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Synthesis, Characterization and Chemistry of Tetrakis(Propargylisocyanide) Copper(I) Complex

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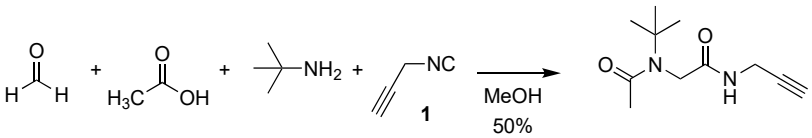
Abstract: The kinetically unstable propargylisocyanide was reacted with the tetrakis(acetonitrile) copper(I) hexafluorophosphate and the formed complex was then involved in a copper-catalyzed alkyne-azide cycloaddition reaction (CuAAC). After the decomplexation of the adduct, the isocyanide was engaged in a Ugi reaction. By such a complexation, reactions can be carried out on the CC triple bond without the constraint of the instability of the free compound or the competitive reactivity of the isocyanide group.

Keywords: isocyanide; copper; cycloaddition; Ugi reaction

1. Introduction

Isocyanides are well-studied compounds, especially for their peculiar reactivity. These isomers of nitriles possess a carbenoid structure due to the atomic arrangement R-NC, which confers these compounds their unique reactivity [1]. In addition to cycloadditions, they are able to react in multi-component reactions (MCRs) like the well-known Passerini [2,3] and Ugi [4–6] reactions. Recently, we described the use of unsaturated isocyanides bearing CC double bonds or triple bonds in such MCRs [7]. We showed that despite their instability, they are interesting building blocks that are able to afford highly functionalized products (Scheme 1). However, their handling remains tedious due to their combined volatility, instability and vile odor. To solve this problem, Zwikker and Stephany [8] described the complexation of two of them (the propargyl and the allenyl isocyanides) to copper(I) in order to stabilize and handle them, knowing that their decomplexation with NaCN proved to be efficient. Nevertheless, except for the isomerization of the propargylic complex into the allenic one with the help of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), their chemistry was not investigated.



Scheme 1. Previous work: reactivity of isocyanide **1** in Ugi reaction.

In this article, we focused our attention on the propargylic copper(I) complex in order to characterize it and investigate its reactivity in Copper-catalyzed Alkyne-Azide Cycloaddition (CuAAC) [9,10]. We thus showed that it was possible to make it react, decomplex the corresponding isocyanide from Cu(I) and subsequently react it in a Ugi reaction. This provides an alternative pathway to the Ugi reaction followed by CuAAC we recently reported. In addition, we showed it was possible to keep the isocyanide function after reacting the CC triple bond.

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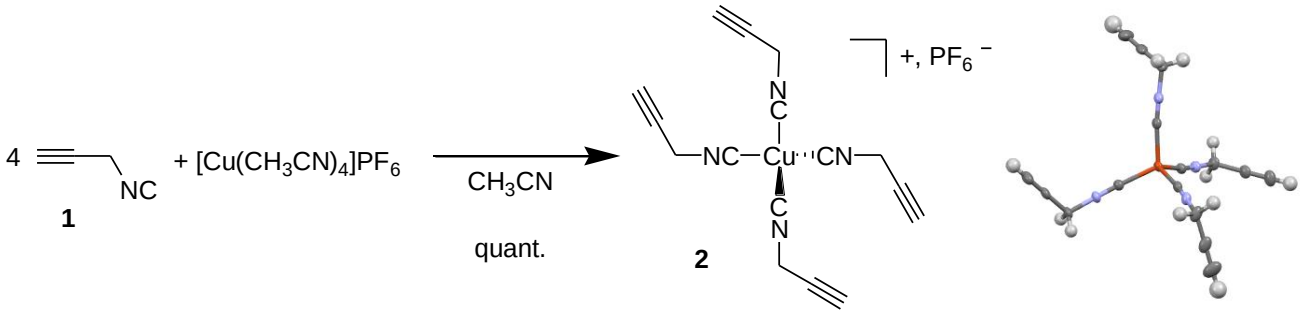
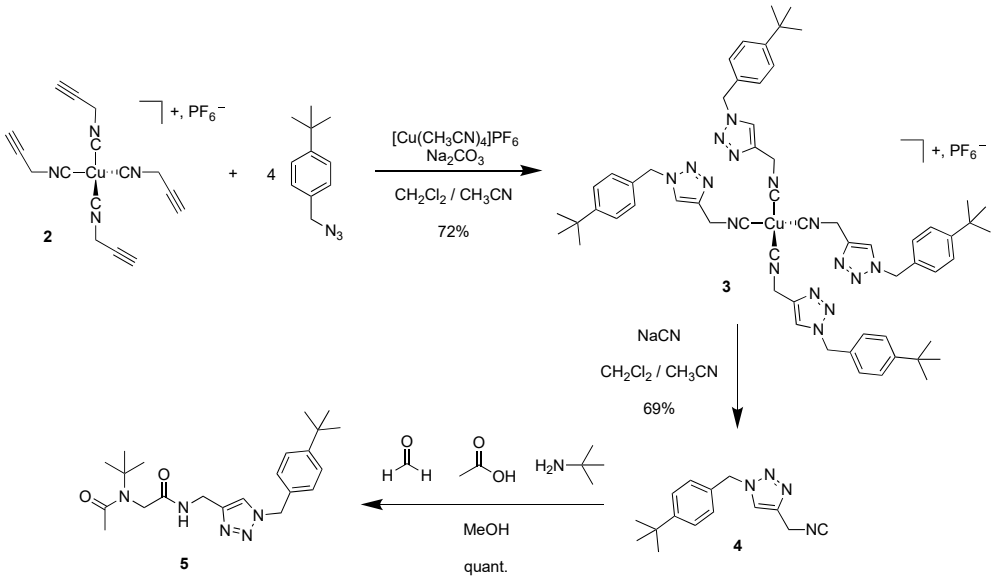
2. Results and Discussion

