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Combined XRD-paramagnetic ^{13}C NMR spectroscopy of 1,2,3-triazoles for revealing copper traces in a Huisgen click-chemistry cycloaddition. A model case

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Abstract: Copper-catalyzed Alkyne-Azide Cycloaddition (CuAAC) click chemistry robustness has been demonstrated over recent years to produce 1,2,3-triazoles with excellent yields at mild conditions with simple purification methods. However, the consequences of having copper paramagnetic traces in final products, which complicate spectroscopic assignments and can produce inaccurate conclusions, has been scarcely discussed. Herein we present a strategy that combines X-Ray Diffraction (XRD) with ^{13}C- paramagnetic Nuclear Magnetic Resonance spectroscopy, in order to demonstrate the presence of paramagnetic metal traces at standard Huisgen synthesis and purification conditions. We also demonstrate that the derivatization of 1,4-disubstituted-1,2,3-triazoles to produce 1,3,4,-trisubstituted-1,2,3.triazolium salts, promotes an efficient removal of Cu(II/I) moieties. Evidence of paramagnetic metal moieties is given using XRD structural analysis of abnormalities in torsional angles between substituents and the 1,2,3-triazole center, in parallel to ^{13}C- paramagnetic NMR chemical shift and line width analysis. As model systems to demonstrate the importance of characterizing paramagnetic traces, we present the synthesis of novel 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole and its derivatized 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-3-methyl-1H-[1,2,3]-triazol-3-ium triflate salt.

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Introduction

[1,2,3]-triazoles are a very well-known class of nitrogen aromatic heterocyclic compounds, continuously widespread in different fields such as synthetic organic chemistry[1], medicinal chemistry[2], polymer science,[3] and catalysis[4], amongst others. Their 1,2,3,-triazo-aromatic scaffolds comprise stable compounds to even acidic/basic hydrolysis conditions or reductive/oxidative environments due to their high aromatic stabilization.[5] Moreover, this framework is relatively resistant to metabolic degradation.[6] In order for an exclusive and high yield of a stereospecific 1,4-disubstituted [1,2,3]-triazole regioisomer, a modular synthetic approach is used: the Huisgen azide-alkyne 1,3-dipolar cycloaddition[7] recently adapted to the "click chemistry" philosophy[8], wherein said cycloaddition is carried out in mild-aqueous conditions to produce high-yield / stereospecific products, using straightforward purification methods (crystallisation or distillation). Some strategies to install highly hindered groups within the heterocyclic ring comprise: increasing the Cu(I) catalyst amount and/or implementing harsh reaction conditions (for instance: microwave radiation combined with longer reaction periods).

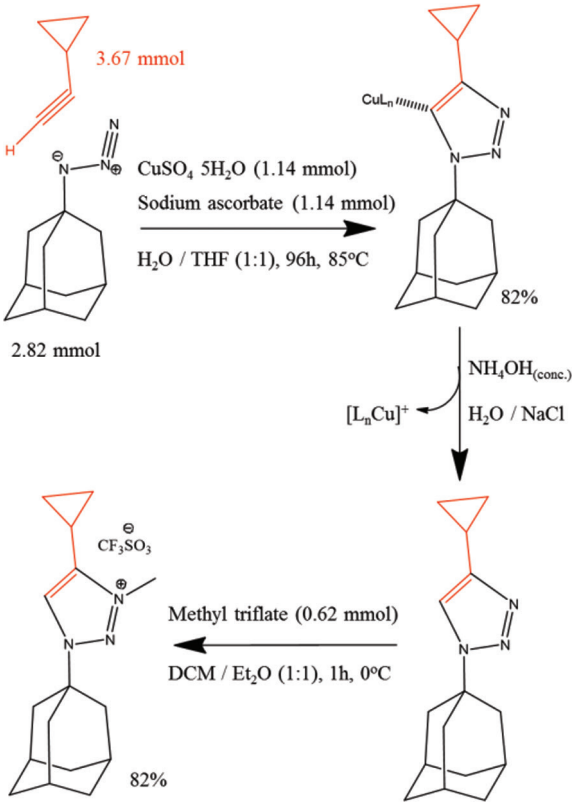
On one hand, adamantane coupled to specific pharmaceutical formulations has provided an excellent lipophilicity due to its absorption, distribution, metabolism, and excretion modulation effects[9]. Examples of molecules with biological activities that include any adamantyl scaffold in their structures are amino adamantane derivatives[10], Rimantadine[11], and Amantadine hydrochloride[12]. On the other hand, the "cyclopropyl fragment" is a versatile player that frequently appears in clinical drug studies.

