

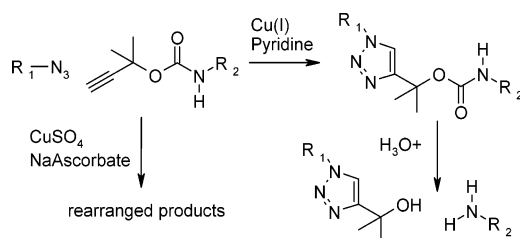
## Click Chemistry with *O*-Dimethylpropargylcarbamate for Preparation of pH-Sensitive Functional Groups. A Case Study

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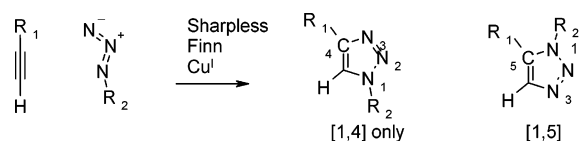


Click chemistry has become an important tool for molecular constructs such as biopolymers. During the development of biodegradable multifunctional poly(ethylene oxide) (PEO) polymers suitable for click chemistry in water, an unexpected reaction leading to a mixture of triazole cycloadducts was observed. This result was attributed to an intramolecular ligand effect, and alternative conditions were evaluated. An efficient method was then implemented allowing the access in high yields to the expected triazolylcarbamate. pH sensitivity of the obtained isopropyltriazolylcarbamate was demonstrated at acidic pH.

In 1963, Huisgen reviewed the [3 + 2] cycloaddition reactions between 1,3 dipoles and unsaturated bonds.<sup>1</sup> When realized under thermal conditions, this reaction generally led to two possible regioisomeric adducts limiting the possible applications of this reaction (Scheme 1), the ratio being governed by steric and electronic factors. Applied to terminal alkynes and azides, this reaction allows access to [1,4] and [1,5] disubstituted 1,2,3-triazoles. In 2001, Sharpless showed in this latter case that the use of Cu(I) salts gave only [1,4] cycloadducts in high yields.<sup>2</sup>

As this reaction can be realized in several solvents, including water, and supports many functional groups, it has been widely used in several ways as “click chemistry”. A selective [1,5] cycloadduct formation was also proposed.<sup>3</sup> Click chemistry has been applied to several types of polymers such as modified carbohydrates<sup>4</sup> or polyamides<sup>5</sup> for biocompatible purposes,

### SCHEME 1. Cycloaddition of Alkynes and Azides



polyphenylacetylenes<sup>6</sup> for material development, and in the field of combinatorial chemistry.<sup>7</sup> Biocompatible and biodegradable polymers for therapeutic usage have been developed for many decades<sup>8</sup> either as carrier systems or to improve physical properties such as solubility. Several strategies were developed to incorporate bioactive molecules into polymers to produce slow releasing systems based on biological transformations such as enzymatic hydrolysis or pH variations,<sup>9</sup> the polymer carrier being usually decomposed. Poly(ethylene oxide) (PEO) polymers have been known for a long time to be biocompatible, nonimmunogenic, and hydrophilic, increasing water solubility, and are approved by the FDA.<sup>10</sup> They are themselves the major polymeric material when higher molecular weight derivatives are used<sup>11</sup> or are integrated in more complex systems as intermediate chains.<sup>12</sup> A PEG-asparaginase bioconjugate has been developed for the treatment of acute lymphoblastic leukaemia.<sup>13</sup> In a project devoted to the development of functional PEO polymers for drug delivery, we were interested in biodegradable modified branched PEO with a moiety designed for the introduction of multipurpose functional groups by click chemistry and also for drug release in biological systems under acidic conditions.<sup>9</sup> Polymer biodegradability can also be obtained by integration of pH-sensitive groups (orthoesters,<sup>14</sup> acetals<sup>15</sup>) in the polymer structure.

