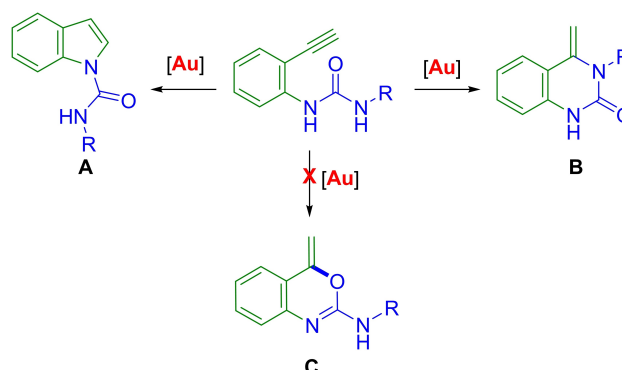


From Thioureas to Thioquinolines through Isolated Benzothiazines by Gold Catalysis

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Abstract: New benzothiazine heterocycles have been formed from thiourea derivatives by using different gold catalysts. The catalyst and the conditions were optimised towards the selective synthesis of six-membered benzothiazine heterocycles, characterised by X-ray diffraction. Interestingly, these organic compounds evolved under gold catalysis in basic medium to achieve the formation of amino thioquinolines through an unprecedented aromatisation process of the heterocycle. The reaction was also carried out stoichiometrically by reaction with gold complexes to afford thioquinolines coordinated to the gold fragment. Benzothiazine, amino thioquinoline heterocycles and gold-derived species have a great potential for biological applications.

Homogeneous gold catalysis continues to attract substantial attention because of its versatility and efficiency, especially in reactions where carbon-carbon unsaturated bonds are involved, such as those in alkynes.^[1] Alkynyl compounds bearing different functional groups have been extensively investigated in gold-catalysed intramolecular cyclisations.^[2] The cyclisation reactions of alkynyl ureas, which selectively undergo either 6-*exo-dig* or 5-*endo-dig* cyclisations, have received much attention. In all cases, nucleophilic attack of the nitrogen atoms gives different heterocycles.^[3] In particular, the gold-catalysed annulation of *o*-alkynylaniline urea species has been studied for several gold catalysts with formation mainly of indole derivatives **A**, due to the hydroamination reaction.^[3] The formation of indoles from *o*-alkynylaniline derivatives is highly favoured by a 5-*endo-dig* cyclisation process, although cyclic quinazolinones **B** are also formed through a 6-*exo-dig* reaction, depending of the choice of the gold catalyst (Scheme 1).^[4] Markovnikov addition generates a



Scheme 1. Cyclisation reaction in *o*-alkynylaniline ureas.

six-membered ring involving π -activation by a single gold species, whereas anti-Markovnikov addition gives a five-membered ring involving dinuclear σ,π -activation.^[4] However, no formation of benzoxazines **C** resulting from the *O*-6-*exo-dig* attack was detected.

In contrast, corresponding studies with *o*-alkynylaniline thioureas have been far less developed. In this case, N- or S-cycloadducts could be obtained, depending on whether N-attack or S-attack occurs.

The closest approach studied is the addition reaction of internal alkynylaniline derivatives substituted with electron-withdrawing groups with aryl isothiocyanates to afford benzothiazine derivatives in a domino Michael addition/cyclisation procedure.^[4,5] In these cases, only the two benzothiazine tautomers **D** or **D'** were isolated; the quinazoline skeleton was not observed (Scheme 2).

Taking these precedents into account, we aimed to synthesise different heterocycles starting from *o*-alkynylaniline thioureas instead of ureas. In addition of the formation of benzothiazines, we envisaged that these molecules could evolve to the more stable thioquinoline heterocycles **E** by a rearrangement (Scheme 2). This reactivity has been proved both under stoichiometric and catalytic conditions. Reaction with gold catalysts/gold complexes in basic media affords the corresponding amino thioquinolines or gold thiolates that have been isolated and structurally characterised for the first time. In this rearrangement, new amino thioquinolines are produced involving C–S bond cleavage and C–C bond formation. Krause and co-workers reported the efficient synthesis of 2,5-dihydrothiophenes by stereoselective cycloisomerisation of α -thioallenes, which is the opposite reaction to the one described here.^[6]

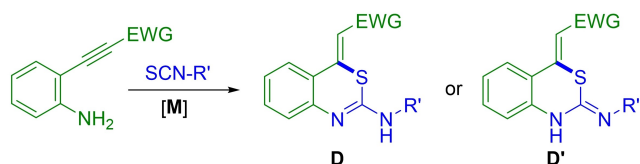
Several thiourea species **1 a–d** were synthesised starting from *o*-ethynylaniline with different isothiocyanates (Scheme 3); they

