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Formation of cinnoline derivatives by a gold(I)-catalyzed hydroarylation of *N*-propargyl-*N*′-arylhydrazines

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ABSTRACT

A study concerning the gold(I)-catalyzed hydroarylation of *N*-propargyl-*N*′-arylhydrazinecarboxylic acid methyl esters is described. The use of the gold complex [XPhosAu(NCCH$_3$)SbF$_6$] as the catalyst in refluxing nitromethane allows the generally rapid and efficient synthesis of a range of functionalized 4-*exo*-methylene-1,2-dihydrocinnolines.

1. Introduction

While being less frequently used than the quinoline heterocycle, the isosteric cinnoline moiety remains a structural unit of choice in medicinal chemistry for the discovery of new biologically active substances (Fig. 1) [1]. The continuous attention which has been paid over the past 50 years to the development of new strategies allowing the efficient synthesis of heterocyclic compounds possessing a cinnoline moiety is mainly due to the exceptional spectrum of pharmaceutical activities exerted by such molecules [1]. The use of cinnoline derivatives in drug design has also been investigated and several tetrahydrocinnolines [2] and 1,2-dihydrocinnolines [3], such as compound **1** or the marketed drugs cinnopentazone **2** and cinnofuradione **3**, have been reported as bioactive molecules.

Given the general interest in the cinnoline motif and following our continuous interest in the field of gold-catalyzed synthesis of nitrogen containing heterocycles [4], we envisaged developing a new access to molecules possessing either a tetrahydro- or a dihydrocinnoline unit in their structure. Our synthetic approach is depicted in Scheme 1. It is based on our recent finding that a wide range of *N*-aminophenyl propargyl malonates **4** can be easily converted into tetrahydroquinolines **5** following a gold(I)-catalyzed hydroarylation process [5,6]. By analogy with this transformation, we surmised that the *N*-propargyl-*N*′-arylhydrazine derivatives **6** might be transformed into the corresponding tetrahydrocinnolines **7** by a nucleophilic addition of the aromatic nucleus onto the gold(I)-activated alkyne [7]. The hydroarylation product **7** would be subsequently converted into 1,2-dihydrocinnolines **8** by treatment with an acid.

It is important to note that the gold(I) formation of tetrahydroquinolines **5** we recently reported could only be performed with substrates **4** possessing a basic nitrogen atom (i.e. R^2 = alkyl or aryl) [8]. Moreover, the efficiency of this transformation was directly associated with the presence of the malonate moiety that was supposed to prevent or limit the coordination of the gold(I) complex with the nitrogen atom probably through steric and electronic effects [9]. These results caused us to initially question the possibility of performing an analogous gold(I)-catalyzed hydroarylation on hydrazine derivatives **6** as it was supposed in this case that the nitrogen atom attached to the aromatic nucleus would be more accessible and therefore more prone to coordination than that in substrates **4**. We report herein our investigations in this domain which have led to the development of a new synthetic approach to functionalized cinnoline derivatives.

2. Results and discussion

N-Propargyl-*N*′-phenylhydrazine derivative **9**, easily and efficiently obtained in a two steps sequence from diethyl azadicarboxylate (DEAD), was first chosen as a model substrate to validate our synthetic approach to tetrahydrocinnolines (Scheme 2).

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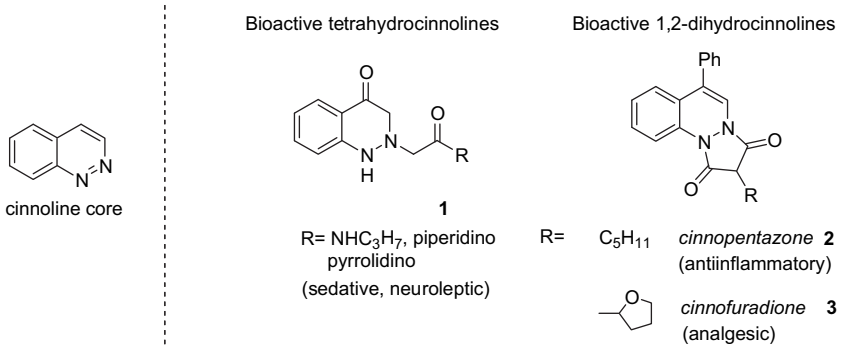
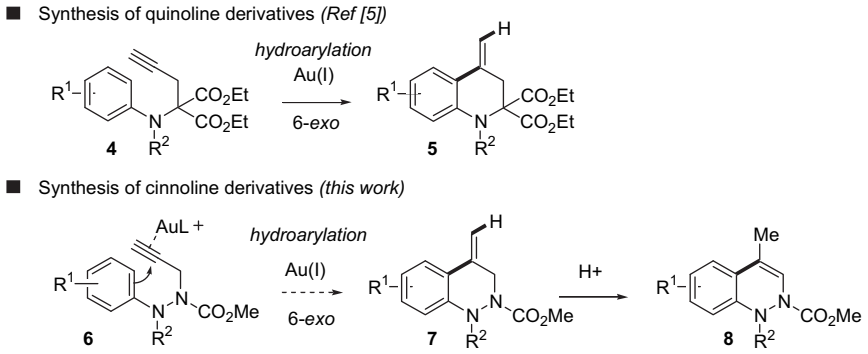


