CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201202828

Propargyl Hydrazides: Synthesis and Conversion Into Pyrazoles Through Hydroamination

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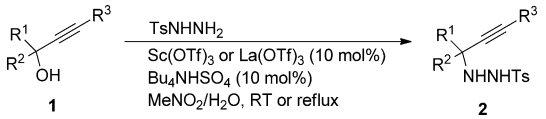
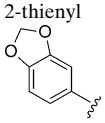
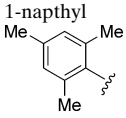
Direct C–N bond forming reactions of propargyl alcohols have received considerable attention because the products, propargyl amines and their derivatives, can be converted into a wide variety of heterocycles through either one-pot or stepwise cyclizations. In particular, propargyl hydrazides have been converted into heterocycles that contain either one or two nitrogen atoms, compounds that exhibit various biological activities.[1] Similarly, alkenyl and propargyl amines and their derivatives can be readily accessed from the corresponding halides,[2] alcohols,[3] esters,[4] and imines[5] using novel methodologies based on metal-catalyzed and metal-free aminations; such transformations can also be carried out in an enantioselective manner.[6] However, methods for preparing alkenyl and propargyl hydrazides are very limited. In particular, propargyl hydrazides are useful intermediates in Mannich-type coupling reactions of aldehydes with hydrazines to generate pyrazoles,[7] which have diverse biological activities, including antihyperglycemic, analgesic, anti-inflammatory, antipyretic, and antibacterial activities.[8] To the best of our knowledge, while there are a few preparative methods for the hydrohydrazination of enynes[9] and the allylation of hydrazones,[10] direct hydrazination of alcohols has not yet been reported.[11] We recently achieved direct Lewis acid catalyzed C–C and C–O bond formation of propargyl alcohols with nucleophiles in $MeNO_2/H_2O$, a reaction medium that provided high regioselectivity and chemoselectivity.[12] We therefore decided to study the more challenging direct hydrazination of propargyl alcohols and a subsequent intramolecular hydroamination that is tunable with either the addition of an acid or a base.

First, we screened nitrogen nucleophiles in the direct Lewis acid catalyzed hydrazination of propargyl alcohols in $MeNO_2/H_2O$ and were pleased to find that the reactions with *p*-tosylhydrazine proceeded to afford the desired propargyl hydrazines (Table 1). The typical reaction conditions developed in our research group for other C–C and C–O bond forming reactions with alcohols were applied to the C–N bond formation with hydrazines: scandium triflate (0.10 equivalents), Bu_4NHSO_4 (0.10 equivalents), $MeNO_2/H_2O$ (10:1), either 30 °C or reflux for 5—15 minutes. Propargyl alcohols containing a sulfur substituent on the alkyne moiety are highly reactive toward hydrazination and afford the propargyl hydrazides even at room temperature. However, alcohols bearing either *n*Bu or Ph R^3 substituents did not react at room temperature, although the hydrazination of these less reactive substrates can be readily achieved under reflux conditions. Hydrazination of phenylsulfanyl cycloalkanols **1l–1n** also provided the corresponding products in satisfactory yields. Dialkyl- and diaryl-propargyl alcohols provided the desired products in moderate yields (Table 1, entries 15 and 16). The structures of the products were confirmed using deuteration experiments. When deuterium oxide was added to the NMR sample of **2c**, the resulting ^1H NMR spectrum no longer showed the characteristic two peaks at δ 4.77 and 6.19 ppm, signals that correspond to the NH protons of the hydrazine moiety. All the other spectral

Table 1. Direct hydrazination of propargyl alcohols.



Entry	R^1	R^2	R^3	*T*/*t*	**2** (Yield [%])[a]
1	Ph	H	Ph	45 °C, 5 h	**2a** (84)
2	*p*-FC_6H_4	H	Ph	50 °C, 1 h	**2b** (67)
3	1-naphthyl	H	Ph	50 °C, 1 h	**2c** (78)
4	Ph	H	*n*Bu	reflux, 7 min	**2d** (68)
5	2-thienyl	H	*n*Bu	RT, 1.5 h	**2e** (96)
6	*p*-$MeOC_6H_4$	H	PhS	RT, 50 min	**2f** (90)
7	2-thienyl	H	PhS	RT, 1.5 h	**2g** (86)
8		H	PhS	50 °C, 13 min	**2h** (65)
9	1-napthyl	H	PhS	50 °C, 40 min	**2i** (98)
10		H	PhS	RT, 1 h	**2j** (98)
11	*p*-FC_6H_4	H	PhS	60 °C, 0.5 h	**2k** (91)
12	$(CH_2)_4$		PhS	50 °C, 1.5 h	**2l** (75)
13	$(CH_2)_5$		PhS	50 °C, 3 h	**2m** (66)
14	$(CH_2)_6$		PhS	50 °C, 15 min	**2n** (68)
15	*n*-pentyl	*n*-pentyl	PhS	RT, 3.5 h	**2o** (64)
16	*p*-FC_6H_4	*p*-FC_6H_4	PhS	reflux, 5 min	**2p** (56)

