ARTICLE

Thiol-yne click reaction: an interesting way to derive thiol-provided catechols

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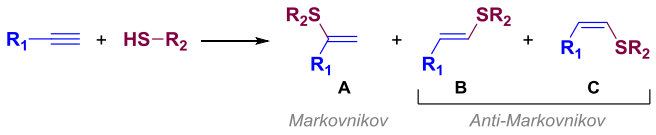
The hydrothiolation of activated alkynes is presented as an attractive and powerful way to functionalize thiols bearing catechols. The reaction has been promoted by a heterogeneous catalyst composed of copper nanoparticles supported on TiO_2 (CuNPs/TiO_2) in 1,2-dichloroethane (1,2-DCE) under heating at 80 ºC. The catalyst could be recovered and reused in three consecutive cycles, showing a slight decrease in its catalytic activity. Thiol derivatives bearing catechol moieties, obtained through a versatile Michael addition, were reacted with different activated alkynes, such as methyl propiolate, propiolic acid, propiolamide or 2-ethynylpyridine. The reaction shown to be regio- and stereoselective towards the anti-Markovnikov *Z*-vinyl sulfide in most of the cases studied. Finally, some of the catechol derivatives obtained were tested as ligands in the preparation of coordination polymer nanoparticles (CNPs), by taking advantage of their different coordination sites with metals such as iron and cobalt.

Introduction

Vinyl sulfides are of great interest because they can be used as versatile building blocks in organic synthesis,[1] as well as intermediates for the synthesis of biologically active compounds[2] and new materials,[3] among others.

Thiol-yne click (TYC) reaction, also known as alkyne hydrothiolation, is one of the simplest and most atom-economical approach to produce alkenyl sulfides from thiols and alkynes.[4,5] TYC reaction commonly occurs in presence of free radicals,[6] strong acids,[7] bases,[8] or transition metals[9] and, as shown in Scheme 1, in principle can lead to one of the regio- and stereoisomeric vinyl sulfides A (branched) through a Markovnikov orientation, B (E linear) and C (Z linear), or give mixtures of them through an anti-Markovnikov orientation (Scheme 1).[10,11]

Regardless of the method used to promote the reaction, it is important to bear in mind that both alkyne and thiol groups are inherently nucleophilic, hence the activation of one or both groups is necessary for the construction of vinyl sulfide.[5] In this sense, the use of activated alkynes, it means alkynes bearing an adjacent electron-withdrawing group (such as carboxylic acid, ester or amide group), resulted in a reduction of the electronic density on the alkyne, thus enhancing the nucleophilic attack of



Scheme 1. Schematic representation of alkyne hydrothiolation

the thiol. The reaction of thiols, especially aliphatic ones, with propiolic acid esters is very slow in the absence of catalysts, but is remarkably accelerated by bases[12] due to the increased concentration of thiolate ions in alkaline solution.[13] Because of its click characteristics, which include a fast, quantitative and selective reaction under mild conditions, the hydrothiolation of activated alkynes has been used in very interesting applications such as the polymer syntheses[14] or post-polymerization modifications,[15,16] the design of covalent adaptable networks (CANs),[17] and the chemoselective modification of amino acids side chains in unprotected peptides.[13,18]

On the other hand, in recent years, an increasing number of works have focused on the synthesis of new bioinspired catechol-based molecules, which have shown to be useful in the fabrication of novel functional materials,[19] including adhesives,[20] capsules,[21] coatings,[22] hydrogels,[23] and in the formation of coordination polymer nanoparticles (CNPs).[24] However, despite extraordinary characteristics of catechol-derived structures, their preparation has been challenging mainly due to the vulnerability of catechol to oxidation. In this way, few synthetic methodologies have been described and among them, relatively lengthy synthetic routes, comprising protection/deprotection of the catechol ring, harsh reaction conditions, and overall poor atom economy were reported.[25]

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According to this, some of us recently reported a systematic and straightforward methodology for the synthesis of functional catechols with thiol pendant groups, obtained by oxidation of the simplest catechol (pyrocatechol) to the corresponding *o*-quinone, followed by conjugated nucleophilic addition of different dithiol molecules.[26,27]

Although there are several examples with catechol derivatives where the thiol-ene reaction has been exploited, the thiol-yne reaction in the presence of catechol moiety has been less explored. To the best of our knowledge, only two very interesting examples have been published related to this issue. A functional copolymer polyPDP, containing blocks with alkyne and catechol pendant groups respectively, easily reacted with 4-arm thiol PEG *via* a TYC reaction under UV exposure, to produce self-adhesive hydrogels.[28] Other study described the reduction of graphene oxide to graphene by alkynyl-terminated dopamine, and post-functionalization with thiols by photochemical click reaction between the alkyne and thiols.[29] As described in both articles, the TYC reaction was activated by UV irradiation, but resulting in a double addition of thiol molecules due to the fact that radicals react faster with the vinyl sulfide intermediate than with the starting alkyne. Thus, no vinyl sulfide could be obtained through the TYC reaction in the presence of catechols.

