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Click Intermediate

Isolation of a Copper(I) Triazolide: A “Click” Intermediate**

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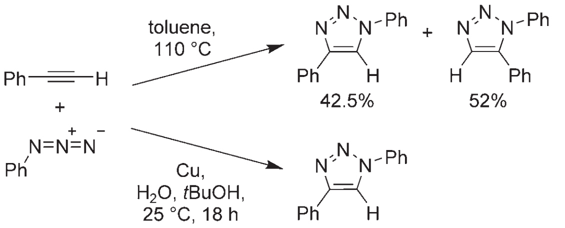
Dedicated to Professor Herbert Mayr on the occasion of his 60th birthday

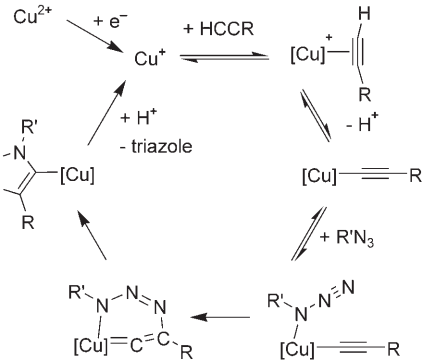
The reaction of alkynes with organoazides has been known as a valuable triazole synthesis for more than a century.[1] It is a typical example of a Huisgen-type 1,3-dipolar cycloaddition.[2] The low regioselectivity and the high reaction temperatures, however, limit the scope of this reaction. Independently, the groups of Meldal and of Sharpless reported an ideal regiospecifity and an extreme rate enhancement in the reaction of terminal alkynes with azides in the presence of copper metal precatalysts or copper salts (Scheme 1).[3] This method has been categorized as a “click” reaction.[4]



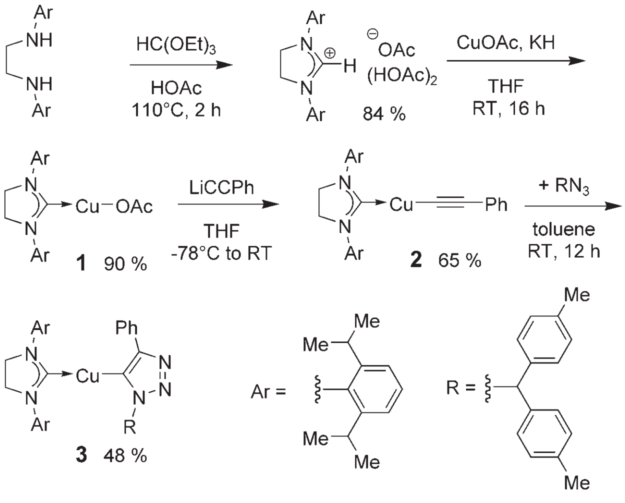
Scheme 1. Concerted Huisgen-type [3+2] cycloaddition (top)[5a] and copper-catalyzed click reaction (bottom).[5b]

A stepwise pathway with copper(I) acetylide catalysts and a copper(I) triazolide intermediate is generally assumed (Scheme 2).[6] Mechanistic investigations by Fokin and Finn revealed that the alkyne–azide click reaction presumably involves dinuclear copper(I) complexes in the rate-determining step.[7]

Since a direct proof of the existence of copper(I) intermediates has remained elusive to date,[8] we considered the isolation and characterization of a molecular copper(I) triazolide complex as a formidable goal in our attempts to unravel the mechanisms of organic reactions catalyzed by transition-metal complexes.[9] Our strategy for the isolation of a triazolide complex comprised the stoichiometric reaction of a copper(I) acetylide complex with a sterically demanding organoazide. In the absence of electrophiles in an aprotic solvent, the resulting copper triazolide species should be stable. However, the preparation of mononuclear copper(I) phenyl acetylides with phenanthroline or phosphane ancillary ligands failed. In our attempts, these ligands dissociated from copper, resulting in precipitation of polymeric copper phenyl acetylide. Since molecular copper(I) acetylide complexes with unsaturated N-heterocyclic carbene (NHC) ligands had already been described,[10] we developed a straightforward synthesis to copper(I) phenyl acetylide complexes with a saturated NHC ligand (Scheme 3).[11] NHC copper(I) halide complexes have only recently been reported as highly active catalysts for triazole click reactions.[12]



Scheme 2. Some proposed mechanistic steps in the alkyne–azide click reaction; [Cu] represents either mononuclear or dinuclear copper(I) complex fragments.



Scheme 3. Preparation of a copper(I) triazolide complex **3**.

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Supporting information (X-ray structure of **1**, preparation procedures and characterization data) for this article is available on the WWW under http://www.angewandte.org or from the author.

