Formation of 1,3-Thiazine Catalyzed by Gold and Isolation of a Rare Tautomer

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ABSTRACT

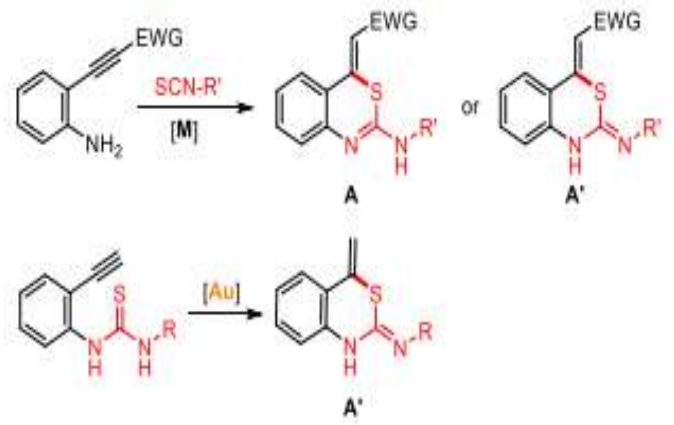
This is the first paper to describe the synthesis of 1,3-thiazine/1,3-thiazinane using gold as a catalyst, followed by its separation. The method described herein has the potential to rapidly and reliably produce a broad range of 1,3-thiazine derivatives in high yields. It's important to keep in mind that, depending on the although the 1,3-thiazine isomer cannot be found in crystalline forms, the 1,3-thiazinane isomer may be synthesized. Isomer. Significant progress toward a new method for the synthesis of chemicals that may have important biological functions has been made in this work, making it notable. Method for identifying and omitting tautomerisms.

INTRODUCTION

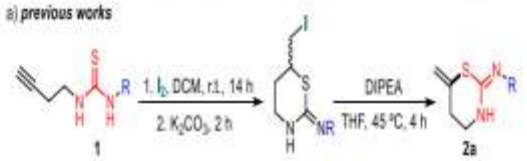
The scientific community has been fueled by the discovery of new ways to efficiently synthesize heterocyclic compounds1, giving chemists a lofty target to go towards in their quest for novel molecules.Techniques for synthesizing that focus on differences between elements.Thiamine, in particular, is a member of the classContrary to the great majority of other possible structural centers,heterocyclic scaffolds that are doable in three different configurations.N and S Atomic PositionsThere are six rings. Because of this, certain species are crucial:Anti-microbial, anti-epileptic and anti-spasmodic properties are only few of the found biological actions.The powers against cancer, insects, fungi, parasites, herbivores, anxiety, inflammation, bacteria, yeast, and mould.Antiviral.3specifically, the research using benzo-1,3-diol isomers stands noteworthy.Many studies focus on thiamine's since they are the most used kind of synthetic alkaloid.Structure for many different kinds of drugs.4 InThe 1,3-thiazines and 1,3-thiazinanes, however, haveexplored.Only a few methods, most of which need superstoichiometric concentrations of the promoter5, have been shown to successfully synthesize benzo1,3-

thiazines via tandem cyclization.Utilization of a metal catalyst for a tandem 6-exo-digest is uncommon.Six-carbon ring cyclization: internal alkynes addition to a ring-opening anilinechemical compounds where the electron-withdrawing groups have been substitutedas a general rule, aryl isothiocyanates may be converted into benzothiazine derivatives.Interchangeablyutilizing the A and A′ forms5,6 Recent developments includebenzothiazine synthesis using a gold catalyst has been reported.Catalyst synthesis beginning at the terminal alkynesforms of harmony (Scheme 1). Interestingly, our technique yielded just the A′ tautomer. 7The importance of these chemical substances just cannot be emphasized enough.The search for cutting-edge synthetic methodsusing readily accessible substrates is a well-established practice.Due to their underlying architecture, the available approaches are limited in their versatility. In

Scheme 1. Synthesis of Benzo-1,3-thiazines



Scheme 2. Use of Stoichiometric Amounts of I_2 in the Synthesis of 1,3-Thiazinanes and Our Hypothesis of Work



