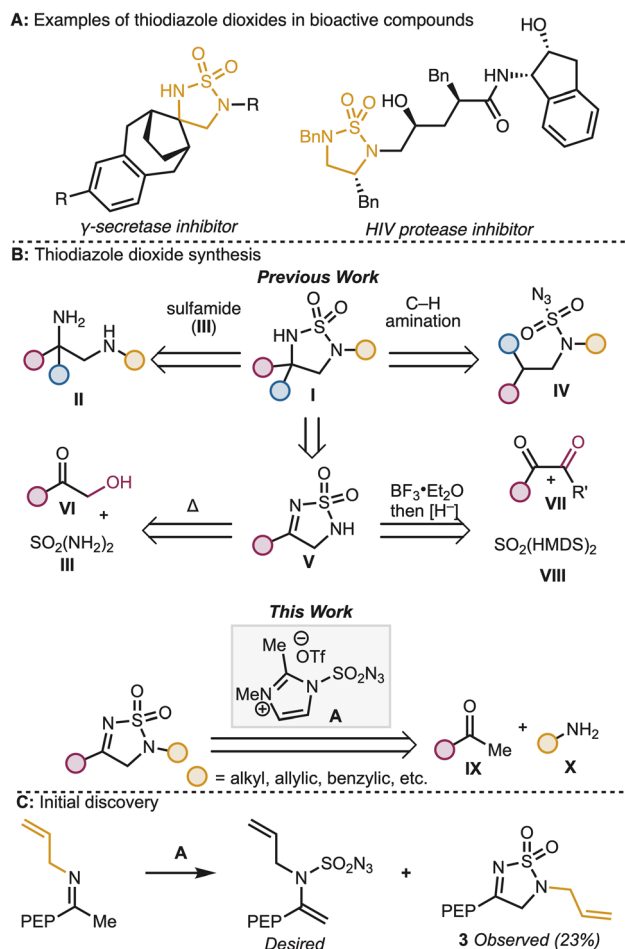**C:** Initial discovery

Desired

3 *Observed (23%)*

Fig. 1 (A) Biologically active molecules containing the thiodiazole dioxide motif. (B) Strategies for the preparation of thiodiazole dioxides. (C) Unexpected formation of thiodiazole dioxide **3**. PEP = *para*-ethoxyphenyl HMDS: hexamethyldisilazide.

