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# One Step Cascade Synthesis of 4,5-Disubstituted-1,2,3-(*NH*)-Triazoles

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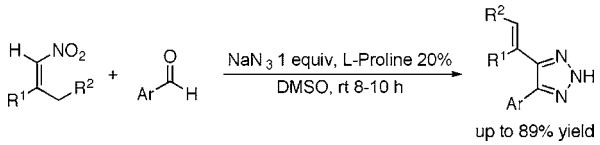
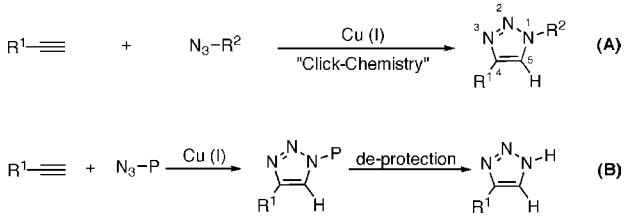
## ABSTRACT




**A Lewis base-catalyzed three-component cascade reaction was developed for the synthesis of 4,5-disubstituted-1,2,3-(*NH*)-triazoles. More than 25 new (*NH*)-triazoles were prepared in good to excellent yields under mild conditions. The availability of the C-4 vinyl group allows easy conversion into other triazole derivatives.**

Since the recent discovery of the Cu-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC, often referred to as "click-chemistry"), the 1,2,3-triazole compounds have received considerable attention from scientists in various fields.[1] Within the last 5 years, the importance of these compounds has been continuously demonstrated in research fields as diverse as material science,[2] chemical biology,[3] and medicinal chemistry.[4]

Despite being a very efficient method for the synthesis of N-substituted triazole (reaction **A**), one limitation of the CuAAC is the lack of reactivity toward unsubstituted azides,




such as $NaN_3$ and $HN_3$. Therefore, to prepare the N-unsubstituted triazoles (NH-triazole) by CuAAC, the organic azides are usually applied with removable N-protecting groups (reaction **B**) followed by deprotection.[5] Meanwhile, the thermal reactions between alkyne and $NaN_3/HN_3$ gave low yields, and the preparation of substituted alkynes was usually challenging and had high costs.[6] Therefore, an efficient synthesis of substituted NH-triazoles (as a complementary approach for the CuAAC reaction) is highly

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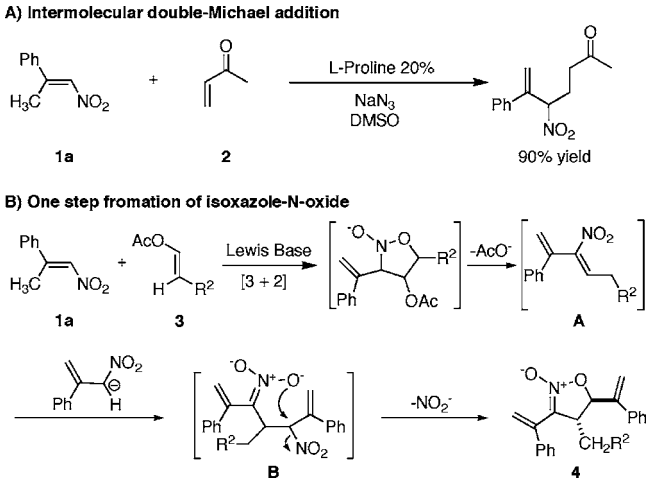
desirable. Herein, we report a L-proline catalyzed cascade reaction as an efficient approach for the synthesis of 4,5-disubstituted-NH-triazoles.

Our interest in developing new synthetic methods by an organo catalyst promoted cascade reaction recently led to the discovery of the successful intermolecular double-Michael addition between nitro and carbonyl activated olefins[7] as shown in Scheme 1A. The key to this new

