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Construction of the 1,5-Benzodiazepine Skeleton from *o*-Phenylendiamine and Propargylic Alcohols via a Domino Gold-Catalyzed Hydroamination/Cyclization Process

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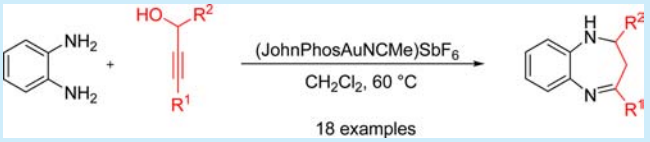
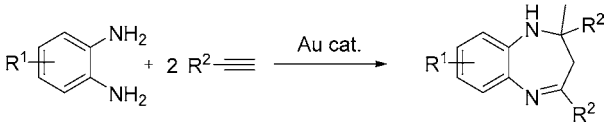
Supporting Information

ABSTRACT: The gold-catalyzed reaction of *o*-phenylendiamine with propargylic alcohols affords 1,5-benzodiazepines bearing different substituents on the 2 and 4 positions. The method allows even for the selective preparation of 4-substituted 1,5-benzodiazepine derivatives.



The 1,5-benzodiazepine nucleus is a structural component of a vast number of biologically active compounds exhibiting a broad spectrum of properties such as antianxiety,[1] antifungal,[2] anthelmintic,[2] antimicrobial,[3] antiviral,[4] analgesic,[5] antiinflammatory,[5] antipyretic,[5] and anxiolytic[6] activities. They have also been shown to possess cholecystokinin-2[7] and cholecystokinin-A[8] receptor antagonistic activities. For this reason, a great deal of attention has been dedicated to the development of synthetic routes to the construction of the 1,5-benzodiazepine skeleton, the great majority of them relying on condensation reactions of *o*-phenylenediamines with a variety of carbonyl derivatives such as ketones, *β*-haloketones, and *α*,*β*-unsaturated carbonyl compounds.[9] Recently, a simple and interesting gold-catalyzed synthesis of 1,5-benzodiazepines from *o*-phenylenediamines and terminal alkynes as alternative precursors has been developed[10] (Scheme 1) providing a new, effective, and atom-economic route to this class of compounds. However, this reaction does not allow for the introduction of different substituents on the 2 and 4 positions. This may represent a limit in some cases and justify efforts to develop more general and versatile procedures.

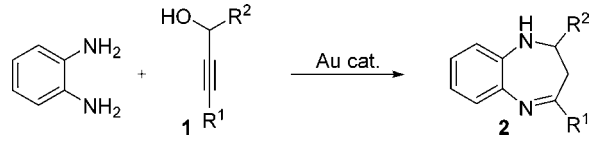
Scheme 1. Gold-Catalyzed Synthesis of 1,5-Benzodiazepines from *o*-Phenylenediamines and Terminal Alkynes



Herein, as part of our ongoing interest in gold-catalyzed assembly of heterocyclic rings,[11] we report just such a process involving the use of *o*-phenylenediamine and readily available propargylic alcohols **1** as building blocks for the synthesis of 1,5-benzodiazepines **2** bearing different substituents on the 2 and 4 positions (Scheme 2).

The development of a protocol for the preparation of **2a** from *o*-phenylenediamine and **1a** was initially explored when we started this research project. Part of our optimization work is summarized in Table 1.

Scheme 2. Gold-Catalyzed Synthesis of 1,5-Benzodiazepines from *o*-Phenylenediamine and Propargylic Alcohols



The initial use of Au(III) catalysts met with failure (Table 1, entries 1−3). However, we were pleased to find that switching to the Au(I) complex (JohnPhosAuNCMe)SbF_6[13] at 25 °C afforded the desired **2a** in 34% yield (Table 1, entry 4). Increasing the reaction temperature to 60 °C led to the isolation of **2a** in a satisfactory 72% yield (Table 1, entry 5). A further increase of temperature to 80 °C gave a lower yield. Compound **2a** was formed in 54% yield after 5 h (Table 1, entry 6), and no better results were obtained prolonging the reaction time (Table 1, entry 7). Most probably the reaction stops because of the decomposition of the catalyst, and longer reaction times lead to the decomposition of **1a**. The role of solvents was briefly investigated, but **2a** was isolated in lower yield both in MeCN and $CHCl_3$ (Table 1, entries 8 and 9).

Thus, 1.2 equiv of *o*-phenylendiamine, 1 equiv of propargylic alcohol, and 0.02 equiv of (JohnPhosAuNCMe)SbF_6 in CH_2Cl_2 at 60 °C were usually employed as standard conditions for the synthesis of 1,5-bezodiazepines when we investigated the generality and the substrate scope of the reaction. In some cases, to increase the reaction rate, a higher catalyst loading (0.03 or 0.05 equiv) was used. Our preparative results are listed in Table 2. A variety of substituents, such as OMe, CN, Br, COOEt, or Cl are tolerated, and the desired 1,5-benzodiazepines are usually isolated in good to high yields. Only with R^2 = *p*-MeO-C_6H_4 moderate yields were obtained (Table 2, entries 3, 15,16).