Because of their diverse array of reactivity, the study of these reagents with a variety of functional groups may give rise to new mechanistic insights and strategies for chemical diversification.
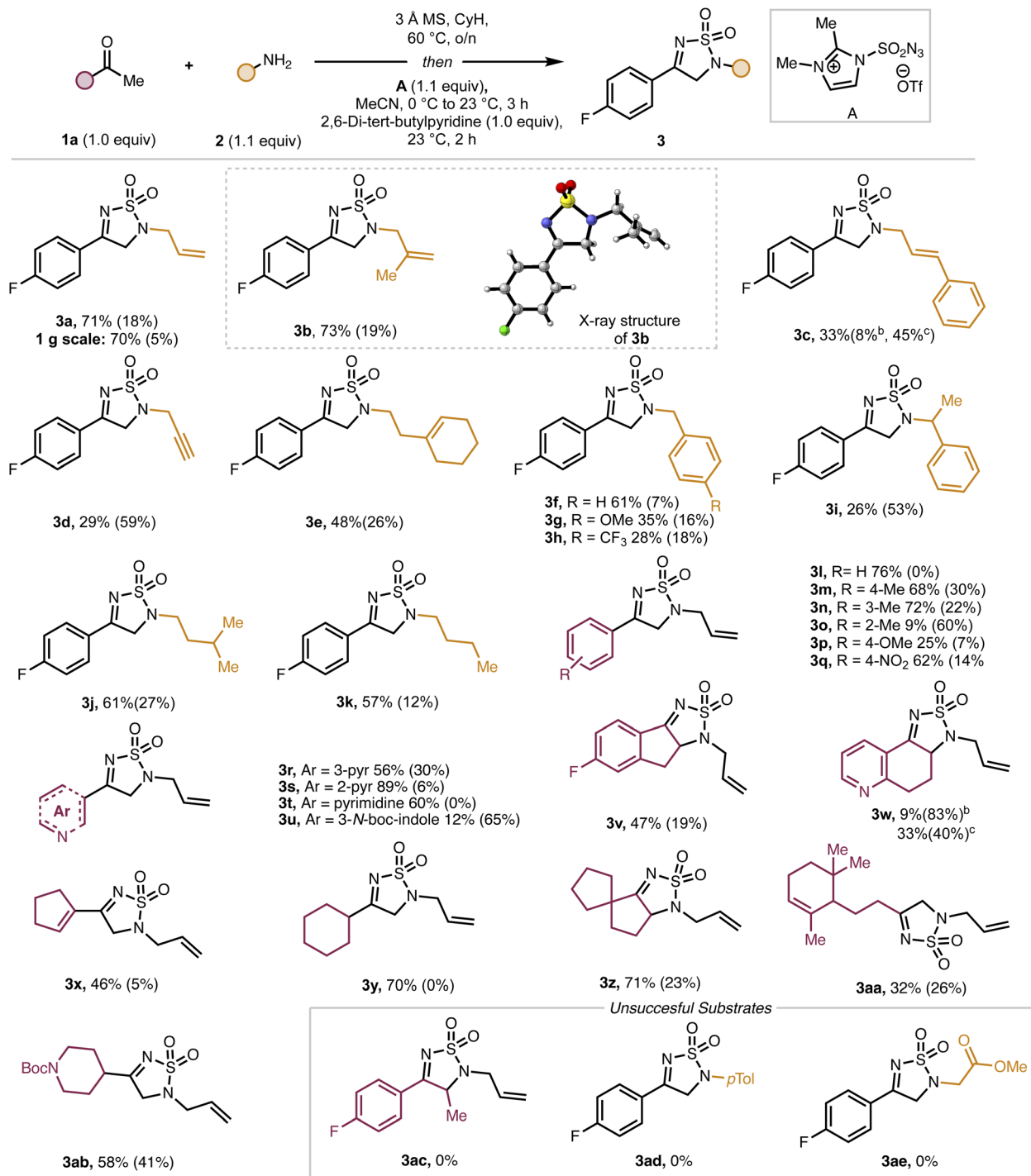
Results and discussion

We first set out to optimize the yield of **3a** (Table 1) by performing the reaction in two steps consisting of imine formation from 4-fluoroacetophenone (**1a**) and allylamine (**2a**), followed by reaction of the imine with **A**. Initial conditions involved stirring **1a** and **2a** in the presence of 3 Å molecular sieves at ambient temperature in cyclohexane. After 24 h, the solvent was removed, the reaction vessel cooled to 0 °C, and a solution of sulfonyl azide **A** in dry MeCN was slowly added. The reaction mixture was then allowed to warm to room temperature yielding the desired thiodiazole (**3a**) in 15% yield along with a 59% yield of recovered ketone (entry 1). The large amount of remaining starting ketone indicated to us that the condensation step (to make the imine) did not reach completion. Increasing the temperature for the imine formation to 60 °C led to a significant increase in overall yield (entry 2). However, running the reaction at 80 °C resulted in mostly decomposition (entry 3). We also speculated that a base additive could facilitate the conversion of the initially formed imine to intermediates such as an enamine en route to the product. Using 2,6-di-*tert*-butylpyridine as a base led to a pronounced increase in the reaction yield (entry 4), with 2, 6-lutidine proving less effective (entry 5). Lastly, we examined other common solvents, including tetrahydrofuran (THF), and dichloromethane (DCM) (entries 6 and 7), which led to decreased yields of **3a**. The optimized conditions (entry 4) also proved viable without the need to remove the cyclohexane solvent needed for imine formation, leading to an efficient one-pot reaction protocol.