On this basis, we attempted to apply TYC reaction to the modification of catechol structures bearing a thiol functionality as end-group. As already mentioned, in most cases the addition of a base to promote the hydrothiolation reaction of activated alkynes, is mandatory. However, catechol moiety is not compatible with a basic media, even if it is moderately basic, due to oxidation to *o*-quinone by atmospheric oxygen or another mild oxidant. An alternative is to carry out the hydrothiolation of alkynes substituted with electron-withdrawing groups and promoted by transition metals, thus taking advantage of the beneficial effect of metal species increasing the nucleophilicity of the thiol. In this context, copper-based catalytic systems are of particular interest since the activation of both the alkyne and the thiol is thought to be the key step in this reaction.[5]

Here we report our results on the thiol-yne click reaction between activated alkynes, substituted with electron-withdrawing groups, and different thiol derivatives bearing catechol pendant moieties. The reaction was regio- and stereoselective towards the anti-Markovnikov *Z*-vinyl sulfide in the vast majority of cases studied. The heterogeneous and low cost CuNPs/TiO_2 catalyst, also showed a high activity and good recyclability. Additionally, some of the vinyl sulfides obtained were used in the preparation of CNPs, taking advantage of their chelating properties.

Results and discussion

The catalysts were prepared by addition of the support to a suspension of freshly prepared copper nanoparticles (CuNPs). The CuNPs were generated by fast reduction of anhydrous copper(II) chloride, using lithium sand and a catalytic amount of DTBB (4,4'-di-tert-butylbiphenyl, 10 mol%) as reducing system, in THF at room temperature (see Scheme S1). The catalysts were ready for use as prepared, after filtration and drying, without any pre-treatment. Different inorganic materials such as activated carbon, nanosized silica coated maghemite (MagSilica®), TiO_2, zeolite Y (ZY), MgO, Al-MCM-41, ZnO and CeO_2 were tested as supports for the CuNPs.

As listed in Table 1, 2-ethynylpyridine and 1-octadecanethiol were used as model substrates in order to test the activity of different catalysts in the TYC reaction. The reaction of 2-ethynylpyridine (0.1 mmol) with 1-octadecanethiol (0.1 mmol) was conducted in the presence of different CuNPs/support catalysts (10 mg) in THF at 25 ºC for 20 hours. The most promising systems are shown in Table 1, entries 1-3. In these cases the regioselectivity was excellent, providing only the anti-Markovnikov adduct but the stereoselectivity was moderate giving an average *Z*:*E* isomers ratio of near 35:65. The observed conversion was low for both CuNPs/TiO_2 and CuNPs/ZnO catalyzed TYC reaction (entries 2 and 3), a 40% of 1-octadecanethiol remaining unreacted. In contrast, the reaction promoted by CuNPs/C catalyst, gave full conversion to disulfide C as the main product, together with vinyl sulfides A and B in less proportion (entry 1). For the reaction catalyzed by CuNPs/TiO_2, an increase in the catalyst loadingsignificantly improved the conversion to products A and B, but with a marked drop in the stereoselectivity (entry 4). In addition, a rise in temperature to 66 °C led to a 77% conversion to the desired products, leaving no unreacted thiol (entry 5). However, the very good conversion towards A and B was accompanied by an increase in the amount of disulfide formed, even working under nitrogen atmosphere.

A similar behavior was observed with the CuNPs/ZnO catalyst, as the conversion also improved at higher reaction temperature and catalyst loading, but in this case the stereoselectivity markedly favoured the *Z*-vinyl sulfide (entry 6). The use of $CuCl_2$ as the catalyst, gave a complete conversion to disulfide C (entry 7). With regard to the reaction solvent, previous reports have shown that the use of THF in presence of Cu (I) and O_2 favors the formation of disulfide product.[30] In view of this, we tested other solvents such as dioxane, DMSO, DCM and 1,2-DCE. As shown in Table 1 (entries 8-11), when the reaction was carried out in DCM, almost the same conversion as in THF was observed but with a

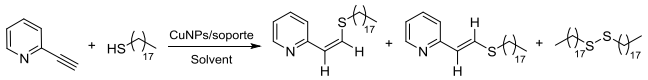


Table 1[a]

