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Regioselective Formation of 2,5-Disubstituted Oxazoles Via Copper(I)-Catalyzed Cycloaddition of Acyl Azides and 1-Alkynes

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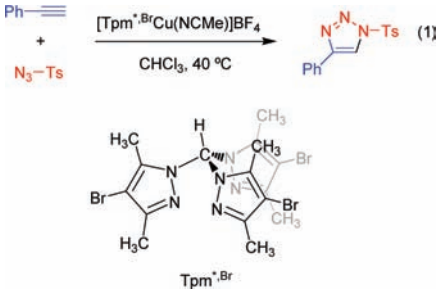
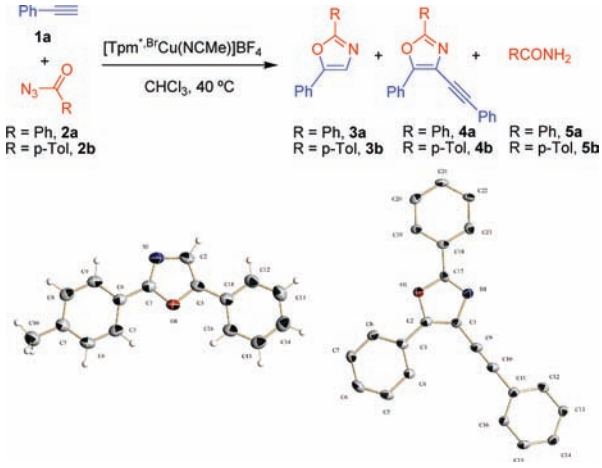
Abstract: The reaction of 1-alkynes with acyl azides in the presence of [Tpm*,BrCu(NCMe)]BF_4 [Tpm*,Br = tris(3,5-dimethyl-4-bromopyrazolyl)methane] as the catalyst provides 2,5-oxazoles in moderate to high yields. This is a novel transformation of the CuAAC type that constitutes a significant variation of the commonly observed [3 + 2] cycloaddition reaction to yield 1,2,3-triazoles.

The copper-catalyzed azide−alkyne cycloaddition (CuAAC) reaction constitutes one of the most interesting examples of click chemistry.[1] Since its discovery,[2] the CuAAC methodology has become a powerful tool with growing applications in different areas such as polymer and material sciences, bioconjugation, and medicinal chemistry.[3] We recently developed a catalytic system for this transformation based on a well-defined and stable Cu(I) complex, [Tpm*,BrCu(NCMe)]BF_4 [Tpm*,Br = tris(3,5-dimethyl-4-bromopyrazolyl)methane], that efficiently promotes the formation of *N*-sulfonyl-1,2,3-triazoles from sulfonyl azides and 1-alkynes under mild conditions (eq 1).[4]



Encouraged by these results, we decided to expand the scope of this reaction using acyl azides, as the formation of the corresponding *N*-benzoyl-1,2,3-triazoles by the [3 + 2] azide−alkyne cycloaddition has remained elusive to date.[5] Under the protocol used for the synthesis of *N*-sulfonyltriazoles,[4] phenylacetylene (**1a**; 1.2 mmol) and benzoyl azide (**2a**; 1.0 mmol) were reacted in chloroform at 40 °C in the presence of catalytic amounts (5 mol %) of [Tpm*,BrCu(NCMe)]BF_4.[6] The azide was consumed after 24 h, as inferred from FTIR spectroscopy of the reaction mixture, from which three compounds were identified. One of them was benzamide, $PhCONH_2$ (29% NMR yield),[7] which resulted from decomposition of the initial azide. The other two compounds, **3a** and **4a**,

Scheme 1. (top) Catalytic Formation of Oxazoles from Direct Reaction of Phenylacetylene and Benzoyl Azides; (bottom) X-ray Structures of Oxazoles **3b** (left) and **4a** (right)



were obtained in a 10:1 ratio and showed all resonances in the 8.2−7.2 ppm region in the ^{1}H NMR spectrum. However, neither the carbonyl resonance nor the ν(CO) band were observed in the ^{13}C NMR and FTIR spectra, respectively. Therefore, the expected formation of the *N*-benzoyl-1,2,3-triazole seemed to have failed following this route. A second experiment carried out using *p*-Me(C_6H_4)CON_3 as the azide led to the same observations: two compounds **3b** and **4b** (along with the corresponding amide derived from that azide) lacking the characteristic spectroscopic data typical of the expected triazoles were isolated. In order to ascertain the nature of the new compounds obtained, single crystals of **3b** and **4a** were grown, and their structures were unambiguously confirmed by X-ray diffraction analysis.[7] To our surprise, they were identified as the oxazoles shown in Scheme 1, and the NMR data were in complete agreement with those formulations.[7]