With optimized conditions in hand, we next investigated the scope of the coupling partners (Scheme 1). Simple allylic amines (see **3a–3b**) perform well in this reaction, while

Table 1 Optimization of reaction conditions

Entry	Temp	Solvent	Additive (1.0 equiv.)	Yield[a] (%)	RSM (%)
1	23 °C	MeCN	—	15	59
2	60 °C	MeCN	—	43	26
3	80 °C	MeCN	—	N/A[b]	N/A
4	60 °C	MeCN	**Di-*tert*-butylpyridine**	**71[c]**	**18[c]**
5	60 °C	MeCN	2,6-Lutidine	48	47
6	60 °C	THF	Di-*tert*-butylpyridine	61	15
7	60 °C	DCM	Di-*tert*-butylpyridine	38	6

[a] Yield was determined by ^{1}H NMR with dimethyl sulfone as an internal standard. [b] Decomposition was observed. [c] Isolated yield. CyH = cyclohexane RSM: recovered starting material MS: molecular sieves.

Scheme 1 Substrate scope of amine. [a]Reaction conditions: see Table 1, entry 4. [b]*p*-Fluoroacetophenone. [c](*E*)-Cinnamylamine. Isolated yield reported. Yield in parenthesis refer to recovered starting material. CyH: cyclohexane MS: molecular sieves.

cinnamyl amine results in reduced yield of the product (**3c**). Propargylic and homoallylic amines are also competent coupling partners giving moderate yields of the desired products (**3d** and **3e**, respectively). Diverse benzylic amines, including those bearing electronically-disparate groups (see **3f–h**) serve competently as coupling partners in the reaction, although α-substitution (see **3i**) leads to decreased yields

compared to other benzylic amines. Finally, aliphatic amines can also be employed, giving the products (**3j–3k**) in moderate to good yields. X-Ray crystallographic analysis of a single crystal of **3b** provided support for the assigned structures. To further establish the practicality of this approach, a gram-scale reaction using **1a** (1.00 g, 7.23 mmol) and **2a** under the standard reaction conditions proceeded without any loss in efficiency to give **3a** in
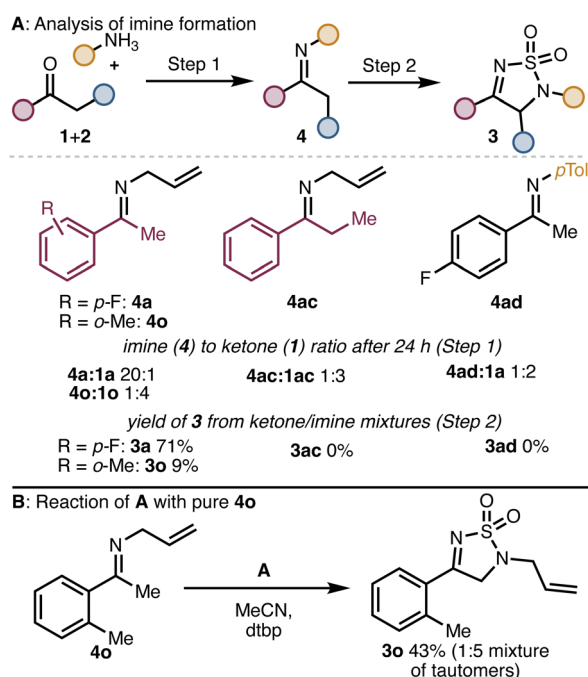
70% yield along with 5% of recovered methyl ketone starting material.

We then investigated the substrate scope of the ketone coupling partner. *Para-* and *meta-*substitution is well tolerated on the ketone coupling partner (see **3m–3n**), while *ortho-*substitution significantly reduces reaction efficiency (see **3o**). Electron-neutral and electron-poor ketones react well (see **3l–3q**), whereas decreased yields are observed for an electron-rich ketone (see **3p**). Various heteroaryl substituted ketones are competent substrates and deliver the corresponding products (**3r–3u**) in up to 89% yield. A series of cyclic aromatic ketones, including 5-fluoro-1-indanone, α-tetralone, and β-tetralone were successful substrates as well. Notably, α-tetralone and β-tetralone led to the same product (**3w**), presumably through diverging pathways (*vide infra*). Finally, vinyl and aliphatic ketones were competent substrates, giving **3x** and **3y–3ab**, respectively. Ketones bearing α-branched, cyclic, groups are superior substrates, whereas linear substrates (*e.g.*, **1aa**) gave lower yields of the desired products (*e.g.*, **3aa**).
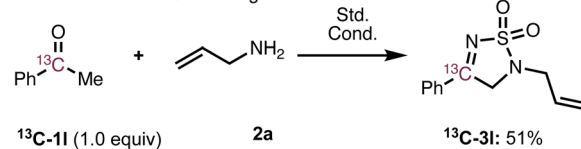
There are also several limitations in the scope of this reaction. Specifically, we found that ketones bearing α-substitution were poor substrates. For example, **3ac** was not formed from the corresponding ketone even upon extended reaction times. Amino acids and anilines also proved to be unsuccessful amine coupling partners.

