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Transition-metal-free multinitrogenation of amides by C-C bond cleavage: a new approach to tetrazoles

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A metal-free brand-new one-pot multinitrogenation of amides for the chemo-, regioselective synthesis of 1,5-disubstituted tetrazoles is depicted. By means of electrophilic amide activation, further C-C bond cleavage and rearrangement, a diverse set of functionalized 1,5-DST derivatives were selectively constructed under mild conditions. As showcased in mechanisms, the chemoselectivity is easily switched by the selection of the starting materials in the reaction.

The cleavage of carbon−carbon bonds is considered as an industrial key technology, and this chemistry has kept appealing in organic fundamental transformation.[1] Among them, transition-metal-catalyzed unstrained C-C bond cleavage has been made impressive progress in recent decades.[2] However, owing to high inertness and highly directed nature, the development of C−C bonds activations lags more behind the traditional C-X (X=halogen), C-M (M=metal), and C-Y (Y =O, N, S, P) bond cleavage, there is obvious scope for the discovery of novel reactions through direct C-C bond functionalization to reach new applications.[3]

In the other hand, the tetrazole ring has attracted significant attention, especially the 1,5-disubstituted tetrazoles (1,5-DSTs), which are widely found in numerous biologically active substances. Some of these scaffolds exhibit various types of biological properties, such as growth hormone secretagogue, antiviral and anti-inflammatory.[4] In 1980, Nohara[5] identified the first tetrazole *N*1 glucuronide in the urine stream of several animals orally dosed with a chromone-derived tetrazole. Those *bio*-structures have showed low toxicity and a wide range of activity (Figure 1).

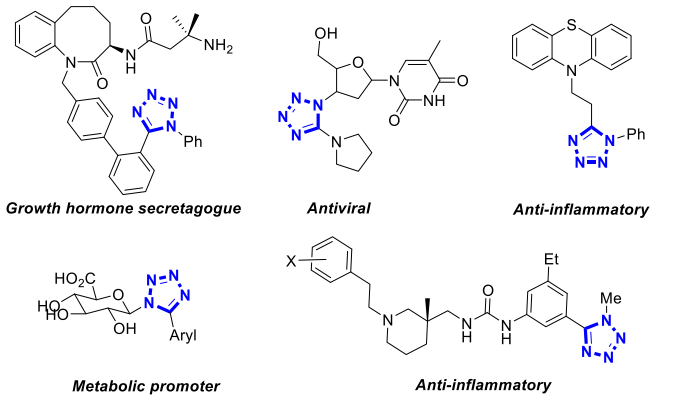
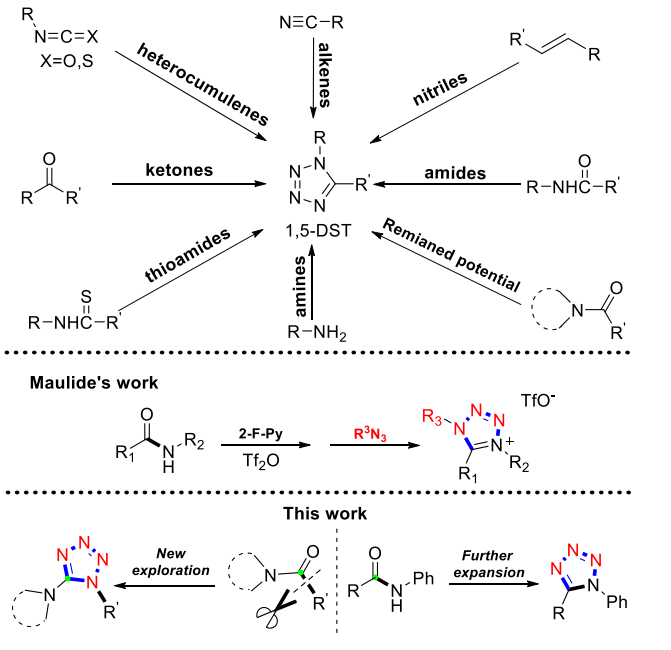


Figure 1 Selected bioactive 1,5-DSTs

In this context, a great number of strategies for synthesizing tetrazoles have been reported (Scheme 1),[6] such as nitriles, alkenes, thioamides, heterocumulines, ketones, amines, amides are considered as common starting materials, and among them, amides have been preferentially selected since they are readily available and enormously utilized.[6a]