1a : n = 1, R = Ph
1b : n = 1, R = 4-(F)C_6H_4
1c : n = 1, R = 3-(F)C_6H_4
1d : n = 1, R = 4-(Cl)C_6H_4
1e : n = 1, R = 4-(Br)C_6H_4
1f : n = 1, R = 4-(CF_3)C_6H_4
1g : n = 1, R = 3,5-(CF_3)$_2C_6H_3$
1h : n = 1, R = 4-(NO_2)C_6H_4
1i : n = 1, R = 4-(CN)C_6H_4
1j : n = 1, R = 3-Pyridyl
1k : n = 1, R = 4-(Me)C_6H_4
1l : n = 1, R = 4-(OMe)C_6H_4
1m : n = 1, R = 1-Naphthyl
1n : n = 1, R = Benzyl
1o : n = 1, R = CH_2CH_2Ph
1p : n = 1, R = Cyclohexyl
1q : n = 2, R = Ph

Figure 1. Synthesized thioureas 1a-q.

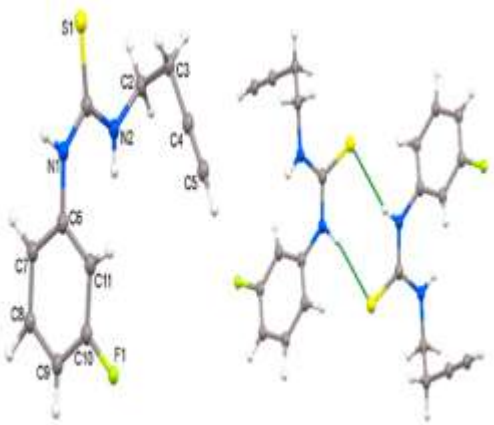


Figure 2. Crystal structure of thiourea 1c and formation of dimers through hydrogen bonding.

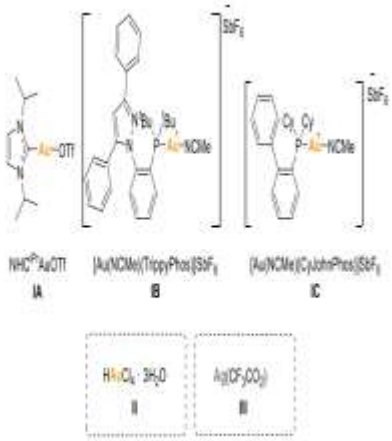


Figure 3. Catalysts tested in the model reaction.

The process is also cutting-edge since it improves catalysis, a revolutionary strategy for collecting rare species that has not been tried before. Keep in mind that every prior attempt at catalysis has ended in failure.Consisting of 1,3-thiazines or 1,3-thiazinanesynthetic monocyclic compounds based on alkynylamines

Table 1. Screening of the Reaction Conditions to Obtain 1,3-Thiazinane 2a or 1,3-Thiazine 2a′ a

entry	cat. (%)	solvent (mL)	temp. (°C)	time (h)[b]	yield (%)[c]
1	IA (5)	MeCN (0.5)	r.t.	47	n.d.
2	IA (5)	MeCN (0.5)	60	172	55
3	IB (3)	MeCN (0.5)	60	24	98
4	IB (3)	CH_2Cl_2 (1)	60	4	92
5	IB (1)	MeCN (0.5)	60	5	91
6	IC (1)	MeCN (0.5)	60	5	99
7	II (5)	MeCN (0.5)	r.t.	47	n.d.
8	II (5)	MeCN (0.5)	60	22	48
9	II (3)	MeCN (0.5)	60	71	n.d.
10	II (1)	MeCN (0.5)	60	71	n.d.
11	II (5)	Toluene (0.5)	r.t.	22	n.d.
12	II (5)	Toluene (0.5)	60	26	n.d.
13	II (5)	THF (0.5)	r.t.	22	12
14	III (10)	MeCN (0.5)	60	45	82

Thiourea 1a (0.1 mmol) was added to a catalyst solution (amount specified) in the solvent given (0.5 mL) TLC (n-hexane/ethyl acetate 5:5) was used to monitor the reaction while it was being stirred at various temperatures. TheEvaporating the reaction product under vacuum after filtering it via silica gel. The 1,3-thiazinane-2a derivatives was found.White as snowthe amount of time until either all of the thiourea 1a is converted or the reaction course to a standstill is shown by TLC. CThe yield was separated by column chromatography.