We hypothesized that inefficient formation of the intermediate imine could account for the poor reaction outcomes observed in several cases. To probe this possibility, we monitored the imine formation for one successful substrate (*i.e.*, to form **3a**) and two unsuccessful substrates (to form **3ac** and **3ad**)
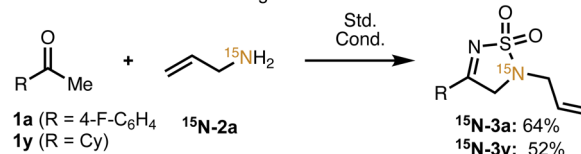

Scheme 2 (A) Ratios of **4** : **3** after 24 h (3 Å MS, CyH, 60 °C) and outcome of subsequent reaction of **A**. (B) Success of reaction with pure **4o** step 1: 3 Å MS, cyclohexane, 60 °C. Step 2: **A**, MeCN, dtbp, 0 °C to r. t. dtbp: 2, 6-ditertbutylpyridine.

Scheme 3 (A) Outcome of reaction with ^{13}C-acetophenone. (B) Outcome of reaction with ^{15}N-allylamine for conditions see Table 1 entry 4.

as well as one low yielding product (**3o**). As shown in Scheme 2, for substrates that reacted poorly or unsuccessfully, only partial conversion of the ketone to the imine was observed. When these ketone/imine mixtures were treated with **A**, product was only obtained from imines **4a** and **4o**. The mixtures containing imines **4ac** and **4ad** returned only starting ketone after treatment with **A** and workup. We then synthesized pure **4o** and subjected it to reaction with **A**. The product (**3o**) was isolated in a much improved 43% yield. From these experiments, we conclude that for some ketone substrates, low yields of the product might result due to incomplete imine formation. However, in some cases (*e.g.*, **3ac**), even substrates that form the imine intermediate efficiently can lead to low yields of the products due to other incompatibility issues (*e.g.*, difficulty with enamine formation).

To gain insight into the reaction mechanism, we chose to conduct a series of studies with isotopically labeled substrates. The use of α-^{13}C acetophenone ([13]C-**1l**) provided thiodiazole dioxide [13]C-**3l** (Scheme 3A) bearing the ^{13}C label at the imine carbon, which suggests that the carbon chain remains intact (*i.e.*, a phenyl migration does not occur). Next, we conducted the reaction with ^{15}N labelled allyl amine, which gave [15]N-**3a** (Scheme 3B) where the ^{15}N label was incorporated only at the amine position and not at the imine nitrogen. This observation indicates that the imine nitrogen in **4** undergoes a 1,2 migration during the course of the reaction. Notably, the nitrogen also migrates when an aliphatic ketone (**1y**) is used to give [15]N-**3y**— further evidence that the aromatic system is not involved or critical to the rearrangement.