Model compound **3** was designed (Scheme 2) to integrate these several requirements. In this study, a minimal methoxy-protected ethylenoxide motif is used and linked to a benzoate ester, for the purpose of biodegradability. The phenyl ring of the benzoate group can also be the central point of multipurpose functionality, provided multiple substitutions. In this work we limited these substitutions by selecting salicylic acid, the phenol group being converted to an azidoether necessary for the click

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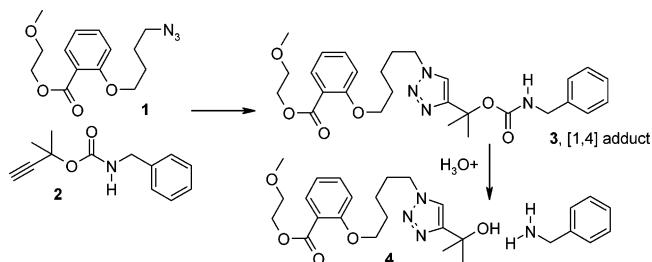
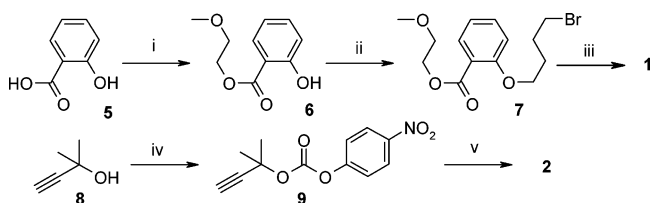
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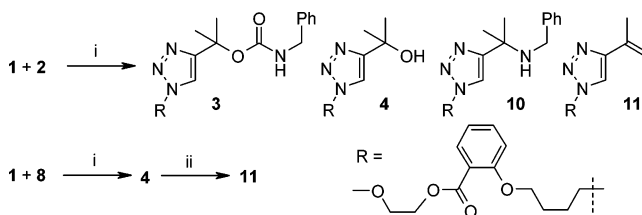
**SCHEME 2. Preparation and Hydrolysis of Model Compound 3**

**SCHEME 3. Preparation of Intermediates 1 and 2<sup>a</sup>**


<sup>a</sup> Conditions: (i) H<sub>2</sub>SO<sub>4</sub>, MeO-(CH<sub>2</sub>)<sub>2</sub>-OH, 44%; (ii) K<sub>2</sub>CO<sub>3</sub>, DMF, Br-(CH<sub>2</sub>)<sub>4</sub>-Br, 80%; (iii) NaN<sub>3</sub>, acetone, 97%; (iv) pNO<sub>2</sub>-Ph-OCO-Cl, pyridine, 72%; (v) BnNH<sub>2</sub>, NEt<sub>3</sub>, 92%.

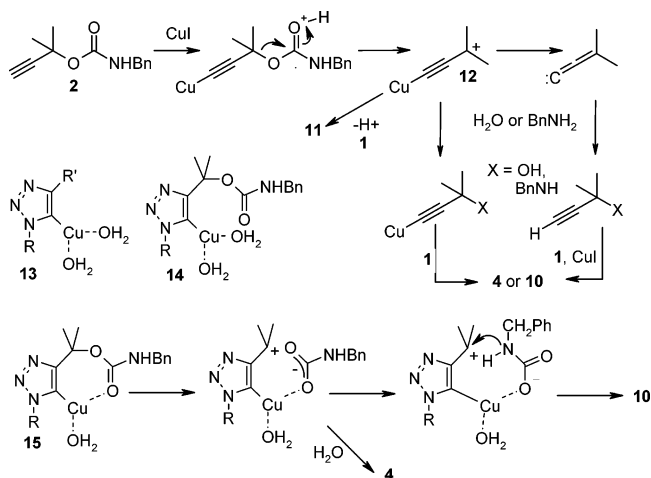
chemistry. The triazole ring obtained by click chemistry can be considered as a substitute for a phenyl ring and is expected to facilitate the acidic cleavage of the carbamate group, especially by preparing an isopropyltriazolylcarbamate,<sup>16</sup> which under acidic hydrolysis will afford alcohol **4** and benzylamine in our case. This cleavage method is an original alternative approach compared to other *N*-triazole deprotections realized under highly acidic conditions (TFA, CH<sub>2</sub>Cl<sub>2</sub>).<sup>17</sup> Thus Sharpless cycloaddition conditions were selected to prepare **3** from azide **1** and propargylcarbamate **2**. Equivalent reactions were described with unsubstituted *O*-propargylcarbamate in a ligation protocol for the synthesis of peptides.<sup>18</sup> Interestingly, the opposite *N*-propargyl<sup>19</sup> and *N*-disubstituted propargylcarbamate<sup>20</sup> cycloadditions were reported.

