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Copper(I)-doped Wyoming's montmorillonite for the synthesis of disubstituted 1,2,3-triazoles

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ABSTRACT

A new catalytic system based on copper(I)-doped Wyoming's montmorillonite was elaborated. This system was studied and was found to catalyze the formation of 1,4-disubstituted 1,2,3-triazoles when starting from azides and alkynes. It was used for the synthesis of a few triazole derivatives to show its usefulness.

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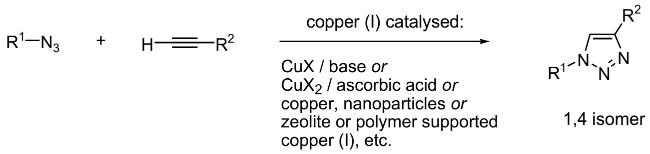
Medicinal chemists, as well as the pharmaceutical industry are continuously seeking new molecules in order to prevent or cure human diseases. The synthesis of small or more complex molecules incorporating a functional group variety that can act as a pharmacophore, or participate in the biological activity, is nowadays a current approach for the preparation of molecular series or libraries.

In this field, the 'click-chemistry' concept has demonstrated its usefulness for the easy, selective, efficient, fast, and powerful preparation of wide range of molecules.[1] Huisgen's dipolar cycloaddition is the best example to illustrate the 'click' approach: under thermal activation, two potentially reactive partners can form a wide range of substitutions on a reaction product, in this case a triazole heterocycle, starting from various organic azides and alkynes.[2]

The discovery of a copper(I) catalysis in this cycloaddition placed this reaction at the summum of the 'clickable' ones.[3] Furthermore, the reaction can be used in several instances, using various conditions that are efficient in most cases: copper(I) systems often in the presence of a base[4] and the redox couple copper(II)/ascorbic acid[5] in organic or organo-aqueous systems are the most commonly used. Heterogeneous catalysis conditions can also be used as illustrated by efficient use of copper salts in zeolites,[6] charcoal,[7] polymer-supported versions,[8,9] metallic copper,[10] and nanoparticles (Scheme 1).[11]



Scheme 1. Huisgen's cycloaddition route to 1,2,3-triazoles in some of its various copper(I) catalyzed conditions.

In our continuous efforts to find new reaction conditions that can be amenable to automated parallel synthesis, we decided to explore the preparation and use of a new heterogeneous catalytic system. The catalyst we were seeking for has to meet both criteria of applicability in automation and ecological considerations. Based on our cooperation program, we decided to evaluate the use of a natural clay as a support for the copper catalyst.

Wyoming montmorillonite is a clay belonging to 2/1 dioctaedric phyllosilicates group. Its composition $[(Si_{3.92}Al_{0.04})(Al_{11.5}Fe_{0.18}Mg_{0.32})(OH)_2]$ in which hydroxylic centers can act as a base, and the possibility to conduct cation exchanges and molecular intercalation, let us believe that copper can be included in such structures in order to make the complete catalytic system.

Purified Wyoming montmorillonite-Na,[12] dried as a thin film at 50 °C,[13] was incubated for 3 h in a 0.15 M copper(I) iodide solution in acetonitrile at room temperature (Scheme 2).

The dried sample, named Wy·CuI, was then submitted to elemental analysis and gave a value of 4.6% for copper, against

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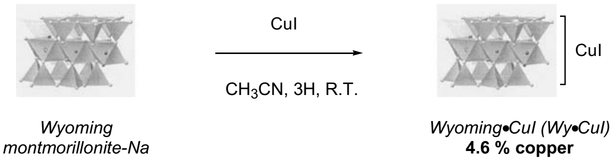


Scheme 2. Preparation of CuI adsorbed Wyoming montmorillonite (Wy·CuI).

<50 ppm for Wy-Na proving its incorporation in the sample. The exact way the copper is included is hard to put in evidence.[14] The incorporation of copper(I) in clays was not much studied due to its relative instability and the pH-dependent redox phenomena occurring inside the clay, even for copper(II).[15] Clays that were cation exchanged with other metals were usually incubated iteratively several times in aqueous solutions of the metal salt for long periods of time.[16]

In our case, incubating the clay overnight with the acetonitrile copper(I) solution turned it blue, indicating the presence of copper(II) salts in the mixture due to oxidation of the cuprous species. We thus decided to select the short incubation time to prepare Wy·CuI keeping in mind that the copper salt may only be adsorbed or partially exchanged with cations.

The Wy·CuI was then tested on model reactions between benzyl azide (**1a**) and methyl propiolate (**2a**), or phenylacetylene (**2b**), to verify its ability to catalyze the triazoles, **1a2a** and **1a2b,** formation (Scheme 3).

We arbitrarily selected an 8 mol % catalytic level, and methylene chloride as a solvent, mainly to compare it with our polymer-supported catalyst.[8] The Wy·CuI activity was compared to crude and Na Wyoming montmorillonites (Wy-crude, Wy-Na), the results being presented in Table 1.