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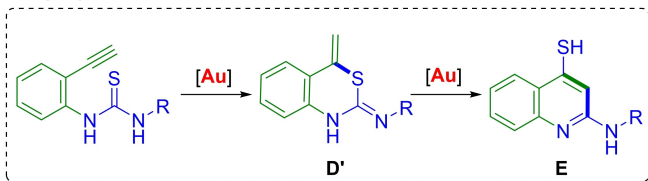
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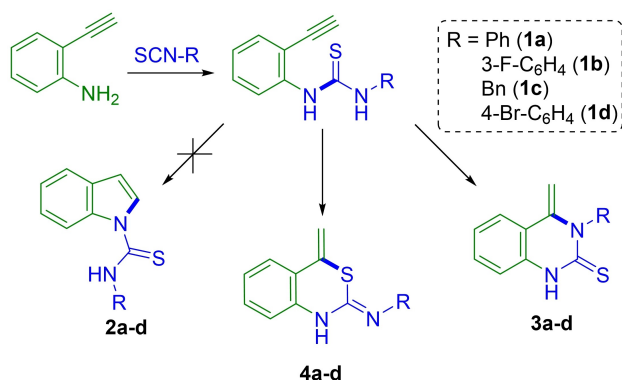
Previous work



This work



Scheme 2. Approaches to the synthesis of benzothiazines **D'** and amino thioquinolines **E** by gold catalysis.



Scheme 3. Possible cyclisation pathways from thioureas **1 a–d**.

were characterised by NMR spectroscopy and mass spectrometry (see the Supporting Information). Moreover, the formation of thiourea **1 a** was supported by X-ray diffraction studies (Figure S1 in the Supporting Information).

Cyclisations of these thioureas were further studied, and Scheme 3 shows all the possible species that could be formed. Hydroamination reactions would give rise to indole **2** or 3,4-dihydroquinazoline rings **3**. In addition, the presence of the sulfur atom, a better nucleophile, could give rise to the benzothiazine heterocycle **4** (Scheme 3).

It is worth mentioning that the heterocyclic compounds derived from benzothiazine **4** or 3,4-dihydroquinazoline **3** are interesting because they can exhibit a broad spectrum of biological and pharmaceutical properties, as for example anti-HIV, anti-tuberculosis, anti-inflammatory, antimicrobial, antifungal, antiviral, antimalarial or antitumor activity.^[7]

Considering this, we decided to explore the reactivity of thioureas **1** by using various gold catalysts to produce the corresponding heterocycles. For this purpose, several gold phosphine complexes such as [AuCl(PPh₃)], [AuCl(JohnPhos)] and [AuCl(CyJohnPhos)] were chosen. Additionally, the influence of the use of stoichiometric amounts of AgNTf₂, AgOTf or AgSbF₆ was also studied. The reaction conditions were optimised by

using the different catalysts and changing the additives or the solvents (Table S1). Study of all these parameters showed that there is no background of the reaction and that the silver salt AgNTf₂ produces only a low conversion to give a mixture of products. Reaction with the gold complexes led to the following observations: [Au(OTf)(PPh₃)] and [Au(NCMe)(JohnPhos)]SbF₆ gave a quantitative conversion to a mixture of **3** and **4**. In contrast, the use of [Au(NCMe)(CyJohnPhos)]SbF₆ led to the selective synthesis of compound **4** in all the samples tested with a catalyst loading of 1 mol%, ethanol being the solvent of choice.

Compounds **4 a–d** were obtained with excellent yields, 90–99% and characterised by NMR spectroscopy, showing characteristic resonances for the CH₂ outside the cycles around 5 ppm. The structure of compound **4 a** was established by X-ray diffraction (Figure 1).^[8] This confirms the proposed pathway in which the nucleophilic attack of the sulfur atom over the alkyne produces a six-membered cycle. The 1,3-benzothiazine species **D'**, in which the amine is located inside the cycle, is observed as corroborated for the N1–C9–N2 distances, which are N1–C9 1.375(5) and N2–C9 1.312(5) Å.

The synthesis of six-membered sulfur and nitrogen heterocycles is not very common, in contrast to the stability and abundance of five-membered thiazole derivatives. For this reason, we envisaged that these compounds could be very reactive in rearrangement reactions in order to give more stable heterocycles through an aromatisation process. Looking closely at the structure, it could be appreciated that an exchange between the sulfur atom and the alkene would give rise to a highly stable thioquinoline heterocycle **E**. Taking into account the high affinity of gold to coordinate to sulfur atoms, especially in the form of thiolate,^[9] in a basic medium, reaction with a gold compound could proceed with coordination of the gold centre to the sulfur atom and a ring rearrangement could create a new amino thioquinoline heterocycle coordinated to gold.