Indeed, the reaction of the copper(I) acetate complex **1** with lithium phenyl acetylide yields a suitable precursor complex **2**. Addition of azidodi-4-tolylmethane to a solution of acetylide **2** in toluene results in the precipitation of a mononuclear copper triazolide complex **3** at room temperature within 12 h. It thus appears that dinuclear copper complexes are not mandatory for Huisgen–Sharpless click reactions, since even mononuclear copper(I) acetylides with extreme steric shielding react with bulky organoazides at room temperature.[13] The reaction rate is comparable to sterically hindered systems of Nolan and co-workers.[12]

Both the acetate complex **1** as well as the triazolide complex **3** are active catalysts in click chemistry. Preliminary results indicate a strong dependence of the reaction rate on the acidity of the medium. The rate-limiting step apparently changes from the protonation of the triazolide complex (H_2O or alkyne as proton source) to the alkyne deprotonation–cycloaddition sequence (excess of acetic acid). Triazolide complex **3** in CD_2Cl_2 reacts quantitatively with acetic acid within minutes at room temperature to give the triazole product and acetate complex **1**.

The crystal structure of the product **3** shows a d^{10} ML_2 copper(I) species with a linear metal coordination environment (Figure 1).[14] The uncharged complex is, electronically, closely related to diorganocuprates with 14 valence electrons.[15] In triazolide **3**, the Cu−C bond lengths to the formally uncharged NHC ligand and to the formally anionic triazolide ligand are essentially equal. The five-membered heterocyclic ligands are coplanar, leading to a conformation with minimal steric repulsion. An *ortho* position of the phenyl substituent is in close vicinity to the copper atom, resulting in the Cu-C2-C3 angle being larger than the Cu-C2-N5 angle.

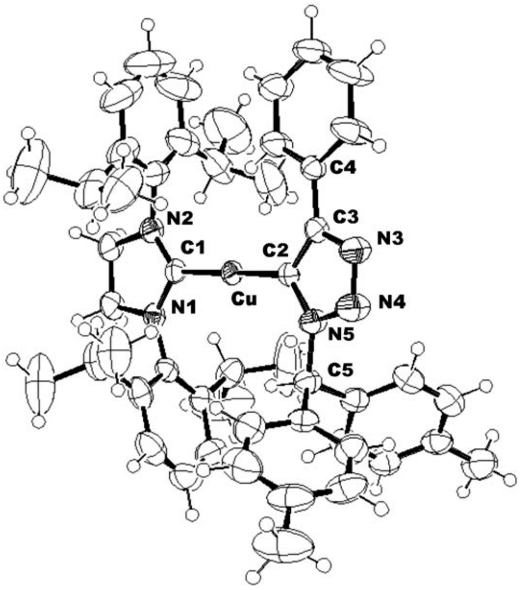

Figure 1. X-ray structure of copper(I) triazolide **3**.[16,17] Disordered CH_2Cl_2 is omitted for clarity; only one of the two complexes **3** in the elemental cell is shown. Average bond lengths [pm] and angles [°] (deviations): Cu–C1 190.9(0.5), Cu–C2 190.4(0.2), Cu–H(o-Ph) 269.1(7.2), C2–C3 139.8(0.3), C3–N3 136.7(0.1), C2–N5 136.8(0.2), N3–N4 131.2(0.5), N4–N5 136.1(0.1), N2–C1 133.2(0.4), N1–C1 134.1-(0.1); C1-Cu-C2 178.0(0.3), Cu-C2-N5 125.3(3.1), Cu-C2-C3 133.7(3.2), C2-C3-C4 130.7(0.3), C2-N5-C5 128.9(0.8). Dihedral angles: N2-C1-C2-C3 1.7(0.2), Cu-C2-N5-N4 178.2(1.9).

In Figure 2, the ^1H NMR spectrum of copper triazolide complex **3** in CD_2Cl_2 is shown. The thermal stability of complex **3** in solution is consistent with its high melting point and decomposition temperature of 235 °C. The complex even resists fragmentation under ESI conditions. For the triazolide substitution pattern present in complex **3**, we have not observed N_2 elimination.

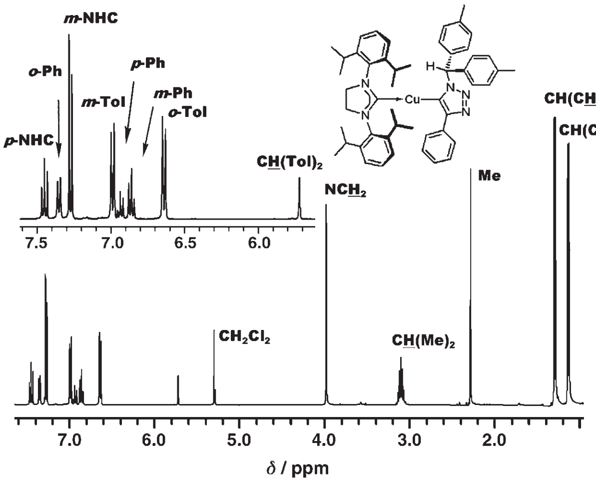

Figure 2. ^1H NMR spectrum of **3**.