Esterification of salicylic acid **5** afforded phenol **6** (Scheme 3, H<sub>2</sub>SO<sub>4</sub>, CH<sub>3</sub>O-(CH<sub>2</sub>)<sub>2</sub>-OH, 44%<sup>21</sup>), which gave after etherification bromoether **7** (dibromobutane, K<sub>2</sub>CO<sub>3</sub>, acetone, 80%). Azide **1** is finally obtained from **7** by bromine substitution (NaN<sub>3</sub>, DMF, 97%). Carbamate **2** was prepared from butynol **8** via the parnitrophenoxycarbonate **9** (pNO<sub>2</sub>-Ph-OCO-Cl, pyridine, 72%) followed by displacement with benzylamine (BnNH<sub>2</sub>, NEt<sub>3</sub>, 92%); **1** and **2** were then reacted using the Sharpless procedure (Scheme 4, CuSO<sub>4</sub>·5H<sub>2</sub>O, NaAscorbate, *t*BuOH/H<sub>2</sub>O 1:1) in order to obtain cycloadduct **3**. <sup>1</sup>H NMR of the crude material revealed the disappearance of the terminal alkyne hydrogen (singlet 2.8 ppm) of the alkyne **2**, and several singlets appeared around 7.5 ppm, attributed to hydrogens from newly formed triazole rings.

Separation allowed the NMR characterization of small amounts of elimination product **11** and expected **3**, and the more

**SCHEME 4. Sharpless Cycloadditions<sup>a</sup>**


<sup>a</sup> Conditions: (i) CuSO<sub>4</sub>·5H<sub>2</sub>O, Na ascorbate, *t*BuOH/H<sub>2</sub>O 1:1; (ii) benzene, *p*-TsOH, reflux Dean-Stark, 45%.

**SCHEME 5. Proposed Mechanism for the Rearrangement Leading to 4, 10, and 11**


polar major compounds alcohol **4** and amine **10**. Identification of **4**, **10**, and **11** was made by ESI MS, comparison with literature data,<sup>22</sup> and for **4** and **11**, by cycloaddition of butynol **8** with **1** and subsequent dehydration, giving identical <sup>1</sup>H NMR spectra compared to the products obtained under Sharpless conditions. Cycloaddition of carbamate **2** with azide **1** is the first example of unexpected results obtained by click chemistry realized in water, which is generally tolerant to various substrates and reactions conditions.<sup>23</sup> Two hypothesis were first considered. Substitution of propargylic acetates by amines catalyzed by Cu(I) salts was described by Murahashi and co-workers<sup>24</sup> with a mechanism shown in Scheme 5. Thus carbocation **12** can be formed from **2** and then be trapped either by water or by the released benzylamine, leading to **4** and **10**, respectively, after cycloaddition. Deprotonation of **12** can also give alkene **11**. Triazoles are good copper chelators<sup>25</sup> and could also be involved in the rearrangement of **3** after cycloaddition. As carbamate **2** and triazole **3** were found stable in the Sharpless conditions, both hypothesis were ruled out.