[a] Yield of isolated product. Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

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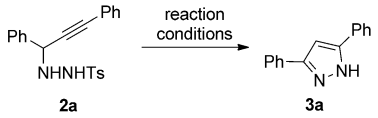
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201202828.

data supported the assignment of the structures as being the indicated propargyl hydrazides. Next, intramolecular cyclization of the propargyl hydrazides using either acid or base was investigated, because in comparison with propargylamines, propargyl hydrazides are less utilized as precursors to useful heterocycles.[13] First, the acid-catalyzed cyclization of propargyl hydrazides was investigated (Table 2).

Using the optimized reaction conditions for the acid-catalyzed cyclization of propargyl hydrazides, the scope of the $AuCl/AgClO_4$ catalyzed cyclization was evaluated. The reac-

Table 2. Screening of acid-catalyzed cyclization of **2a**.



2a **3a**

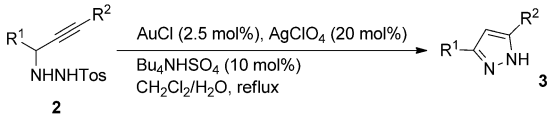
Entry	Reaction conditions	Yield **3a** [%]	Yield **2a** [%]
1	$AgClO_4$ (10 mol%), CH_2Cl_2, RT, 1.2 h	62	
2	CuOTf (10 mol%), CH_2Cl_2, RT, 1.5 h	40	
3	CuI (10 mol%), CH_2Cl_2, RT, 1.2 h		47
4	$Yb(OTf)_3$ (10 mol%), CH_2Cl_2, reflux, 3 h		24
5	$La(OTf)_3$ (10 mol%), CH_2Cl_2, reflux, 3 h		4
6	AuCl (10 mol%), DCE, reflux, 5 min	36	
7	$AgClO_4$ (10 mol%), $MeNO_2$, reflux, 3.5 h	84	
8	AuCl (20 mol%), CH_2Cl_2, RT, 45 min	72	
9	AuCl (2 mol%), TBAC (10 mol%) CH_2Cl_2/H_2O, reflux, 2 h	67	
10	$AgClO_4$ (2 mol%), TBAB (10 mol%) CH_2Cl_2/H_2O, RT, 2 h	58	
11	AuCl (5 mol%), $AgClO_4$ (15 mol%) TBAS (20 mol%), CH_2Cl_2/H_2O, reflux, 2 h	96	2
12	AuCl (5 mol%), $AgSbF_6$ (15 mol%) TBAS (20 mol%), CH_2Cl_2/H_2O, reflux, 3 h	66	16
13	AuCl (2.5 mol%), $AgClO_4$ (20 mol%) TBAS (20 mol%), CH_2Cl_2/H_2O, reflux, 7 h	91	

TBAB = tetra-*n*-butylammonium bromide, TBAC = tetra-*n*-butylammonium chloride, TBAS = tetra-*n*-butylammonium hydrogen sulfate.

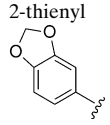
tions of hydrazides with R^1 substituents, pFC_6H_4 and 1-naphthyl, gave pyrazoles **3b** and **3c**, respectively (Table 3, entries 1 and 2). The use of hydrazides bearing a *n*-butyl group instead of a phenyl group as the R^2 substituent gave good yields of the corresponding products (Table 3, entries 3 and 4). Similarly, the reactions of phenylsulfanyl hydrazides proceeded to completion faster than the hydrazides bearing *n*-butyl and phenyl groups in and gave the corresponding excellent yields (Table 3, entries 5—10). Furthermore, the cyclization of ethynylcycloalkylhydrazides was investigated using the $AuCl/AgClO_4$ reaction conditions (Scheme 1). The yield of pyrazoles decreases as the size of the cycloalkyl groups increases (5- to a 7-membered ring), the side products being β-elimination products, that is, ethynylcycloalkenes.

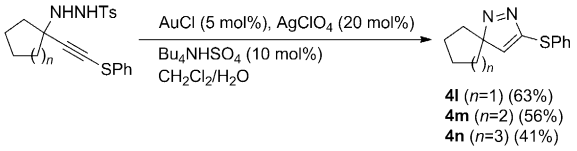
On the basis of the above results and our previous studies, a plausible reaction mechanism for the intramolecular cyclization of the propargyl hydrazides is outlined in Scheme 2. First, gold activates the acetylenic group of the propargyl

Table 3. $AuCl/AgClO_4$-catalyzed cyclization of propargyl hydrazides.



