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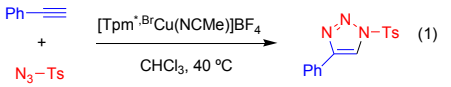
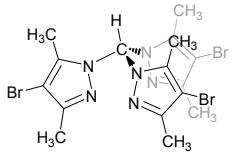
Abstract: The reaction of 1-alkynes with acylazides in the presence of [Tpm*,BrCu(NCMe)]BF_4 (Tpm*,Br = tris(3,5-dimethyl-4-bromopyrazolyl)methane) as the catalyst provides 2,5-oxazoles in moderate to high yields. This is a novel transformation of CuAAC type, that constitutes a significant variation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

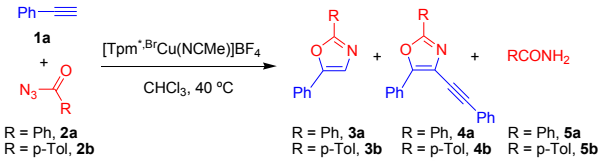
The copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction constitutes one of the most interesting examples of click chemistry.[1] Since its discovery,[2] the CuAAC methodology has become a powerful tool with growing applications in different areas such as polymer and material sciences, bioconjugation and medicinal chemistry.[3] We have 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 ligand) that efficiently promoted the formation of N-sulfonyl-1,2,3-triazoles from sulfonyl azides and 1-alkynes under mild conditions (eq 1).[4]

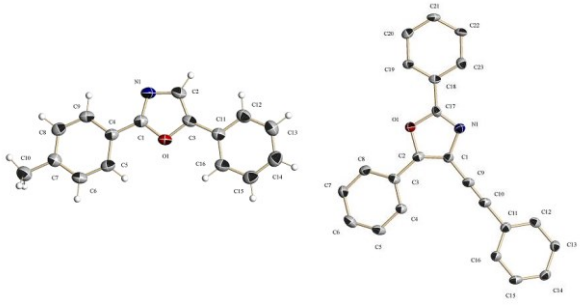




Tpm*,Br

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





Scheme 1. Top: catalytic formation of oxazoles from direct reaction of phenylacetylene and benzoyl azide. Bottom: X-ray structures of oxazoles **3b** (left) and **4a** (right).

1,2,3-triazol 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) that lacked from 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 unambiguously confirmed by X-ray diffraction analysis.[7] To our surprise, they were identified as the oxazoles shown in Scheme 1, the NMR data being in complete agreement with those formulations.[7]

The oxazole heterocycle is an important structural motif in many natural product, drugs and biologically active compounds.[8] Two types of strategies are commonly used to prepare substituted oxazole derivatives: synthesis of acyclic precursors and their subsequent cyclization[9] or 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 propargylation/cycloisomerization tandem reaction.[12] Although reliable and high yielding, some of these reactions require harsh conditions incompatible with sensitive functional groups. In this context, protocols based on metal-catalyzed reactions under mild conditions are desirable. While the reaction of acyl azides and alkynes has been previously investigated,[13] it is worth pointing out that, to the best of our knowledge, the formation of an oxazole ring from a copper-catalyzed azide/alkyne cycloaddition (CuAAC) reaction reported herein finds no precedent in the literature.[14]

Table 1. Screening conditions for Tpm*,BrCu(I)-catalyzed oxazoles formation.[a]

Entry	Solvent	Temp (º 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 performed with phenylacetylene (1.2 mmol), benzoyl azide (1.0 mmol), catalyst (0.05 mmol), in solvent (1 mL) for 24 h. [b]Determined by ^{1}H NMR of the crude, based on an internal standard. [c]Reaction time = 12 h. [d]CuI as catalyst precursor.