DFT studies made by Sharpless and co-workers<sup>26</sup> showed that a copper intermediate **13** is formed in water during the cycloaddition process. On the other hand, Kebarle and co-

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**TABLE 1. Conditions for CuI-Catalyzed Cycloadditions of **1** with **2** and **3**:**10**:**11** Ratios Obtained<sup>a</sup>**

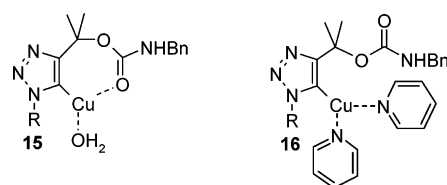
entry	base	solvent	<b>3</b> : <b>10</b> : <b>11</b> relative %	isolated yields
1	DIPEA <sup>a</sup>	toluene	38.5:47.4:14.1 <sup>c</sup>	30:37:11
2	DMF <sup>a</sup>	toluene	35.7:50.0:14.3 <sup>d</sup>	— <sup>f</sup>
3	pyridine <sup>a</sup>	toluene	76.9:0:23.1 <sup>d,e</sup>	— <sup>f</sup>
4	pyridine	pyridine	97.5:0:2.5 <sup>e</sup>	85:0:2:2
5	bipyridyle <sup>b</sup>	toluene	76.9:15.4:7.7 <sup>d,e</sup>	— <sup>f</sup>

<sup>a</sup> General conditions: 0.1 mmol alkyne, 0.1 mmol azide, 0.01 mmol CuI, 0.1 mmol amine, 1 mL of solvent. <sup>b</sup> 0.2 mmol catalyst. <sup>c</sup> Determined from isolated products. <sup>d</sup> Determined from <sup>1</sup>H NMR crude mixture. <sup>e</sup> Incomplete reaction. <sup>f</sup> Not determined.

worker<sup>27</sup> determined in the gas phase the following bonding order for several ligands of Cu(I): amines > R-CONR'<sub>2</sub> > RCOOR' > H<sub>2</sub>O. From this literature information, a mechanism can be postulated with the formation of intermediate **14**, with carbamate bonding properties considered equivalent to those of ester or amide and stronger than water. Thus **15** can be formed by displacement of one molecule of water by the carbamate group, facilitated by a possible steric hindrance of the gem dimethyl group,<sup>28</sup> leading to **10** by an intramolecular rearrangement or to **4** by water trapping. Water as solvent affording alcohol **4**, other reaction conditions were considered.<sup>7,29</sup>

Toluene was selected as solvent, CuI as the catalyst, and several amines as ligands were tested (Table 1). The best condition was determined conveniently by the <sup>1</sup>H NMR spectrum of the crude material, several hydrogen signals being easily quantified in the mixture (Figure 2, Supporting Information). Reacting **1** and **2** in toluene, CuI, and DIPEA (Table 1, entry 1) produced the carbamate **3**, with amine **10** as the major product, and small amounts of alkene **11**. As expected, in absence of water, alcohol **4** was not detected. DMF (Table 1, entry 2) gave quite the same results as DIPEA, and only Pyridine<sup>7a</sup> gave an improvement (Table 1, entry 3) with **3** being the major product but with incomplete reaction. Interestingly, **10** was not observed in these conditions.

Higher solvation of the copper acetylide by pyridine is postulated according to Kebarle, by the fact that aromatic amines, such bipyridyles, were used to improve click chemistry applications<sup>30</sup> and that polar organic solvents better dissolved Cu(I) salts.<sup>31</sup> Improvement of cycloaddition between pegylated azides and acetylenic amide in CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O due to better solubility of organic reacting materials was also reported.<sup>32</sup> To increase the yield obtained with the toluene/pyridine system, cycloaddition was then conducted in pyridine only, and **3** was obtained in high yield, with traces of elimination product **11** (Table 1, entry 4 and Figure 2E, Supporting Information). Alternatively, with a bipyridyle/toluene system **3** was obtained as the major compound, with incomplete reaction (Table 1, entry 5 and Figure 2D, Supporting Information), underlining this

**FIGURE 1.** Proposed bonding ligand effect.

solvating effect. This latter condition was not optimized but a complete conversion can be expected by longer reaction time or higher bipyridile loading.