In summary, the isolation of a molecular copper(I) triazolide complex is direct evidence for the existence of such structures, which have to date only been assumed as intermediates in the Huisgen–Sharpless click reaction. With click intermediates at hand, mechanistic studies can go beyond indirect kinetic measurements of reaction mixtures towards the direct investigation of elementary steps.

Experimental Section

Azidodi(4-tolyl)methane (0.385 g, 1.62 mmol) was added to a Schlenk flask charged with **2** (0.600 g, 1.08 mmol) and dry toluene (10 mL) under an N_2 atmosphere. The solution was stirred at room temperature. After 4 h, a colorless solid began to precipitate. After an additional 8 h, the precipitate was collected by filtration and washed with toluene. The solid was dissolved in CH_2Cl_2 and filtered through Celite 500. Pentane was added to the filtrate, and the solution cooled to −20 °C. The precipitate was collected and dried in vacuo, affording 414 mg (48.4 %) of the product as colorless crystals. Single crystals of **3** suitable for an X-ray diffraction study were grown from CH_2Cl_2 at room temperature by slow diffusion of pentane. ^1H NMR (399.92 MHz, CD_2Cl_2): $\delta = 1.13$ (d, $^3J_{HH} = 7$ Hz, 12 H, $CH(CH_3)_2$), 1.29 (d, $^3J_{HH} = 7$ Hz, 12 H, $CH(CH_3)_2$), 2.29 (s, 6 H, Aryl-CH_3), 3.10 (sept$_{pseudo}$, $^3J_{HH} = 7$ Hz, 4 H, $CH(CH_3)_2$), 3.98 (s, 4 H, NCH_2), 5.72 (s, 1 H, Tol_2CH), 6.64 (d, $^3J_{HH} = 8.0$ Hz, 4 H, *o*-Tol), 6.86 (t$_{pseudo}$t$_{pseudo}$, $^3J_{HH} = 7.2$ Hz, $^4J_{HH} = 1.2$ Hz, 2 H, *m*-C_6H_5), 6.94 (tt, $^3J_{HH} = 7.2$ Hz, $^4J_{HH} = 1.2$ Hz, 1 H, *p*-C_6H_5), 6.99 (d, $^3J_{HH} = 8.0$ Hz, 4 H, *m*-Tol), 7.27 (d, $^3J_{HH} = 8.0$ Hz, 4 H, *m*-NHC), 7.35 (dd, $^3J_{HH} = 7.2$ Hz, $^4J_{HH} = 1.6$ Hz, 2 H, *o*-C_6H_5), 7.45 ppm (t, $^3J_{HH} = 8.0$ Hz, 2 H, *p*-NHC). $^{13}C\{^1H\}$ NMR (100.56 MHz, CD_2Cl_2): $\delta = 20.8$ (Aryl-CH_3), 23.6 ($CHCH_3$), 25.1 ($CHCH_3$), 29.0 ($CHCH_3$), 54.2 (NCH_2), 70.0 (Tol_2CH), 124.7 (*p*-C_6H_5), 125.0 (*m*-NHC), 125.3 (*o*-C_6H_5), 128.2 (*m*-C_6H_5), 128.2 (*m*-

Tol), 128.9 (s, *o*-Tol) 130.0 (s, *p*-NHC), 135.0 (*o*-NHC), 136.3 (*ipso*-C_6H_5), 136.7 (*p*-Tol), 138.8 (*ipso*-Tol), 146.9 (*ipso*-NHC), 152.2 (triazolide-C), 154.6 (triazolide-C), 204.7 ppm ($N_2\mathit{C}Cu$). MS (+p ESI): m/z (%) = 792.406 (100.00) [$M^+(^{63}Cu)+H$], 793.411 (45.50) [$M^+(^{63}Cu)+2H$]. IR: $\tilde{\nu} = 3057$ (w), 2962 (s), 2924 (s), 2868 (m), 2097 (w), 1602 (w), 1513 (m), 1481 (m), 1459 (s), 1428 (s), 1385 (m), 1364 (w), 1327 (m), 1274 (s), 1182 (m), 1058 (w), 988 (m), 805 (s), 788 (m), 770 (s), 758 cm^{-1} (s). M.p. 235 °C (decomp). Elemental analysis (%) calcd for $C_{50}H_{58}CuN_5$: C 75.77, H 7.38, N 8.84; found: C 75.24, H 7.33, N 8.73. CCDC-625315 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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