We first reproduced the synthesis of the tetrakis(propargylisocyanide) copper(I) complex **2** by mixing four equivalents of propargylisocyanide **1** with one equivalent of tetrakis(acetonitrile) copper(I) hexafluorophosphate in acetonitrile to afford the expected complex quantitatively (Scheme 2). The only difference with the original publication [8] is the counter-ion, which is PF_6^- here instead of BF_4^- or ClO_4^- as in the previous case. We were able to confirm the structure of this complex by X-ray crystallography, in addition to the usual techniques (^1H and ^{13}C NMR spectroscopy, see the Supplementary Materials). The geometry around the copper atom is a slightly distorted tetrahedron, with C-Cu-C comprised between 104 and 115°. The fact that crystals suitable for X-ray diffraction could be obtained at room temperature confirmed the great stability of this compound, while propargylisocyanide slowly decomposes at −30 °C in pure form. This observation encouraged us to continue this study and evaluate the reactivity of this compound.



Scheme 2. Synthesis of copper(I) complex **2** and its X-ray structure. Ellipsoids are drawn with 50% probability; PF_6^- counter-ion was removed for clarity. Orange: copper; grey: carbon; blue: nitrogen; white: hydrogen.

This complex **2** was reacted with an excess of 4-*tert*-butylbenzylazide (6.7 equiv.) in the presence of $[Cu(CH_3CN)_4]PF_6$ (1.1 equiv.) and Na_2CO_3 (1.3 equiv.) in a mixture of dichloromethane and acetonitrile at room temperature overnight. The corresponding Cu(I) complex **3** bearing four triazole units was isolated in a satisfying yield of 72% after silica column chromatography, showing again the stability of such a complex. This also demonstrated the ability of this kind of compound to be further functionalized. The corresponding isocyanide was subsequently decomplexed from copper using an excess of NaCN (14 equiv.) to isolate the free isonitrile **4** bearing a triazole function in 69% yield. It is noteworthy that isonitrile **4** could not be isolated from direct CuAAC (2 mol% of CuI, di(isopropyl)ethylamine (3 equiv.) as a base and toluene as solvent), showing the importance of complexing it before reaction (only the starting azide was observed by NMR spectroscopy). Finally, the latter was reacted in Ugi conditions with *tert*-butylamine, acetic acid and formaldehyde in methanol overnight to form quantitatively the corresponding Ugi-product **5** that we already described using another pathway (Scheme 3) [7]. This shows that after functionalization, the isocyanide was able to react according to a Ugi reaction, instead of subsequently functionalizing the Ugi product.



Scheme 3. Synthesis of compound **5** from copper(I) complex **2**.

3. Materials and Methods

Reactions were monitored by thin layer chromatography (Merck TLC 0.25 mm silica gel plates 60 F_{254}) and visualized under UV irradiation at 245 nm and $KMnO_4$ staining solution. Compounds were purified by flash column chromatography using Geduran silica gel 60 (43−60 µm). Melting points were measured on a Stuart® SMP10 melting point apparatus. NMR spectra were recorded on a Bruker (Wissembourg, France) Avance spectrometer at 23 °C, 400 MHz for proton and 100 MHz for carbon. Spectra were recorded in deuterochloroform referenced to $CHCl_3$ (^{1}H, 7.26 ppm) or $CDCl_3$ (^{13}C, 77.2 ppm) and in deuterodimethyl sulfoxide referenced to $(CD_3)(CD_2H)SO$ (^{1}H, 2.50 ppm) or $(CD_3)_2SO$ (^{13}C, 39.5 ppm). Chemical shifts (δ) are reported in ppm and coupling constants (*J*) are reported in Hertz. The following abbreviations are used to describe multiplicity: s-singlet, br s-broad singlet, d-doublet, t-triplet, q-quadruplet, hept-heptuplet and m-multiplet, quadr. moment-quadrupole moment. HRMS spectra were recorded on a Maxis$^+$ (Bruker Daltonics, Bremen, Germany) and Q-Exactive (Thermo Fischer Scientific, Bremen, Germany), depending on the targeted structure.