To test this hypothesis, benzothiazines **4 a–d** were reacted with stoichiometric ratios of different gold compounds. We first used the [Au(acac)PPh₃] species, in which the acac ligand is able to act as base, or gold-phosphine derivatives such as [AuCl(PPh₃)] or [AuCl(JohnPhos)] with addition of KOH as the base.^[10] The result is the formation of a new heterocycle, an amino thioquinoline species **5** or **6**, after an aromatisation process and with the gold centre coordinated to the sulfur atom as thiolate outside the cycle (Scheme 4). In the process, one of the C–S bonds is cleavage and two new C–C bonds are formed. As we observed,

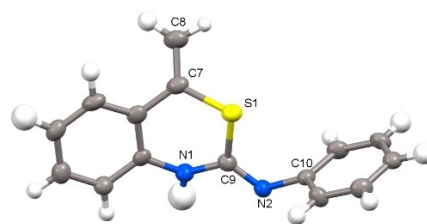
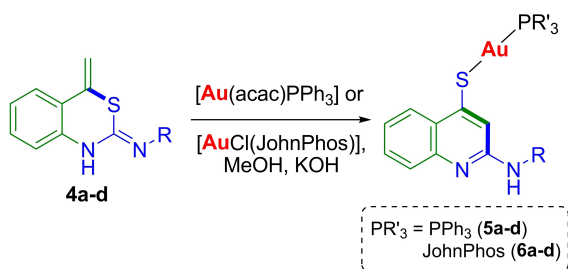


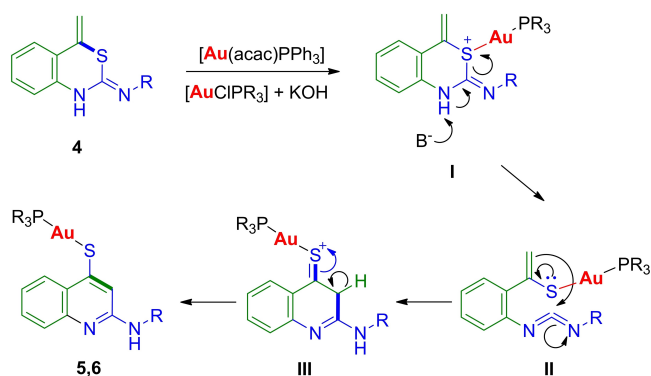
Figure 1. ORTEP diagram of 1,3-benzothiazine **4 a**. The ellipsoids represent 50% probability.



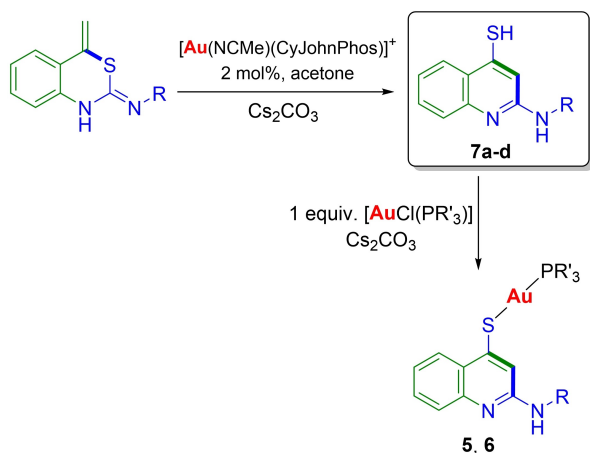
Scheme 4. Preparation of complexes 5 a–d and 6 a–d.

the reaction has some generality as it works with different gold-phosphine complexes under different conditions.

The transformation of 4 in complexes 5 or 6 occurs only in the presence of a base and with a stoichiometric ratio of the gold complex. Consequently, the rearrangement from 4 in the absence of a base must be very slow because it is not detected during the catalytic reaction time from 1. In the ^1H NMR spectra, the resonances of the two protons of the double bond have disappeared, and the number of aromatic protons has increased because now all the protons, with the exception of the NH



Scheme 5. Proposed mechanism for the synthesis of complexes 5 and 6.



Scheme 6. Preparation of amino thioquinolines 7 and further reaction to produce 5 or 6.

outside the cycle, are aromatic. The ^{13}C spectra also corroborate the formation of a thioquinoline heterocycle. The mechanism for the formation of derivatives 5 a–d and 6 a–d is proposed in Scheme 5, starting from the benzothiazine heterocycles 4. Initially, the AuPPh_3^+ or the Au(JohnPhos)^+ fragment would coordinate to the sulfur atom to give I and, consequently, the sulfur would be positively charged. At the same time, the base, acetylacetonate or KOH, would deprotonate the NH of the species I. This would result in the formation of carbodiimide intermediate II with cleavage of the sulfur-carbon bond and opening of the ring. Subsequent reorganisation by the addition of the alkene to the carbodiimide would generate the formation of a new species III. Finally, aromatisation of the ring would give rise to the gold amino thioquinoline derivatives 5 and 6 (Scheme 5).