The oxazole heterocycle is an important structural motif in many natural products, drugs, and biologically active compounds.[8] Two types of strategies are commonly used to prepare substituted oxazole derivatives: (1) synthesis of acyclic precursors and their subsequent cyclization[9] and (2) functionalization of the parent oxazole ring.[10] Recently, a metal-catalyzed cyclization of propargylic alcohols with amides for the synthesis of oxazoles has been developed.[11] In a very recent contribution, *p*-toluenesulfonic acid has been shown to catalyze a tandem propargylation/cycloisomerization reaction.[12] Although reliable and high-yielding, some of these reactions require harsh conditions that are incompatible with sensitive functional groups. In this context, protocols based on metal-catalyzed reactions under mild conditions are desirable. While the reaction of acyl

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Table 1. Screening Conditions for Tpm*,BrCu(I)-Catalyzed Formation of Oxazoles[a]

entry	solvent	temp (°C)	conv. (%)[b]	(**3a** + **4a**)/**5a**[b]
1	$CHCl_3$	40	>95	3:1
2	$CHCl_3$	60	>95	1.2:1[c]
3	$CHCl_3$	25	14	>99:1
4	THF	40	93	1.2:1
5	MeOH	40	<2	–
6[d]	$CHCl_3$	40	<2	–

[a] Reactions were performed with phenylacetylene (1.2 mmol), benzoyl azide (1.0 mmol), and catalyst (0.05 mmol) in solvent (1 mL) for 24 h. [b] Determined by ^{1}H NMR analysis of the crude mixture using an internal standard. [c] Reaction time = 12 h. [d] CuI was used as the catalyst precursor.

azides and alkynes has been investigated previously,[13] it is worth pointing out that, to the best of our knowledge, the formation of an oxazole ring from a CuAAC reaction as reported herein has no precedent in the literature.[14]

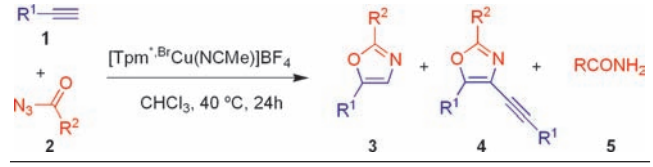
After this seminal experiment, we decided to investigate the reaction conditions in order to improve the selectivity (Table 1) using **1a** and **2a** as the reactants. We found that temperature exerted an important influence on the efficiency of oxazole formation. The selectivity (for oxazoles vs benzamide) provided at 40 °C decreased markedly as the temperature was raised to 60 °C (entry 2). However, full selectivity for the formation of oxazoles was observed at room temperature, although with low conversion (entry 3). Solvents other than chloroform did not improve the yield (entries 4 and 5). Finally, it is also worth mentioning that when CuI was employed as the catalyst precursor, no reaction was observed, indicating a crucial role of the Tpm*,Br ligand (i.e., the Tpm*,BrCu core) in this transformation. This is in agreement with the previously proposed accelerating effect of ligands in click reactions.[15]

Under the optimal conditions based on the use of chloroform as the solvent and 40 °C as the reaction temperature, we examined the scope with regard to the azide and alkyne components (Table 2). An array of 2,5-disubstituted oxazoles (**3a**−**s**) were prepared in moderate to good yields (43−82%) with the appearance of trisubstituted oxazoles (**4a**−**s**) incorporating two molecules of the initial alkynes as minor byproducts. The $RCONH_2$ amides and/or unreacted starting azides completed the mass balance. In all cases, only the 2,5-disubstituted oxazoles were observed, with no evidence of the formation of the 2,4-disubstituted isomers, indicating complete control of the regioselectivity. As the data in Table 2 show, the nature of the substituents on the benzoyl azides affects the efficiency of the reaction: electron-rich azides led to higher yields of oxazoles **3** than those with electron-withdrawing groups on the phenyl rings (Table 2, entries 1−4). The use of arylacetylenes provided the oxazoles in similar yields with little influence of the electronic effect of the substituents.

However, when alkylacetylenes were employed, the yields decreased (entries 13−15 and 19), a feature also observed in several CuAAC reactions leading to triazoles.[16] Heteroaromatic substituents were also tolerated in both the alkyne (entries 10−12) and the azide (entries 16−19). Alkynes of the type $XCH_2C{\equiv}CH$ (X = Cl, OH) or $Me_3SiC{\equiv}CH$ did not afford the desired oxazoles. Overall, the scope of this new reaction seems to be quite broad, although the development of future more active catalysts is needed to improve the yields for the less reactive substrates.