We were glad to discover that the Wy·CuI was catalyzing the reaction and giving a complete regioselective conversion into the 1,4 isomer of **1a2a** and **1a2b** after overnight (18 h) reaction time. Interestingly, formation of the triazole nucleus **1a2a** was also observed with Wy-crude and Wy-Na. In this case, the yields were lower, 50% and 39%, and some of the 1,5 isomer was formed (9–1 ratio in favor or the 1,4 one). However, phenylacetylene (**2b**) did not give any reaction with the natural clays. The results obtained without solvent were quite similar.[17] Wy·CuI gave the same excellent yield and selectivity for **1a2a** and **1a2b**, whereas Wy-crude and Wy-Na gave good conversions only for **1a2a**, around 80%. Wy-Na gave a 9–1 isomeric mixture of the 1,4 and 1,5 isomers, while Wy-crude was in this case 1,4-selective.

The reaction observed in the case of methyl propiolate (**2a**) seems to be due to a higher reactivity toward benzyl azide (**1a**) of this alkyne when compared to phenylacetylene (**2b**).[18] This should be the consequence of the electron-withdrawing carboxylate group. As a matter of fact, in the absence of any catalyst in the solvent free version, the triazole **1a2a** was formed at 50%.[19]

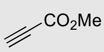
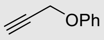
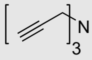
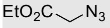
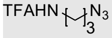
The Wy·CuI catalyst was then tested for its generality through the synthesis of a small library of 12 triazoles (Table 2). The catalyst was efficient for the formation of the triazoles reaching an average of 90%. Benzyl azide (**1a**) and ethyl azidoacetate (**1b**) reacted quite well with methyl propiolate (**2a**), phenylacetylene (**2b**), phenyl propargyl ether (**2c**), and tripropargylamine (**2d**) in 97% and 93% average. In the case of *N*-(3-azidopropyl)trifluoroacetamide (**1c**), the yields were lower (80% average). This was due to solubility problems of the reaction products that prevented a good recuperation (*the use of acetonitrile for final washings gave a better recuperation yield*). However, the catalyst gave good yields for most synthesized triazoles that were isolated by a simple filtration to separate the catalyst and by solvent evaporation. The products were isolated in a pure form without traces of copper.

Table 1
Results of the reaction of benzyl azide (**1a**) and methyl propiolate (**2a**) and phenylacetylene (**2b**) in the presence of clays to form the triazoles **1a2a** and **1a2b** (*NMR conversions and isomeric ratios*)[a]

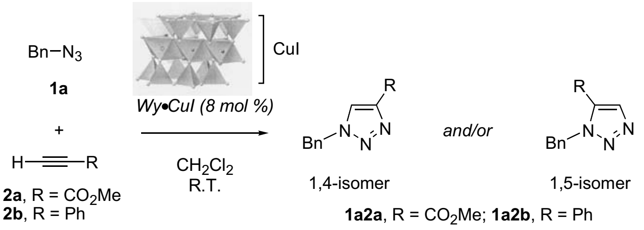
Solvent	Triazole	Wy-crude[b] (Yield, ratio)[d]	Wy-Na[b] (Yield, ratio)[d]	Wy•CuI[b,c] (Yield, ratio)[d]
CH_2Cl_2[e]	**1a2a**	50%, 9/1	39%, 9/1	99%, 10/0
	1a2b	0%	0%	99%, 10/0
none	**1a2a**	81%, 10/0	80 %, 9/1	99%, 10/0
	1a2b	0%	0%	99%, 10/0

[a] On a 0.5 mmol scale, 1 equiv alkyne **2a**, 1.1 equiv azide **1a**.
[b] 55 mg of clay.
[c] 55 mg Wy·CuI = 8 mol %.
[d] Estimated by ^1H NMR. The first number refers to the 1,4 isomer, the second to the 1,5 one.
[e] 18 h reaction.

Table 2
Yields for the synthesis of a small library of triazoles by reaction between azides **1a–c** and alkynes **2a–d** catalyzed by Wy·CuI[a]

	 **2a**	 **2b**	 **2c**	 **2d**[b]
PhCH$_2$–N$_3$ **1a**	99%[c]	99%	93%	99%
 **1b**	99%	99%	92%	83%
 **1c**	98%	76%	57%	90%

[a] On a 0.5 mmol scale, 1 equiv alkyne **2**, 1.1 equiv azide **1** in CH_2Cl_2, 55 mg (8 mol %) Wy·CuI, 18 h reaction time.
[b] 3.3 equiv azide were used.
[c] Isolated yields. All compounds gave correct mp, IR, ^1H, ^{13}C NMR and LC–MS analyses.