Based on the electrophilic activation of amides, various chemical transformations have been emerged by using triflic anhydride (Tf_2O) over the years,[7,8] particularly, Maulide and his co-workers' have worked on tetrazolium salts[8j] (Scheme 1) and our work team has recently exploited a valuable chemoselective strategy to furnish quinolone derivatives.[9] Inspired by these noteworthy works, we noticed that multinitrogenation with metal-free process would be an intriguing new challenge. Consequently, we tried to design a new reaction pathway to get triazoles from $TMSN_3$ and amides, the system didn't provide any eye-catching transformation in the initial investigation. Nevertheless, under the ceaseless



Scheme 1 Strategy design to 1,5-DSTs

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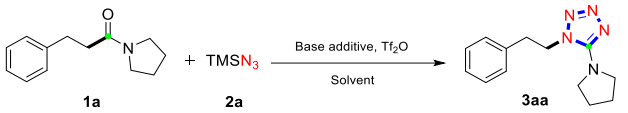
Table 1 Optimizing of the reaction conditions[a]

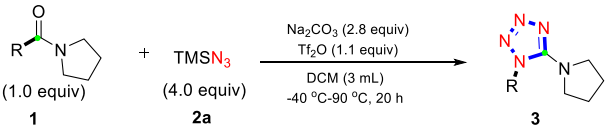


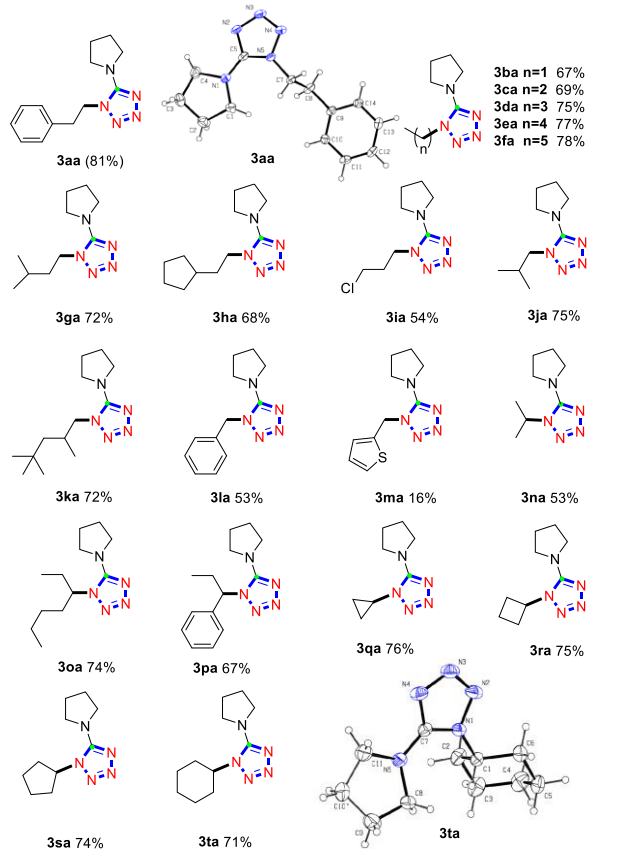
1a 2a 3aa

Entry	Base additive	Temp (°C)	Solvent	Yield (%)[d]
1[b]	2,6-lutidine	80	DCM	trace
2	2,6-dichloropyridine	80	DCM	trace
3	2-chloropyridine	80	DCM	trace
4	NaH	80	DCM	41
5	K_2CO_3	80	DCM	28
6	Na_2CO_3	80	DCM	50
7	Na_2CO_3	90	DCE	47
8	Na_2CO_3	90	toluene	trace
9	Na_2CO_3	90	1,4-dioxane	N,D
10[c]	Na_2CO_3	90	DCM	81

[a] Reaction conditions: To a mixture of amide **1a** (0.2 mmol, 1.0 equiv), $TMSN_3$ (3.0 equiv) and base additive (2.6 equiv) in DCM (3.0 mL) was added Tf_2O (1.1 equiv) at -78 °C under Ar atmosphere. After 20 min, the reaction mixture was stirred at the reported temperature. [b] Base (2.0 equiv) was used. [c] $TMSN_3$ (4.0 equiv), base additive (2.8 equiv), Tf_2O (1.1 equiv) were added at -40 °C. [d] Isolated yields. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, DCE = 1,2-dichloroethane, DCM = dichloromethane.