We also found that only terminal alkynes undergo this process. In addition, experiments carried out with Ph−C≡C−C≡C−Ph (a plausible precursor of **4a**) as the reactant failed. Thus, the formation of the trisubstituted oxazoles **4** should proceed along the reaction path that leads to disubstituted derivatives **3.** The lack of reactivity

Table 2. Scope of the Reaction[a]

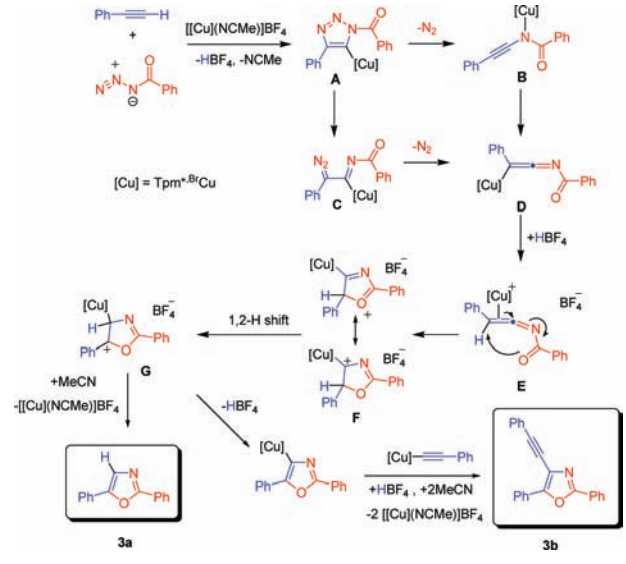


entry	R^1	R^2	**3**	yield (%)[b]	**4**	yield (%)[b,c]
1	Ph	Ph	**3a**	60	**4a**	6
2	Ph	*p*-MeC_6H_4	**3b**	77	**4b**	4
3	Ph	*p*-$MeOC_6H_4$	**3c**	82	**4c**	<2
4	Ph	*p*-$NO_2C_6H_4$	**3d**	14	**4d**	<2
5	*p*-MeC_6H_4	Ph	**3e**	61	**4e**	6
6	*p*-MeC_6H_4	*p*-MeC_6H_4	**3f**	56	**4f**	5
7	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	**3g**	63	**4g**	6
8	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	**3h**	43	**4h**	<2
9	*p*-BrC_6H_4	*p*-$MeOC_6H_4$	**3i**	52	**4i**	<2
10	3-thienyl	Ph	**3j**	49	**4j**	7
11	3-thienyl	*p*-MeC_6H_4	**3k**	46	**4k**	4
12	3-thienyl	*p*-$MeOC_6H_4$	**3l**	59	**4l**	<2
13	1-propyl	Ph	**3m**	18[d]	**4m**	<2
14	1-butyl	Ph	**3n**	17[d]	**4n**	<2
15	cyclopropyl	*p*-$MeOC_6H_4$	**3o**	24[d]	**4o**	4
16	Ph	2-thienyl	**3p**	41	**4p**	<2
17	*p*-MeC_6H_4	2-thienyl	**3q**	38	**4q**	<2
18	*p*-$MeOC_6H_4$	2-thienyl	**3r**	36	**4r**	<2
19	cyclopropyl	2-thienyl	**3s**	18[d]	**4s**	3

[a] Reactions were performed with phenylacetylene (1.2 mmol), benzoyl azide (1.0 mmol) and catalyst (0.05 mmol) in $CHCl_3$ (1 mL) for 24 h at 40 °C. [b] Isolated yield based on azide (average of two runs). The remaining initial azide was converted into $RCONH_2$ and/or recovered unreacted. [c] Yields of <2% for compounds **4** correspond to products that could not be isolated because of the extremely low conversion. [d] Reaction was performed at 60 °C.

of internal alkynes and the regioselective formation of 2,5-disubstituted oxazoles could be a consequence of the formation of copper acetylide as the first step of the reaction, followed by a [3 + 2] cycloaddition reaction with the azide (Scheme 2), in a manner similar to the well-known mechanism for the formation of *N*-substituted-1,2,3-triazoles.[5,17−21] However, in our case, the conversion of the copper triazolyl intermediate **A** into the corresponding triazole does not take place. Presumably, intermediate **A** could be transformed into the copper ketenimide species **D** through species **B** or **C**.[5,19,21] Protonation of the ketenimide would trigger

Scheme 2. Plausible Mechanism for the Formation of Oxazoles from 1-Alkynes and Acyl Azides



a rearrangement and cyclization of the organic fragment to give **F** (two resonance forms shown in Scheme 2) in a manner that is similar but not identical to that previously proposed by Gevorgyan and co-workers for the formation of pyrroles.[22] A 1,2-hydrogen shift[23] would afford **G**, from which **3a** would be formed with the concomitant release of the catalyst. The origin of the trisubstituted oxazoles would be explained by proton loss from intermediate **G** followed by coupling with a copper acetylide.

In conclusion, we have found a novel route for the catalytic and regioselective synthesis of 2,5-disubstituted oxazoles from simple reactants such as 1-alkynes and acyl azides using a copper(I) catalyst precursor. Work aimed at the development of more active and selective catalysts and of a more complete understanding of the mechanism of this transformation is currently underway.

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Supporting Information Available: Detailed experimental procedures, analytical and spectroscopic data, and crystallographic data for **3b** and **4a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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