Our results can be rationalized according to Figure 1. In water, the C–O single bond of the carbamate is probably weaker due to donor ligand effect of the C=O bond. The formation of a stabilized carbocation is also favored and both effects are expected to lead to carbamate bond breaking. Using a stronger ligand such as pyridine disrupts the carbonyl bonding to copper, stabilizing the C–O single bond in **16**. This conclusion is consistent with the results reported in Table 1, with the following ligand strength for our current reaction: pyridine > bipyridyle > DMF = DIPEA > H<sub>2</sub>O.

Having in hand a practical method to prepare carbamate **3**, acidic hydrolysis was then evaluated. Two pH buffers were selected: pH 1 (HCl/KCl buffer, Normex dose) and pH 4 (citric acid buffer). A 10 mg portion of **3** was mixed with 0.5 mL of *tert*-butanol to help dissolution in 10 mL of buffer, and 1 mL samples were neutralized and analyzed at 0.5, 1, 2.5, 4, 6.5, 22, 48, 72, and 96 h. Evolution of the remaining carbamate **3** was compared to the formation of alcohol **4** (**3** + **4** = 100%). Hydrolysis at pH 1 appeared to be a fast process (Figure 3 and 4, Supporting Information), as most of the carbamate was hydrolyzed at 0.5 h and completely disappeared after 2.5 h. At pH 4, about 50% hydrolysis (*t*<sub>1/2</sub>) is obtained at 20 h, and 75% at 72 h (3 days).

In conclusion, this work is to our knowledge the first example of click chemistry applied to *O*-dimethylpropargyl carbamates. Initial attempts to run the reaction in the water system described by Sharpless led to unexpected products, a result attributed to the lability of the *O*-propargylcarbamate group in the presence of Cu(I) salts. The use of nonpolar solvent such as toluene with amines or Cu(I) chelating agents highlighted the importance of the solvating effect for this unwanted result. Changing the reaction medium to pyridine as solvent allows the formation of a stable copper intermediate **16**, giving a practical method for the cycloaddition of such propargylcarbamates. Hydrolysis of carbamate **3** was then validated at acidic pH levels, showing the potential use of such triazole systems in this kind of applications. Work is in progress in our laboratory for the development and optimization of these new types of pH sensitive releasing systems for chemical or biochemical applications.

## Experimental Section

**Toluene Cycloaddition Conditions.** Alkyne (0.1 mmol) and azide (0.1 mmol) were dissolved in toluene (1 mL). CuI (1.9 mg, 0.01 mmol) and amine (0.1 mmol) were then added. After stirring overnight at ambient temperature, solvent and amine were removed under reduced pressure at 40 °C, and the residual oil was purified by preparative TLC (silica, AcOEt/EP 50:50). Depending on solvent used (Table 1), amine **10**, carbamate **3**, and alkene **11** were obtained in various ratios.

**Pyridine Cycloaddition Conditions.** Alkyne (0.1 mmol) and azide (0.1 mmol) were dissolved in pyridine (1 mL). CuI (1.9 mg,

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0.01 mmol) was then added. After stirring overnight at ambient temperature, pyridine was removed under reduced pressure at 40 °C, and the residual oil was purified by preparative TLC (silica, AcOEt/EP 50:50), giving carbamate **3** (43.8 mg, 85%, yellow oil) and alkene **11** (0.85 mg, 2.4%, colorless oil).

