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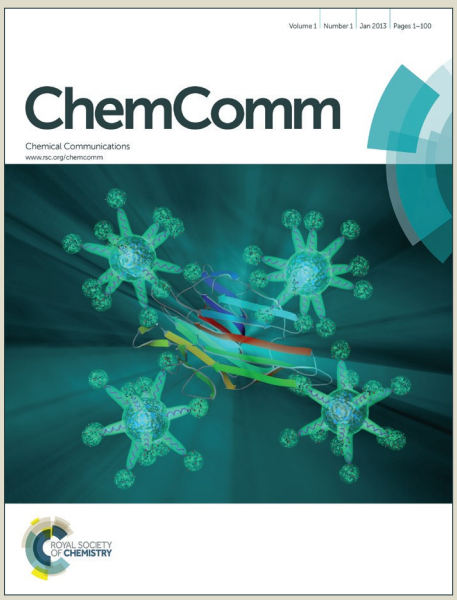

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O-Transfer-facilitated Cyclizations of Propargylamides with $TMSN_3$: Selective Synthesis of Tetrazoles and Dihydroimidazoles†

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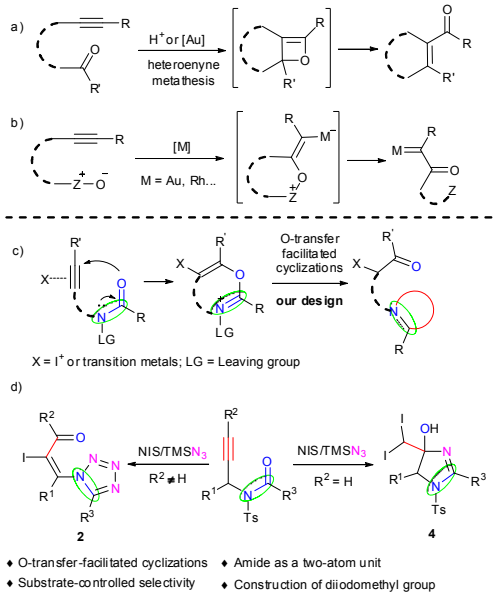
An unprecedented formal [3+2] annulation of propargylamides with $TMSN_3$ to deliver functionalized tetrazoles is developed. Oxygen-atom transfer (OAT) from amide group to C≡C bond was realized via a NIS-triggered-cyclization/ring-opening cascade pathway. The OAT process enables the amide to serve as a two-atom unit in the reactions. Notably, in situ umpolung of azide occurred when terminal propargylamides were employed in this reaction, providing an array of diiodomethylated dihydroimidazoles.

Cyclization of alkynes containing adjacent nucleophilic centers has emerged as an exceptionally mild and practical approach for the synthesis of functionalized carbo- and heterocycles.[1] Among them, cyclizations of ketone-, amine *N*-oxide-, nitro-, sulfoxide-, and nitrone-alkynes involving an intramolecular oxygen transfer process have been investigated.[2,3] For example, alkyne-carbonyl metathesis of ketone-alkynes to produce oxygen transferred carbocycles through a [2+2] pathway has been reported (Scheme 1a).[2] Transition-metal-catalyzed oxygen transfer reactions of alkynes possessing the polar Z^+-O^- groups have been proposed to generate reactive α-oxo carbenoids, allowing the generation of various carbonyl compounds (Scheme 1b).[3] However, despite these achievements, oxygen-atom transfer (OAT) from amide into alkynes has never been reported before.

Recently, propargylamides have been well studied as versatile precursors for the synthesis of 5- or 6-membered oxa-heterocycles.[4,5] As our continued efforts to explore new reaction patterns of *N*-tosyl propargylamides,[5] we envisaged that whether oxygen-atom transfer could facilitate the cyclizations of propargylamides with nucleophilic coupling partners to deliver some unexpected aza-heterocycles (Scheme 1c). Indeed, by employing $TMSN_3$ as the coupling partner, the iodocyclization of internal *N*-Ts propargylamides furnished various tetrazoles **2**, whereas that of terminal substrates gave dihydroimidazoles **4** (Scheme 1d). Intramolecular OAT from the amide groups to carbon-carbon triple bonds was observed in both cyclizations. The OAT process enables the amide to serve as a two-atom unit in the reactions. Thus, we have realized the O-transfer-facilitated cyclizations of propargylamides with $TMSN_3$ to selectively construct functionalized tetrazoles[6,7] and diiodomethylated dihydroimidazoles[8] for the first time. Herein, we report the preliminary results of our investigations.