Solvents such as acetonitrile (anhydrous 99.8%), methanol (99.8%) and dichloromethane (anhydrous, ≥99.8%) were directly purchased from Sigma-Aldrich (Saint-Quentin-Fallavier, France).

The commercial reagents employed in the synthesis were tetrakis(acetonitrile) copper(I) hexafluorophosphate (97%, Sigma-Aldrich), *tert*-butylamine (≥99.5%, Sigma-Aldrich), formaldehyde (ASC reagent, 37 wt.% in H_2O, Sigma-Aldrich), acetic acid (glacial, ACS reagent, ≥99.7%, Sigma-Aldrich), Na_2CO_3 (anhydrous powder, Sigma-Aldrich), $MgSO_4$ (anhydrous powder, Sigma-Aldrich) and NaCN (reagent grade, 97%, Sigma-Aldrich).

Single crystal diffraction data were collected on a D8 Venture Bruker AXS diffractometer with multilayer monochromatized Mo-Kα radiation. Structures were solved by the dual-space algorithm using the SHELXT program [11] and then refined with full-matrix least-squares methods based on F^2 (SHELXL program) [12]. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. H atoms were finally included in their calculated positions and treated as riding on their parent atom with constrained thermal parameters.

4-*tert*-Butylbenzylazide [13] and propargylisocyanide [8] were synthesized according to published procedures.

3.1. Tetrakis(propargylisonitrile) Copper(I) Hexafluorophosphate **2**

To a −20 °C cooled solution of tetrakis(acetonitrile) copper(I) hexafluorophosphate (2.24 g, 6.0 mmol, 0.25 equiv.) in acetonitrile (12 mL), was added under dinitrogen a cooled solution of propargylisonitrile (1.56 g, 24.0 mmol, 1.0 equiv.) in acetonitrile (4 mL). The resulting solution was allowed to reach room temperature and stirred for 20 min. The mixture was concentrated under high vacuum and the solid obtained was diluted with dichloromethane. The organic phase was then washed with water. The organic layers were gathered, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 2.81 g of the desired tetrakis(propargylisonitrile) copper(I) hexafluorophosphate **2** (quantitative yield) as a white solid. Suitable crystals for X-ray diffraction were grown by slow evaporation of an acetonitrile solution of compound **2**.

^{1}H NMR (400 MHz, DMSO-d_6) δ 4.93 (d, 2H, *J* = 2.6 Hz), 3.73 (t, 1H, *J* = 2.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 138.5 (m (quadr. moment)), 77.4, 73.7, 33.4; ^{19}F NMR (376 MHz, DMSO-d_6) δ-70.2 (d, *J* = 712 Hz); ^{31}P NMR (162 MHz, DMSO-d_6) δ-144.2 (hept, *J* = 711 Hz).

Crystal data: $C_{16}H_{12}CuF_6N_4P$, M = 468.81 g mol^{-1}, T = 150(2) K, monoclinic, space group = *C* 2/c, a = 5.4651(6) Å, b = 22.311(2) Å, c = 16.4771(18) Å, β = 94.038(4)°, V = 2004.1 (4) Å3, Z = 4, Dc = 1.554 g cm^{-3}, absorption coefficient = 1.231 mm^{-1}, F(000) = 936, reflections collected = 13,996, independent reflections = 2290 (Rint = 0.0446), data/restraints/parameters = 2290/0/128. Final R indices (I > 2σ): R1 = 0.0513. R indices (all data): wR2 = 0.1401, goodness-of-fit on F^2 of 1.049.