Some notable pharmaceutical properties that are influenced by the cyclopropane ring include, amongst others, intrinsic lipophilicity[13], metabolic stability[14], and binding to target proteins[15]. Some drugs that contain a cyclopropyl fragment are Trametinib (renal carcinoma drug), Volasertib B1/6727 (selective PLK1 inhibitor for acute myeloid leukemia) and Vaniprevir (hepatitis C virus). Given the proven effectiveness of both a 1,2,3-triazole core and adamantyl-cyclopropyl substituents in different pharmaceutical formulations, as for other applications stressed above, it is thought a natural step to test clinical advantages of 1-adamantyl-4-cyclopropyl-1,2,3-triazole scaffolds. A further advantage of 1,4-disubstituted 1,2,3-triazoles is the simplicity and flexibility of their use in derivatizations (for instance to produce 1,3,4-trisubstituted 1,2,3-triazolium salts, precursors of N-heterocyclic carbene metal complexes, used as organocatalysts for key SN regioselective arrangements or as ionic liquids[16-17]).

Despite the significant number of reports enhancing the synthetic advantages of a one-pot step to regiospecifically unite azides and terminal acetylenes to form 1,4-disbstituted 1,2,3-triazoles with the aim of Cu (I) catalyzed ligation[1, 18-19], few have discussed the efficient removal of metal traces in Copper - Catalyzed Alkyne-Azide Cycloaddition (CuAAC) "click" reactions[20]. Presence of Cu (I) or its paramagnetic Cu (II) raw material could produce inaccurate conclusions in terms of molecular assignments. For instance, paramagnetic species (with unpaired electrons in metals' d-shells) in proximity to organic centers will produce important changes in experimental ^{1}H and/ or ^{13}C NMR spectra of said organic species. Major spectral modifications comprise temperature-dependent large line widths and/or chemical shift dispersions. Active electron paramagnetic spin relaxation broadens signals from nuclei near paramagnetic centers by a direct dipolar coupling interaction between the unpaired electron spin with nuclear spins in the vicinity[21-22]. Furthermore, the appearance of a Fermi-contact shift contribution in the isotropic chemical shift promotes shift dispersions of neighboring nuclear spins, an effect that nowadays can be straightforwardly described with the calculation of an electron-spin density interaction with molecular orbitals of organic centers, using Density Functional Theory approach[23-24]. However, solution-state ^{13}C detected paramagnetic NMR spectroscopic studies of samples directly or indirectly affected by active electron-spin interactions have been scarcely reported[25].

In contrast, when paramagnetism is present as copper traces in CuAAC processes, said presence could not necessarily be unambiguously assigned with X-Ray Diffraction (XRD) data, typically using copper K(α) radiationto collect data, due to known polychromatic radiation effects of some paramagnetic species present in the monocrystal when an intense beam of wavelength equal to 1.5418 Å is used.

In the present work, we report for the first time the synthesis of the 1,4-disubstituted 1,2,3-triazole: 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole, its treatment with ammonia solution as standard removal strategy of copper traces and, finally, its derivatization to 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-3-methyl-1H-[1,2,3]-triazol-3-ium triflate salt (Scheme 1). Both 1,4-disubstituted and 1,3,4-trisubstituted compounds were crystallized for exhaustive XRD structural analysis. Finally, ^{13}C detected paramagnetic NMR spectroscopy of the 1,4-disubstituted molecule, its ammonia washed



Scheme 1. Synthetic route for the present Huisgen "Click chemistry" reaction and experimental conditions to produce the 1,4-disubstituted triazole: 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole, followed by its treatment with ammonia solution as standard removal strategy of copper traces and final derivatization to produce the 1,3,4-trisubstituted triazole: 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-3-methyl-1H-[1,2,3]-triazol-3-ium triflate salt. As stated in reference 18, the one-pot 1,3-dipolar copper catalyzed cycloaddition promotes the Cu-addition in position 5 of the 1,2,3-triazol, whereas its presence and ineffective removal, could explain the paramagnetic effects discussed in the present work.

byproduct and the 1,3,4-trisubstituted triazole were carried out to confirm the presence of copper paramagnetic traces. Clinical advantages of novel triazole molecular architectures and their metal-related toxicity are out of the scope of the present study, and will be published elsewhere.

Results and discussion

The synthesis of 1,4-disubstituted and 1,3(methyl),4-trisubstituted 1,2,3-triazoles with adamantyl and cyclopropyl scaffolds as promising molecules with lipophilicity and metabolic stability are described (see Scheme 1 and synthetic details in Experimental, *vide infra*). First, the 1,4-disubstituted-1,2,3-triazole was prepared following standard Huisgen 1,3-cycloaddition copper catalyzed conditions, with expected high yields (above 80%). After carrying out standard purification methods for all molecules herein presented (Experimental, *vide infra*)[4, 16, 26], high quality monocrystals of : 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole (Figure 1) and 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-3-methyl-1H-[1,2,3]-triazol-3-ium triflate salt (Figure 2) were collected for XRD studies (see Crystallography section, *vide infra*). Key geometrical data of both crystallographic data is presented in Figure 3. The same purified samples as well as that obtained from the washing ammonia solution of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole were dissolved in deuterated $CDCl_3$ for ^{13}C-NMR studies (Figure 4).