**Scheme 1**



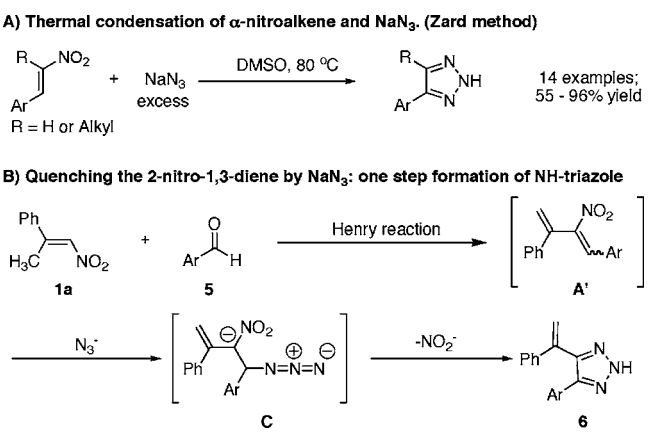

methodology was the introduction of a $\beta$-alkyl group on the nitroalkene, which allowed the $\beta$-elimination to give the allylic nitro compounds as the stable product rather than the highly reactive nitroalkenes. Moreover, we recently discovered that the treatment of nitroalkene **1** with electron enriched olefins gave isoxazole-*N*-oxide as shown in Scheme 1B.[8] The potential applications of functional 1,2,3-triazole derivatives and the recent discovery of organo catalyst mediated cascade reactions mentioned above initiated our interest in extending this approach to the synthesis of NH-triazoles through cascade reactions from simple, readily available starting materials.

Besides the CuAAC approach, another method for the synthesis of 1,2,3-triazole is the 1,3-dipolar cycloaddition between $\beta$-nitrostyrene and $NaN_3$, which was first reported by Zefirov in 1971.[9] With DMSO as the solvent at room temperature, the authors reported the formation of 4-phenyl-1,2,3-triazole in 65% yield. However, a recent study by Quiclet-Sire and Zard indicated that this result was not reproducible.[10] Instead, they developed an optimized approach using an α-substituted nitroalkene and an excess amount of $NaN_3$ (2−4 equiv) at 80−90 °C. With the optimized condition, some NH-triazoles were prepared in good to excellent yields (54%−96%). However, as pointed out by the authors, the reaction yields highly depended on the substrates, and the synthesis of the olefin precursor was challenging (unfavored equilibrium in the Henry reaction) and in some cases gave low yields. Therefore, as a general problem, all the thermal cyclization approaches suffered from limited substrate scope.

In our recently reported cascade double-Michael addition between nitroalkene **1a** and enone **2**, a formal allylic nitro nucleophile was generated under mild conditions. Moreover, the attempt on [3 + 2][11] cycloaddition of **1a** and electron-rich alkene **3**, forming isoxazole-N-oxide **4**, revealed the formation of 1,3-diene **A** as activated intermediate. We then wondered whether $N_3^-$ could quench the diene intermediate to produce NH-triazole **6**, which would avoid the synthesis of α-nitroalkene starting material (more complicated 1,2-disubstituted nitroalkenes) in the 1,3-dipolar cycloaddition and significantly increase the reaction substrate scope.

Our initial attempt was to treat **1a** and **3** with the addition of $NaN_3$ to quench intermediate **A**. However, only isoxazole **4** was obtained with no formation of triazole, even in the presence of excess $NaN_3$. It suggested that the 1-alkyl diene **A** is a highly reactive intermediate, which was fully quenched by allylic nitro carbanion and not by the $N_3^-$. To avoid this nitro carbanion addition, an alternate approach was designed by treating nitroalkene **1** with aryl aldehyde **5** to form the 1-aryl diene **A′** followed by $N_3^-$ 1,3-dipolar cycloaddition to give triazole **6** (Scheme 2B). As expected, the reaction of

**Scheme 2**




nitroalkene **1a**, benzylaldehyde, and $NaN_3$ produced the desired 1,2,3-NH-triazole **6a** at room temperature. The screening of the reaction conditions is summarized in Table 1.

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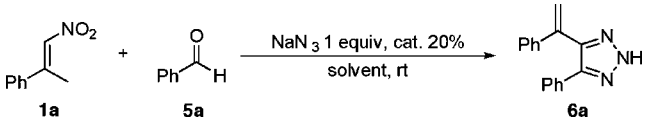
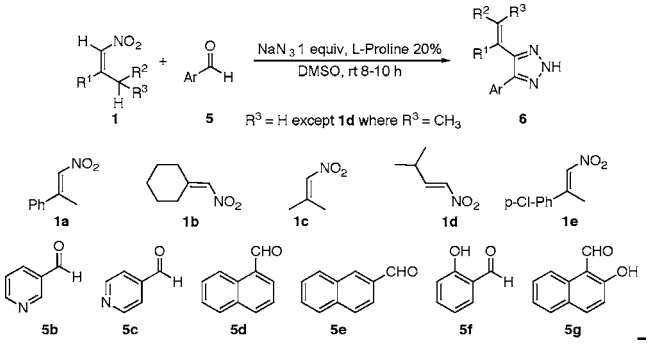
**Table 1.** Screening of the Reaction Conditions[a]