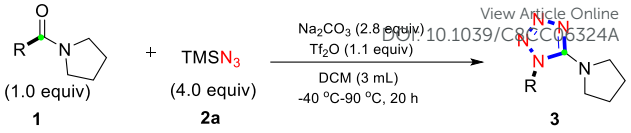
Table 2 Scope of the amide substrates[a,b]

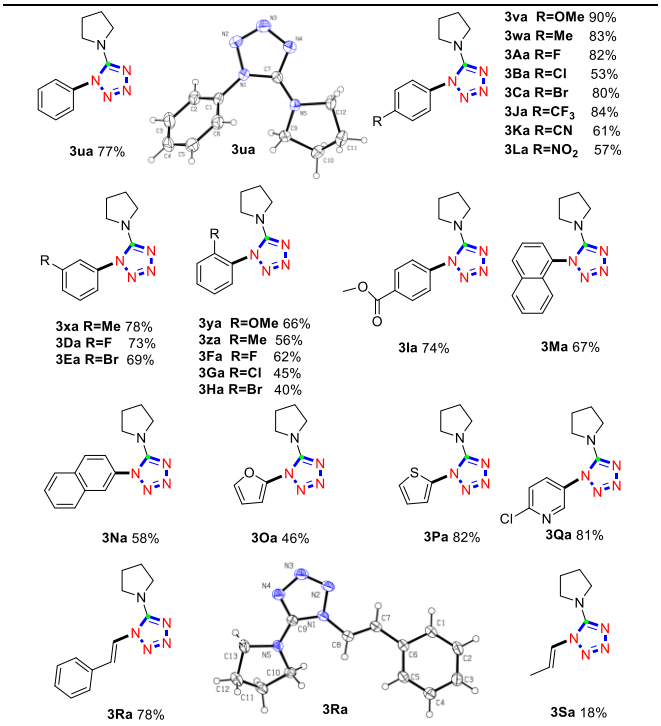




[a] All reactions were carried out on 0.2 mmol scale under Ar atmosphere (amide as 1.0 equiv). [b] Isolated yields.

Table 3 Substrate scope of the amides[a,b]





[a] All reactions were carried out on 0.2 mmol scale under Ar atmosphere (amide as 1.0 equiv). [b] Isolated yields.

progression, it turned out to be a brand-new result and the outcome was confirmed as 1,5-disubstituted tetrazole by X-ray crystal structure analysis subsequently. Thus, we herein report a metal-free multinitrogenation of amides with spontaneous C-C bond cleavage and rearrangement to offer multi-*N*-atom-loading structure: 1,5-disubstituted tetrazoles.

At the outset, the tertiary amide **1a** was selected as a model substrate to explore this transformation (Table 1). The reaction was conducted in the presence of $TMSN_3$, 2,6-lutidine and Tf_2O at 80 °C with no new product came out. After screening different base additives, we gladly tracked out an appealing outcome and the productivity reached pleasant 50% with Na_2CO_3 as the crucial base support (Table 1, entry 6). An evaluation of solvents showed that the frequently-used solvent CH_2Cl_2 (DCM) had a beneficial effect for this transformation. With the adjustment of ratio between base and Tf_2O, we ultimately used 2.8/1.1 ratio of Na_2CO_3 and Tf_2O as the optimal option. The highest efficiency was achieved by increasing the amount of $TMSN_3$ to 4.0 equiv at 90 °C, therefore generating the desired product **3aa** in 81% yield (Table 1, entry 10).

With the optimal reaction conditions in hand, we got started to survey the compatibility of this reaction. As shown in Table 2, this new method can be applied with a wide range of substituents, thus giving 1,5-DST derivatives in generally good to excellent yields. Firstly, amides with chain alkyl groups were examined and the substrates underwent favourably to produce 1,5-DSTs (Table 2, **3aa-3ka**). When a halogen was linked to the amide, the desired product could also be obtained in 54% yield (Table 2, **3ia**), which allows significant opportunity for further functionalization, especially in pharmacological demand. Furthermore, benzyl amide and thiophenolamide afforded the desired product in acceptable yields of 53% and 16%, respectively (Table 2, **3la**, **3ma**). Amides bearing

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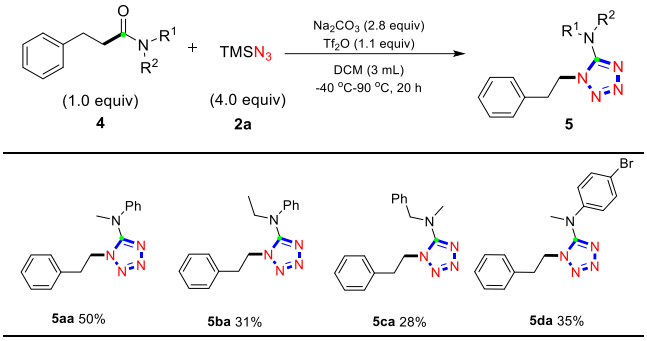
Table 4 Substrate scope of the amides[a,b]



[a] All reactions were carried out on 0.2 mmol scale under Ar atmosphere (amide as 1.0 equiv). [b] Isolated yields.

