COMMUNICATION

Gold-Catalyzed Sequential Amination/Annulation Reactions of 2-Propynyl-1,3-dicarbonyl Compounds

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Abstract: The gold(III)-catalyzed sequential amination/annulation reaction of 2-propynyl-1,3-dicarbonyl compounds **1** with primary amines **2** produces 1,2,3,5-substituted pyrroles **4** in moderate to high yields.

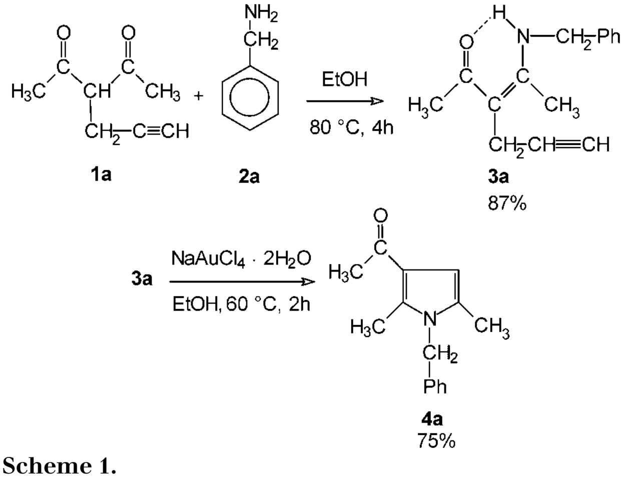
Keywords: amination; cyclization; gold; 2-propynyl-1,3-dicarbonyls; pyrroles

The recent trends in organic reaction development are oriented towards synthetic efficiency to alleviate their environmental impact. Homogeneous catalysis, promoted by complexes of transition metals, represents a methodology that perfectly meets the requirements for the design of environmentally friendly procedures for the synthesis of organic compounds.[1] Furthermore, the traditional stepwise formation of target molecules is being increasingly replaced by domino reactions.[2] Indeed, it would be much more efficient if one could form several bonds in one sequence without isolating the intermediates, changing the reaction conditions, or adding reagents. It is obvious that this type of reaction would allow the minimization of waste since, compared to stepwise reactions, the amount of solvents, reagents, and energy would be dramatically decreased.

Following our studies towards the development of new synthetic methods for heterocycles through transition metal-catalyzed domino reactions,[3] we planned to prepare functionalized pyrroles from 2-propynyl-1,3-dicarbonyl compounds using a simpler, and more efficient one-pot procedure compared to the classical stepwise methodology.[4]

We previously reported the synthesis of simple and fused pyrroles through sequential addition/elimination/annulation reactions[5a,5b] of 2-propynyl ketones with benzylamine and ammonia. Surprisingly, the reaction of 2-propynyl-1,3-dicarbonyl compounds **1** failed to give the target pyrrole derivative **4**. The reaction of the 3-acetyl-5-hexyn-2-one (**1a**) with the benzylamine (**2a**) in dry toluene or ethanol under reflux led to the formation of the enaminone derivative **3a** which was unable to undergo an annulation reaction under the reaction conditions. Very likely, the *5-exo-dig* annulation reaction of **3** as well as those of a variety of alkynes containing nucleophiles near the alkyne moiety depends on an intriguing combination of electronic, coordinating, and medium factors.[6] Various metal salts of groups 9, 10, and 11 have been reported to effectively catalyze the intramolecular addition of the nitrogen to alkynes.[7a–7c] Indeed, the regioselective cycloamination of the enaminone **3a** to give the target compound **4a** can be easily accomplished under the catalytic action of $NaAuCl_4 \cdot 2\,H_2O$ (Scheme 1).

The above formation of **4a** can be suggested to proceed by the *anti*-addition of nitrogen and gold moieties in a *5-exo-dig* manner to the acetylenic bond to give a vinylaurate species. The following protonolysis of the sp^2-C-Au bond and isomerization reactions afford the pyrrole **4a**. The regio-/chemoselective interaction to the acetylenic bond is one of the interesting features of gold(III) catalysis.[8]



Scheme 1.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/asc/ or from the author.

$$\mathbf{1a} + \mathbf{2a} \xrightarrow[40\ ^\circ\mathrm{C}]{\mathrm{M^+X^-,\ EtOH}} \mathbf{4a} \qquad (1)$$

Table 1. Transition metal-catalyzed synthesis of pyrrole **4a** from **1a** and **2a.**