**Carbamate (3).** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.85 (s + m, 8H), 2.20 (m, 2H), 3.39 (s, 3H), 3.69 (m, 2H), 4.03 (t, 2H, *J* = 5.75 Hz), 4.24 (d, 2H, *J* = 5.95 Hz), 4.44 (m, 4H), 5.2 (sb, 1H), 6.91 (d, 1H, *J* = 8.28 Hz), 6.97 (t, 1H, *J* = 7.67 Hz), 7.28 (m, 5H), 7.44 (ddd, 1H, *J* = 1.8, 7.8, 15.7 Hz), 7.65 (s, 1H), 7.81 (dd, 1H, *J* = 1.6, 7.8 Hz). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 26.4, 27.3, 28.1, 45.0, 50.2, 59.3, 64.1, 68.2, 70.9, 76.8, 113.4, 120.5, 120.7, 121.6, 127.7, 127.8, 128.9, 132.2, 134.0, 139.0, 152.3, 158.8, 155.7, 166.5. HRMS (ESI) calcd for [M<sup>+</sup>] C<sub>27</sub>H<sub>34</sub>N<sub>4</sub>O<sub>6</sub> 510.60, found (M + Na)<sup>+</sup> 533.2358.

**2-{4-[4-(1-Benzylamino-1-methyl-ethyl)-[1,2,3]triazol-1-yl]-butoxy}-benzoic Acid 2-Methoxyethyl Ester (10).** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.53 (s, 6H), 1.86 (m, 2H), 1.97 (sb, 1H), 2.2 (m, 2H), 3.39 (s, 3H), 3.50 (s, 2H), 3.68 (m, 2H), 4.05 (t, 2H, *J* = 5.8 Hz), 4.41 (m, 2H), 4.48 (t, 2H, *J* = 7.0 Hz), 6.91 (d, 1H, *J* = 8.4 Hz), 6.97 (td, 1H, *J* = 0.8, 7.6 Hz), 7.22 (m, 1H), 7.27 (m, 4H), 7.43 (ddd, 1H, *J* = 1.8, 7.5, 8.3 Hz), 7.56 (s, 1H), 7.83 (dd, 1H, *J* = 1.8, 7.7 Hz). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 26.0, 27.0, 28.4, 47.9, 49.8, 52.3, 58.9, 63.7, 67.8, 70.6, 113.0, 120.1, 120.3, 126.7, 128.25, 128.31, 131.8, 133.6, 140.9, 154.7, 158.8, 166.0. HRMS

(ESI) calcd for [M<sup>+</sup>] C<sub>26</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub> 466.59, found (M + Na)<sup>+</sup> 489.2485.

**2-[4-(4-Isopropenyl-[1,2,3]triazol-1-yl)-butoxy]-benzoic Acid 2-Methoxyethyl Ester (11).** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.86 (m, 2H), 2.11 (s, 3H), 2.21 (m, 2H), 3.40 (s, 3H), 3.70 (m, 2H), 4.05 (t, 2H, *J* = 5.9 Hz), 4.43 (m, 2H), 4.49 (t, 2H, *J* = 6.9 Hz), 5.07 (t, 1H, *J* = 1.5 Hz), 5.68 (s, 1H), 6.92 (d, 1H, *J* = 8.3 Hz), 7.0 (td, 1H, *J* = 0.8, 7.6 Hz), 7.44 (ddd, 1H, *J* = 1.7, 7.4, 9.1 Hz), 7.65 (s, 1H), 7.83 (dd, 1H, *J* = 1.7, 7.8 Hz). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 21.0, 26.3, 27.5, 50.2, 59.3, 64.1, 68.3, 71.0, 112.6, 113.4, 120.2, 120.6, 120.7, 132.1, 134.0, 134.1, 149.1, 158.8, 166.4. HRMS (ESI) calcd for [M<sup>+</sup>] C<sub>26</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub> 359.43, found (M + Na)<sup>+</sup> 382.1743.

**Acknowledgment.** The authors thank CNRS for financial support.

**Supporting Information Available:** Experimental procedure and analytical data for compounds **1**, **2**, **3**, **4**, **6**, **7**, **9**, **10**, and **11**, and acidic hydrolysis of **3**. HPLC analysis of compounds **3**, **4**, and **10** and example of chromatograms for time-dependent acidic hydrolysis of compound **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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