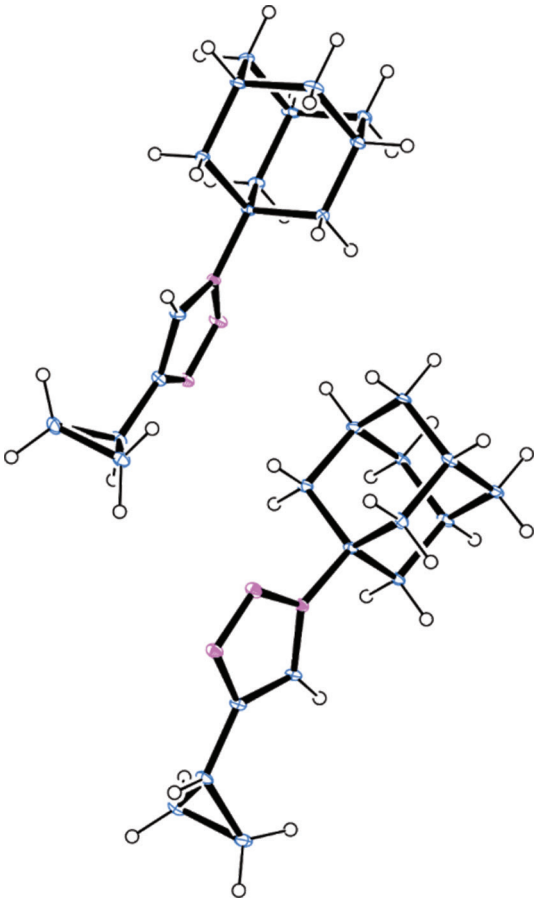


Figure 1. XRD Ortep plot of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole with 50% probability thermal ellipsoids for non-H atoms. Atomic labels, crystallographic data, fractional atomic coordinates, isotropic and atomic displacements as well as geometrical parameters are reported within the supplementary material. CCDC accession number: **1896662**.

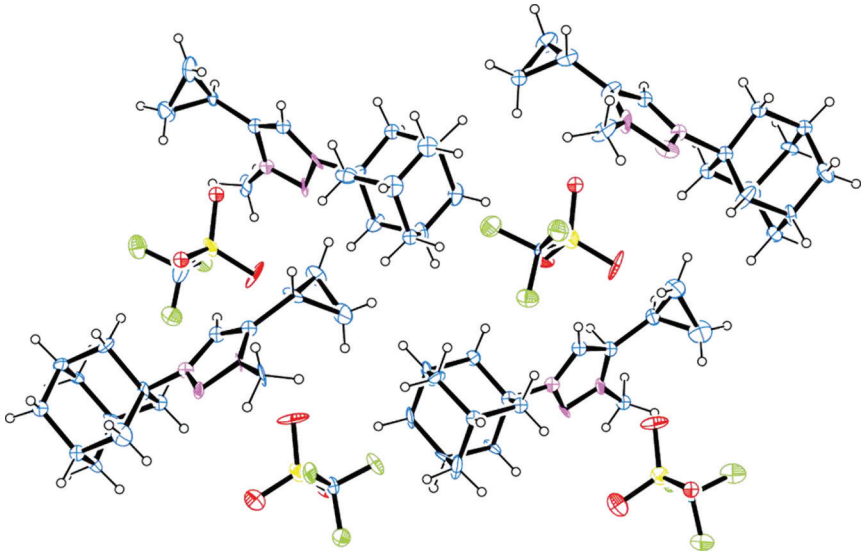


Figure 2. XRD Ortep plot of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-3-methyl-1H-[1,2,3]-triazol-3-ium triflate salt with 50% probability thermal ellipsoids for non-H atoms. Atomic labels, crystallographic data, fractional atomic coordinates, isotropic and atomic displacements as well as geometrical parameters are reported within the supplementary material. CCDC accession number: **1896671**.