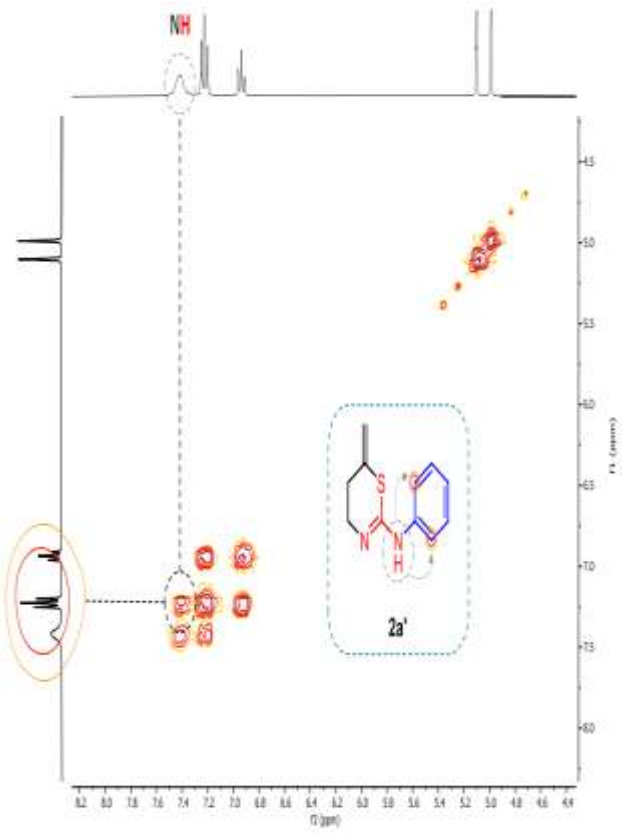


Figure 4. COSY NMR (300 MHz, CD_3COCD_3) spectrum for compound 2a'.

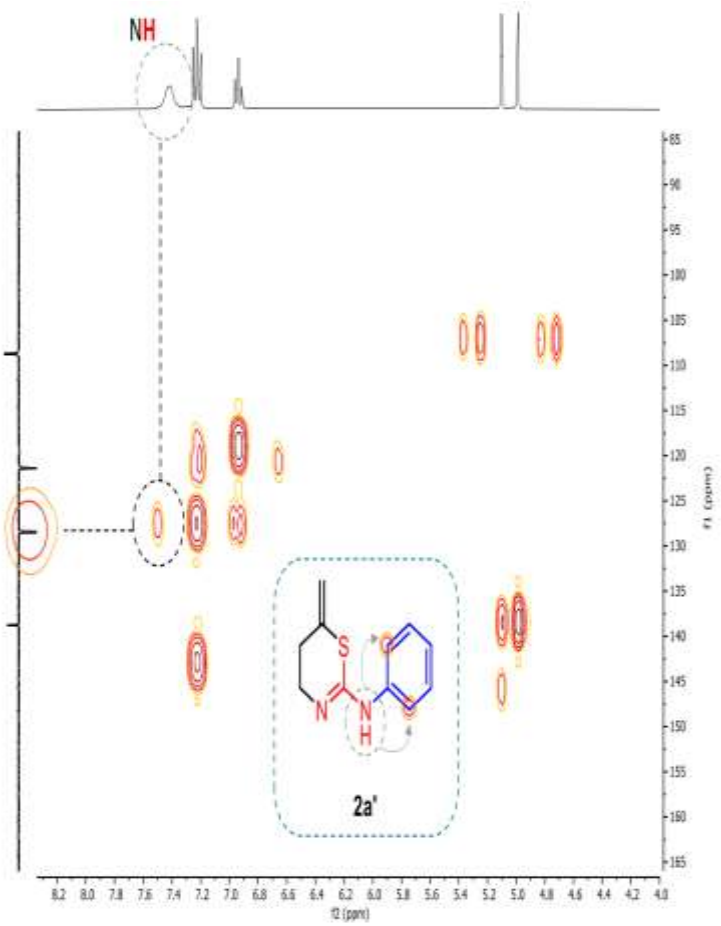


Figure 5. HMBC NMR (300 MHz, 75 MHz, CD3COCD3) spectrum for compound 2a′.

