



Zeo-click synthesis: Cu^I-zeolite-catalyzed one-pot two-step synthesis of triazoles from halides and related compounds

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ABSTRACT

Cu^I-zeolites proved to be an efficient heterogeneous catalyst for the one-pot two-step synthesis of triazoles from halides or tosylates, sodium azide, and alkynes. The step and atom economies of this cascade reaction as well as water used as solvent and catalyst recycling make such synthesis a truly green process. With selected substrates, the peculiar roles of Cu^I-zeolites as catalysts were highlighted.

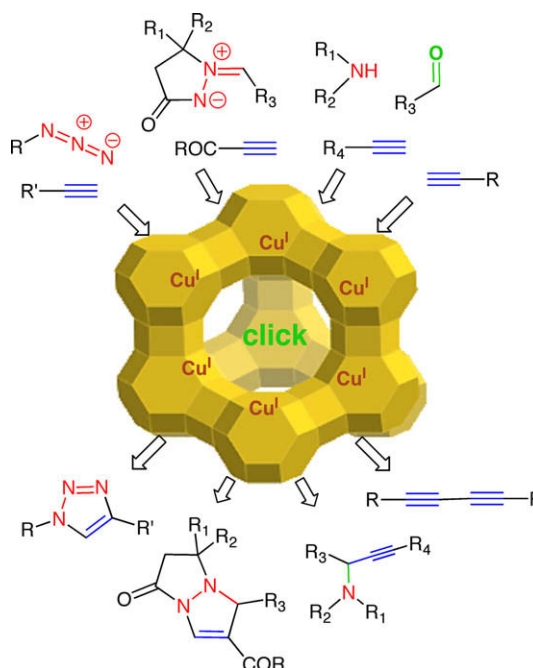
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Environmental concern dramatically rose during the last two decades, leading to the emergence of the concept of ‘Green Chemistry’.¹ One of the major challenges that chemists are facing today is the development of new transformations that are not only efficient, selective, and high-yielding but also environmentally benign. Thus, Green Chemistry aims at the implementation of sustainable and safe chemical processes, while minimizing wastes production and energy consumption.

Within this context, we are developing the ‘zeo-click’ synthesis, that is, organic synthesis based on catalysis with metal-doped zeolites, combining the best of both homogeneous and heterogeneous catalyses. This new class of heterogeneous catalysts proved easy to prepare, easy to handle, and recyclable. They can be applied to a large panel of reaction types for generating various substances quickly and reliably by regio- and stereoselectively joining small units together (Scheme 1).² These useful properties fulfilled most of the Green Chemistry criteria; they are also close to the chemical ‘philosophy’ introduced by Sharpless in 2001 under the name ‘click chemistry’.³

The Meldal–Sharpless Cu^I-catalyzed version⁴ of the Huisgen cycloaddition⁵ between organic azides and terminal alkynes became the archetype of ‘click’-reactions and numerous applications have since been developed.⁶ In parallel, we set up an alternative version using Cu^I-zeolites as stable and recyclable catalysts (Scheme 1).^{2a–c} However, from sustainability and safety point of

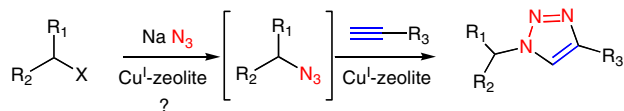
views, this version was still not perfect, being performed in toluene and with preformed organic azides. We thus tried to combine the



Scheme 1. The zeo-click concept and reactions catalyzed by Cu^I-zeolites.^{2a–g}

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Scheme 2. Cu^I-zeolite-catalyzed one-pot reaction of organic halides and related compounds with sodium azide and alkynes.

organic azide preparation with the cycloaddition in a single zeolite-catalyzed operation run in safer solvents and we reported herein our results revealing that water was a perfect medium for such cascade reactions best catalyzed by Cu^I-USY. A few examples of such cascade reactions have recently been described,⁷ including supported catalyst⁸ but only two mentioned the use of heterogeneous catalyst, that is, copper nanoparticles on carbon or on alumina.⁹ So far, no example promoted by zeolites has been reported.