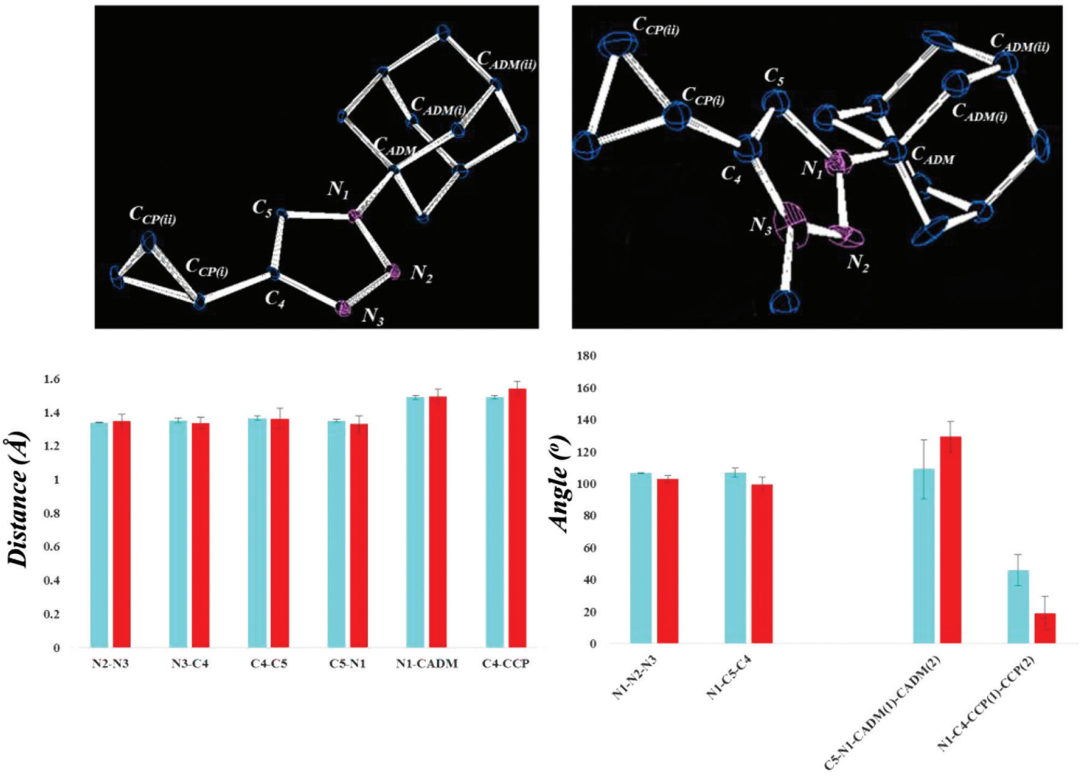


Figure 3. Key geometrical parameters (Å, °) of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole (blue histograms) and 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-3-methyl-1H-[1,2,3]-triazol-3-ium triflate salt (red histograms). Standard deviations of bonds [± 0.005-0.01, blue histograms]; [± 0.03-0.06, red histograms] and angles [± 0.31-2.8, blue histograms]; [± 1.9-4.6, red histograms] between asymmetric units in both crystal structures are represented as error bars.

The crystal structure of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole (T= 100K) presents two independent molecules within its asymmetric unit of the defined Monoclinic $P2_1$ space group. The derivatized 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-3-methyl-1H-[1,2,3]-triazol-3-ium triflate salt (T = 298 K) crystal structure is, in contrast, built up with four crystallographic independent molecules within its triclinic space group. Comparisons between both crystal structures were possible by obtaining mean geometric parameters of both 1,4-disubstituted (Z=2) and 1,3,4-trisubstituted (Z=4) 1,2,3-triazoles, displayed in Figure 3 (depicting standard deviations as error bars within the histograms), highlighting the following observations:

- Both 1,2,3-triazole pentacycles present expected bond N-N (1.33 – 1.34 Å), N-C (1.33 – 1.35 Å) and C-C ranges (1.36 Å), confirming the effective Cu catalytic cycloaddition of a Huisgen process.
- An equivalent triazole – adamantyl distance of N_1-C_{ADM} of 1.49 Å between both crystal structures is as well within the expected ranges of substituent values of N-C bonds in triazoles.
- The effect of methyl substitution in the triflate salt might be regarded as follows: elongation of the C_4-$C_{CP(i)}$ bond distance (1.54 Å) and the distortion of the N_1-C_5-C_4 angle (99.7°) of the triazole ring, with respect expected ranges (respectively C_4-$C_{CP(i)}$ = 1.49 Å, N_1-C_5-C_4 = 106.9° observed in 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole), mostly due to the ionic triazolium-triflate stabilization.