Nitrogen migrations of this type are known for enamine/azide cycloadditions.[12] These cycloadditions can generate amino-triazolines which can in turn generate amino-aziridines (Fig. 2A). Each of these species can further transform in several ways, including through C–C bond cleavage (Type I)[13] and migration of a carbon (Type II),[13a–d,14] nitrogen (Type III),[13e,14b,c,15b] or hydride (Type IV)[10,13e,14a,15] substituent (Fig. 2A). Product mixtures are often observed, and the selectivity is dictated by the nature of the substituents on both the enamine
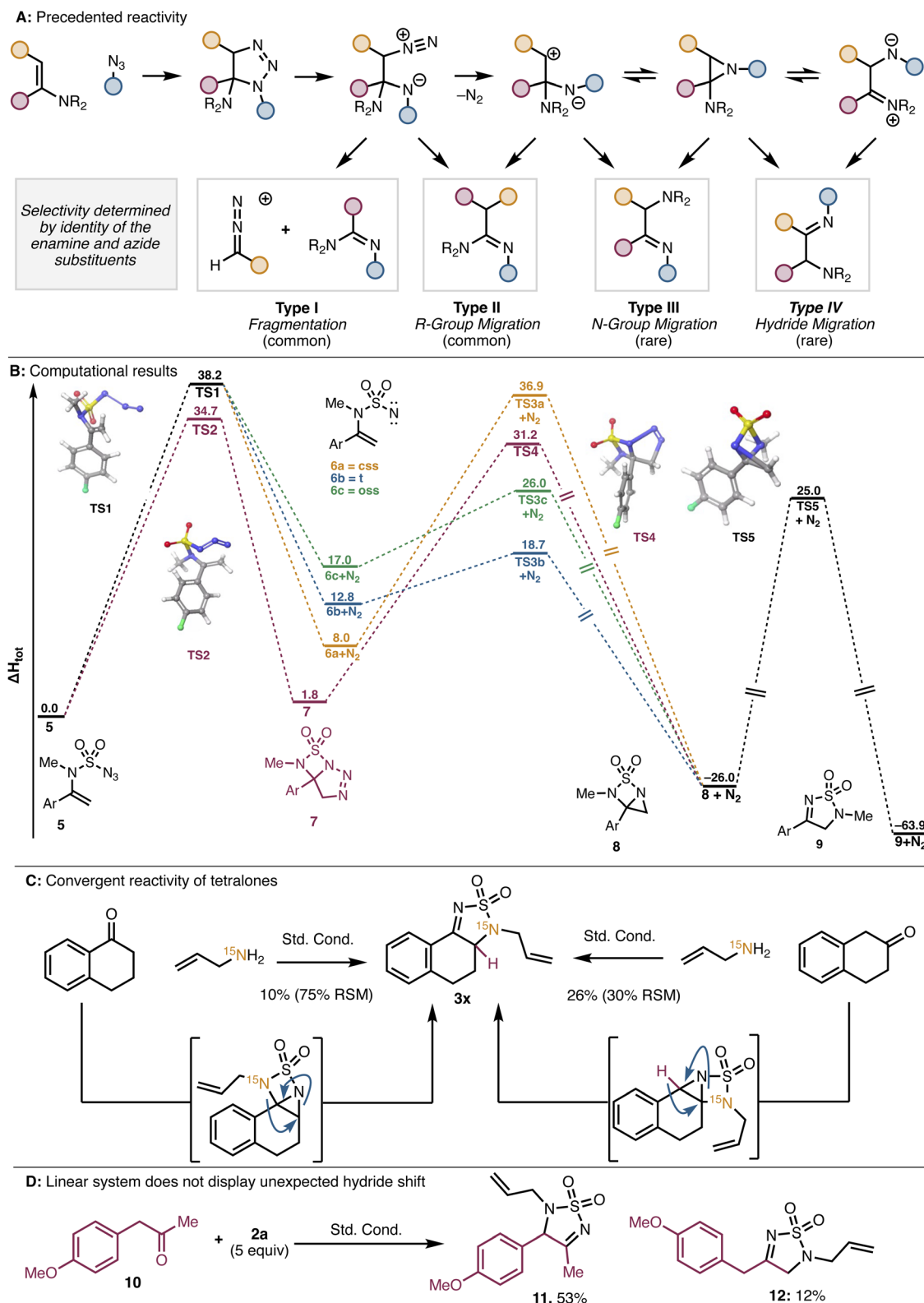
Fig. 2 (A) Rearrangements of amino–triazolines. (B) DFT investigation of possible reaction pathways (values given in kcal mol⁻¹). (C) Reactivity of tetralone substrates (css: closed shell singlet. oss: open shell singlet. t: triplet).