Compound[a]	Catalyst	Time (h)	Yield [%] of **4a**[b]
1a	$NaAuCl_4$	1	100
1a	CuI	24	100
1a	$ZnCl_2$	24	34[c]
1a	Na_2PdCl_4	1	100
1a	$AgNO_3$	6	71

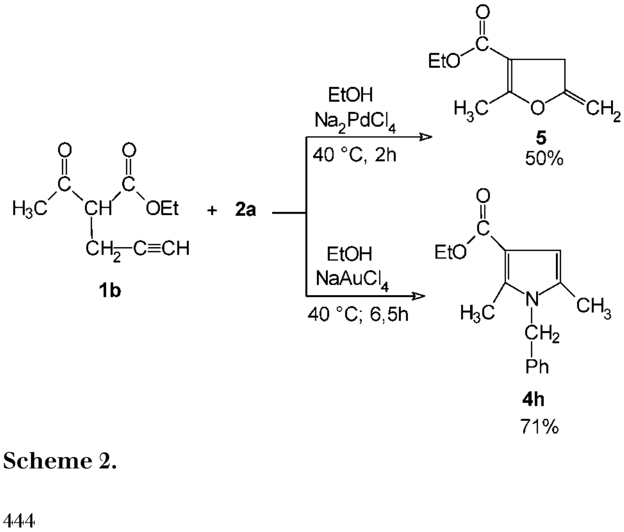
[a] Unless otherwise stated, reactions were carried out at 40 °C in ethanol under a nitrogen atmosphere using the following molar ratios: **1**:**2**:M^+X^- = 1:1.5:0.05.

[b] Yields refer to single runs, are given for pure isolated products, and are based on **1**.

[c] The derivative **3a** has been isolated in 34% yield.

Moreover, the pyrrole **4a** could be obtained in moderate to quantitative yields in the presence of phosphane-free metal catalysts through a sequential amination/annulation/protonolysis/isomerization reaction (Equation 1, Table 1).

Gold catalysts[9] have been reported to show a higher activity compared to Pd[10] in the intramolecular amination of acetylenic substrates and to Pd[11]/Ag[12] catalysts in the C-O intramolecular bond formation through nucleophilic attack of OH groups to a carbon-carbon triple bond. In our cases $NaAuCl_4$ had the further specific quality of accelerating the condensation of ketones with primary amines. Depending on the nature of the 2-propynyl-1,3-dicarbonyl partner, the competitive formation of 5-methylene-4,5-dihydrofuran derivatives through tandem intramolecular oxymetalation/protonolysis reactions[3] could be prevailing over the formation of the pyrrole nucleus. The reaction of ethyl 2-acetyl-4-pentynoate (**1b**) with **2a** (Scheme 2), i.e., led chemoselectively to the formation of 2-methyl-3-acetyl-5-methylene-4,5-dihydrofuran (**5**) in the presence of Na_2PdCl_4 as catalyst. By contrast, the formation of the pyrrole **4h** was observed by using $NaAuCl_4 \cdot 2\ H_2O$ instead of Na_2PdCl_4 as catalyst. The formation of **5** in higher yield (70%) at r.t. than at 40 °C (50%) suggested that the decomposition of **5** to some extent under the reaction conditions could be responsible of the lower yield of **5** compared to **4h**.

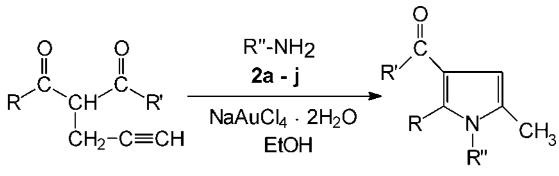


Scheme 2.

The above results clearly point out that the condensation reaction of **1** with primary amines must be faster than the oxymetalation reaction to allow the chemoselective formation of the pyrrole nucleus. To shed light on this point, **1a** was allowed to react with **2a** at room temperature for 12 h in ethanol in the presence of the gold catalyst, leading to the formation of a mixture of the enaminone **3a** (66% yield) and the pyrrole **4a** (29% yield). On the other hand, we failed to obtain a valuable amount of amination derivatives on treating **1a** with **2a** under the same reaction conditions but without the gold catalyst. Although $ZnCl_2$,[13] $AlCl_3$,[14] $TiCl_4$,[15] and other Lewis acids[16] have been reported to be efficient catalysts and water scavengers in the condensation of ketones with amines, to the best of our knowledge this is the first example of a gold-catalyzed amination of ketones. The development of clean, mild and efficient protocols for condensation reactions of carbonyl derivatives with amines is currently a synthetic challenge.[17] Similarly, when the system was extended to other 2-propynyl-1,3-dicarbonyl compounds and primary amino groups, the gold(III)-catalyzed sequential amination/annulation/protonolysis/ isomerization reactions to give pyrroles **4** turned out to be quite general (Equation 2 and Table 2).