Entry	Catalyst (Cu mg)	Solvent	Temp. (ºC)	Conv. A + B (%)[b]	Conv. C (%)[b]	Selectivity Z : E
1	CuNPs/C (10)	THF	25	23	77	40:60
2	CuNPs/TiO_2 (10)	THF	25	44	15	32:68
3	CuNPs/ZnO (10)	THF	25	31	30	31:69
4	CuNPs/TiO_2 (30)	THF	25	65	14	43:57
5[c]	CuNPs/TiO_2 (30)	THF	66	77	23	49:51
6	CuNPs/ZnO (15)	THF	66	44	10	70:30
7	$CuCl_2$ (100)	THF	66	-	100	-
8	CuNPs/TiO_2 (30)	Dioxane	90	[d]	-	37:63
9	CuNPs/TiO_2 (30)	DMSO	70	-	100	-
10	CuNPs/TiO_2 (30)	DCM	40	75	22	85:15
11	CuNPs/TiO_2 (30)	DCE	80	82	18	86:14
12	TiO_2 (0)	DCM	40	-	60	-

[a] Conditions: alkyne (0.1 mmol), thiol (0.1 mmol), catalyst, solvent (2 mL) and a reaction time of 20 h.
[b] Conversion determined by ^{1}H-NMR analysis of the crude mixture.
[c] Reaction carried out under a N_2 atmosphere.
[d] Conversion could be not calculated due to the presence of many by-products.

notably improved stereoselectivity to *Z*-vinyl sulfide (*Z*/*E* ratio = 85/15) (entry 10). Moreover, the use of 1,2-DCE as the solvent and the possibility that higher temperatures could be reached, substantially improved the conversion to the desired product and reduced the amount of disulfide formed (entry 11). The use of 1,2-DCE in the hydrotiolation reaction, has been previously reported by other authors leading to excellent results.[31,32]

Finally, no conversion to products A and B was observed in the presence of the support alone (entry 12). In view of these experimental observations, the best conditions found were those corresponding to entry 11 in Table 1.

The copper-on-titanium oxide catalyst was characterized by different techniques. The copper content in the catalysts, ca. 6.4–7.0 wt%, was determined by inductively coupled plasma optical emission spectroscopy (ICP-MS). Analysis by TEM revealed the presence of small spherical aggregates with an average size of 30 ± 15 nm, homogeneously distributed over seed-like form particles of the support with a length between of 100-300 nm (see Figures S1 and S2). Energy-dispersive X-ray (EDX) analysis on various regions showed copper on the small spherical aggregates located on the surface, whereas titanium was detected mainly in the seeds particles (Figure S3). Performing Electron Energy Loss Spectroscopy (EELS) on those small spherical aggregates, confirmed the presence of copper.

The heterogeneous nature of the CuNPs/TiO_2 catalyst led us to test its recyclability. Thus, the hydrothiolation of propiolamide with 1-octadecanothiol was carried out and the catalyst could be recovered by filtration, washed with DCM and reused at least 3 times without significant loss of regio- and stereoselectivity. As shown in Figure 1, the conversion value showed a drop of about 10% in the activity of the first cycle, but remained constant along the last two cycles.

With the optimized conditions in hand, the scope of the TYC reaction was studied for a series of alkynes (2), mainly terminal ones, with several thiols bearing catechol pendant groups. The starting catechols were synthesized according to the procedure previously reported by some of us, which is based on the attachment of dithiolated chains to pyrocatechol in two stages (see Scheme 2a).[26] Pyrocatechol is first oxidized to *o*-benzoqui-

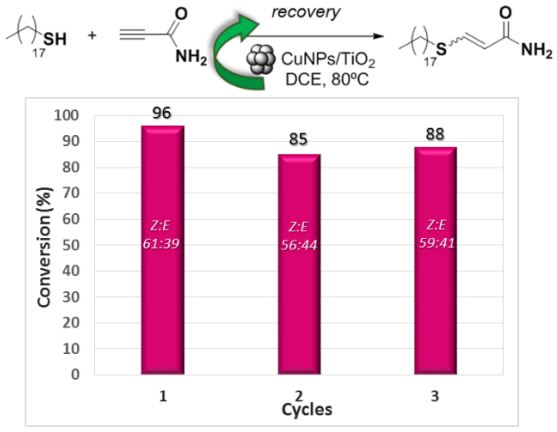
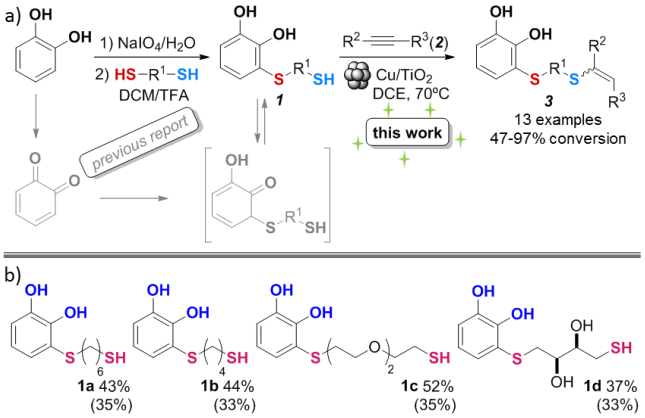


Figure 1. Recycling of the CuNPs/TiO_2 catalyst in the synthesis of 3-(heptadecylthio)acrylamide.



