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One-Pot Synthesis of 3,4,5-Trisubstituted 1,2,4-Triazoles via the Addition of Hydrazides to Activated Secondary Amides

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Supporting Information

ABSTRACT: A general approach has been developed for the one-pot synthesis of 3,4,5-trisubstituted 1,2,4-triazoles from secondary amides and hydrazides via triflic anhydride activation followed by microwave-induced cyclodehydration. In addition, the 1,2,4-triazole moiety is shown to be a useful directing group for Ru-catalyzed C−H arylation. Access to 1,2,4-triazolophenanthridine can be achieved from the reaction products using a Pd-catalyzed intramolecular C−H functionalization reaction.

The 1,2,4-triazole motif has attracted considerable interest in the fields of medicinal and coordination chemistry as well as in materials science.[1] For example, this five-membered ring scaffold is found in numerous biologically active compounds[2] and pharmaceuticals, including maraviroc,[3] triazolam,[4] and sitagliptin.[5] Notably, this heterocycle is used as an amide *cis*-bond isostere for both peptide mimicry and drug design, where it can improve the pharmacological properties of the corresponding lead compound.[6] 1,2,4-Triazoles have also been extensively studied as ligands for mononuclear and oligonuclear metal coordination, exhibiting interesting physical properties.[7] Recent applications illustrate that the incorporation of the 1,2,4-triazole ligand into functional heteroleptic Ir(III) complexes affords a sky-blue emission with attractive quantum yields for potential use in organic light emitting diodes (OLEDs).[8]

Owing to its broad spectrum of functions, a number of synthetic methods have been developed for the synthesis of substituted 1,2,4-triazoles **3** (Figure 1).[1] The most commonly investigated pathways involve cyclodehydration of *N*-acylamidrazone derivatives **2**, which can be formed from various precursors, such as amides **1**,[1] amidrazones **4**,[9] *N*′-acetyl-*N*,*N*-dimethylhydrazonamides **5**,[10] oxadiazoles **6**,[11] and *N*-acylhydrazides **7**.[12] Substituted 1,2,4-triazole derivatives are also synthesized from dichloroaldazines **8** by treatment with anilines at 170 °C.[13] Unfortunately, most of the methods require multistep synthetic procedures as well as the use of nonreadily available starting materials and/or are limited to a methyl substituent at the C-5 position (R^3 = Me).[10]

Considering the ubiquity of substituted 1,2,4-triazoles in synthetic and applied chemistry, from both step-economy and medicinal chemistry perspectives, a process that allows the direct synthesis of 1,2,4-triazoles from secondary amides is of high interest. The formation of such a heterocycle via the addition of hydrazides to activated amide derivatives have been reported by different research groups (Figure 2). These methods include the use of chloromethylene amides[14] **9a**, imidates **9b**,[15] thioamides **9c**,[6a,16] thioimidates **9d**,[17] and

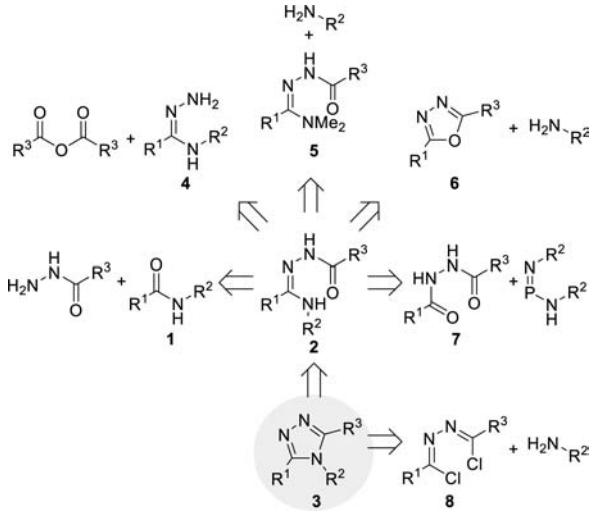

Figure 1. Different synthetic pathways leading to 3,4,5-trisubstituted 1,2,4-triazoles.