However, abnormalities within the high resolution crystal structure of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole have been observed at the level of torsional angles. Important deviations of the torsional angles between the triazole ring and its 1,4-substituents are observed between asymmetric molecules within the unit cell: C_5-N_1-$C_{ADM(i)}$-$C_{ADM(ii)}$ = 96° (I), C_5-N_1-$C_{ADM(i)}$-$C_{ADM(ii)}$ = 122° (II); N_1-C_4-$C_{CP(i)}$-$C_{CP(ii)}$ = 53° (I), N_1-C_4-$C_{CP(i)}$-$C_{CP(ii)}$ = 39° (II). Said torsional angles retain consistency and remain in higher agreement with respect to expected values, for its triflate triazolium salt counterpart: C_5-N_1-$C_{ADM(i)}$-$C_{ADM(ii)}$ = 127° (I), C_5-N_1-$C_{ADM(i)}$-$C_{ADM(ii)}$ = 145° (II), C_5-N_1-$C_{ADM(i)}$-$C_{ADM(ii)}$ = 123° (III), C_5-N_1-$C_{ADM(i)}$-$C_{ADM(ii)}$ = 132° (IV); N_1-C_4-$C_{CP(i)}$-$C_{CP(ii)}$ = 0° (I), N_1-C_4-$C_{CP(i)}$-$C_{CP(ii)}$ = 18° (II), N_1-C_4-$C_{CP(i)}$-$C_{CP(ii)}$ = 20° (III), N_1-C_4-$C_{CP(i)}$-$C_{CP(ii)}$ = 24° (IV).

Despite its higher symmetry, less asymmetric molecules per unit cell (Z=2), higher symmetry between molecules in the unit cell (standard deviations of bonds and angles

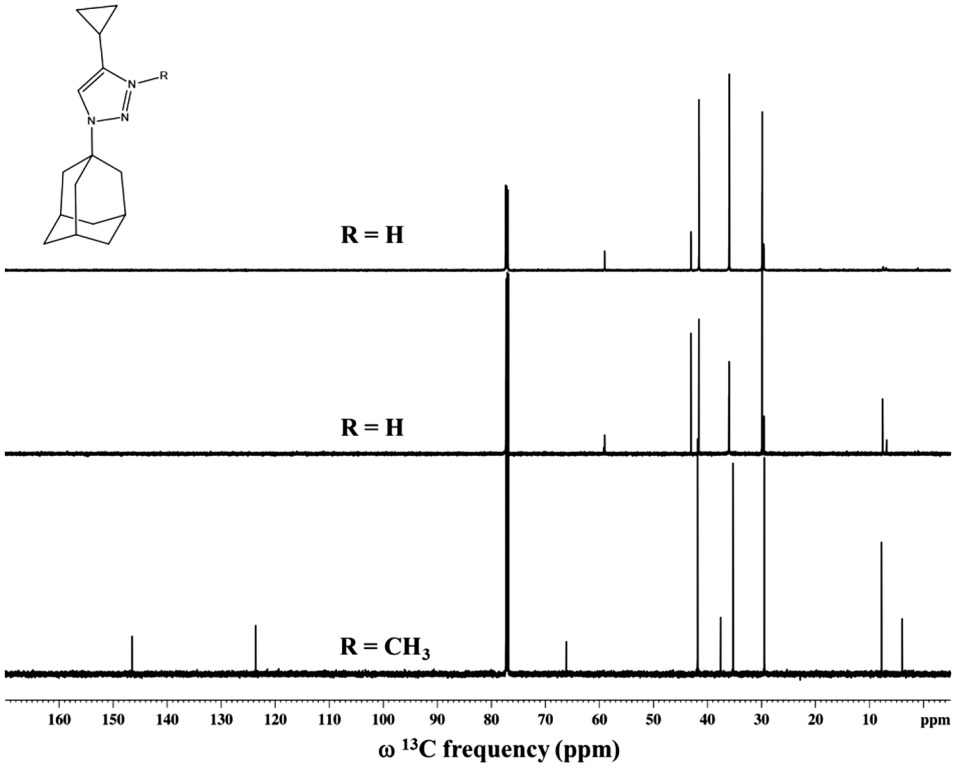


Figure 4. ^{13}C-direct excitation NMR spectra of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole (top), the ammonia washing by-product (middle) and 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-3-methyl-1H-[1,2,3]-triazol-3-ium triflate salt (bottom), carried out at exact experimental conditions.

respectively in the ranges of [± 0.005-0.01], [± 0.31-2.8]) and better discrepancy index (R_{int} = 0.031) with respect to the triazolium triflate crystal structure (Z= 4, standard deviations of bonds and angles respectively in the ranges of [± 0.03-0.06], [± 1.9-4.6] and R_{int} = 0.176), observed abnormalities of torsional angles between triazole ring and substituents in 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole, might suggest the presence of additional electronic density not observed with the present XRD experimental and instrumental conditions. Orthogonal methods shall shed light to explain said discrepancies.