Following two chemical reactions, alkynylanilines utilize stoichiometric quantities of I2 to complete the molecule (Scheme 2a). 8 That being said, we will keep looking for theat the moment, our efforts are concentrated on developing novel metal-catalyzed processes.To learn more about the chemical composition of these previously unknown substances,9 and thanks to the use of gold catalysts, we now have a more effective prototype.Scheme 2b

is a procedure that uses butyl thiourea as its first ingredientderivatives.

RESULTS AND DISCUSSION

To put this theory to the test, first high-yielding and selective synthesis of thiourea 1 batteries was performed (Figure 1 and see the Supplementary Materials).NMR research has found several interesting properties of thioureas 1.X-ray diffraction analysis verified 1c's structural integrity.(Second of three images) Both the S1 and C1 distances are 1.6917(18), whereas the C and S distances are 1.6917(18). (18).The corresponding formulas for the N-distances are N1C1 = 1.347(2) and N2C2 = 1.339. (2) Å,typical of substances based on thiourea Knowledge ofby the formation of NH bonds with the sulphur atomthe surrounding molecular atmosphere as well.10Thus, there is considerable academic interest in the catalytic cyclization of these thioureas.Figure 3 depicts test settings and metal catalysts.What a possible version of Table 1 may look like. Diverse phosphates andany and all reactions between gold and N-heterocyclic carbines,Common salts include chloroauric acid and silver trifluoroacetate.Got pickedconsidering any and all possible changes and constraints,components that make up (catalysts, temperature, solvent, and concentration of catalysts),As a result, we know that the best circumstances exist whenoptimal results (as high as 99 percent for IB and IC catalysts).5 hours of response time at a loading of 1amount of moles (in 60 C MeCN in 0.5 mL) (See Table, Columns 5 and 6)The results and speed of action provided by Catalyst IB are comparable.When the temperature and the loading of the catalyst are kept stable, IC performs better.Isfavored because of its convenience in both acquisition and production.

Having to do with the phosphate. We've also done a proof, just in case.Researching the catalytic potential of [Au(NCMe)(JohnPhos)]SbF6,John Phos phosphate, a phosgene analogue, provides the best conditions for the reaction.Difficult circumstance, yet we accomplished a lot anyhow.Median response time (99% in 5 hours). Nonetheless, the Au (III)In particular, catalytic reactions II with Ag(I) (entry 8 in Table 1) and III with Ag(I) (item 14 in Table 1)Despite their catalytic potential, the cyclization of (Table 1),Increasing the catalytic loading of theorem from 5% to 10% is necessary.The delays were also noted to be 22 and 45 hours

in length.without triggering a radical change in perspective Understanding ofMeCN was the most promising option, maybe because of thebecause MeCN is present in the catalyst.Dependence on this solvent for effective communication betweena ligand for a catalyst that participates in the chemical cycle.

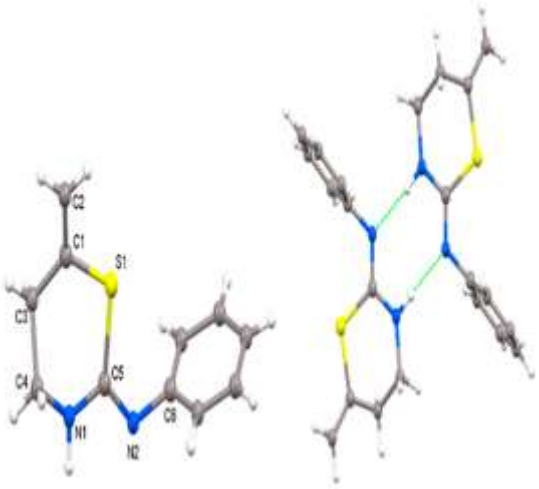


Figure 6. Crystal structure of 1,3-thiazinane 2a and association through hydrogen bonding.