Scheme 2. a) Thiol conjugate addition and hydrothiolaton of alkynes. b) Synthesized Michael adducts with their respective conversion values. Isolated product yields are indicated in brackets.

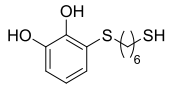
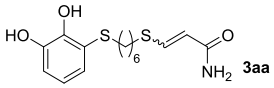
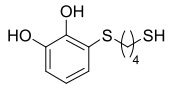
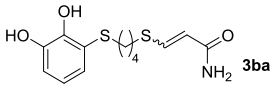
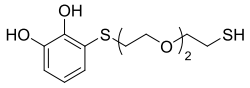
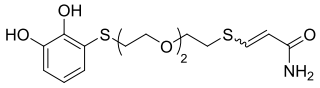
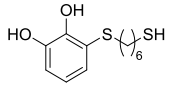
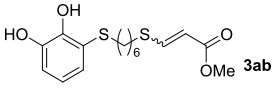
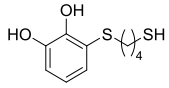
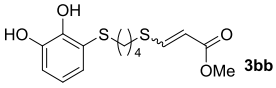
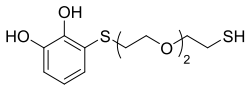
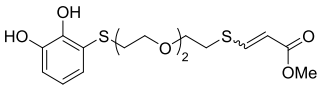
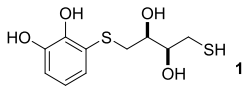
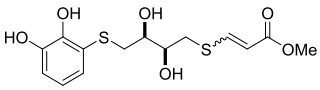
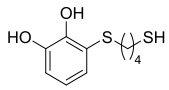
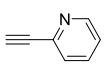
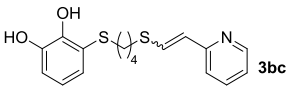
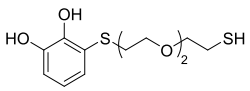
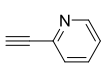
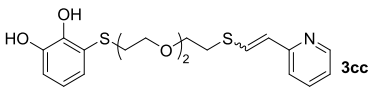
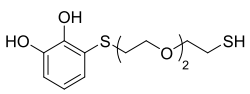
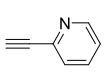
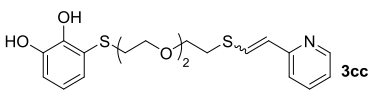
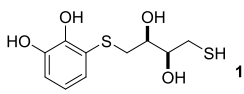
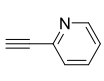
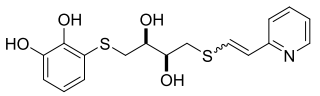
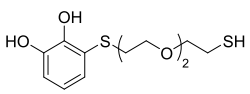
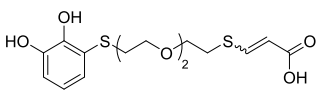
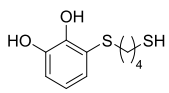
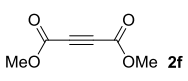
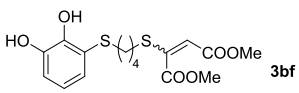
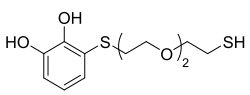
none with $NaIO_4$ in an aqueous solution. Then, the solution is extracted with DCM, and the dry organic extracts are added over a solution of a dithiol and an excess of trifluoracetic acid (TFA) in DCM. At this point, the thiol produces a nucleophilic attack on the quinoid ring, giving a keto-enol intermediate that spontaneously tautomerizes into the substituted catecholic form, yielding the Michael adduct **1**.

Applying this previously reported procedure, four Michael adducts were obtained with conversions in the range of 37-52% (Scheme 2b). Although the conversion values to the Michael adduct may seem to be rather low, it should be noted that the oxidation step from pyrocatechol to quinone occurs around 75% of conversion, so leaving at least 25% of the starting dithiol unreacted. Considering this, and referencing the values of mono-adduct obtained to that initial 75% of quinone, the conversion values would be around 52-75%.