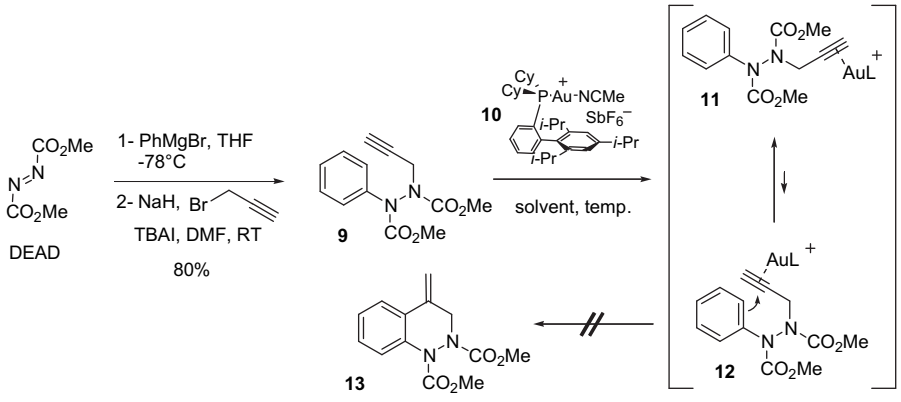
Fig. 1. Example of bioactive 1,2-dihydro- and tetrahydrocinnolines.



Scheme 1. Synthetic approach to cinnoline derivatives.

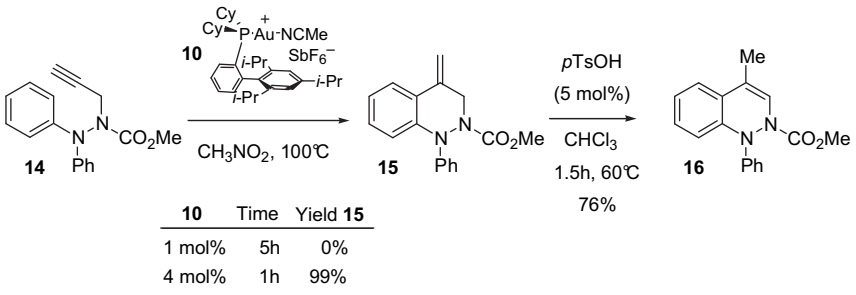
However, under the optimal catalytic conditions previously used for the hydroarylation of *N*-aminophenyl propargyl malonates **4** (1 mol% of gold complex [XPhosAu(NCCH$_3$)SbF$_6$] **10** in refluxing nitromethane) [5], no formation of the *exo*-methylene tetrahydrocinnoline **13** could be observed. Using a higher catalyst loading or changing the nature of the solvent and the reaction temperature was not beneficial. Such a negative result might be attributed to the presence of two possible conformers **11** and **12** among which the cyclizing one (**12**) should be less favoured due to a steric interaction and/or a dipole repulsion between the two carboxymethyl moieties. The reduced nucleophilicity of the phenyl nucleus, due to the presence of the carboxymethyl group on the nitrogen atom attached to the aromatic, might also be invoked to explain the inertness of **9** [5]. To circumvent this problem and in order to increase the nucleophilicity of the aryl group, one of the carbamate moiety was therefore replaced by another phenyl group (Scheme 3).