Assuming the presence of copper catalyst traces, nuclear magnetic resonance chemical shift- and particularly ^{13}C-line widths at half-height ($\nu_{1/2}$) analysis, provide unequivocal evidence of the presence of paramagnetic effects. Figure 4 presents the ^{13}C-NMR spectra of the 1,4-disubstituted-1,2,3-triazole, before (top) and after (middle) copper removal procedure with NH_4OH, as well as 1,3,4-trisubstituted-1,2,3-triazoleum salt (bottom). Chemical shift inspection of the CuAAC cycloaddition product prior to any ammonia washing procedure, reveals only the presence of adamantyl carbon spin systems. Cyclopropyl and triazole carbon resonances are not observed, strongly suggesting the presence of fast electron spin relaxation from paramagnetic Cu (II) that will broaden ^{13}C signals from nuclei in close proximity to the paramagnetic center (See Scheme 1). As elsewhere discussed[20], nonquantitative ammonia removal of copper traces produces a by-product with a non-negligible quantity of paramagnetic copper, as revealed in the ^{13}C-NMR spectrum of washed 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole (Figure 4, middle). Cyclopropyl NMR resonances also appear, but not those from the 1,2,3-triazole moiety. ^{13}C-NMR chemical shift analysis of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-3-methyl-1H-[1,2,3]-triazol-3-ium triflate salt reveals the presence of all adamantyl, cyclopropyl and 1,2,3-triazole spin systems, strongly suggesting the better copper removal with methyl triflate. However in order to conclude the effectiveness in removing paramagnetic effects of 1,2,3-triazoles, a deeper inspection must be done by line width analysis. First, ^{1}H-NMR line widths (see Experimental) of all molecules herein presented reveal line-broadening effects in all cases that produce, in turn, non-exploitable spectra which are difficult to assign. 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole, its ammonia treated by-product and the 1,3,4-trisubstituted-1,2,3,triazolium salt present proton line widths in the range of, respectively: 20.3 Hz (only adamantyl broad resonance is observed), 6.25 – 13.28 Hz and 4.12 – 20.55 Hz.

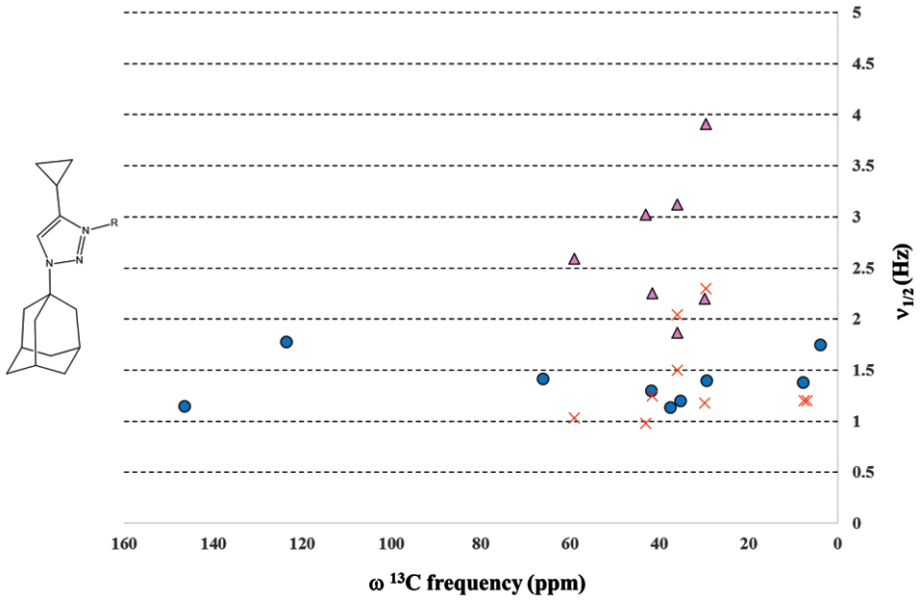


Figure 5. ^{13}C-detected chemical shifts as a function of measured line widths at half height ($\nu_{1/2}$) of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole (magenta triangles), the ammonia washing by-product (red crosses) and 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-3-methyl-1H-[1,2,3]-triazol-3-ium triflate salt (blue circles).

In contrast, ^{13}C line widths –less dependent to paramagnetic effects[22]- reveal carbon line broadening of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole, its ammonia treated by-product and the 1,3,4-trisubstituted-1,2,3,triazolium salt in the range of, respectively: c.a. 2-4 Hz, 1-2.5 Hz and 1-2 Hz (Figure 5). Proton and carbon line widths serve, in turn, to disentangle the presence of paramagnetic effects in all cases. However, a significant improvement of copper removal is done when methyl triflate is used.