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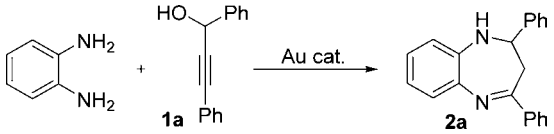
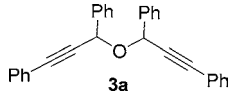
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solv	temp (°C)	time (h)	2a yield %[b,c]
1	$NaAuCl_4{\cdot}2H_2O$	CH_2Cl_2	25	8	−(91)
2	$NaAuCl_4{\cdot}2H_2O$	CH_2Cl_2	60	18	−(95)
3	$AuBr_3$	CH_2Cl_2	60	18	−(34)[d]
4	(JPAuNCMe)SbF_6[e]	CH_2Cl_2	25	48	34 (62)
5	(JPAuNCMe)SbF_6[e]	CH_2Cl_2	60	24	72 (4)
6	(JPAuNCMe)SbF_6[e]	CH_2Cl_2	80	5	55 (24)
7	(JPAuNCMe)SbF_6[e]	CH_2Cl_2	80	48	54 (14)
8	(JPAuNCMe)SbF_6[e]	MeCN	60	24	52 (25)
9	(JPAuNCMe)SbF_6[f]	$CHCl_3$	60	24	52(29)

[a]Unless otherwise stated, reactions were carried out on a 0.5 mmol scale using 1 equiv of 1,3-diphenyl-2-propyn-1-ol **1a**, 1.2 equiv of *o*-phenylendiamine, and 0.02 equiv of catalyst in 2 mL of solvent. [b]Yields are given for isolated products. [c]Figures in parentheses refer to the recovered **1a**. [d]The dimeric ether derivative **3a**, very likely formed via gold-catalyzed propargylic substitution,[12] was isolated in 54% yield as a diastereoisomeric mixture.



[e]JP = JohnPhos.

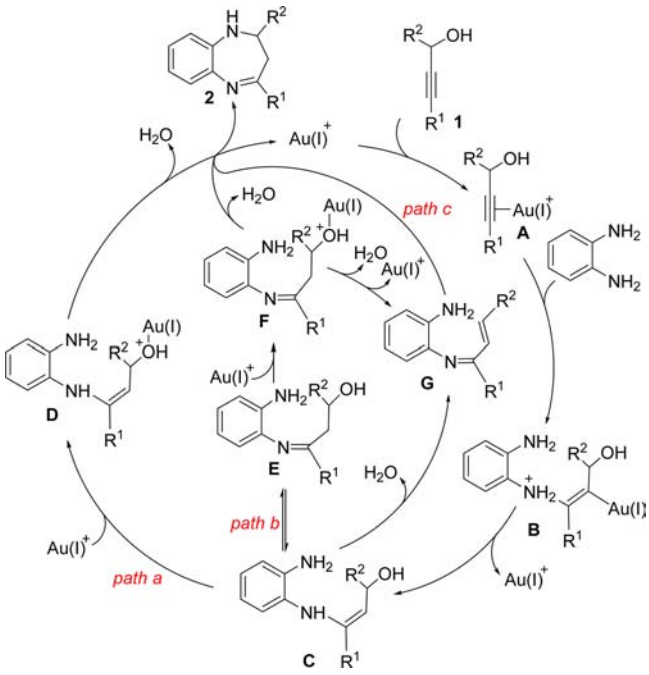
Table 2. Gold-Catalyzed Synthesis of 1,5-Benzodiazepines (2) from Propargylic Alcohols (1)[a]

	propargylic alcohol, **1**				
entry	R^1	R^2	cmpd	time (h)	product, **2** (yield %)[b]
1	Ph	Ph	**1a**	24	**2a** (72)
2	*p*-MeO-C_6H_4	Ph	**1b**	16	**2b** (62)
3	Ph	*p*-MeO-C_6H_4	**1c**	20	**2c** (34)
4	*p*-Me-C_6H_4	Ph	**1d**	30	**2d** (57)
5	Ph	*p*-Me-C_6H_4	**1e**	20	**2e** (62)
6	*p*-CN-C_6H_4	Ph	**1f**	24	**2f** (64)[c]
7	Ph	*p*-CN-C_6H_4	**1g**	24	**2g** (56)
8	*m*-MeO-C_6H_4	Ph	**1h**	24	**2h** (66)
9	Ph	*m*-MeO-C_6H_4	**1i**	7	**2i** (67)
10	*p*-Br-C_6H_4	Ph	**1j**	24	**2j** (66)[c]
11	Ph	*p*-Br-C_6H_4	**1k**	24	**2k** (65)
12	Ph	*m*-Br-C_6H_4	**1l**	24	**2l** (59)
13	*p*-EtOOC-C_6H_4	Ph	**1m**	9	**2m** (67)[c]
14	*p*-Cl-C_6H_4	Ph	**1n**	10	**2n** (70)[c]
15	*p*-EtOOC-C_6H_4	*p*-MeO-C_6H_4	**1o**	10	**2o** (32)[c]
16	*p*-MeO-C_6H_4	*p*-MeO-C_6H_4	**1p**	24	**2p** (45)
17	Ph	Et	**1q**	9	**2q** (70)[d]
18	Ph	H	**1r**	24	**2r** (77)
19	H	Ph	**1s**	72	−[e]