We then studied the conjugation of dithiols molecules bearing an apolar alkyl chain (1,6-hexanedithiol and 1,4-butanedithiol, 1a and 1b, respectively), a polar moiety (2,2-(ethylenedioxy)diethanethiol, 1c) and pendant hydroxyl groups (DL-dithiothreitol, 1d). The carbon chain between both thiol groups should be intended as a spacer in the catechol derivative, providing a degree of flexibility, as well as enough spatial separation when needed. Moreover, changes in the polarity of the spacer could modify the solubility of these adducts in aqueous or polar media. Additionally, the procedure for the obtention of Michael adducts **1**, could be successfully scaled up to a 9 mmol scale, keeping the same conversion value as that of the reaction carried out in 1 mmol scale.

The results of TYC reaction between the prepared Michael adducts 1a-d and different activated alkynes with adjacent electron-withdrawing groups, are presented in Table 2. The starting alkynes were readily synthesized from methyl propiolate and acetylenedicarboxylic acid, respectively (see Experimental Section). Under the optimized conditions shown in Table 1, the alkyne (0.4 mmol) and the thiol (0.4 mmol) were then reacted upon heating in 1,2-DCE at 80 ºC in the presence of the CuNPs/TiO_2 catalyst (120 mg, 30.2 mol%). Fortunately, the hydrothiolation of propiolamide (2a) with 1a

Table 2[a]

Entry	Michael adduct	Alkyne	Time (h)	Product	% Conv.[b,c]	Selectivity *Z*:*E*
1	 **1a**	 **2a**	41	 **3aa**	86 (40)	83:17
2	 **1b**	 **2a**	22	 **3ba**	87 (53)	86:14
3	 **1c**	 **2a**	24	 **3ca**	97 (69)	85:15
4	 **1a**	 **2b**	48	 **3ab**	78 (39)	82:18
5	 **1b**	 **2b**	48	 **3bb**	90 (46)	86:14
6	 **1c**	 **2b**	48	 **3cb**	78 (36)	79:21
7	 **1d**	 **2b**	72	 **3db**	45 (23)	90:10
8	 **1b**	 **2c**	24	 **3bc**	67 (50)	81:19
9	 **1c**	 **2c**	24	 **3cc**	69 (37)	58:44
10[d]	 **1c**	 **2c**	24	 **3cc**	60	52:48
11	 **1d**	 **2c**	46	 **3dc**	53 (21)	64:36
12	 **1c**	 **2e**	96	 **3ce**	47 (14)	99:1
13	 **1b**	 **2f**	24	 **3bf**	92 (31)	52:48
14	 **1c**	**2f**	24	**3cf**	90 (63)	40:60

[a] Conditions: alkyne (0.4 mmol), Michael adduct (0.4 mmol), catalyst (120 mg, 30.2 mol%), DCE (4 mL) and heating at 80 ºC. [b] Conversion determined by ^{1}H-NMR analysis of the crude mixture.
[c] The yields of products are shown in brackets. [d] Conditions: alkyne (0.4 mmol), Michael adduct (0.5 mmol), catalyst (120 mg, 30.2 mol%), DCE (4 mL) and heating at 80 ºC.

produced an excellent conversion to 3aa with a very good stereoselectivity (*Z*/*E* ratio = 83/17) after 41 hours (Table 2, entry 1). Similar promising results were obtained with Michael adducts 1b and 1c (entries 2 and 3). When other activated alkynes such as methyl propiolate 2b were tested, the products of the TYC reaction followed a similar trend as that observed for 2a, that is good to excellent conversions into the anti-Markovnikov vinyl sulfide and very good *Z* stereoselectivity (entries 4-7).

Interestingly, the corresponding *s-cis* and *s-trans* rotamers were detected for both products in entries 3 and 6. It is known that this type of conformers are usually observed in acyclic α,β-unsaturated esters, amides or carboxylic acids.[33] In our

case, both the *cis* isomer and s-*cis* rotamer were the major products, with a 1:1 ratio between them.

When 2-ethinyl pyridine (2c) was used as the starting alkyne, the conversions were significantly lower than those observed with propiolamide (2a) and methyl propiolate (2b). In all cases it was observed that much of the starting thiol was quickly oxidized to the corresponding disulfide, a considerable amount of 2c remaining unreacted (entries 8-11). The use of an excess of the thiol (1.25 equivalents) produced practically no change in conversion to 3cc (entry 10, footnote c).