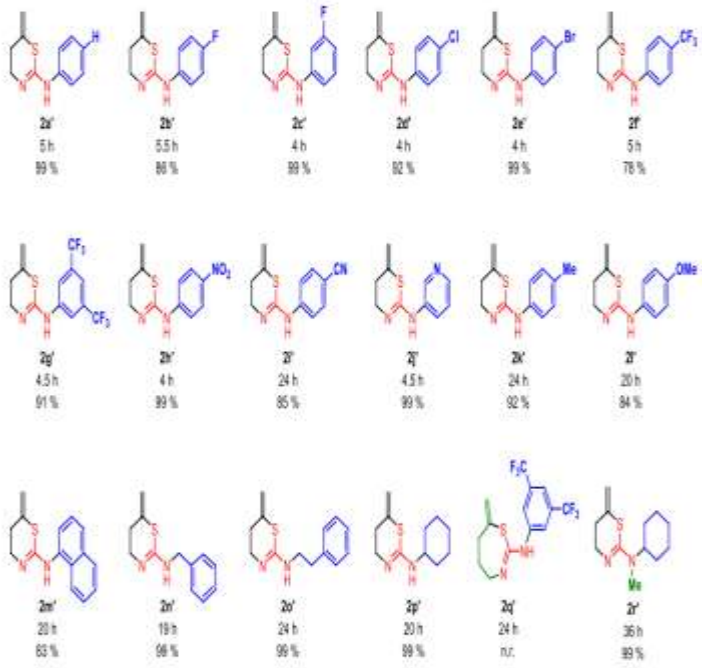


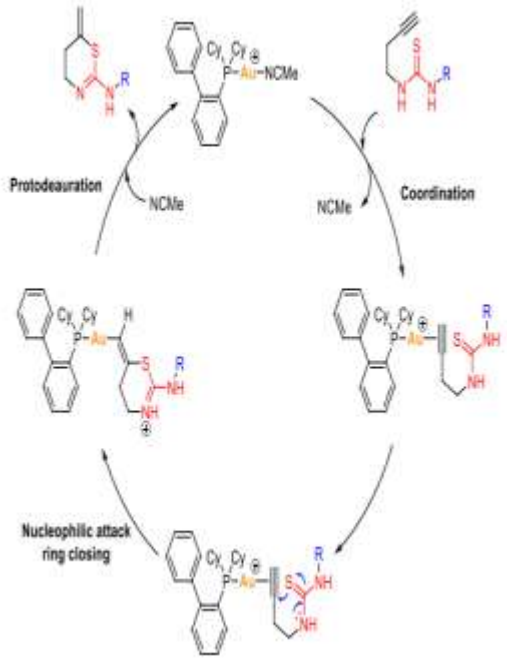
Figure 7. Synthesis of tautomers 2a′–p′ characterized in solution. N.r.: no reaction observed.

Both the 1,3-thiazinane tautomer 2a and the 5,6-dihydro-4H-1,3-thiazine tautomer 2a′ exist in equilibrium, therefore it was necessary to identify the species that were formed.As a result, this unexpectedly crucial factor has been neglected inliterature that is similar to that which has already been printed. Due to the scarcity of information on this topic, there isn't much literature available.Numerous nuclear magnetic resonance (NMR) investigations were performed on the compounds.So that we may better understand the framework. There has been a great deal of study, some of

which is of high quality.Cosmic-Orbital Spectroscopy (COSY) (Figure 4) and the High-Momentum Breakdown Spect (Figure 5).A coupling reaction would occur if 1,3-thiazinane 2a were to form in solution.In the ring, between the CH2 and the NH.On the other hand, the correlation was found solely between the NH andProtons from the aromatic and cosmological areas may be found in some of the remaining 1,3-thiazines.2′ (see Fig (please see the Additional Materials for other COSY spectra).We may provide further instances upon request; however, the CH2 ofring. This led some to speculate that NH does not participate in the cycle (as2a′ when exhaustive study and sustained mental effort are required forwe were able to confirm the presence of this crucial link by doing these investigations.Additionally, the NH and MeV levels are linked in the HMBC spectra.The generated tautomer is in accordance with the observed aromatic C.This is seen in Figure 5.