3.2. Tetrakis(1-(4-(tert-butyl)benzyl)-4-(isocyanomethyl)-1H-1,2,3-triazole) Copper(I) Hexafluorophosphate **3**

To a solution of **2** (100 mg, 0.21 mmol, 1.0 equiv.) tetrakis(acetonitrile) copper(I) hexafluorophosphate (86 mg, 0.23 mmol, 1.1 equiv.) in dichloromethane (3.0 mL) and acetonitrile (1.0 mL) was added under dinitrogen 4-(*tert*-butyl)benzyl azide (270 mg, 1.43 mmol, 6.7 equiv.) and Na_2CO_3 (30 mg, 0.28 mmol, 1.3 equiv.). The resulting solution, stirred for 18 h at 25 °C, was monitored by TLC (dichloromethane/MeOH (97:3), R_f: 0.3) until the complete consumption of **2**. The mixture was concentrated under reduced pressure to give a mixture of **3** and an excess of 4-(*tert*-butyl)benzyl azide. The resulting solid was purified by column chromatography (SiO_2, eluent: CH_2Cl_2/acetone from 100:0 to 0:100) to remove the excess of 4-(*tert*-butyl)benzyl azide and gave **3**. Yield 189 mg (72%); orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (br s, 1H), 7.34 (d, 2H, *J* = 8.4 Hz), 7.23 (d, 2H, *J* = 8.4 Hz), 5.40 (br s, 2H), 4.86 (br s, 2H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 140.9 (m (quadr. moment)), 138.9, 130.7, 128.5, 126.2, 125.1, 54.6, 38.0, 34.7, 31.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.0 (d, *J* = 713 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ -144.2 (hept, *J* = 713 Hz).

HRMS (ESI) *m/z* $[M - PF_6]^+$ calcd. for $C_{60}H_{72}N_{16}Cu$: 1079.54164, found: 1079.5415.

3.3. 1-(4-(tert-Butyl)benzyl)-4-(isocyanomethyl)-1H-1,2,3-triazole **4**

To a solution of NaCN (73 mg, 1.48 mmol, 14 equiv.) in dichloromethane (1.0 mL), acetonitrile (0.5 mL) and water (0.5 mL) was added **3** (130 mg, 0.11 mmol, 1 equiv.) and the resulting solution was stirred for 1.5 h at 20 °C. The biphasic mixture was diluted with dichloromethane, then the organic phase was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure and gave **4**. Yield 74 mg (69%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (br s, 1H), 7.41 (d, 2H, *J* = 8.4 Hz), 7.22 (d, 2H, *J* = 8.4 Hz), 5.49 (s, 2H), 4.72 (br s, 2H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3 (m (quadr. moment)), 152.3, 140.9, 131.1, 128.1, 126.2, 122.1, 54.2, 37.9 (t (quadr. moment), *J* = 7.32 Hz), 34.7, 31.3.

3.4. N-(tert-butyl)-N-(2-(((1-(4-(tert-butyl)benzyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-2-oxoethyl)acetamide **5**

In a three-neck round-bottom flask under dinitrogen containing a solution stirred at 0 °C of *tert*-butylamine (19 mg, 0.256 mmol, 1.0 equiv.), formaldehyde (23 mg, 37% in water, 0.256 mmol, 1.0 equiv.), acetic acid (15 mg, 0.256 mmol, 1.0 equiv.) in MeOH (2.5 mL), was added a cooled solution of isonitrile **4** (65 mg, 0.256 mmol, 1.0 equiv.) in MeOH (0.5 mL). The mixture was stirred for 18.5 h at 28 °C and monitored by TLC (CH_2Cl_2/MeOH (97:3), R_f: 0.20). The greenish solution was concentrated under reduced pressure and gave **5**. Yield 102 mg (quantitative yield); beige solid (mp: 118 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (br s, 1H), 7.38 (d, 2H, *J* = 8.2 Hz), 7.19 (d, 2H, *J* = 8.2 Hz), 6.83 (br s, 1H), 5.46 (s, 2H), 4.54 (br s, 2H), 3.95 (s, 2H), 2.02 (s, 3H), 1.37 (s, 9H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 170.1, 152.1, 144.7, 131.4, 127.9, 126.1, 122.2, 57.8, 54.1, 49.9, 34.9, 34.7, 31.3, 28.7, 25.4.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd. for $C_{22}H_{33}N_5O_2Na$: 422.2527, found: 422.2526.

4. Conclusions

In this article, we showed that it was possible to react the CC triple bond of kinetically unstable propargylisocyanide after complexation to Cu(I) and release the corresponding isocyanide to make it react in the Ugi reaction.

Supplementary Materials: The following supporting information can be downloaded online, Figure S1: ^{1}H NMR spectrum of **2**; Figure S2: ^{13}C NMR spectrum of **2**; Figure S3: ^{19}F NMR spectrum of **2**; Figure S4: ^{31}P NMR spectrum of **2**; Figure S5: ^{1}H NMR spectrum of **3**; Figure S6: ^{13}C NMR spectrum of **3**; Figure S7: ^{19}F NMR spectrum of **3**; Figure S8: ^{31}P NMR spectrum of **3**; Figure S9: ^{1}H NMR spectrum of **4**; Figure S10: ^{13}C NMR spectrum of **4**; Figure S11: ^{1}H NMR spectrum of **5**; Figure S12: ^{13}C NMR spectrum of **5**.

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Data Availability Statement: CCDC 2238883 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44-1223-336033.

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