imidoylbenzotriazoles **9e**.[18] However, these approaches suffer from various limitations, such as the use of excess activating reagent (which oftentimes must be removed before the cyclodehydration step), the use of toxic metals, the isolation of the activated reactant, long reaction times, sensitivity to steric hindrance of starting materials, and an overall narrow scope in terms of substitution diversity at the C-3, N-4, and C-5 positions. Therefore, developing general and practical one-flask procedures to access multiple 3,4,5-trisubstituted 1,2,4-triazole derivatives from readily available secondary amides is desirable. To address these previous issues, we decided to pursue an operationally simple trifluoromethanesulfonic anhydride (Tf_2O) mediated activation strategy toward **3** while employing

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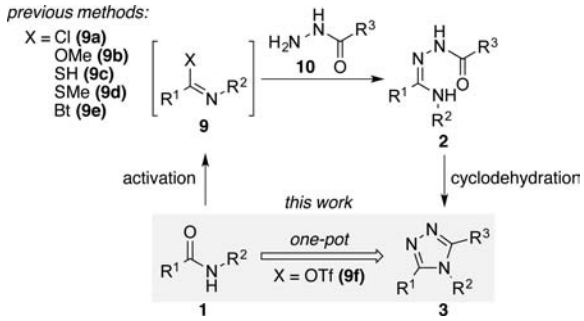
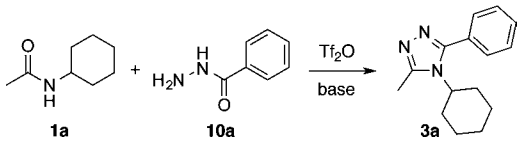


Figure 2. Synthesis of 3,4,5-trisubstituted 1,2,4-triazoles via activated amides as intermediates.

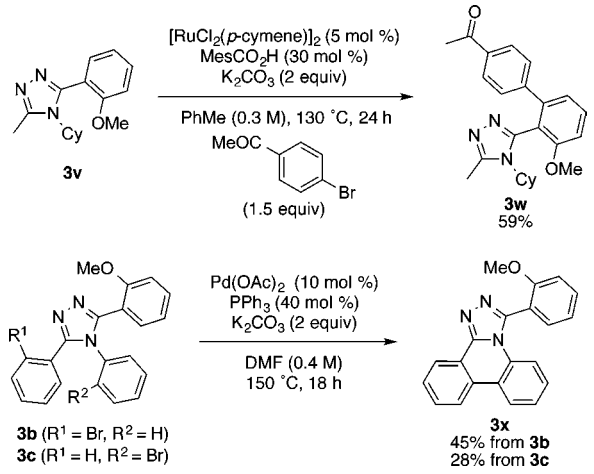
Table 1. Optimization for the Activation/Cyclodehydration



entry	base[a]	solvent (0.3 M)	μW temp (°C)	time (h)	yield 2a[b] (%)
1	none	DCE	110	1	27
2	2-FPyr	DCE	110	1	52
3	2-FPyr	DCE	140	1	68
4	2-FPyr	DCE	140	2	85
5	2-FPyr	DCM	140	2	81

[a]Conditions: **1a** (1.0 mmol), solvent (0.3 M), 2-FPyr (1.1 equiv), Tf_2O (1.1 equiv) at 0 °C for 10 min, then **10a** (1.1 equiv) and μW heating for the given time. [b]Yields determined by ^1H NMR analysis using Ph_3CH as an internal standard.