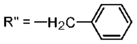
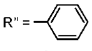
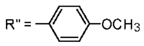
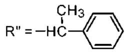
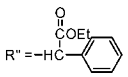
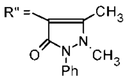
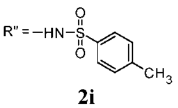
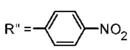
Various functional groups were tolerated in the amino framework. Subsequent application of this procedure to (*R*)-(+)-1-phenylethylamine (**2e**) (Table 2, entry 5) led to the corresponding chiral pyrrole derivative **4e** in an enantiomeric excess of 98% (the ee was determined by HPLC analysis on a CHIRACEL OD column in comparison of racemic **4e**). Further investigations on the synthesis of enantiopure pyrrole derivatives are in progress. When **1d** was allowed to react with **2j** (Table 2, entry 12) only the pyrrole **4l**, derived from the regioselective amination of the aliphatic carbonyl group, was isolated from the reaction mixture. Products of the gold-catalyzed addition of ethanol[18] or water[19] as well as catalytic oxidation of amines[20a,20b] were not observed.

In summary, because of the simple experimental procedure, mild conditions, easy availability of the starting materials, and ability to incorporate a variety of functional groups, the present method represents a valuable tool for the synthesis of 1,2,3,5-tetrasubstituted pyrroles. The gold(III)-catalyzed condensation reaction of ketones with amines is under investigation because it promises to overcome some of the draw-



1a - d **4a - l** (2)

Table 2. Synthesis of 1,2,3,5-substituted pyrroles 4[a],[b]

Entry	Compounds **1**	Compounds **2**	Yield [%] of **4**
1	R = R‘ = -CH_3 **1a**	 **2a**	100 **4a**
2	**1a**	 **2b**	78 **4b**
3	**1a**	 **2c**	100 **4c**
4	**1a**	R'' = $-CH_2CH{=}CH_2$ **2d**	52[c] **4d**
5	**1a**	 **2e**[d]	96 **4e**
6	**1a**	R'' = $-CH_2COOEt$ **2f**	78[e] **4f**
7	**1a**	 **2g**[f]	49[c] **4g**
8	R = -CH_3; R‘ = -OEt **1b**	**2a**	71 **4h**
9	**1b**	 **2h**	100 **4i**
10	**1b**	 **2i**	100 **4j**
11	R = -Ph; R‘ = -Ph **1c**	**2a**	50 **4k**
12	R = -CH_3; R‘ = -Ph **1d**	 **2j**	78 **4l**

[a] Unless otherwise stated, reactions were carried out at 40 °C in ethanol under a nitrogen atmosphere using the following molar ratios: **1**:**2**:$NaAuCl_4$ = 1:1.5:0.05

[b] Yields refer to single runs, are given for pure isolated products, and are based on **1**.

[c] **4d** was isolated in 80% yield in the presence of Na_2PdCl_4 as catalyst.

[d] (R)-(+)- enantiomer.

[e] Reaction was carried out at 60 °C.

[f] (D,L).

backs caused by more vigorous reagents and drastic reaction conditions. Currently, we are examining the extension of this procedure to the synthesis of enantiopure pyrrole derivatives via the gold(III)-catalyzed sequential amination/annulation/protonolysis/isomerization reaction of 2-propynyl-1,3- dicarbonyl compounds with chiral primary amines and chiral α-amino esters.

Experimental Section

Typical Procedure for Compound 4a

To a solution of **1a** (70 mg, 0.51 mmol) and benzylamine (**2a**; 81 mg, 0.76 mmol) in ethanol (3 mL) $NaAuCl_4 \cdot 2\,H_2O$ (10 mg, 0025 mmol) was added at room temperature under a nitrogen atmosphere. The reaction mixture was heated at 40 °C and stirred for 2 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate, 95/5) to give **4a**; yield: 120 mg (quantitative).

Acknowledgements

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