The treatment of compound **14** with 1 mol% of gold complex **10** in refluxing nitromethane did not allow the formation of the desired cinnoline derivative **15**. However, the use of a higher

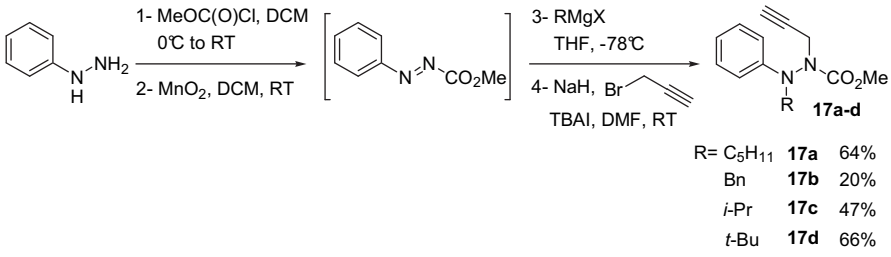


10	SolventT	emp.	Time	Yield 13
1 mol%	CH_3NO_2	100℃	3h	0%
4 mol%	CH_3NO_2	100℃	24h	0%
4 mol%	toluene	110℃	24h	0%

Scheme 2. Hydroarylation attempt with arylhydrazine **9**.



Scheme 3. Hydroarylation attempt with arylhydrazine **14**.



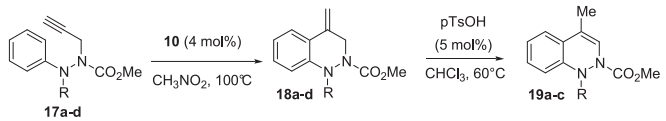
Scheme 4. Four steps/1 purification procedure for the synthesis of phenylhydrazine derivatives **17a**–**d**.

loading of the catalyst (4 mol%) had a remarkable effect since the *exo*-methylene tetrahydrocinnoline **15** was obtained in 99% yield after only 1 h of reaction [10]. Notably, no formation of 1,2-dihydrocinnoline **16** that could be formed by a gold-catalyzed isomerization of the *exo*-methylene functionality was observed under these conditions [11]. Isomeric compound **16** could however be obtained in a good yield (76%) by a simple subsequent treatment of **15** with a catalytic amount of *p*TsOH (5 mol%) in refluxing chloroform.

Having in hand an efficient catalytic system for the conversion of substrate **15** into tetrahydrocinnoline **16**, we next decided to study its applicability to other substrates. We first focused our attention on the variation of the substituent at the nitrogen atom attached to the phenyl ring. For this purpose, a series of *N*-alkylated substrates **17a**–**d** were synthesized from phenylhydrazine in a practical 4 steps/1 purification procedure (Scheme 4). With the exception of benzyl derivative **17b**, this synthetic route proved to be efficient and the desired substrates for the hydroarylation reaction **17a**–**d** were obtained in yields ranging from 47–66%.

We were pleased to see that the treatment of substrates **17a**–**d** with 4 mol% of **10** in refluxing nitromethane also led to the rapid formation (1–3 h) of the corresponding *exo*-methylene tetrahydrocinnoline **18a**–**d** in generally high yields (25–99%) (Table 1).

Table 1
Hydroarylation of *N*-substituted phenylhydrazine derivatives **17a**–**d**.



R		Time (h)	Yield[a] (%)		Time (h)	Yield[a] (%)
C_5H_{11}	**18a**	2.5	99	**19a**	1	91
Bn	**18b**	1.5	87	**19b**	0.5	80
i-Pr	**18c**	1	96	**19c**	0.5	75
t-Bu	**18d**	3	25			

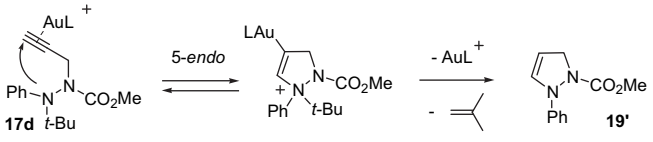
[a] Isolated yields.

The transformation tolerated either a primary (pentyl or benzyl) or a secondary (isopropyl) alkyl group on the nitrogen atom. A low yield (25%) was however obtained in the case of the *N*-*tert*-butyl substituted substrate **17d**. A possible competitive 5-*endo* nucleophilic addition of the *tert*-butylamino group onto the activated alkyne, which would lead to the formation of a probably unstable dihydropyrazole **19′** after fragmentation of the *t*-Bu-N bond, might be responsible for this loss of efficiency (Scheme 5) [12]. Compounds **18a**–**c** could also be easily isomerized into 1,2-dihydrocinnolines **19a**–**c** under acidic conditions.

We next turned our attention to the possibility of performing the hydroarylation on substrates possessing variously substituted aromatic nuclei. *para*-Substituted phenylhydrazine derivatives **20a**–**g** were then synthesized following the same practical route than that used for the formation of compounds **17a**–**d** (see Scheme 4) and subsequently reacted with gold catalyst **10**.