Organic azides are usually prepared from the corresponding halides or related sulfonate species by nucleophilic substitution with sodium azide. It is worth reminding here that nucleophilic substitution can be accelerated in the presence of various salts, acting as Lewis acid toward the leaving group.¹⁰ Cu^I-zeolites could therefore play a dual role, helping at the first nucleophilic substitution step and catalyzing the second cycloaddition step (Scheme 2).

Benzyl bromide and phenyl acetylene were selected as model compounds to find the appropriate conditions for the required Cu^I-zeolite-catalyzed one-pot synthesis of triazoles from halides. As Cu^I-USY often proved to be the best catalyst in other Cu^I-zeolite-catalyzed reactions,² we first screened various conditions with this modified zeolite as the catalyst with an amount of zeolite doped with copper corresponding to 10 mol % of copper(I) ions¹¹ as in our earlier work (Table 1). For comparison purposes with our earlier work, we checked the behavior in toluene and in a few other solvents. As one would expect for S_N type reaction, apolar or poorly polar solvents did not allow for any transformation, whatever the temperature (entries 1–3). More polar solvents proved more effective (entries 4–10). At room temperature, acetonitrile only gave trace amount of the expected product, while at reflux, the conversion remained low (entries 4 and 5). The more polar DMF gave the cascade product in good yield at room temperature (entry 6). Under the same conditions, the polar and protic methanol gave better result (entry 7). Water proved to be the best solvent

Table 1
Conditions screening for Cu^I-zeolite-catalyzed one-pot synthesis of triazoles from halides^a

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield ^b (%)
1	Cu-USY	Tol	20–110	15	0 ^c
2	Cu-USY	Tol-THF	20–70	15	0 ^c
3	Cu-USY	THF	20–70	15	0 ^c
4	Cu-USY	MeCN	20	15	Traces
5	Cu-USY	MeCN	80	15	22 ^c
6	Cu-USY	DMF	20	15	71
7	Cu-USY	MeOH	20	15	80
8	Cu-USY	H ₂ O	20	15	50 ^d
9	Cu-USY	H ₂ O	50	15	60 ^d
10	Cu-USY	H ₂ O	90	15	98
11	Cu-ZSM5	H ₂ O	90	20	23 ^d

^a The reaction was conducted under anoxic conditions.

^b Isolated yields of pure product after complete conversion unless otherwise stated.

^c The starting materials were recovered.

^d Mixture of benzyl derivatives was also recovered.

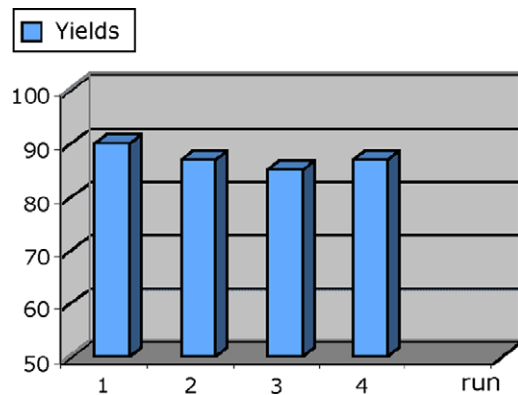


Figure 1. Recycling of Cu^I-USY for the reaction between BnBr and phenylacetylene.

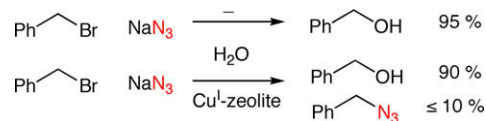
for this one-pot two-step transformation, especially at 90 °C (entries 8–10). Interestingly, the observed approximate rates tend to follow the Grunwald–Winstein relationship¹² and related solvent scales¹⁰ defined for S_N reaction, suggesting the S_N step as the limiting one in this cascade. Furthermore, the higher the ionizing power of the solvent is,¹³ the higher is the cascade reaction efficiency, suggesting S_N1 type mechanism for the first step.

Under the same conditions, other zeolites were far less effective as exemplified with Cu^I-ZSM5¹¹ (entry 11) in agreement with our earlier studies on the ‘click’ step.^{2a,b} These results highlighted the role played by the zeolite internal structures (channel system for ZSM5 vs cages for USY) and their Si/Al ratios (15 for ZSM5 vs 3 for USY).