| | solvent | cat.[b] | temp (°C) | time (h) | convn (%)[c] | yield (%)[d] |
|---|---|---|---|---|---|---|
| 1 | DMSO | | rt | 12 | 40 | 28 |
| 2 | DMSO | | 80 | 10 | 100 | 35 |
| 3 | DMSO | L-Pro | rt | 8 | 100 | 90 |
| 4 | DMSO | pyrrolidine | rt | 8 | 15 | 12 |
| 5 | DMSO | pyrrolidine/AcOH | rt | 8 | 20 | 14 |
| 6 | DMSO | DMAP | rt | 8 | 35 | trace |
| 7 | DMSO | DIPEA (1.0) | rt | 8 | 30 | trace |
| 8 | DMSO | NaOt-Bu (1.0) | rt | 8 | trace | trace |
| 9 | DMSO | glycine | rt | 8 | 90 | 20 |
| 10 | DMSO | $P(OMe)_3$ | rt | 20 | trace | trace |
| 11 | DMSO | imidazole | rt | 20 | 40 | trace |
| 12 | THF | L-Pro | rt | 12 | 58 | 45 |
| 13 | MeCN | L-Pro | rt | 12 | 58 | 55 |
| 14 | MeOH | L-Pro | rt | 12 | 65 | 64 |
| 15 | Acetone | L-Pro | rt | 12 | 48 | 40 |
| 16 | $MeNO_2$ | L-Pro | rt | 20 | 60 | 56 |

[a] Reactions were carried out at room temperature, **1a:5a** = 1:2. [b] 20% catalyst loading. [c] Conversion based on the consumption of the starting material **1a** from NMR. [d] NMR yield was determined by 1,3,5-trimethoxybenzene as internal standard.

**Table 2.** Reaction Substrate Scope[a]




| entry | 1 | 5 | time (h) | yield (%)[b] |
|---|---|---|---|---|
| 1 | **1a:** $R^1$ = Ph; $R^2$ = H | Ar = Ph | 8 | **6a:** 89 |
| 2 | **1a** | Ar = p-$NO_2$-Ph | 8 | **6b:** 88 |
| 3 | **1a** | Ar = m-$NO_2$-Ph | 8 | **6c:** 85 |
| 4 | **1a** | Ar = o-$NO_2$-Ph | 8 | **6d:** 81 |
| 5 | **1a** | Ar = p-CN-Ph | 8 | **6e:** 78 |
| 6 | **1a** | Ar = p-Cl-Ph | 8 | **6f:** 74 |
| 7 | **1a** | Ar = p-OMe-Ph | 8 | **6g:** 40[d] |
| 8 | **1a** | Ar = 2,6-di-Cl-Ph | 8 | **6h:** 76 |
| 9 | **1a** | **5b** | 8 | **6i:** 76 |
| 10 | **1a** | **5c** | 8 | **6j:** 75 |
| 11 | **1a** | **5d** | 8 | **6k:** 81 |
| 12 | **1a** | **5e** | 8 | **6l:** 83 |
| 13 | **1a** | **5g** | 8 | **6m:** 56[d] |
| 14 | **1b:** $R^1$; $R^2$ = -$(CH_2)_4$- | Ar = Ph | 8 | **6n:** 72 |
| 15 | **1b** | Ar = p-$NO_2$-Ph | 8 | **6o:** 78 |
| 16 | **1b** | Ar = p-Cl-Ph | 8 | **6p:** 74 |
| 17 | **1b** | **5c** | 8 | **6q:** 71 |
| 18 | **1b** | **5d** | 10 | **6r:** 73 |
| 19 | **1b** | **5f** | 8 | **6s:** 65[d] |
| 20 | **1c:** $R^1$ = $CH_3$; $R^2$ = H | Ar = p-$NO_2$-Ph | 10 | **6t:** 58[e] |
| 21 | **1c** | **5c** | 8 | **6u:** 55 |
| 22 | **1d:** $R^1$ = H; $R^2$ = $R^3$ = Me | **5c** | 8 | **6v:** 56 |
| 23 | **1e:** $R^1$ = p-Cl-Ph; $R^2$ = H | **5c** | 8 | **6w:** 81 |

[a] Compounds **1** (1.0 equiv), **5** (2.0 equiv), L-Pro (20%), and $NaN_3$ (1 equiv) were dissolved in DMSO (0.2 M of **1**) and stirred at rt. Reactions were monitored by TLC. [b] Isolated yields. [c] **6t** was characterized by X-ray crystallography. [d] Heating at 80 °C.