Scheme 1. An overview of oxygen transfer reactions of functionalized alkynes

Our initial studies were carried out using internal propargylamide **1a** as substrate, NIS as iodine source, and $TMSN_3$ as coupling partner. When the reaction was performed in DCE at 60 °C, 1,5-disubstituted tetrazole **2a** was obtained. The structure of **2a** was unambiguously confirmed by X-ray crystallography.[9] It is noteworthy that the most known synthesis of tetrazoles involves the cycloaddition reactions between azides and nitriles.[7] Nonetheless, our method provides an appealing alternative for the

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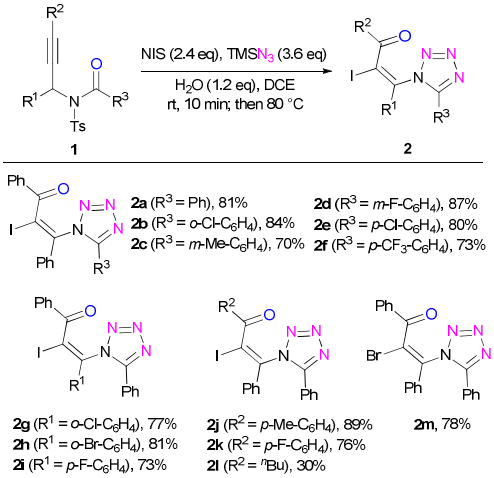
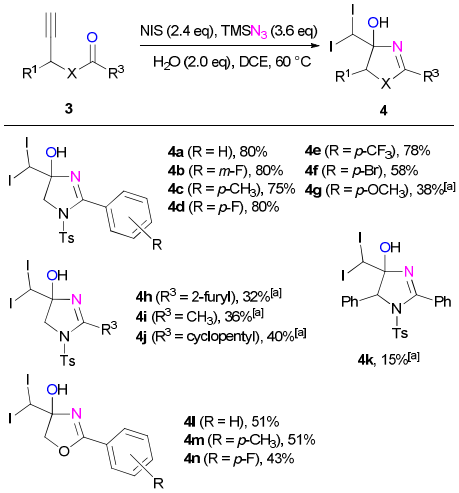
† Electronic Supplementary Information (ESI) available: General experimental procedures, characterization data, ^1H and ^{13}C NMR spectra and X-ray crystallographic analysis of compounds **2a** (CCDC 1026405) and **4a** (CCDC 1026409). For ESI and crystallographic data in CIF or other electronic format, see DOI: 10.1039/x0xx00000x

synthesis of functionalized tetrazoles from amides and azides,[10] which prompted us to screen the reaction conditions for this process (see the Supporting Information). Gratifyingly, the reaction of **1a** with NIS (2.4 equiv), $TMSN_3$ (3.6 equiv) and H_2O (1.2 equiv) in DCE at 80 °C delivered tetrazole **2a** in 81% yield (Scheme 2). The scope of this transformation was further examined (Scheme 2). Propargylic amides possessing a broad variety of aromatic motifs in R^1, R^2 and R^3 groups underwent this reaction smoothly, providing the corresponding tetrazoles (**2b–2k**) in good yields. The electronic effects and the positions of the substituents on the phenyl ring had less influence on the results. However, when aliphatic moiety was employed as R^3 (e.g. R^3 = Me) or R^1 (e.g. R^1 = ^{i}Pr) group, no reactions occurred. Butyl substituent in R^2 group was also tolerated, albeit with lower yield (**2l**). Moreover, NBS could also trigger this cyclization(**2m**), whereas NCS gave no desired product.

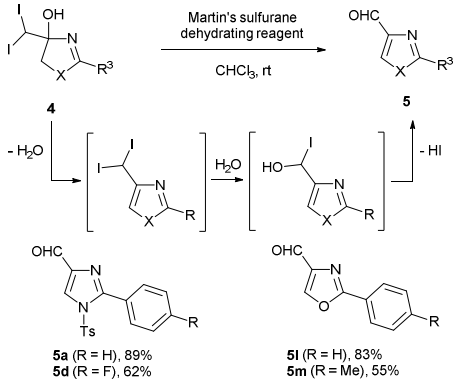


Scheme 2. Direct transformation of internal propargylic amides into tetrazoles. Reaction conditions: **1** (0.20 mmol), NIS (0.48 mmol), $TMSN_3$ (0.72 mmol), H_2O (0.24 mmol), DCE (3.0 mL), at RT for 10 min, then 80 °C for 2–8 h; isolated yields are given.