Conclusions

This work presents a strategy to reveal the presence of paramagnetic copper (II) traces in a standard Huisgen CuAAC cycloaddition click-chemistry process, using as a model system the novel synthesis of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole and its derivatized 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-3-methyl-1H-[1,2,3]-triazol-3-ium triflate salt. Chemical shift and line widths analysis in paramagnetic NMR spectra strongly suggest the presence of copper traces that mostly affect cyclopropyl and 1,2,3-triazole spin systems, due to their proximity to the paramagnetic center. Particularly a Cu-C_5 adduct is the most plausible possibility that could explain carbon line broadening of said ^{13}C resonances in 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole and its ammonia washing solution product. This result, in turn, might explain the torsional angle abnormalities of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole substituents, observed in XRD 3D-data carried out with a Cu K(α) radiation beam. Whereas close copper centers could promote said structural distortions, paramagnetic copper centers would not be directly observed by XRD when diffraction patterns are collected with a radiation beam of wavelength = 1.5418 Å, as commonly used in organic chemistry.

Experimental

1.1. Synthesis of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole

1-Adamantane azide (500 mg, 2.82 mmol), and cyclopropylacetylene (243 mg, 3.67 mmol) were suspended in a mixture of water (7 mL) and THF (7 mL). Copper sulphate (180 mg, 1.14mmol), and sodium ascorbate (224 mg, 1.14 mmol) were added to the mixture and the full set was stirred for 96 hours at 85 °C in a pressure tube. After cooling, all volatiles were removed by evaporation and the residue was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with H_2O (2 × 50 mL), brine (2 × 30 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was precipitated with pentane (150 mL) to give the crude triazole as a bluish compound (551 mg, 82%). The residue was redissolved in 30 mL of CH_2Cl_2 and passed through a nylon membrane 0.45 µm (Titan 3,

Thermo Scientific) in order to get rid of non-soluble particles. Crystals were grown by slow diffusion of the crude bluish triazole in diethyl ether at 4 °C. After four days micro crystals were collected and chosen for mono crystal X-ray experiments. ^1H NMR: δ 1.409 (m, 5H, $\nu_{1/2}$ = 20.3 Hz); ^{13}C NMR: δ 29.51 ($\nu_{1/2}$ = 3.91 Hz), 29.81 ($\nu_{1/2}$ = 2.20 Hz), 35.91 ($\nu_{1/2}$ = 1.87 Hz), 35.95 ($\nu_{1/2}$ = 3.12 Hz), 41.52 ($\nu_{1/2}$ = 2.25 Hz), 43 ($\nu_{1/2}$ = 3.02 Hz), 58.99 ($\nu_{1/2}$ = 2.59 Hz).

1.2. Ammonia washing solution of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole

In order to get rid of copper salts in the 1-adamantyl-4-cyclopropyl-1,2,3-triazole compound, washings with NH_4OH were conducted. The compound was redissolved in 30 mL of CH_2Cl_2 and poured into a separating funnel. 15 mL of a concentrated solution of aqueous ammonia (NH_4OH) was added. Mechanical stirring of both aqueous and organic phases was carried out. Afterwards, both phases were left to settle down. The upper layer was removed, whilst all organic layers were collected. Washings with ammonia comprised as well the addition of 10 mL of water and 10 mL of a saturated NaCl solution. After washings and phases' separation, a bluish compound was obtained by evaporation of CH_2Cl_2 with a rotatory evaporator. ^1H NMR: δ 0.843 (m, 2H, $\nu_{1/2}$ = 9.81 Hz), 0.94 (m, 2H, $\nu_{1/2}$ = 13.28 Hz), 1.65 (s, 2H, $\nu_{1/2}$ = 8.06 Hz), 1.67 (s, 4H, $\nu_{1/2}$ = 8.44 Hz), 1.7 (s, 4H, $\nu_{1/2}$ = 8.68 Hz), 1.72 (s, 2H, $\nu_{1/2}$ = 8.99 Hz), 1.80 (s, 4H, $\nu_{1/2}$ = 11.93 Hz), 1.82 (s, 12H, $\nu_{1/2}$ = 6.25 Hz), 2.16 (s, 5H, $\nu_{1/2}$ = 11.34 Hz), 2.22 (s, 5H, $\nu_{1/2}$ = 6.53 Hz), 2.26 (s, 3H, $\nu_{1/2}$ = 11.72 Hz), 7.3 (s, 1H, $\nu_{1/2}$ = 6.73 Hz); ^{13}C NMR: δ 6.79 ($\nu_{1/2}$ = 1.2 Hz), 7.53 ($\nu_{1/2}$ = 1.2 Hz), 29.47 ($\nu_{1/2}$ = 2.3 Hz), 29.83 ($\nu_{1/2}$ = 1.18 Hz), 35.93 ($\nu_{1/2}$ = 2.04 Hz), 35.98 ($\nu_{1/2}$ = 1.5 Hz), 41.54 ($\nu_{1/2}$ = 1.25 Hz), 43.00 ($\nu_{1/2}$ = 0.98 Hz), 58.99 ($\nu_{1/2}$ = 1.03 Hz).