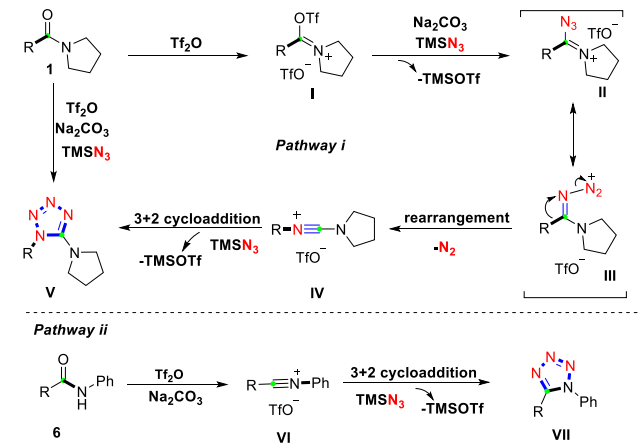
α-substituted chain alkyl groups performed well under the standard conditions giving the corresponding products in moderate to good yields (**3na**-**3pa**). The effect of the strained cycloalkyl moiety was tested as well. The related substrates were tolerated to give the corresponding products in high yields (Table 2, **3qa**-**3ta**). The exclusive structures of **3aa** and **3ta** were specifically confirmed by X-ray crystal structure analysis in Table 2.

Our attention next turned to explore the capability of diverse benzamides (Table 3). To our delight, benzamides with different functional groups were impressively tolerated in this protocol (Table 3, **3ua**-**3Sa**). Among them, benzamides with *α*- and *β*-naphtyl substituent efficiently participated in the reaction and provided the desired product in good yields (Table 3, **3Ma**, **3Na**). Notably, heteroaromatic amides bearing furyl, thienyl and pyridyl were also compatible under the reaction conditions (Table 3, **3Oa**-**3Qa**). The structures of **3ua** and **3Ra** were confirmed by X-ray crystal structure analysis.

The substrates with various alkyl and aryl groups at *N* were further studied. The system offered the desired products as expected, and the yields were acceptable (Table 4). Based on these results, it was found that the pyrrolidine substituted amides were the most efficient components in this chemistry.

Encouraged by these observations, the plausible mechanism—pathway **i** was proposed to support this appealing versatile protocol in Scheme 2. The Tf_2O-mediated activation of amide was expected to generate highly electrophilic adduct **I**. The subsequent nucleophilic attack of $TMSN_3$ on adduct **I** led to intermediate **II**, which could be transformed to intermediate **IV** through an acid-catalyzed rearrangement process.[10] In this process, the Na_2CO_3 played a role of promoting generation of indtermediate **II**, **III** (more detials see supporting information). Furthermore, the high migratory aptitude of **R** group, either aromatic or aliphatic groups, exhibited the unique regioselectivity of this

Scheme 2 Proposed mechanisms



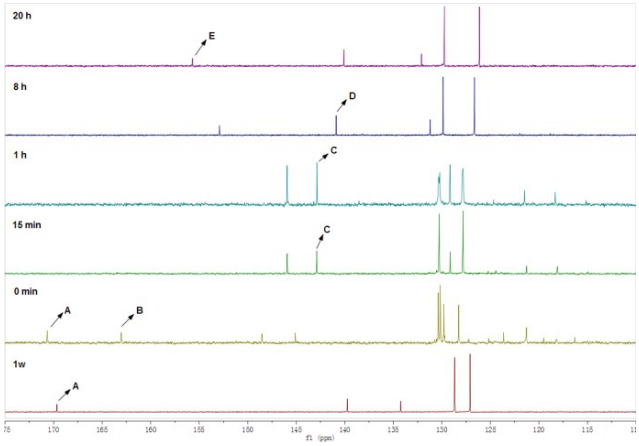


Figure 2 Transformation of **3wa** monitored by **^{13}C NMR** spectroscopy (**100MHz**, **$CDCl_3$**). **A** = **1w** carbonyl carbon, **B**, **C** and **D** = transforming signals assigned to original **1w** carbonyl carbon, **E** = **3wa** imine carbon.