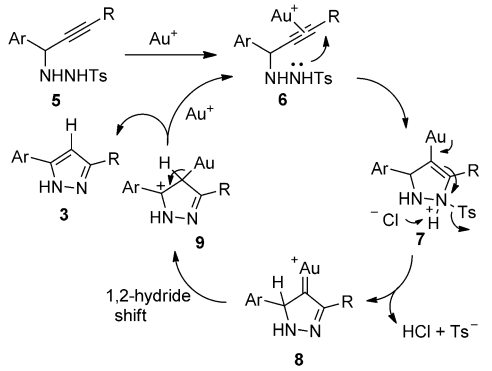
2 **3**

Entry	R^1	R^2	*t* (h)	**3** (Yield [%])
1	p-FC_6H_4	Ph	8	**3b** (97)
2	1-naphthyl	Ph	10	**3c** (97)
3	Ph	*n*Bu	3	**3d** (79)
4	2-thienyl	*n*Bu	1.5	**3e** (70)
5	p-$MeOC_6H_4$	PhS	1.5	**3f** (98)
6	2-thienyl	PhS	2.5	**3g** (91)
7		PhS	2	**3h** (61)
8	1-napthyl	PhS	3.5	**3i** (95)
9	2,4,6-$Me_3C_6H_2$	PhS	2.5	**3j** (90)
10	p-FC_6H_4	PhS	4	**3k** (98)



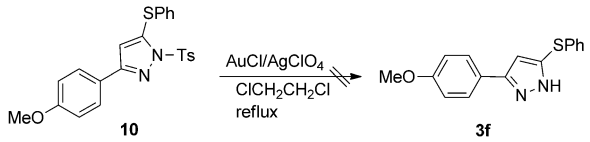
4l (*n*=1) (63%)
4m (*n*=2) (56%)
4n (*n*=3) (41%)

Scheme 1. $AuCl/AgClO_4$-catalyzed transformation of 1-ethynyl-1-hydrazinocycloalkanes.



Scheme 2. Proposed reaction mechanism.

hydrazide **6**, which leads to a gold-substituted pyrazoline intermediate **7** through an intramolecular 5-*endo*-dig cyclization. The elimination of both tosylate and hydrogen chloride from **7** generates gold(I)-stabilized intermediate **8**.[14] The 1,2-hydride shift of intermediate **8** gives the benzyl cation **9**, which could release the gold(I) catalyst with concomitant formation of product **3**. To determine if a different mechanism is operating, the desulfonylation of **10** to give **3f** was attempted under the same reaction conditions that were used for the intramolecular cyclization (Scheme 3). This reaction did not proceed at all at room temperature; however, under reflux for 8 hours, the desired **3f** was obtained in 56% yield, accompanied by the tosylhydrazide **10** (44%).

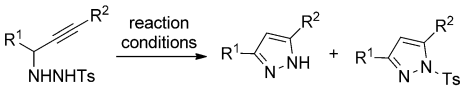


Scheme 3. Attempted desulfonylation of tosyl pyrazoles.

The difficulty in achieving the desulfonylation reaction under acidic conditions suggests that **10** is not an intermediate in the catalytic cycle and that elimination of the tosyl group occurs in the manner in which it is depicted in Scheme 2.

In addition to the AuCl/$AgClO_4$-catalyzed reaction, the base-promoted cyclization of propargyl hydrazides was also investigated (Table 4). Surprisingly, when using either

Table 4. Base-promoted cyclization of propargyl hydrazides.



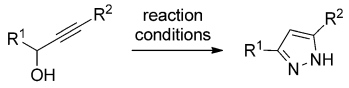
Entry	R^1	R^2	Reaction conditions	Product (Yield [%])
1	Ph	Ph	Cs_2CO_3 (1.2 equiv) acetone, RT, 4.5 h	**10a** (88)
2	2-thienyl	*n*Bu	Cs_2CO_3 (1.2 equiv) acetone, RT, 3 h	**10e** (42)
3	*p*-$MeOC_6H_4$	PhS	LDA (2 equiv) THF, RT, 4 h	**10f** (55)
4	*p*-$MeOC_6H_4$	PhS	*t*BuOK (3 equiv) *t*BuOH, reflux, 3.5 h	**3f** (69)
5	*p*-$MeOC_6H_4$	PhS	NaH (1 equiv) THF, 0 °C, 2 h	**10f** (60) **3f** (15)
6	*p*-FC_6H_4	PhS	Cs_2CO_3 (1.2 equiv) acetone	**10h** (43)
7		PhS	LDA (2 equiv) THF, RT, 20 min	**10i** (49)

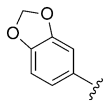
LDA = lithium diisopropylamine.

cesium carbonate or LDA, *N*-tosylpyrazoles were obtained as the sole product, instead of 1*H*-pyrazoles. On the other hand, when sodium alkoxides were used, such as sodium methoxide and *t*BuOK in the appropriate alcoholic solvent, the desulfonylated pyrazole **3f**, which was obtained using the acid-catalyzed cyclization of the propargyl hydrazides, was obtained. The use of sodium hydride in THF gave a mixture of **10f** and **3f** (Table 4, entry 5).