Having established the transformations of internal propargylamides, we wondered whether the chemo- and regioselectivity of the reactions can be tuned by changing the substituents on the amides. To our delight, when terminal propargylamide **3a** was subjected to the same conditions, diiodomethylated dihydroimidazole **4a** was obtained.[9] Since dihalogen-derived compounds have been shown to possess useful biological activity,[11] this reaction might be applicable to prepare analogous diiodomethylated heterocycles.[12] After careful screening of the reaction conditions (see the Supporting Information), we observed that the desired product **4a** could be obtained in 80% yield at 60 °C (Scheme 3). Variations on the acyl moiety (R^3) were first examined. Both electron-withdrawing and electron-donating substituents (R) on the phenyl ring were compatible with this transformation, giving the corresponding dihydroimidazo-4-ols **4b–4g** in moderate to good yields. It is noteworthy that when *p*-OCH_3 substituted propargylamide **3g** was submitted to the standard conditions, no desired product was formed. Pleasingly, switching the solvent to 1,4-dioxane could provide dihydroimidazole **4g** in 38% yield. It turns out that 1,4-dioxane is much more effective than DCE for the cyclization of heteroaryl- and alkyl-derived substrates. For example, 2-furyl, methyl and cyclopentyl substituents in R^3 group (**3h–3j**) were all well tolerated with the reaction. Unexpectedly, the R^1 group significantly influences the reactivity. When phenyl group was employed as R^1, dihydroimidazole **4k** was only obtained in 15% yield. Gratifyingly, the protocol can be further extended to oxygen-linked propargylic carboxylates bearing various aromatic moieties (**3l–3n**), furnishing the products in moderate yields. It is noted that neither NBS nor NCS could promote the cyclization of **3a**.



Scheme 3. Substrate scope. Reaction conditions: **3** (0.20 mmol), NIS (0.48 mmol), $TMSN_3$ (0.72 mmol), H_2O (0.40 mmol), DCE (3.0 mL), 60 °C, 8–18 h; isolated yields are given. [a] 1,4-dioxane (3.0 mL) was used as solvent.

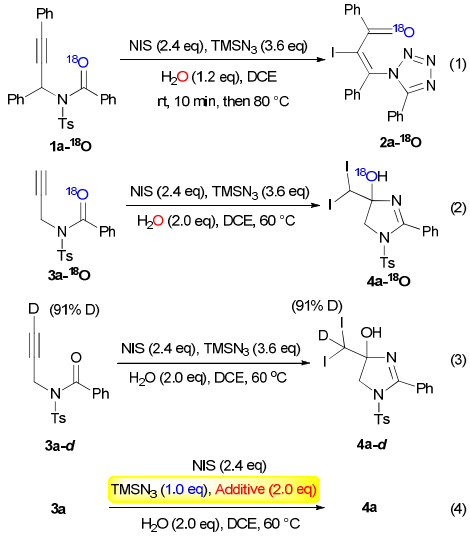


Scheme 4. Synthesis of heterocyclic carbaldehydes. Reaction conditions: **4** (0.20 mmol), Martin's sulfurane dehydrating reagent (0.40 mmol), $CHCl_3$ (2.0 mL), at room temperature for 12–18 h; isolated yields are given.

To illustrate the synthetic potential of the products, additional investigations were performed on their further transformations. Pleasingly, we found that the resulting dihydroimidazo-4-ols and dihydrooxazo-4-ols could be efficiently converted into the corresponding carbaldehydes in the presence of Martin's sulfurane dehydrating agent in $CHCl_3$ (Scheme 4).[13] The elimination of H_2O leads to diiodomethylimidazoles or diiodomethyloxazoles, followed by nucleophilic substitution and elimination of HI to furnish the final products in 55–89% yields. This general protocol can be readily applied for the construction of diversified heterocyclic carbaldehydes under mild conditions.

To probe the reaction mechanism, isotopic labelling experiments were first conducted. When ^{18}O was incorporated into the carbonyl group of propargylamide **1a** [Eq. (1)] or **3a** [Eq. (2)]