The formation of these heterocyclic compounds was corroborated by X-ray diffraction studies for two of these species, one with triphenylphosphine 5 a and the other with the JohnPhos ligand 6 a (Figure 2).

The structure of complex 5 a showed a Au1-P1 distance of 2.2585(12) Å and Au1-S1 2.3337(13) Å, which are very similar to those found in 6 a, Au1-P1 2.2773(14) and Au1-S1 2.3255(14) Å. The main difference between both structures is that in 5 a short intermolecular aurophilic interactions of $\text{Au1}\cdots\text{Au1}$ 3.0426(4) Å are formed, probably because of the lower steric hindrance in the PPh_3 derivative. The distances within the quinoline rings confirm their aromaticity, with N–C bond lengths of N1–C3 1.315(6), N1–C4 1.373(7), N2–C3 1.387(7), N2–C10 1.401(7) Å in 6 a and similar values for 5 a. The geometry around the gold centre is slightly distorted from linearity, with angles of P1-Au1-S1 175.62(4)° in 5 a and P1-Au1-S1 171.46(5)° in 6 a.

The next aim was to achieve this rearrangement in a catalytic way to give rise to the amino thioquinoline species. For this purpose, we used the same gold catalyst, $[\text{Au}(\text{NCMe})(\text{CyJohnPhos})]\text{SbF}_6$ (2 mol%), in the presence of a mild

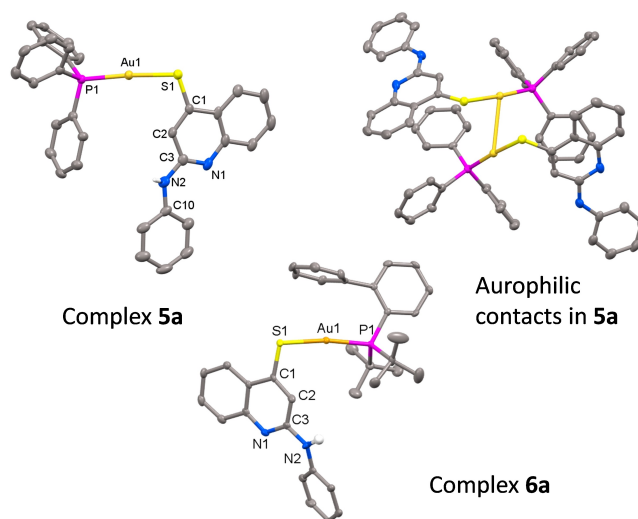


Figure 2. ORTEP diagrams of complexes 5 a and 6 a. Ellipsoids represent 50% probability. Hydrogen atoms, with the exception of the N–H, have been omitted for the sake of clarity.

base such as Cs_2CO_3 . Optimisation indicated acetone to be the most suitable solvent, as in ethanol or dichloromethane mixtures of compounds were obtained, which could arise from partial oxidation of the thiol species to the disulfide or inactivation of the catalyst by coordination to the desired thiol species.

The reaction works under mild conditions at room temperature with a characteristic change from colourless to the yellow colour of the thiol derivatives **7**. The NMR spectra agree with the formation of thioquinoline derivatives, as the vinyl protons disappear, and the aromatic protons agree with the presence of a quinoline moiety. Moreover, the proton of the SH group appears at around 4 ppm. The mass spectra also show the presence of the molecular peaks.

In order to corroborate the formation of these species, further reaction with $[\text{AuCl}(\text{PR}_3)_3]$ compounds were carried out to achieve the expected complexes **5** or **6** (Scheme 6).

In summary, we have studied the cyclisation of *o*-alkynylthioureas with gold catalysts through selective nucleophilic attack of the sulfur atom on the alkyne. New benzothiazine heterocycles were formed and characterised by X-ray diffraction. Interestingly, and probably because of the poorer stability of these six-membered rings compared with the five-membered, it was possible to promote a rearrangement process towards ring aromatisation by reaction with gold complexes. The benzothiazines reacted with gold complexes in the presence of a base to form novel amino thioquinolines coordinated to the gold centre, through an unprecedented aromatisation process of the heterocycle. Interestingly, we have also succeeded in the synthesis of free amino thioquinoline heterocycles by gold catalysis. This is an interesting approach for the preparation of different heterocycles, benzothiazines and amino thioquinolines, which are interesting scaffolds alone or combined with gold that deserve further investigation of their biological properties.^[11,12]

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: benzothiazine · catalysis · gold · thioquinoline · thiourea

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