After this seminal experiment, we decided to investigate the reaction conditions in order to improve the selectivity (Table 1), with **1a** and **2a** as the reactants. We found that temperature exerted an important influence on the efficiency of oxazole formation. The selectivity (intended as oxazoles vs benzamide) provided at 40 ºC decreased markedly as the temperature was raised to 60 ºC (entry 2). However, full selectivity toward 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 employing CuI as the catalyst precursor, no reaction was observed, assessing a crucial role of the Tpm^{*,Br} ligand, i. e., the Tpm*^{,Br}Cu 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 ºC 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**) was prepared in moderate to good yields (43-82 %), with the appearance of a trisubstituted oxazol (**4a-s**) that incorporated two molecules of the initial alkyne, as a minor byproduct. 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, assessing a complete control of the regioselectivity. As inferred from data in Table 2, the nature of the substituents on the benzoyl azides affected 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 yield, with no much influence of the electronic effect of the substituents.

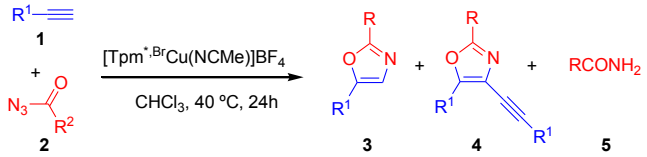


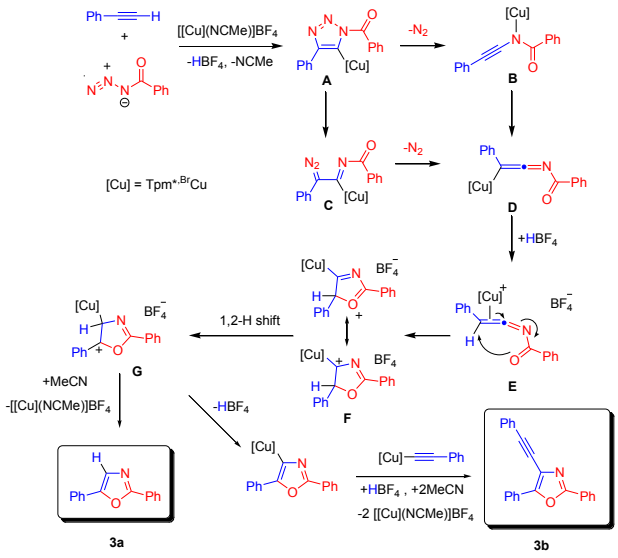
Table 2. Scope of the reaction.[a]

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

However, when alkylacetylenes were employed, the yields decreased (entries 13-15, 19), a feature also observed in several CuAAC reactions leading to triazoles.[16] Heteroaromatic substituents were also tolerated both in the alkyne (entries 10-12) as well as in the alkyne (entries 16-19). Alkynes of type X-CH_2CCH (X = Cl, OH) or Me_3SiCCH did not afford the desired oxazoles. Overall, the scope of this new reaction seems to be quite broad, the development of future more active catalysts being needed to improve the yields for the less reactive substrates.

We have also found that only terminal alkynes undergo this process. In addition, experiments carried out wit Ph-C≡C-C≡C-Ph as reactant (a plausible precursor of **4a**) failed. Thus, the formation of the trisubstituted oxazoles **4** should form along the



Scheme 2. Plausible mechanism for the formation of oxazoles from 1-alkynes and acyl azides.

reaction path that leads to disubstituted derivatives **3.** The lack of reactivity 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 similar manner 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 triazol does not take place. Presumably, intermediate **A** could be transformed into the ketenimide-copper species **D** through species **B** or **C**. [5,19,21] Protonation of the ketenimide would trigger a rearrangement and cyclization of the organic fragment to give **F** (two resonance forms shown in Scheme 1) in a similar, but not identical, manner 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 from intermediate **G**, by a proton loss 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 to the development of more active and selective catalysts as well as to fully understand the mechanism of this transformation is currently underway.

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Supporting Information Available. Detailed experimental procedures, analytical and spectroscopic data and crystallographic information files in CIF format.

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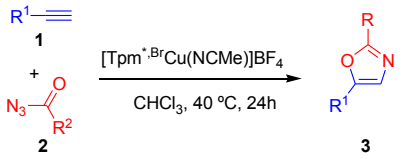
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