[a]Unless otherwise stated, reactions were carried out at 60 °C on a 0.5 mmol scale using 1 equiv of propargylic alcohol **1**, 1.2 equiv of *o*-phenylendiamine, and 0.02 equiv of JohnPhosAuNCMe)SbF_6 in 2 mL of CH_2Cl_2. [b]Yields are given for isolated products. [c]0.03 equiv of catalyst. [d]0.05 equiv of catalyst. [e]Compound **1s** was recovered in 50% yield.

Apparently, as shown by comparing a variety of substrates with R^1 = Ph (Table 2, entries 1, 5, 7, 9, 11, 12, 17, and 18), the presence of a strongly electron-donating substituent on the propargylic carbon has a deleterious effect on the reaction outcome, most probably on the cyclization step (Scheme 3).

Scheme 3. Proposed Reaction Mechanism



However, the benzodiazepine derivative is isolated in good yield when the same strongly electron-donating substituent is bound to the acetylenic terminus (Table 2, entry 2). The method can be successfully applied to propargylic substrates bearing an alkyl substituent on the propargylic carbon (Table 2, entry 17) and to unsubstituted propargylic derivatives (Table 2, entry 18). In the latter case, 4-substituted 1,5-benzodiazepine derivatives can be selectively accessed. With propargylic alcohols bearing terminal acetylenic groups, however, the reaction met with failure. For example, no evidence of benzodiazepine product was attained when **1s** was subjected to standard conditions. The starting propargylic alcohol was recovered in 50% yield, and a variety of products were formed that we have not investigated.

As to the reaction mechanism, we believe that the reaction proceeds through a domino hydroamination/substitution[14] sequence involving the basic steps shown in Scheme 3. The hydroamination intermediate **C** is formed through the intermediacy of **A** and **B**. Then, the intermediate **C** is converted into **2** via intramolecular substitution of the carbon−nitrogen bond for the activated carbon−oxygen bond (*paths a* and/or *b*).[15,16] Alternatively, compound **2** is generated from **G** (*path c*) through a conjugate addition reaction (possibly, via the intervention of Au^+).

The intervention of an alternative mechanism that involves a domino propargylic substitution/hydroamination[17] process has been ruled out on the basis of the following experiment: **1b** was treated under standard conditions with aniline instead of *o*-phenylendiamine. If the first event in the reaction of the nitrogen nucleophile with **1b** were a gold-catalyzed propargylic substitution, formation of the substitution derivative **4b** should be potentially expected. No evidence for the formation of such a derivative was found after 24 h, whereas the *α,β*-unsaturated imine **6b**[18] was isolated in 42% yield along with a 15% of **7b**

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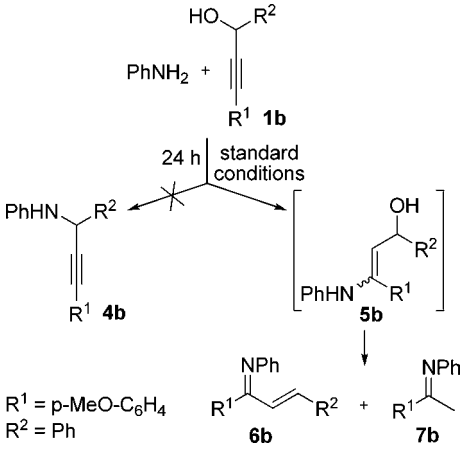
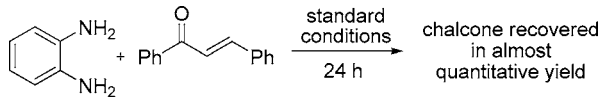
(isolated as single isomer whose configuration was not established; **1b** was recovered in 17% yield), suggesting that a hydroamination intermediate **5b** is initially formed as well as that its dehydration to an α,β-unsaturated derivative can take place under reaction conditions (Scheme 4).

Scheme 4. Reaction of Aniline with 1b



In addition, the starting materials were recovered in almost quantitative yield when *o*-phenylendiamine was treated with chalcone under standard conditions (Scheme 5), supporting the

Scheme 5. Reaction of *o*-Phenylendiamine with Chalcone



view that α,β-unsaturated carbonyl compounds, which might form from propargylic alcohols through the Meyer–Shuster rearrangement,[19] are not involved in the present synthesis.

In conclusion, an efficient gold-catalyzed approach to the construction of the 1,5-benzodiazepine skeleton from readily available starting materials has been developed. The reaction affords 1,5-benzodiazepines bearing different substituents on 2 and 4 positions and tolerates important functional groups such as OMe, CN, Br, COOEt, and Cl. The method allows for the selective preparation of 4-substituted 1,5-benzodiazepine derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01720.

Experimental details, characterization data of all compounds, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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