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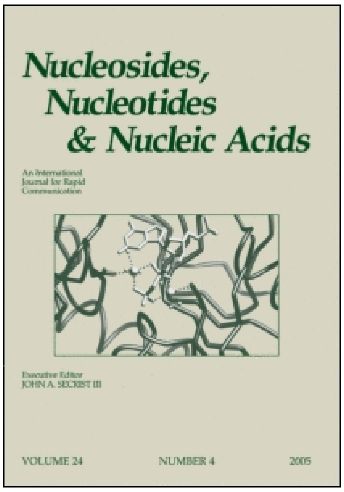

Nucleosides, Nucleotides and Nucleic Acids

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Study of Different Copper (I) Catalysts for the "Click Chemistry" Approach to Carbanucleosides

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STUDY OF DIFFERENT COPPER (I) CATALYSTS FOR THE "CLICK CHEMISTRY" APPROACH TO CARBANUCLEOSIDES

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□ *We compare herein the scope of three copper (I) catalysts on the synthesis of various 1,4-disubstitued-1,2,3-triazolo-carbanucleosides through a microwave (and thermic) assisted Huisgen 1,3-dipolar cycloaddition. The tetrakis(acetonitrile)copper hexafluorophosphate* ([$Cu(CH_3CN)_4$]PF_6)*, the imidazoline(mesythyl)copper bromide (Imes)CuBr, and the copper/copper sulfate Cu(0)/*$CuSO_4$ *(II) mixture have been chosen for this study. Their influence in a catalytic amount will be analyzed according to the substituent of the alkyne, the solvent, or the heating method.*

Keywords Carbanucleosides; Huisgen; 1,3-dipolar cycloaddition

INTRODUCTION

Pharmacomodulation has become fundamental in drug discovery and has played a major role in the research of new treatment for viral infectious diseases. However, the discovery and process optimization of potential agents is often slow, expensive, and involves complex synthesis. Click Chemistry, proposed by Sharpless,[1] has emerged as a fast and efficient approach to simplify compound synthesis. To be defined as "click," a reaction

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must respond to a set of stringent criteria: it must be of wide scope, giving very high yields with a large range of starting materials and providing stereospecific products. Moreover, a click reaction requires simple conditions as the process is usually insensitive to oxygen and water, requires no protection or chromatographic purification, and generates easily removed byproducts. The Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes is one of the best known and powerful click reactions (2). This reaction is also termed the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). The resulting 1,2,3-triazoles have been studied intensively for many years due to their antiviral and antimicrobial activities. This cycloaddition offers complete regioselectivity, giving the 1,4-isomer if catalyzed by copper (I), and can be improved by the use of microwave irradiation. Thus, as part of our drug discovery program, we compare herein the scope of three copper (I) catalysts on the synthesis of various 1,4-disubstitued-1,2,3-triazolo-carbanucleosides through a microwave (and thermic) assisted CuAAC.

RESULTS AND DISCUSSION

The most powerful click reaction, the Huisgen 1,3-dipolar cycloaddition between an azide and a terminal alkyne, generates in a fast, reproducible, and quantitative way, a large variety of five-membered heterocycles. The resulting 1,2,3-triazoles have been studied intensively for many years due to their antiviral and antimicrobial activities.[2] Most of the time, the reaction affords, under thermal condition, both 1,4 and 1,5 disubstitued regioisomers[3] (Figure 1).

However, since the discovery in 2002 of copper (I) catalysts, this cycloaddition offers a complete regioselectivity, giving exclusively the 1,4-isomer (Figure 2).

The use of a copper catalyst, like the use of microwave irradiation,[4] also considerably decreases reaction times and temperatures. As shown in Figure 2, the catalysis of the Huisgen cycloaddition starts by the formation of a Cu(I) acetylide via initial π-complex formation then subsequent

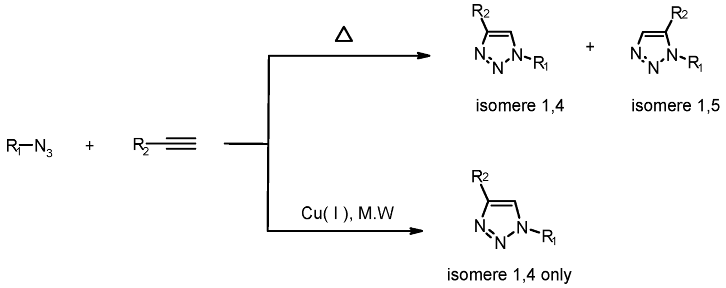


FIGURE 1 Huisgen cycloaddition under thermal heating or in the presence of a copper catalyst under microwave irradiations.