and the azide components. Importantly, our system differs from those described in the literature in several ways. Most notably, our reaction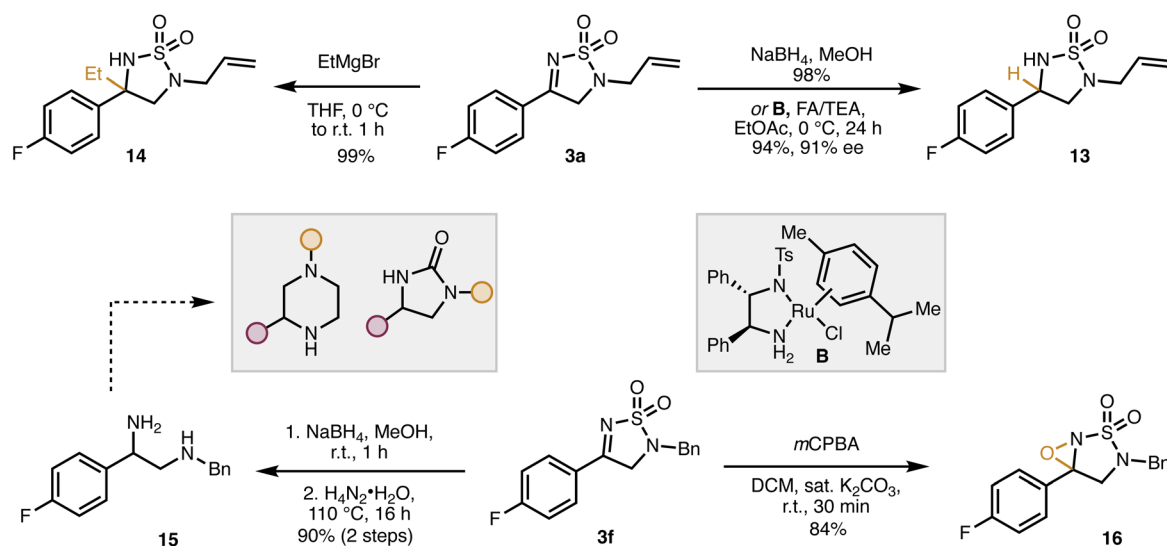 proceeds through an imine formed from a primary amine (see Scheme 3A) rather than an enamine formed from a secondary amine (see ref. 12–15). Additionally, sulfamoyl azide **A** is able to react with the imine *at sulfur*, to generate

a sulfamoyl enamine. These key differences, as well as the superb selectivity for the Type III nitrogen migration that we observe, led us to further investigate the reaction pathway with DFT. For ease of computation, calculations were performed with a model enamine (**5**), where the *N*-allyl group is modified to *N*-Me. Structure minima were generated with DFT or UDFT in the gas phase in Jaguar (B3LYP-D3/6-31G+*). Transition structures were identified using coordinate scans, linear synchronous transit, quadratic synchronous transit, or a combination thereof, at the same level of theory.

We considered two possible pathways to access the amino-aziridine precursor to the Type III product. Pathway 1 involving loss of nitrogen followed by (2 + 1) cycloaddition, and Pathway 2 involving (3 + 2) cycloaddition followed by nitrogen extrusion (Fig. 2B). To interrogate Pathway 1, we first identified a transition state corresponding to loss of nitrogen from **5** (**TS1**) to form nitrene **6** in one of three spin states. At this stage, (2 + 1) cycloaddition would generate aziridine **8** through the respective transition structure, which subsequently undergoes exothermic rearrangement *via* **TS5** to give final product **9**. For Pathway 2, we were able to identify a transition state for the intramolecular cycloaddition of the azide and enamine (**TS2**) in **5**, which results in the formation of triazoline **7**. A transition structure for the direct conversion of **7** to **9** by either a concerted or stepwise mechanism could not be identified. However, **TS4** was identified, corresponding to loss of nitrogen from triazoline **7** to give **8**. Analogous to the first pathway, **8** could undergo exothermic rearrangement to give the final product (**9**). The computationally computed barrier for the (3 + 2) cycloaddition at **TS2** is 3.5 kcal mol^{-1} lower than the barrier for loss of nitrogen at **TS1**, suggesting the former is the favored pathway. Consistent with the isotope labelling experiments discussed above, one of the C–N aziridine bonds is lengthened at **TS5**, and the imaginary frequency at this transition structure corresponds to atomic motion of the C and N atoms involved in the bond rearrangement.