As a result of this resolution, we can now say with certainty thatHence, we may deduce that the answer is 2a′. (5,6-dihydro-4H-1,3-thiazine).The undisputed leader in its field.Despite what nuclear magnetic resonance seems to suggest (NMR),A monoclinic phase crystallized from the aforementioned tautomer.X-ray crystallography allowed us to determine the exact structure of chemical 2a.Experiments Involving Diffraction Rays (Figure 6).New information has been revealed thanks to the discovery of a crystal structure.The N H group is located within the ring, whereas the N C group is located on the periphery.The ring, which contradicts the purported appearance insolution. When chemical 2a is kept, it creates two distinct crystal forms.molecules. Distances between the ring's nitrogen and carbon atoms (N1-C) and carbon atoms (C1-C) are 1.451(4) nm.They are different in many ways, yet they both draw attention to theconnectable to the thiazinane element. The amine bond forms because to the 1.285 angstrom C5-N2 bond length (3). There are 2.012 Gigapascals of force between the dimers thanks to the N, H, and N hydrogen bondsÅ.

Scheme 3. Gold-Catalyzed Formation of 5,6-Dihydro-4H-1,3-thiazines 2′



If the crystalline packing of the solid state has a big enough energy advantage over the solvated state, then this unexplained phenomenon may be explained.reaction between two tautomers in a solution that yields a third tautomerform crystals when exposed to a certain solutionAs the eleventh best, it's well worth the cost.The fact that the two tautomers have been separated is significant here.Common case in which, even if the tautomers by themselves area crystal forms while they're in solution, but after they're out, their existence is much more malleable.Mixture. This is why we suggest tautomeric equilibrium toability to modify itself by triggering a phase shift,Altering the medium's inherent properties. Yet, on the other side,that it is possible to verify that a solution equilibrium existseach tautomer at a rate that permits thorough investigation. An instance whenCrystal packaging seems to be the best option here.tautomers, however only one is found in water at detectable levels. the potential for combining two types of construction materialsprogressions or groups of states originating from the sameIt is still possible for us to collaborate with all of them.

Independent of one another to reach a new synthetic stage.When the time is right for a response, we investigated the one fluid ounce of thiourea following these directions. Figure 7: A Visual RepresentationDisplay the individual 2′-tautomers that have been isolated and characterised.Products whose primary purpose is to address a specific problem.

We typically received 100% yields after just a few minutes of response time. The reaction times of 1kp thioureas and those with electron-withdrawing groups in the aromatic ring were discovered to be different.In addition, 2k′p′ products were obtained

byhigh levels of harvest success. Thiourea 1i, a nitrile-containing compound, was likewise in demand.There is a larger latency compared to other triggersubstrates, even if thiazine 2i′ was synthesized with minimum effortfruitful consequences there is a specified deadline for answers in this protocol.To obtain the seven-member ring 2q′. But the solutionproven unsuccessful when applied to the same situations. Interesting, wedone some work with MeI to methylate 2p′, and the ensuing N-methyl-1,3-Thiazine 2r′ was effectively isolated in statistically relevant amounts from an exceptionally sterile environment.Reaction. This catalyst is alsotechnique, a supersized version was run. In this situation,It was found that 1 mmol of 1a could be transformed into 2a′ in83% (169.6 mg), however with more slow response times (24 h) (24 h). Onexperimental findings and gold's chemical composition,An explanation for these observations is provided.outcomes attained (Scheme 3). (Scheme 3). In Plan 3, we have...

CONCLUTION

For the first time, we detail the gold-catalyzed production of 1,3-thiazine/1,3-thiazinane derivatives, beginning with a series of thiourea derivatives containing the butynyl groupmoiety. By using the tried and true method, new doors of opportunity have been unlocked.An efficient method for the rapid synthesis of 1,3-thiazine derivativesa number of times, with only a modest amount of catalyst being used each time. We need to consider the big picture:Alternatively, the technique may open up a variety of structuralButyl amines have two functional groups: onesub-components of isothiocyanatecompounds. The derivative of pentynyl amine is currently not in widespread usage.Despite the favourable circumstances, the intended outcome did not materialise.It's possible that a new seven-personThe Rings of a Scaffold It is intriguing to note that the two tautomers werediscovered depending on the chemical's reactivity and its state, and in theThe 1,3-thiazinane isomer was formed during the crystallisation process.

In this case, the 1,3-thiazine isomers was found in the liquid. The contents of this bookis an abbreviation for an approach to chemical innovation with promising promise,chemicals that have a pivotal role in biology and are given high priority instudying how to categories tautomerism theoretically.

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