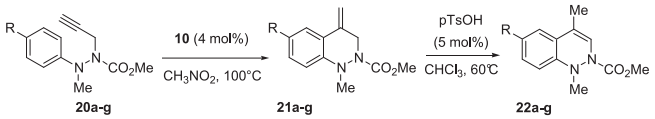
As seen from the results compiled in Table 2, the nature of the *para* substituent had no noticeable influence on the efficiency of the reaction. Substrates **20a**–**f** bearing either an electron-donating group (OMe), an electron-withdrawing group (CO_2Et, CN, CF_3) or an halogen atom (F, Cl) on the aryl nucleus reacted equally to give the corresponding *exo*-methylene tetrahydrocinnolines **21a**–**f** in good to excellent yields (63-99%). The reaction times were however increased to 5–18 h. Compounds **21a**–**f** could be subsequently isomerized into the corresponding 1,2-dihydrocinnolines **22a**–**f** by treatment with a catalytic amount of *p*TsOH. A limit in reactivity was however reached with the electron poor *para*-nitrophenyl derivative **20g** which did not furnish the desired tetrahydrocinnoline **21g** even after a prolonged reaction time.

The formation of cinnoline derivatives from *ortho*- and *meta*-substituted aryl substrates was next investigated (Scheme 6). For



Scheme 5. Possible competitive reaction in the case of substrate **17d**.

Table 2
Hydroarylation of *para*-substituted phenylhydrazine derivatives **20a**–**g**.



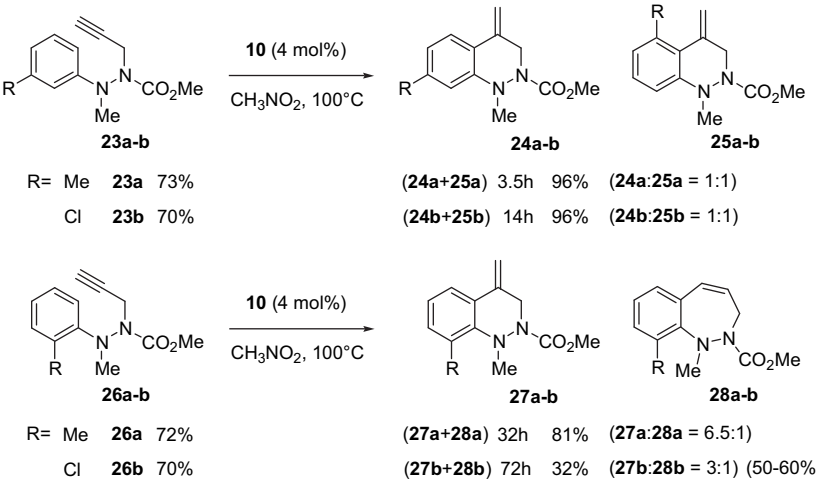
R		Yield[a] (%)		Time (h)	Yield[b] (%)		Time (h)	Yield[b] (%)
MeO	**20a**	60	**21a**	9	83	**22a**	1	88
Cl	**20b**	71	**21b**	18	99	**22b**	1	95
F	**20c**	99	**21c**	13	79	**22c**	1	75
CO_2Et	**20d**	71	**21d**	14	86	**22d**	1	81
CN	**20e**	87	**21e**	5	63	**22e**	4.5	73
CF_3	**20f**	77	**21f**	17	76	**22f**	1.5	67
NO_2	**20g**	71	**21g**	24	0			

[a] Global yield for the formation of **20** from the corresponding arylhydrazine.
[b] Isolated yields.

difficult in these cases due to a probable unfavorable steric interaction in the cyclization transition state between the methyl group on the nitrogen atom and the substituent at the *ortho* position of the aryl group. This possible steric interaction might also be invoked to explain the unexpected formation of compounds **28a**,**b** (minimizing the interactions between the methyl group and the *ortho* sustituent in the cyclization transition state might allow the direct competitive formation of a new 7-membered cycle).