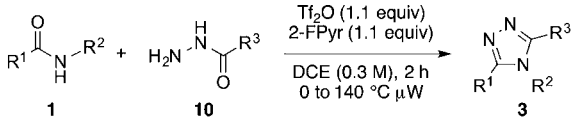
Scheme 2. Novel Metal-Catalyzed C−H Functionalization of 3,4,5-Trisubstituted 1,2,4-Triazoles

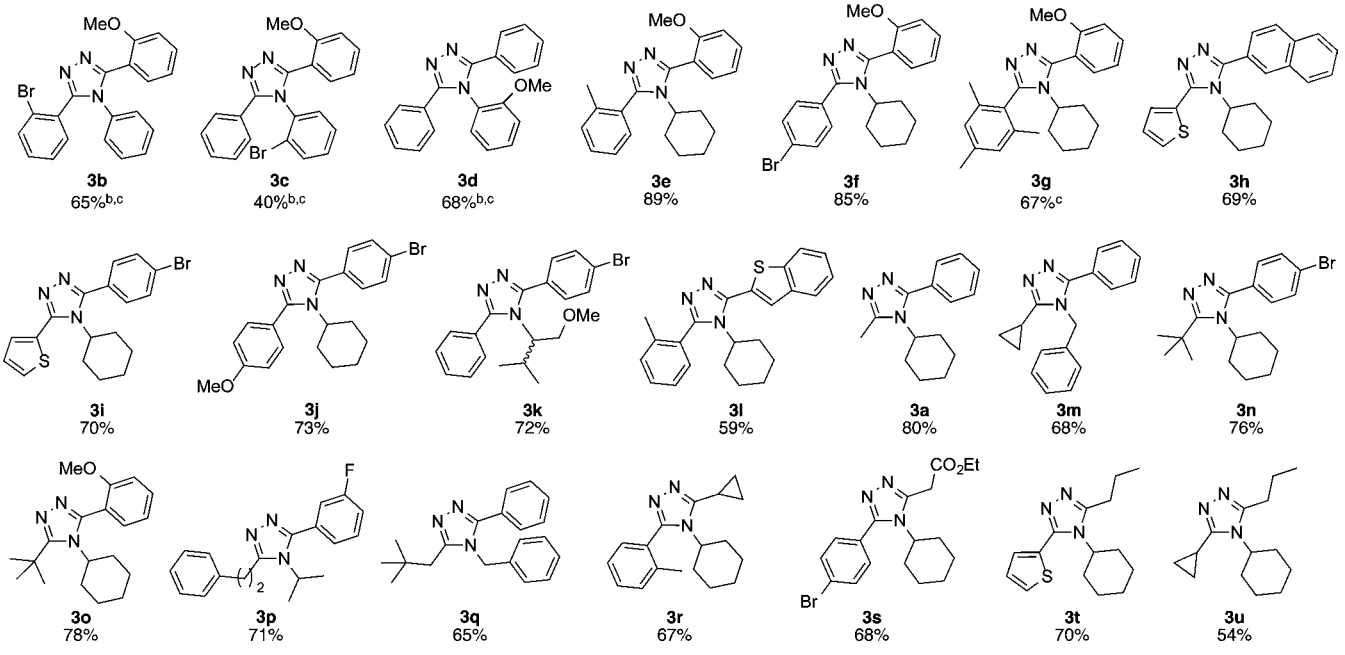


readily available secondary amides **1** and hydrazides **10** (Figure 2).

Various methods based on the chemoselective electrophilic activation of secondary amides with Tf_2O in the presence of 2-halopyridine and a suitable nucleophile have been disclosed by our group[19] and others.[20] These processes allowed the expedient and efficient synthesis of valuable functional groups, including aldehydes, imimes, amines, ketone, ketimines, and imidazopyridines.[19] Inspired by these previous achievements, we envisioned that the versatility and the electrophilicity of imidoyl triflate **9f** would allow it to be a suitable candidate for the rapid nucleophilic addition of hydrazides at a low

Scheme 1. Tf_2O-Mediated One-Pot Synthesis of 3,4,5-Trisubstituted 1,2,4-Triazoles[a]





[a]Isolated yields. [b]Activation performed with DCM from −78 to 0 °C. [c]Cyclodehydration was performed for 4 h.