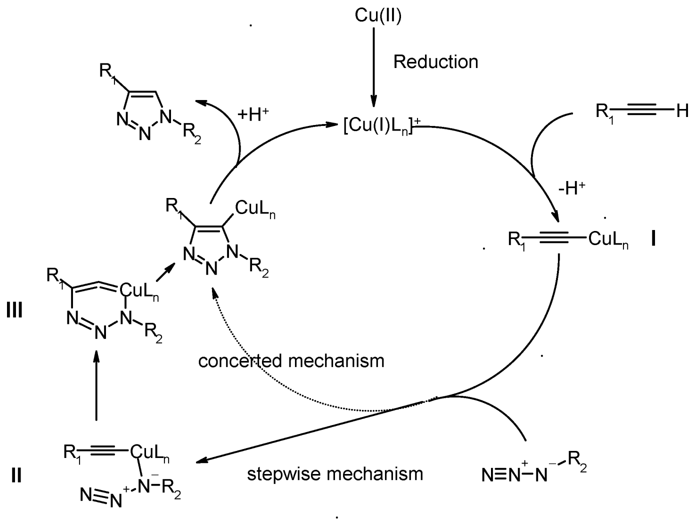
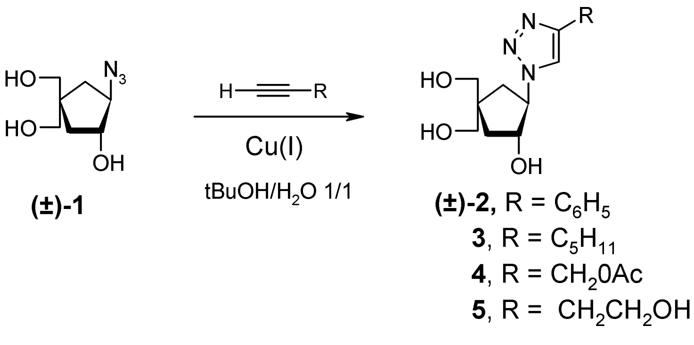


FIGURE 2 Catalytic cycle of the Huisgen cycloaddition.

deprotonation to afford the σ-acetylide Cu(I) complex (**I**). The density functional theory calculations, proposed by Fokin and Sharpless,[5] reveal that the copper catalyzed reaction proceeds in a stepwise mechanism over a concerted mechanism.

Thus, as part of our drug discovery program, we compare herein the influence of three copper (I) catalysts (with respect to the substituent of the alkyne and the heating method) on the synthesis of 1,4-disubstitued-1,2,3-triazoles. *Tetrakis(acetonitrile)copper hexafluorophosphate* ($[Cu(CH_3CN)_4]PF_6$), *imidazoline(mesythyl)copper bromide (Imes)CuBr,* and an equimolar *mixture of copper/copper sulfate* $Cu(0)/CuSO_4(II)$ were chosen for this study. Various 1,2,3-triazolo-carbanucleosides (**2–5**) were thus synthesized through the Huisgen 1,3-dipolar cycloaddition with a simple and efficient method (Scheme 1). The results of the present study are gathered in Table 1.



SCHEME 1 Synthesis of carbanucleosides by the CuAAC.

TABLE 1 Efficiency of three catalysts for microwaves or thermic CuAAC.

		80 mol% Cu(0/20 mol% $CuSO_4$		5 mol% $[Cu(CH_3CN)_4]PF_6$		5 mol% ImesCuBr	
Products		Δ H_2O/tBuOH 1/1	MW H_2O/tBuOH 1/1	Δ H_2O/tBuOH 1/1	MW H_2O/tBuOH 1/1	Δ H_2O/tBuOH 1/1	MW H_2O/tBuOH 1/1
1	**2**	**40 min** conv. 100% yield 98%	**2 min** conv. 100% yield 98%	**13 h** conv. 100% yield 99%	**15 min** conv. 100% yield 98%	**5 days** conv. 95% yield 91%	**9 h** conv. 100% yield 94%
2	**3**	**5 days** conv. 80% yield 75%	**1 h** conv. 100% yield 98%	**5 days** conv. 0% yield 0%	**10 h** conv. 79% yield 60%	**5 days** conv. 51% yield 40%	**2 h** conv. 100% yield 93%
3	**4**	**Immediate** conv. 100% yield 96%	**Immediate** conv. 100% yield 95%	**5 days** conv. 73% yield 17%	**2 min** conv. 100% yield 92%	**2 h** conv. 100% yield 70%	**5 min** conv. 100% yield 93%
4	**5**	**2 min** conv. 100% yield 95%	**2 min** conv. 100% yield 95%	**5 days** conv. 75% yield 71%	**2 h** conv. 100% yield 92%	**1 h** conv. 100% yield 96%	**15 min** conv. 100% yield 96%

All the reactions were performed in the presence of 50 mg of **1**, 1.05 equivalent of alkyne and the copper catalyst in 2 ml of a water-*tert*-butanol mixture. The temperature was set at 75°C for the thermal heating and at 125°C under microwave irradiation. Almost all the cycloadditions were realized with complete and rapid conversion of the azido-carbocycle into the desired carbanucleoside. We have noticed that microwave irradiation considerably reduced the reaction time and increased the conversion compared to the thermal results (Table 1). Generally, 1,4-disubstitued triazoles obtained from alkynes with polar substituents (acetate and ethanol, entries 3–4) were easier to obtain than triazoles with non-polar substituents (phenyl and pentyne, entries 1–2). The reaction time decreases with the polarity of the substituent.

Different treatments were followed according to the carbanucleoside. 1,4-disubstitued triazoles with non-polar substituents (enties 1–2) were isolated with very good yields after a simple extraction in ethyl acetate and salt saturated water. 1,4-disubstitued triazoles with polar substituents (entries 3–4) required filtration on silica gel column chromatography to eliminate the salts, since the products had too much affinity for the aqueous layer. The regioselectivity of the ligation leading to 1,4-disubstitued-[1,2,3]-triazole moiety was confirmed by NMR using $^1H,^{13}C$ long range correlation spectra (HMBC).

Finally, the catalytic efficiency of Cu(0)/$CuSO_4$(II) and $[Cu(CH_3CN)_4]PF_6$ is comparable in term of percentage of conversion. Reaction times are generally longer with the $[Cu(CH_3CN)_4]PF_6$. A high percentage of conversion and increasing times are observed with ImesCuBr.

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