We hypothesize that the preference for Type III reactivity over either Type I or Type II arises from the sulfur dioxide group connecting the two nitrogens. This tether would make amidine formation difficult due to developing strain en route to a four-membered heterocycle. Although we cannot rule out an intermolecular enamine/azide cycloaddition, the product selectivity suggests that the S–N bond forms prior to rearrangement. Additionally, we propose that the nitrogen rearrangement accounts for the convergent reactivity of α- and β-tetralone. In the case of α-tetralone, the expected Type III nitrogen migration is observed (as confirmed by ^{15}N NMR; see Fig. 2C). In the β-tetralone system, however, the nitrogen does not migrate. Instead, the observed product results from Type IV hydride migration (see Fig. 2A and C). We posit that in this case, the nitrogen shift is disfavored by developing "peri-strain" between the ortho hydrogen on the aromatic ring and the *N*-allyl substituent. In all other cases, the migrating group is moving away from the aromatic ring, leading instead to a lessening of any unfavorable interactions between the nitrogen substituent and the aromatic protons. On the basis of this hypothesis, we anticipated that a linear analog of β-tetralone (*e.g.*, phenyl-acetone) should give only the expected nitrogen shift product because of the absence of "peri-strain" in this conformationally flexible system. Indeed, using **10** and **2a** in the thiadiazole dioxide forming reaction, we isolated only the two expected products that involve a nitrogen shift (*i.e.*, **11**, arising from an intermediate benzylic enamine and **12**, arising from a terminal enamine intermediate). This observation supports our hypothesis that the conformational rigidity of the α-tetralone system leads to the unique reactivity that is observed in that case.

With empirical and computational support for our proposed mechanism secured, we then set out to demonstrate the synthetic utility of our dihydro-1,2,5-thiodiazole 1,1-dioxides (Scheme 4). For example, tetrahydro-1,2,5-thiodiazole dioxide **13** is obtained through either reduction with sodium borohydride or enantioselective transfer hydrogenation using

Scheme 4 Synthetic transformations of dihydro-1,2,5-thiodiazole dioxide. FA/TEA: formic acid/triethylamine (~5 : 2).

ruthenium catalyst B to give **13** in high yield and, in the case of the transfer hydrogenation, good enantiomeric excess (91% ee).[6] In addition to hydrides, **3a** is a competent electrophile for carbon nucleophiles, exemplified by the addition of ethyl magnesium bromide to form **14**. The cyclic sulfamide moiety can also be opened to 1,2 diamine **15** by heating with hydrazine. This process allows for easy and modular access to diamines which are precursors to a variety of biologically relevant structural motifs (imidazolidinones, *etc.*).[16]

Sulfonyl imines are well-established precursors to *N*-sulfonyl oxaziridines, a very useful class of oxygen-transfer reagents.[17] Accordingly, the dihydro-1,2,5-thiodiazole dioxide **3f** was readily converted to the corresponding oxaziridine (**16**) by oxidation with *meta*-chloroperoxybenzoic acid (*m*CPBA). The modular nature of our method should allow for the synthesis of a diverse array of oxaziridines which could aid in the discovery of new reagents for oxygen transfer.

Conclusions

In conclusion, we have developed an efficient method for the conversion of commercially available methyl ketones and primary amines to dihydro-1,2,5-thiodiazole dioxides in a one-pot protocol using 2,3-dimethylimidazole-1-sulfonyl azide. The overall transformation constitutes a highly modular three-component coupling and provides a general and practical approach to diversified drug-like thiodiazole dioxides. The transformation displays a reasonably broad functional group tolerance. A proposed reaction mechanism is supported by isotopic labelling of nitrogen and carbon atoms in the amine and ketone coupling partners, respectively. The subsequent transformation of thiodiazole dioxides into other compounds of medicinal relevance was also demonstrated.

Data availability

Data supporting the work in this publication are available *via* the ESI and associated crystallographic data.†

Author contributions

This manuscript was written by P. S. and K. P. with input from I. S., R. S., T. P. L., P. G. R. and M. A. P. P. G. R. first characterized the unexpected thiodiazole dioxide product. The majority of the synthetic work was carried out by K. P. and P. S. Experiments were designed by P. S. and R. S. with input from M. A., T. P. L. and P. G. R. All calculations were carried out by I. S. under the supervision of M. S., T. P. L, P. G. R., M. A., and R. S. supervised the project.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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