Among the terminal alkynes tested, certainly, the lowest conversion was obtained with propiolic acid (entry 12, 47%), even after 96 hours of reaction. However, in this case, the stereoselectivity to the *Z*-isomer was excellent with a *Z*:*E* ratio of 99:1. On the other hand, the internal alkyne dimethyl acetylenedicarboxylate 2f gave the best conversion values when reacted with Michael adducts 1b and 1c (entries 13-14). It is well known that the higher reactivity of 2f is due to the low electron density on the triple carbon-carbon bond which is connected to two carbonyl groups. Following this trend, when we tried to carry out the reaction using acetylenedicarboxylic acid, the conversion to the hydrothiolation product was relatively good. However, a considerable amount of decarboxylated product was observed.

With regard to the reaction time, it is important to note that all thiols used (Michael adducts) are aliphatic and have different carbon-chain lengths. As has already been reported,[10,12a,31] in many cases aliphatic thiols required both longer reaction times and higher temperatures, to achieve satisfactory conversions, compared to aromatic ones.

While the conversions observed along Table 2 were from good to excellent, when the crude reaction products were purified, a significant decrease in the isolated product yields was observed. This fact was mainly attributed to catechol numerous interactions,[34] such as non-covalent forces and chemical bonding, with both TiO_2 and silica present in the catalyst and the stationary phase in the chromatographic column, respectively. A strategy that worked very effectively in some cases, was to carry out washings of the crude reaction mixture with different mixtures of solvents (see Experimental Section). For example, the products 3ca and 3bc could be recovered with only a loss of about 25% compared to the conversion values determined by NMR. On the other hand, it is important to note that practically in all cases, the relationship between the *Z* and *E* isomers was maintained even after column chromatography purification. This can be observed in the Supporting Material, Section S3, which shows that in most cases, the *Z*:*E* ratio in the isolated product is practically the same as in the reaction crude (see Table 2).

Application of Compounds 3 as Ligands in the Synthesis of CNPs

In a preliminary way and taking into account the experience of some of us in the preparation of CNPs for different purposes such as contrast agents,[35] carriers in HIV/AIDS therapy[36] or platforms for drug deliver;[37]we decided to carry out the preparation of CNPs with some of the synthesized ligands and different metallic salts such as $FeCl_3 \cdot 6H_2O$ and $CoCl_2 \cdot 6H_2O$. The synthesis of CNPs is very straightforward and consists of mixing the organic ligand in EtOH under magnetic stirring, and adding drop by drop the metallic salt dissolved in water, over the alcoholic phase. Following this methodology, several of the

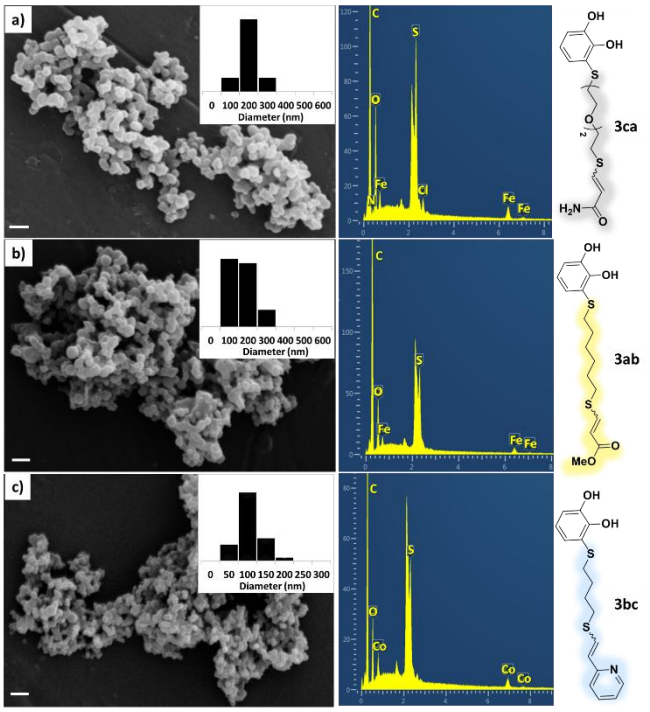


Figure 2. SEM micrographs, histograms and EDX spectra for CNPs prepared by mixing: a) 3ca ligand with Fe (III), b) 3ab ligand with Fe (III) and c) 3bc ligand with Co (II). Scale bars are 500 nm.

ligands synthesized were tested with Fe(III), showing the formation of iron-catecholate complex in all cases as the solution instantaneously turned to blue-violet, followed by the formation of a precipitate. Then, it was centrifuged and washed several times with water and EtOH, and analyzed by SEM and EDX (Figure 2). Among the cases evaluated, only some of them presented characteristics of a regularly structured material. For example, Figures 2a and 2b show SEM micrographs of the nanoparticles generated by the combination of ligands 3ca and 3ab with the $FeCl_3 \cdot 6H_2O$ salt, respectively. The images revealed the formation of oval-shaped nanoparticles, arranged in chains and clusters, with average diameters between 100-300 nm. Moreover, EDX analysis evidenced the presence of S, C, O and Fe elements in the entire analyzed surface.