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temperature, combined with a sequential cyclodehydration of the *N*-acylamidrazone intermediate **2**. We first investigated previously reported conditions[19] by performing the activation of amide **1a** at 0 °C in DCE in the presence of 2-fluoropyridine (2-FPyr) as a base. The in situ addition of hydrazide **10a** to the activated species afforded a reasonable 52% yield for triazole **3a**, following cyclodehydration at 110 °C for 1 h under microwave (μW) irradiation (Table 1, entry 2). By performing the cyclodehydration at 140 °C for 2 h, the corresponding triazole was obtained in 85% yield (entry 4). The reaction could also be performed successfully when employing DCM as solvent (entry 5).

To expand the scope of the one-pot activation/nucleophilic addition/cyclodehydration sequence, various amides and hydrazides were evaluated under our optimized reaction conditions (Scheme 1). To our delight, the triazole synthesis is applicable to a wide variety of substitution patterns at the C-3, N-4, and C-5 positions. Triaryl triazoles **3b**–**d** are obtained in moderate to good yields, as observed with other methods. *N*-Alkyl-substituted triazoles **3e**–**l** bearing different functional groups are well tolerated in the methodology. The combination of *N*-alkyl with other C-aryl/alkyl substituents **3a** and **3m**–**t** is also possible, in which different amides and hydrazides can be successfully employed. The procedure can also be extended to the synthesis of trialkyl-substituted triazole **3u** in 54% yield. Even substrates with a steric bias, which are difficult to obtain by previous methods (such as **3g**, **3n**, and **3o**), are currently produced in moderate to good yields under our optimized conditions. Moreover, the described method tolerates the presence of some heterocycles, such as thiophene-yl (**3h**, **3i**, **3t**) and benzothiophene-yl groups (**3l**).

Given the plethora of methodologies that exploit nitrogen-based chelating groups for transition-metal-catalyzed C–H functionalization,[21] we sought to take advantage of the two contiguous nitrogen atoms at *N*-1 and *N*-2 of the 1,2,4-triazole to selectively perform a Ru-catalyzed C–H arylation at the *ortho* position of the C-3 aryl substituent (Scheme 2).[22] Nonoptimized conditions using the $[RuCl_2(p\text{-cymene})]_2$ complex as the catalyst were applied to triazole **3v** in the presence of bromoacetophenone as the coupling partner. The monoaryl product **3w** was obtained in moderate yield (59%), demonstrating the efficiency of the 1,2,4-triazole motif as a directing group for C–H arylation.

To further expand the elaboration of 1,2,4-triazoles toward the synthesis of more complex heterocycles, a Pd-catalyzed intramolecular C–H activation reaction was carried out (Scheme 2).[23] Starting from triazoles **3b** or **3c**, 1,2,4-triazolophenanthridine **3x** was isolated in 45% and 28% yield correspondingly. Although the phenanthridine scaffold is found in bioactive natural alkaloids and medicinally relevant compounds,[24] there are only scarce examples of processes allowing the synthesis of 1,2,4-triazolophenanthridines.[25]

In summary, we successfully developed a general one-pot synthesis of 3,4,5-trisubstituted 1,2,4-triazoles from readily available secondary amides and hydrazides via triflic anhydride activation followed by microwave-induced cyclodehydration. The method is effective at relatively short reaction times while using minimal amounts of activating reagent. The conditions were applied to the synthesis of a variety of 3,4,5-trisubstituted 1,2,4-triazoles with different alkyl/aryl substitution patterns. Moreover, trisubstituted triazoles were proved to be useful handles for both intramolecular Pd-catalyzed and intermolecular Ru-catalyzed C–H functionalization reactions toward the synthesis of triazolophenanthridine and highly substituted triazole. Current efforts in our group are directed toward the expansion of the scope of such C–H functionalization reactions, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, NMR spectra, and X-ray and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

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