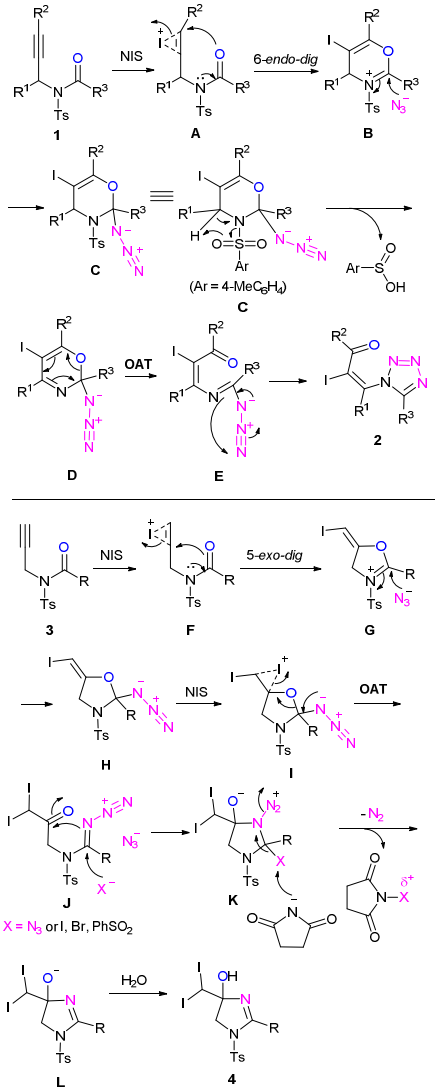
respectively, ^{18}O-labeled products were observed for both cyclizations. Besides, when $H_2{}^{18}O$ was employed in the reactions, only normal products **2a** and **4a** were obtained (see the Supporting Information). These results indicate that intramolecular OAT from amide group to carbon-carbon triple bond occurs in the reaction process. The deuterated substrate **3a-*d*** underwent this reaction efficiently to afford the desired product **4a-*d*** without any loss of deuterium (see the Supporting Information), which implies that the terminal C–H bond of alkyne is not cleaved in the reaction and the proton of hydroxyl group originates exclusively from H_2O [Eq. (3)].



Entry	Additive	Yield of **4a**
A	none	trace (<5%)
B	NaI	39%
C	KBr	58%
D	$PhSO_2Na$	15%
E	NaN_3	23%
F	$TMSN_3$	78%

Notably, only one equivalent of azide or nitrogen atom is ultimately incorporated into the product, while much excess amount of $TMSN_3$ (3.6 equiv) is required to promote the reactions. This phenomenon indicates that the role of $TMSN_3$ is not only limited to be a nucleophile (or coupling partner), but might be a counteranion.[14] Meanwhile, in situ umpolung of azide[15] may also occur in the reaction. To confirm this hypothesis, control experiments were then carried out [Eq. (4), entries A–F]. Indeed, the reaction of **3a** with 1 equivalent of $TMSN_3$ only gave trace amount of **4a** [Eq. (4), entry A]. In contrast, with the assistance of other anions (e.g. I^-, Br^- and $PhSO_2^-$), non-negligible amount of product could be produced [Eq. (4), entries B–D]. It is noteworthy that the using of NaN_3 as additive could also promote this reaction [Eq. (4), entry E], albeit with much lower yield than its $TMSN_3$ analogue [Eq. (4), entry F].

On the basis of these preliminary mechanistic studies, a plausible mechanism is proposed (Scheme 5). In the case of internal substrate **1**, an attack of the carbonyl oxygen atom onto the I^+-activated carbon-carbon triple bond via a 6-*endo-dig* cyclization mode produces intermediate **B**. The iminium ion of **B** can be trapped by an azide anion formed in situ from $TMSN_3$ and H_2O, followed by the elimination of 4-methylbenzenesulfinic acid[5a] and retroelectrocyclization to give O-transfer intermediate **E**. Finally, an intramolecular cyclization affords tetrazole **2**. In contrast, a 5-*exo-dig* cyclization of terminal substrate **3** occurs, resulting in the formation of intermediate **H**. The activation of exo-cyclic double bond by I^+ and intramolecular OAT lead to the ring opening product **J**. The in situ formed azidocarbenium ion[14] is likely to be surrounded by azide anion through a contact ion pair. Subsequently, an excess of azide anion acts as another molecule of nucleophile to promote the cyclization and furnish intermediate **K**. Ultimately, the succinimide anion traps the azide group of **K** (when X = N_3), releasing *N*-azide succinimide by an umpolung step, followed by protonation to generate the desired product **4**. However, attempts to isolate or detect the byproduct *N*-azide succinimide did not succeed, which was presumably due to its lability in the reactions. Fortunately, the molecular weight of *N*-phenylsulfonyl succinimide (239.0) was detected by LC-MS when $PhSO_2Na$ was employed in the reaction [Eq. (4), entry D], thus providing an indirect evidence to support the proposed mechanism.



Scheme 5. Proposed mechanism

In conclusion, we have developed the O-transfer-facilitated cyclizations of propargylamides with $TMSN_3$ to

selectively afford functionalized tetrazoles and diiodomethylated dihydroimidazoles. OAT from amide group to C≡C bond was realized via a NIS-triggered-cyclization/ring-opening cascade pathway. This process enables the amide to serve as a two-atom unit in the cyclizations. The resulting products can be further transformed into the corresponding heterocyclic carbaldehydes. We expect our findings can be applicable to develop new reaction patterns of amides.

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