Figure 2c shows the results obtained by analysis of the precipitate formed by mixing compound 3bc, provided with a pyridinic ring, and a Co(II) salt. Thus, the SEM micrograph revealed the formation of oval-shaped nanoparticles grouped in chains and clusters, with an average size of 100 ± 50 nm. Meanwhile, the EDX showed the presence of S, C, O and Co elements on the entire analyzed surface. This result was very interesting since the traditional methodology for preparing

CNPs in our group has been by mixing the metallic salt with two types of ligands: corresponding to a catechol derivative and to a ditopic *N,N´*-ligand (1,4-bis(imidazole-1-ylmethyl)benzene (bix) or 4,4'-bipyridyl). In this way, it is estimated that the general structure achieved is that represented in the Figure S4.[38] However, more recently it has been determined that depending on the metallic salt used, there could be a higher proportion of coordinated catechol than bix, or quite the opposite, affecting both the structure of the polymer obtained as well as the correct elucidation of its repeating unit. The synthetic approach here presented, would allow us to have in the same ligand either the catechol group and the pyridine ring, both able to coordinate with the metal. It is important to mention that those ligands 3 without a pyridine ring in their structure, were not able to form a precipitate with Co(II). Moreover, those ligands such as 3cc bearing a pyridinic ring, but with a longer spacer chain, were less prone to form a precipitate, giving a slight turbidity, even after 24 hours.

Conclusions

In summary, we have reported an interesting approach for the formation of anti-Markovnikov *Z*-vinyl sulfide with catechol pendant groups, via a thiol-yne click reaction, promoted by CuNPs/TiO_2. Although there are numerous reports in which the alkyne hydrothiolation is carried out employing activated alkynes, the thiol-yne reaction in presence of catechol moiety has hardly been explored. By using our method, various catechol derivatives were obtained with good to excellent conversions. However, due to the chelating power of catechol, both the separation of the product from the catalyst and the purification by chromatographic column were not very effective. A successful solution for some cases consisted in making washes with mixtures of solvents of low to medium polarity, taking advantage of the high polarity of the compounds obtained. In this way, pure compounds could be obtained in yields quite close to those reported as conversions of the starting materials. Finally, as a proof-of-concept to demonstrate the potential of this type of new compounds as ligands, we have carried out the preparation of CNPs with some of the synthesized ligands and metallic salts such as Fe(III) and Co(II).

Experimental

General

All moisture sensitive reactions were carried out under a nitrogen atmosphere. Anhydrous tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl. All starting materials were of the best available grade (Aldrich, Merck, Alfa Aesar) and were used without further purification. Nitric acid 69 % and hydrochloric acid 30 % for analysis of metal traces were purchased from Scharlab SL. Standard solution of Cu was obtained from Perkin Elmer. Commercially available copper(II) chloride dihydrate was dehydrated upon heating in oven (150 °C, 45 min) prior to use for the preparation of CuNPs. Column chromatography was performed with Merck silica gel 60 (0.040–0.063 µm, 240–400 mesh) and hexane/EtOAc as eluent. Reactions were monitored by thin-layer chromatography on silica gel plates (60F-254) visualized under UV light and/or using
FeCl3 in water as stain. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-300 spectrometer using
CDCl3 or CD3OD as solvents. Nitric acid 69 % and metal traces and clorhydric acid 30 % for analysis of metal traces by ICP-MS were purchased from Scharlab SL. Standard solution of Cu was obtained from Perkin Elmer.
For CuNPs/TiO_2 characterization, TEM and STEM images, together with EDX and EELS spectra, were obtained with a FEI Tecnai G2 F20 coupled to an EDAX detector and a Quantum SE 963 Gatan Imaging Filter (GIF). The samples were prepared by casting a drop of the corresponding sample dispersion on a holey carbon copper grid, and then evaporating off the solvent at room temperature. Copper content in the supported catalyst was determined by ICP-MS NexION 300X from Perkin Elmer. Before their use, all glass material was washed with HNO3 40 % for 72 h and rinsed with MiliQ water. Plastic material was washed with HNO_3 0.5 % and rinsed with miliQ water previous use. Standard solution of 1000 ppm Cu in 5 % HNO3 was diluted up to 1 ppm and used to prepare calibration curve (20, 40, 80, 120 and 240 ppb Cu). Samples' digestion was carried out in 3 mL of concentrated ultrapure HNO_3/HCl (1:1) in a Milestone ETHOS EASY microwave digestor. The microwave system was set at 1800 W with a temperature ramp of 25 min up to 230 °C being kept for 15 min more at this temperature. Digested samples were diluted with HNO_3 0.5 % to a final dilution of 1/100, 1/400 and 1/1000 for being analyzed.
For CNPs characterization, SEM images were performed in a LEO EVO 40XVP operated at 10 kV coupled to an EDX detector Oxford X-Max 50. Samples were prepared by drop casting of the corresponding dispersion on an aluminum tape followed by evaporation of the solvent under room conditions. Then were metallized with gold in a sputter coater.