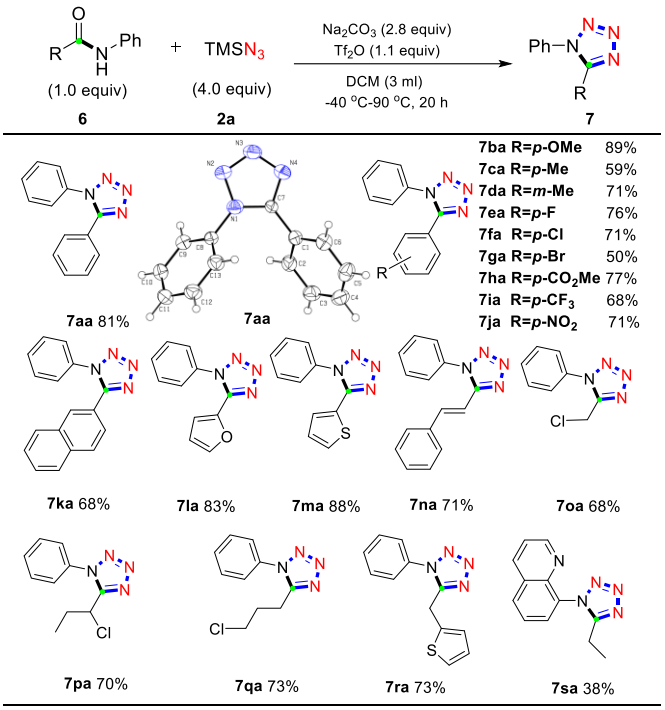
transformation. The intermediate **IV** was attacked by $TMSN_3$ once again, and underwent 1,3-dipolar cycloaddition[11] to produce the desired 1,5-DST product **V** ultimately.

Aimed to further understand this chemistry, the process of the symbolic transformation of **3wa** was monitored by **^{13}C NMR** spectroscopy (Figure 2). We can see that the signal **A** at 169 ppm was assigned to the carbonyl carbon of **1w** originally. After Tf_2O-activated, the signal **A** started to decline and signal **B** 163 ppm appeared, which was corresponding to intermediate **I** in pathway **i** (Scheme 2). Heated at the reported temperature and reacted with $TMSN_3$, the signal **C** 143 ppm came up and became stronger to point to intermediates **II** and **III**, represented the process from nuleaophilic attack and C-C bond cleavage to rearrangement. Around 8 h reaction time, the signal **D** 141 ppm of **IV** was settled successively (details and anyalsis of further water-quenching experiment of **IV** have been dispalyed in supporting information), and the signal **E** 153 ppm of the exact product **3wa** set up eventually at 20 h complete reaction time.These results clearly verify that the turnover-limiting step of this chemistry—Tf_2O-activated process takes place in short time and the nucleophilic attack from $TMSN_3$ is probably an endothermic reaction process. The transformation among the proposed intermediates happens step by step, and they are afforded as transient ions, therefore, difficult to separate from the reaction mixtures.

This captivating reaction transformation gave us further anticipation to explore secondary amide substrates which might occur via a different pathway **ii** (Scheme 2). The conceivable reaction results displayed in Table 5. The secondary amides bearing both aromatic and aliphatic groups were transferred into the desired 1,5-DST motifs with moderate to high yields (Table 5, **7aa**-**7sa**). The reaction further exhibited conspicuous chemo- and regioselectivity to create single structure. On the behalf of the desired products in Table 5, the exclusive structure of **7aa** was unambiguously confirmed by single-crystal X-ray analysis. The examples prosperously illustrate the practicability and compatibility of this chemistry and highlight the flexibility of this methodology.

In a conclusion, we have developed a metal-free easy-organized high chemo- and regioselective synthesis of 1,5-disubstituted tetrazoles through C-C bond cleavage under mild

Table 5 The 3+2 cycloaddition of amides[a,b]



[a] All reactions were carried out on 0.2 mmol scale under Ar atmosphere (amide as 1.0 equiv). [b] Isolated yields.

conditions. This chemistry: 1) possesses a fabulous reaction flexibility, undergoes different mechanisms with different starting materials, and showcases a certain diversity of the reaction; 2) splits the C-C bond and builds up a new C-N bond in one step; 3) generates a nitrogen multiloading process between C-C bond atoms and achieves a desired high bioactive value structure straightforwardly. More related studies on amides activation are ongoing in our laboratory.

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