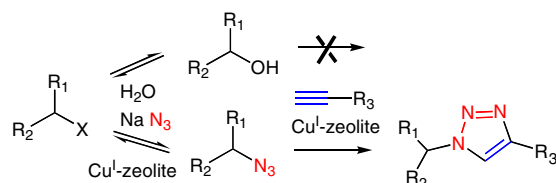
The same reaction with benzyl bromide and phenyl acetylene was also used for examining the catalyst’s behavior and its role in each step of the cascade reaction.

Interestingly, the Cu^I-USY catalyst could be reused four times without significant yield loss provided the catalyst is reactivated between each run (Fig. 1).

Due to the aqueous conditions used, leaching of copper(I) species could be expected, although the solubility of copper(I) salts in water is low. This aspect was investigated by premixing Cu^I-USY in water at different temperatures and after 20 h, that is, a time longer than the usual reaction time, and filtration, all reagents were added to the corresponding solution and their evolution was monitored. Reaction occurred slowly, revealing that some leaching was indeed possible especially at 90 °C. However, the oxidation state of the thus liberated copper species proved important. With degassed solution and under nitrogen or argon, leaching accounts for less than 10% of conversion over 20 h depending on the temper-



Scheme 3. Cu^I-USY role in nucleophilic substitution with sodium azide.



Scheme 4. Cu^I-zeolite role in the one-pot cascade reaction between sodium azide, alkyne and halide.

Table 2
One-pot Cu^I-zeolite-catalyzed synthesis of triazoles from halides and related compounds^a

Entry	Halide	Alkyne	Triazole	Yield ^b
1 2	BnCl	Ph—C≡C		0 62 ^c
3	BnBr	Ph—C≡C		90
4 5	BnOTs	Ph—C≡C		28 58 ^c
6	BnOTf	Ph—C≡C	—	0 ^d
7	BnBr	<i>p</i> CF ₃ Ph—C≡C		98
8	BnBr	<i>p</i> CH ₃ Ph—C≡C		89
9	BnBr	<i>n</i> Hex—C≡C		75
10	BnBr			72
11	BnBr	HO—(CH ₂) ₄ —C≡C		58
12		Ph—C≡C		73
13		Ph—C≡C		88
14 15	EtBr	Ph—C≡C		0 57 ^e
16 17	PrI	Ph—C≡C		0 64 ^e
18	MeOOC—CH ₂ —Br	Ph—C≡C		61
19		Ph—C≡C		80
20 21		Ph—C≡C		62 87 ^c
22		Ph—C≡C	—	0

^a The reaction was conducted under anoxic conditions (see the general procedure below).

^b Yields of isolated pure products.

^c Performed in a 1:1 mixture of water and ethanol.

^d Decomposition was observed.

^e Performed in a 1:1 mixture of water and dioxane.

ature, while in the presence of air, this increased to 20%. Not so surprisingly, leaching is thus more or less important according to the solubility of copper ions in water.

Knowing the Cu^I-zeolite-catalyzed cycloaddition step,^{2a-c} we investigated in more detail the first substitution step, that seemed to be the limiting step as shown above. This was performed by comparing the reaction of sodium azide and benzyl bromide alone in the presence or not of Cu^I-USY. Unexpectedly, the solvolysis product, that is, benzyl alcohol, was the major product isolated under both conditions (Scheme 3). This reaction was almost quantitative without catalyst, while some by-products could be detected in the presence of Cu^I-zeolite, among which was the expected benzyl azide, accounting for around 5–10% of the whole mixture.

These interesting results suggested that in the presence of Cu^I-zeolite, the azide and the bromide are forced to react together, probably through confinement into zeolite cages, while without zeolite, the major but less reactive nucleophile present, that is, water, led to the product. It is worth noting that the amount of benzyl azide observed in these experiments corresponded to the zeolite copper(I) loading (10%), suggesting a stoichiometric nucleophilic substitution promoted by copper(I) under these conditions, as for Ag-assisted nucleophilic substitutions.¹⁴ These results also revealed that equilibrium or competitive reactions occurred and are shifted if alkyne is also present in the mixture, suggesting a more S_N1 than any other type mechanism (Scheme 4).

With these results in hands, we then looked at the scope of this Cu^I-zeolite-catalyzed one-pot synthesis of triazoles from halides and related compounds (Table 2).