Preparation of the CuNPs/TiO_2 Catalyst

Anhydrous copper(II) chloride (404 mg, 3 mmol) was added to a suspension of lithium (63 mg, 9 mmol) and 4,4'-di-tert-butylbiphenyl (DTBB, 80 mg, 0.3 mmol) in THF (10 mL) at room temperature under a nitrogen atmosphere. The reaction mixture, which was initially dark blue, rapidly changed to black, indicating that the suspension of copper nanoparticles was formed. This suspension was diluted with THF (10 mL) followed by the addition of the TiO_2 (2.4 g). The resulting mixture was stirred for 1 h at room temperature, quenched with water and then filtered. The solid was successively washed with EtOH (15 mL) and dried under vacuum.

Preparation of Michael adducts 1

For the preparation of 1a-d, 2 mmol of the corresponding dithiol was dissolved in 3 mL of CH_2Cl_2 in a Schlenk flask under nitrogen. For more polar dithiols, 3mL of a 1:2 mixture MeOH:CH_2Cl_2 was used. To this solution, 460 µL of trifluoroacetic acid (TFA, 2 mmol) were added with stirring. In a separate flask, a solution of 468 mg of $NaIO_4$ (2.2 mmol) in 80 mL of H_2O was prepared and cooled in an ice bath. 220 mg of pyrocatechol (2 mmol) dissolved in 1 mL of Et_2O were added to the aqueous solution and left stirring vigorously for 15 min. The orange-reddish *o*-benzoquinone was extracted with 4x15 mL of CH_2Cl_2, and the organic phase was dried over anhydrous Na_2SO_4, filtered and immediately added to the dithiol solution. The reaction mixture was stirred in the dark at room temperature under nitrogen for 6 h. After this, the solvent and the TFA were evaporated under reduced pressure and the crude was purified by flash column chromatography (hexane-EtOAc) to give the corresponding Michael adducts. Compounds 1a-d were characterized by comparison of their physical and spectroscopic data with those described in the literature (see Supplementary Information S3).[26]

Preparation of alkynes

Synthesis of propiolamide, 2a.[39] Methyl propiolate (2 mmol) was dissolved in 4 equivalents of 25% NH_3/H_2O (8 mmol) and stirred at -78 ºC for 1 h. Then, all volatile compounds were removed under reduced pressure. While solvent removal, the corresponding amide precipitated easily. A further purification was not necessary, yielding 126 mg (91%) of compound 2a. White needles. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.17 and 5.90 (broad s, 2H, N*H*$_2$), 2.86 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.6 (C), 77.2 (C), 74.4 (CH).

Synthesis of dimethyl acetylenedicarboxylate, 2f.[40] To 4 mL (97 mmoles) of methanol in a round-bottomed flask was added in small portions with cooling 0.84 mL of concentrated sulfuric acid. To this cooled solution was added 570 mg (5 mmol) of acetylenedicarboxylic acid. The flask was fitted with an adapter and left under nitrogen and at room temperature for 1 day. The solution was extracted with diethyl ether (5 x 5 mL). The ether extracts were combined and washed successively with 5 mL of cold water, 5 mL of saturated sodium bicarbonate solution and 5 mL of cold water and then dried over anhydrous calcium chloride. A further purification was not necessary, yielding 625 mg (88%) of compound 2f. Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.78 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.9 (C), 74.3 (C), 53.2 (CH_3).

General Procedure for the Synthesis of Vinyl Sulfide 3 Catalyzed by CuNPs/TiO_2

The Michael adduct **1** (0.4 mmol) and alkyne **2** (0.4 mmol) were added to a reaction tube containing CuNPs/TiO_2 (120 mg, 30.2 mol% Cu) in 1,2-DCE (4 mL) under air. The reaction mixture was warmed to 80°C and monitored by TLC until total conversion of the starting material. The catalyst was removed by filtration and washing with hexane-AcOEt. Finally, the filtrate was concentrated under vacuum and the product was purified by column chromatography to give the corresponding vinyl sulfide **3**. Full data for all compounds are provided below (see Supplementary Information S3).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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