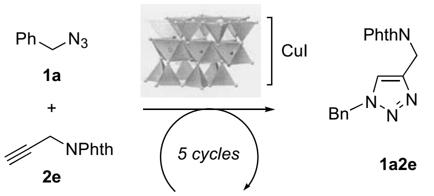
Scheme 3. Reaction of benzyl azide (**1a**) and methyl propiolate (**2a**) and phenyl acetylene (**2b**) in the presence of Wy·CuI to form disubstituted triazoles **1a2a** and **1a2b**.

The stability of copper(I) in the Wy·CuI was then tested qualitatively by its color change. Samples of Wy·CuI have to be used quite readily since a blue coloration due to copper(II) appeared after one week. This stability of Wy·CuI seemed to increase after its use in organic media for triazole formation.

The same sample was used in a cycle of five reactions, separated from one week, without getting much colored or loosing its activity in the synthesis of **1a2e**, starting from azide **1a** and alkyne **2e** (Scheme 4).

The reaction gave a quantitative yield for all the five cycles. Furthermore, the sample was still active after up to three months.

The kinetics of the reaction leading to **1a2e** was also evaluated by comparison with both a homogeneous (CuI/Et$_3$N) and heterogeneous (A-21·CuI) catalytic systems in the same solvent at room



cycle	yield (%)
1	99
2	99
3	99
4	99
5	99

PhthN : phthalimide

Scheme 4. Recycling stabilized Wy·CuI in the reaction of benzyl azide (**1a**) with *N*-propargyl phthalimide (**2e**) to prepare triazole **1a2e**.

temperature.[8] While using CuI/Et$_3$N, the reaction was complete in 3 h, with A-21·CuI in 5 h and with Wy·CuI in 15 h. Faster reactions observed in the case of our reference systems can be attributed to the presence of an amine (base) functionality helping the formation of the copper(I) acetylide. Our Wy·CuI system can, however, be advantageously compared to other published heterogeneous systems that are not easier to prepare, and for which longer reaction times are required.[6–11]

We presented in this Letter the easy preparation of a new supported catalyst for the Huisgen's cycloaddition. The Wyoming montmorillonite-supported copper(I) iodide (Wy·CuI) was found to catalyze efficiently the formation of several triazoles, starting form organic azides and terminal alkynes. The catalyst can be recycled without activity loss. All the reactions but a few gave very good yields of triazoles that were isolated by simple filtration work-up. We think that this catalyst based on a natural and non-toxic clay can find many applications for the synthesis of triazole derivatives. Further work on these systems will be reported in due course.

Typical procedures. Preparation of the supported catalyst (Wy·CuI): Purified Wyoming montmorillonite-Na (film) (170 mg) was added to a solution of copper(I) iodide (1.4 g, 7.0 mmol) in acetonitrile (50 ml), and gently shaken on an orbital stirrer for 3 h at room temperature. The film was washed with actonitrile (2 × 15 ml), CH$_2$Cl$_2$ (2 × 15 ml) and dried at 50 °C. Elemental analyses gave a copper content of 4.57%. Wy-Na was submitted to the same analysis and copper was not detected below 50 ppm.

Synthesis of 1-benzyl-4-phthalimidomethyl-1,2,3-triazole (**1a2e**): Benzyl azide (**1a**, 73 mg, 0.55 mmol) and *N*-propargyl phthalimide (**2e**, 93 mg, 0.50 mmol) were dissolved in CH$_2$Cl$_2$ (2 mL). Wy·CuI (55 mg, 0.04 mmol, 8 mol %) was added and the mixture was stirred at room temperature for 18 h. The reaction mixture was filtered on sintered glass, and the catalyst was washed with CH$_2$Cl$_2$ (3 × 2 mL). Evaporation of the solvent gave the product **1a2e** as a white solid (158 mg, 99%). mp = 179–181 °C. FTIR: ν 3110, 3076, 3038, 2849, 1771, 1708, 1432, 1402 and 1097 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.97 (*s*, 2H), 5.49 (*s*, 2H), 7.25–7.37 (*m*, 5H), 7.51 (*s*, 1H), 7.70–7.85 (*m*, 4H) ppm. ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 33.1, 54.2, 122.7, 123.4, 128.1, 128.7, 129.1, 132.0, 134.1, 134.5, 143.1, 167.6 ppm. LC–MS: ELSD 98%, R_t = 9.10 min, m/z 319 [M+H]$^+$.

For the solvent-free version on the same scale, the azide (0.55 mmol) and alkyne (0.55 mmol) were mixed in a small test tube. The catalyst was added at once and the reaction was left to stand overnight. The products were recuperated with CH$_2$Cl$_2$ (3 × 2 mL), filtration, and evaporation.

Caution: Even if no noticeable temperature rise was detected in the solvent-free reaction with Wy·CuI on this scale, the cycloaddition can be quite exothermic and should not be attempted on a larger scale, without being aware of explosion risks.

Acknowledgments

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