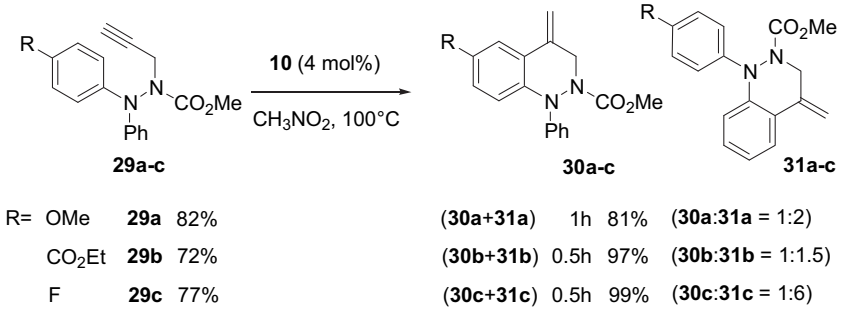
We finally focused our attention on the hydroarylation of hydrazine derivatives possessing a phenyl group and a substituted aryl groups attached to the same nitrogen atom (Scheme 7).

The reactions of substrates **29a**–**c** were rapid and extremely efficient whatever the nature of the substituent at the *para* position of the second aromatic nucleus. Surprisingly, little selectivity was observed in the case of substrates **29a** and **29b** bearing respectively an electron donating alkoxy group and an electron-withdrawing ester group. In these cases, tetrahydrocinnolines **31a** and **31b**, resulting from the attack of the unsubstituted aromatic ring onto the gold-activated



Scheme 6. Hydroarylation of *ortho*- and *meta*-substituted phenylhydrazine derivatives **23a**,**b** and **26a**,**b**.

meta-substituted substrates **23a**,**b**, the hydroarylation step could be efficiently performed but mixtures of tetrahydrocinnolines **24a**,**b** and **25a**,**b** were obtained as the result of an unselective nucleophilic addition of the aryl nucleus onto the gold-activated alkyne. In the case of *ortho*-substituted substrates **26a**,**b**, the hydroarylation proved to be more difficult and longer reaction times were required. Moreover, mixtures of products were isolated in these cases. While the tetrahydrocinnolines **27a**,**b** remained the major products, they were isolated in mixture with variable amounts of compounds **28a**,**b** which were formed following a competitive 7-*endo* hydroarylation process. The hydroarylation might be more alkyne, were found to be the major compounds. This poor selectivity is unexpected as one would have supposed that the more electron rich aromatic moiety would have been the more probable nucleophilic partner in the hydroarylation process. The result obtained with substrate **29c** was even more surprising. The presence of a simple fluorine atom at the *para* position of one of the aromatics dramatically increased the selectivity. In this case, the nucleophilic addition of the unsubstituted phenyl ring on the alkyne was predominant. While only little effect of the fluorine atom onto the selectivity of the reaction might have been expected, tetrahydrocinnoline **31c** was formed as the major compound. The rationalization of the observed



Scheme 7. Competitive hydroarylation experiments with diarylhydrazine derivatives **29a**–**c**.

selectivity is difficult as it cannot be easily explained by simply considering the involvement of electronic and/or steric effects. These results will lead us to look into the exact nature of the hydroarylation mechanism since the one initially presented in Scheme 1 appears to be too simplistic in the light of these final observations.

3. Summary

In summary, we have shown that a series of *N*-propargyl-*N*′-arylhydrazines can be efficiently converted into functionalized *exo*-methylene tetrahydrocinnolines following a hydroarylation process catalyzed by a gold(I) complex. This new synthetic procedure is extremely practical since the hydroarylation substrates can be easily obtained in a 4 steps/1 purification procedure from commercially available arylhydrazines. The transformation was found to be compatible with the presence of different aryl or alkyl groups on the nitrogen atom attached to the aromatic nucleus and tolerates various aromatic substituents [13]. Notably, the reaction was performed on substrates possessing a basic nitrogen atom. The possible coordination of the electrophilic gold (I) complex [XPhosAu($NCCH_3$)SbF_6] **10** with this nitrogen atom should therefore be ineffective or at least not strongly competitive with the coordination to the alkyne moiety and its subsequent activation. The hydroarylated compound could also be subsequently isomerized into the corresponding 1,2-dihydrocinnolines under catalytic acidic conditions. Further studies related to the synthesis of other polycyclic heteroaromatics by a gold-catalyzed hydroarylation reaction as well as studies concerning the elucidation of the exact mechanism of the process are underway.

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[9] A very low yield of the desired quinoline derivative was obtained when the malonate group was omitted, see Ref. [5].
[10] A more favourable coordination of the nitrogen atom with the gold complex in hydrazine derivative **14** might be responsible for the higher loading of gold catalyst required (by comparison with the formation of quinoline derivatives **5**, see Ref. [5]).
[11] This contrasts with our previously reported synthesis of quinoline derivatives **5** for which a partial gold-catalyzed isomerization of the *exo*-methylene function was generally observed, see Ref. [5].
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