1.3. Synthesis of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-3-methyl-1H-[1,2,3]-triazol-3-ium triflate salt

Reaction mixture of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole (100 mg, 0.41 mmol) was poured into a mixture of DCM/Et_2O (5: 5 mL) in a pressure vessel and cooled down to 0 °C. Methyl triflate was added (100 mg, 0.62 mmol) at said cold conditions and stirred for 1 hour. The mixture was left with stirring to reach room temperature, then heated up to 90 °C for 5 h. Evaporation of all volatiles afforded the corresponding crude triazolium salt as an off-white powder (138 mg, 82%). The residue was precipitated with pentane (150 mL) to give the crude triazolium salt. The residue was redissolved in 30 mL of CH_2Cl_2 and passed through a nylon membrane of 0.45 µm thickness (Titan 3, thermo scientific) in order to get rid of non-soluble particles. Crystals were grown by slow diffusion of the crude triazolium salt in diethyl ether at 4 °C. After two days, appropriate mono crystals were collected and carefully for mono crystal X-ray experiments. ^1H NMR: δ 1.057 (d, 2H, $\nu_{1/2}$ = 11.18 Hz), 1.25 (d, 2H, $\nu_{1/2}$ = 15.69 Hz), 1.79 (s, 7H, $\nu_{1/2}$ = 8.67 Hz), 1.98 (m, 1H, $\nu_{1/2}$ = 20.55 Hz), 2.25 (s, 6H, $\nu_{1/2}$ = 6.79 Hz), 2.30 (s, 3H, $\nu_{1/2}$ = 11.54 Hz), 8.29 (s, 1H, $\nu_{1/2}$ = 4.12 Hz); ^{13}C NMR: δ 3.91 ($\nu_{1/2}$ = 1.75 Hz), 7.73 ($\nu_{1/2}$ = 1.38 Hz), 29.43 ($\nu_{1/2}$ = 1.4 Hz), 35.22 ($\nu_{1/2}$ = 1.2 Hz), 37.50 ($\nu_{1/2}$ = 1.14 Hz), 41.77 ($\nu_{1/2}$ = 1.3 Hz), 66.08 ($\nu_{1/2}$ = 1.42 Hz), 123.6 ($\nu_{1/2}$ = 1.78 Hz), 146.47 ($\nu_{1/2}$ = 1.15 Hz).

Crystallography

Diffraction data of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole was obtained at 100 K, whilst testing of its 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-3-methyl-1H-[1,2,3]-triazol-3-ium triflate salt counterpart was carried out at room temperature on a Bruker APEX II CCD diffractometer, using a Cu K(α) radiation beam of 1.5418 Å. Crystal structure solution and refinements were developed with the Bruker SHELXTL package. Non H-atoms were refined with anisotropic displacement factors, whilst H-atoms were geometrically positioned, with fixed displacement factors. All crystallographic data have been deposited in the Cambridge Crystallographic Data Centre with accession numbers **1896662 and 1896671**.

Nuclear Magnetic Resonance Spectroscopy

All spectra were recorded on a Bruker 600 AVANCE III HD spectrometer equipped with a 5mm 1H / D TXI probehead with z-gradient. To guarantee best line widths in the presence of paramagnetic effects, all samples were rigorously shimmed in all possible x,y,z axes, with the use of the Topshim gui routine (TopSpin 3.7) and manually verified with the aid of the lock signal. The following experiments were carried out:

1. 1D-^1H 90° pulse direct excitation: A total of 64 transients were collected into 22 K complex data points, with a spectral width of 7812 Hz and acquisition times of 1.4 s producing an experimental time of 6'51''. No apodization function was used prior to Fourier Transform.

2. 1D-^{13}C 90° pulse direct excitation: A total of 2048 transients were collected into 58 K complex data points, with spectral widths of 36232 Hz and acquisition times of 800 ms with a recovery delay of 20 s per scan, producing an experimental time of 11h 12'6''. No apodization function was used prior to Fourier Transform.

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Supplementary Material: Supplementary material, comprising X-Ray diffraction detailed data including atomic labels, crystallographic data, fractional atomic coordinates, isotropic and atomic displacements, as well as geometrical parameters of 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-1H-1,2,3-triazole (CCSD accession number 1896662) and its derivatized 1-((3s,5s,7s)-adamantan-1-yl)-4-cyclopropyl-3-methyl-1H-[1,2,3]-triazol-3-ium triflate salt (CCSD accession number and 1896671), can be found in the online version

Conflict of Interest Disclosure: The authors declare either no competing financial interest, or any Conflict of Interest.

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