We first screened different electrophiles, classically used in nucleophilic substitutions for comparison with bromides. Benzyl chloride was not reactive in water whatever the temperature (entry 1). However, despite a lower polarity and ionizing power of the solvent,^{12,13} the cascade reaction occurred in rather good yield if ethanol was added as the co-solvent, although less efficiently than starting from benzyl bromide (entry 2 vs 3). Solubility problem was thus clearly responsible for the lack of reactivity. Benzyl tosylate also proved to be not so reactive in pure water but more reactive than benzyl chloride since the expected triazole was isolated although in low yield (entry 4 vs 1). In water–ethanol mixture, a similar yield was now achieved (entry 5 vs 2). In contrast to halides, no solvolysis product could be detected under these reactions. The corresponding triflate was too sensitive for practical use (entry 6).

Being the best starting material, benzyl bromide was used to screen various alkynes. The triazoles corresponding to the expected cascade reaction were usually obtained in good to excellent yields (entries 7–11). The results were consistent with those observed in the zeo-click reaction from preformed azides.^{2a-c}

More functionalized benzyl bromides could also be efficiently engaged in this cascade reaction. For example, *o,o'*-dichlorobenzyl bromide gave the corresponding triazole in high yield, despite the hindrance brought by the two large ortho substituents (entry 12).

Allylic bromide reacted as well as its benzyl counterpart. Interestingly, the results gained by submitting a 90:10 mixture of α - and γ -crotonyl bromides under the present conditions revealed that some equilibration of the allyl moiety occurred, yielding a 77:33 mixture of N- α - and γ -crotonyl triazoles, still in favor of the α -product (entry 13). This classical product spread¹⁰ suggested again S_N1 rather than S_N2 or S_N2' type mechanism for the first step, but with ion pairing minimizing scrambling. It is worth noting here that the zeolite pores could be viewed as large solvent cages,¹⁵ favoring ion pairing, and even acting as stabilizer for cations.¹⁶

Non activated halides could also react but their conversion was more or less effective depending on the substitution at the halogenated carbon. Primary halides reacted as expected, the iodide being more reactive than the corresponding bromide,

giving higher yield of triazoles (entries 14–17). Solubility problems again required the addition of a co-solvent in these cases. However, α -bromo keto derivatives such as methyl 2-bromoacetate or bromo-acetophenone proved readily reactive in pure water and gave the corresponding triazoles in good to high yields (entries 18 and 19).

Secondary bromides reacted better than their primary counterparts. In pure water, the triazole derived from 2-bromobutane was produced in good yield, and in high yield when a co-solvent was added (entries 20 and 21 vs 14 and 15). The better results achieved with secondary bromides compared to those from similar primary ones supported again S_N1 rather than S_N2 or any other substitution mechanism for the first step of this cascade reaction.

Unfortunately, *tert*-butyl bromide led to mixtures of products, while adamantyl bromide remained untouched (entry 22). For the former, decomposition and/or elimination seemed to be the major processes whatever the conditions. For the latter, the rigid and bridgehead structure of adamantyl bromide prevents substitution through S_N2 mechanism and barely limits S_N1 reaction. At least, the absence of product and solvolysis product ruled out any other substitution mechanism under the present conditions.

In conclusion, we have developed a Cu^I-zeolite-catalyzed one-pot synthesis of triazoles from halides or tosylates, sodium azide, and alkynes. The step and atom economy of this cascade reaction as well as the green solvent used make such one-pot two-step synthesis a truly green process. The results obtained suggest for the first step a S_N1 mechanism in which the Cu^I-doped zeolite plays several roles, first as the Lewis acid, second as the solid solvent, probably stabilizing cation intermediates, and third as the entropic driver through confinement effect.¹⁶

General procedure: To a suspension of Cu^I-USY (20 mg/mmol) in degassed water (2 mL/mmol) under argon were successively added sodium azide (1.1 equiv), the halide or tosylate (1 equiv), and the alkyne (1 equiv). The mixture was then heated to 90 °C overnight (15 h). When no alkyne could be detected, the mixture was allowed to cool and then filtered over Nylon[®] membrane (0.2 μ m). The solid was rinsed with water and ethyl acetate. The aqueous phase was then extracted with ethyl acetate. The organic layer was then dried and the solvent evaporated. The resulting crude mixture was then purified by chromatography.

Acknowledgments

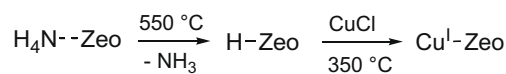
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