The treatment of sodium azide with **1a** and **5a** in DMSO gave the NH-triazole **6a** in poor yield without the addition of a Lewis base (LB) catalyst (entry 1). As reported in our previous paper, sodium azide not only is the reactant but also serves as the Lewis base in the activation of **1a**. However, as a less effective Lewis base catalyst, the reaction proceeded slowly at room temperature. Increasing the reaction temperature resulted in the significant polymerization of the nitroalkene **1a** (entry 2). Further addition of different Lewis base catalysts revealed proline as the best catalyst. Screening of the solvents gave DMSO as the solvent of choice. Considering the low cost, good reaction performance, and easy handling, L-proline was selected as the catalyst. The optimal reaction condition is shown in entry 3. Different nitroalkene and aromatic aldehydes were then applied to evaluate the reaction substrate scope, and the results are shown in Table 2.

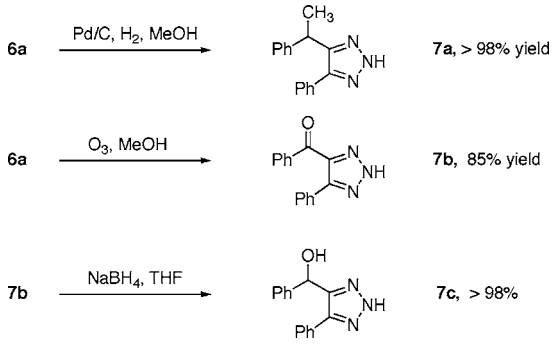
As shown in Table 2, a large number of aryl aldehydes and $\beta$-alkyl nitroalkenes are suitable for this transformation. Various 4,5-disubstituted NH-triazoles can be efficiently synthesized from this cascade process. Based on the reaction mechanism shown in Scheme 2B, the major competing side reaction is the polymerization of the nitroalkene **1**. Therefore, less hindered nitroalkenes (**1c**, **1d**) gave moderate yields of **6** due to the decomposition of **1**. An excess amount of aldehyde (2.0 equiv) was also found to be important for the best product yields. The application of a stoichiometric amount of aldehyde (1.0 equiv) generally gave 10−20% lower yields of **6**, varying by substrates. This may be due to the formation of oxidative $NO_2^-$ byproduct, which causes the decomposition of the reactant aldehyde. The electron density on the aryl group of the aldehydes also influences the reaction performance. Nonsubstituted aromatic aldehydes and electron deficient aromatic aldehydes work well in this cascade approach. Electron-donating group substituted aryl aldehydes (entries 7, 13, 19), on the other hand, gave poor yields at room temperature (less than 20%). This is due to slow kinetics in the Henry reaction and the competition of compound **1** polymerization. Raising the reaction temperature to 80 °C produced the desired triazole **6** in good yields.

Substituted azides (n-hexanyl azide and phenyl azide) have also been applied in this cascade process, and no triazole product was observed. This is probably due to the slow 1,3-dipolar addition between substituted azide and diene intermediate **A′**, which can be associated with either weaker nucleophilicity of the azide or slow elimination of $NO_2^-$. However, as a good nucleophile, the NH-triazoles can be

further functionalized in a regio- and enantioselective manner through readily available reactions, such as alkylation,[12] acetylation,[13] and Michael addition,[14] thereby allowing the formation of fully substituted 1,2,3-triazoles in simple steps.

Compared to the thermal-1,3-dipolar addition (Zard's method), this cascade approach generates the activated intermediate in situ. This method successfully avoids the difficult synthesis of the α-nitroalkene reactants (i.e., 1 vinyl-2-aryl nitroalkene), therefore significantly extending the reaction substrate scope. Moreover, the application of *β*-alkyl nitroalkene **1** allows the formation of a more reactive nitroalkene (1,3-diene) intermediate, which leads to mild reaction conditions and easy incorporation of other functional groups on the C-4, C-5 side chain. Some examples of side-chain modification are shown in Scheme 3.

**Scheme 3**




In conclusion, based on the Lewis base-catalyzed cascade nitroalkene-aldehyde-azide condensation, a new synthesis for NH-1,2,3-triazole was developed. The overall yields of this reaction are good, especially taking into consideration that this cascade method combines two reactions in "one-step". Notably, many of the products reported in Table 2 cannot be prepared from the CuAAC reaction (lack of reactivity at internal alkyne) nor by the thermal 1,3-dipolar cyclization (difficulty in the preparation of highly functional olefins). With the advantages of readily available starting materials, mild reaction condition and high atom-efficiency, this method provides a complementary approach for the synthesis of substituted 1,2,3-NH-triazoles. Development of these compounds as asymmetric ligands is currently under investigation and will be reported in due course.

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**Supporting Information Available:** Experimental details, spectrographic data, and XRD information. This material is available free of charge via the Internet at http://pubs.acs.org.

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