Next, the direct synthesis of pyrazoles from propargyl alcohols was attempted (Table 5). Notably, the use of 5 mol% AuCl provided the pyrazoles **3f** and **3h**. A combination of scandium triflate and gold chloride was also efficient for this procedure (Table 5, entries 3, 6, and 7). Therefore, this metal-catalyzed tandem hydrazination–desulfonylation–cyclization process represents a one-step synthesis of pyrazoles from propargyl alcohols with *p*-tosyl hydrazine.

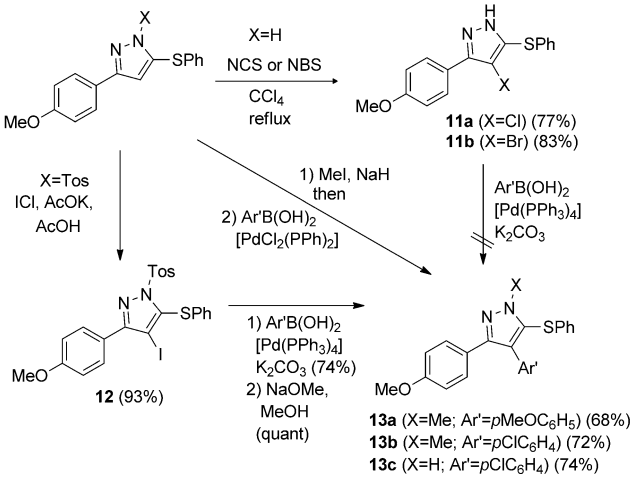
Table 5. Direct synthesis of pyrazoles from propargyl alcohols.



Entry	R^1	R^2	Reaction conditions	Product (Yield [%])
1	Ph	Ph	$Sc(OTf)_3$ (10 mol%) $AgClO_4$ (20 mol%) $MeNO_2$, RT, 5 h	**3a** (90)
2	Ph	*n*Bu	$Sc(OTf)_3$ (10 mol%) $AgClO_4$ (20 mol%) AuCl (5 mol%) 50 °C, 20 min	**3d** (67)
3	*p*-$MeOC_6H_4$	PhS	$Sc(OTf)_3$ (5 mol%) AuCl (5 mol%) 40 °C, 2 h[a]	**3f** (83)
4	2-thienyl	PhS	$Sc(OTf)_3$ (5 mol%) AuCl (5 mol%) reflux, 5 min[a]	**3g** (74)
5		PhS	$Sc(OTf)_3$ (5 mol%) AuCl (5 mol%) 50 °C, 45 min[a]	**3h** (82)
6	1-naphthyl	PhS	AuCl (10 mol%) 50 °C, 5 h[a]	**3i** (63)
7	*p*-FC_6H_4	PhS	AuCl (10 mol%) 60 °C, 3 h[a]	**3k** (57)

[a] $MeNO_2/H_2O$ (10:1), Bu_4NHSO_4 (20 mol%).

Finally, the transformation of sulfanyl pyrazoles was demonstrated using previously reported methods (Scheme 4). 1,3,5-Triarylsubstituted pyrazoles have been used in halogenation–arylation protocols with arylboronic acids (Suzuki coupling process) to give 1,3,4-triarylpyrazoles.[15] Halogenation of the NH pyrazoles using either *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) readily afforded the chlorinated derivative **11a** and the brominated derivative **11b**, respectively; however, the subsequent palladium-catalyzed arylation of the NH halopyrazoles with arylboronic



Scheme 4. Transformations of sulfanyl pyrazoles.

acids did not proceed to give the 3,4-diarylpyrazoles.[7e,16] Next, *N*-methylation and arylation were attempted using the same procedure. On the other hand, the *N*-tosylpyrazoles underwent arylation and desulfonylation to afford **13a** via 4-iodopyrazole **12** in excellent yields. The cross-coupling of heteroaryl halides is extensively used for preparing pharmaceutical intermediates; however, these procedures suffer from deactivation of the metal catalysts because of the binding of these metals with heteroatom moieties, such as NH, OH, CO_2H, SH, and NH_2. To overcome the problem of catalyst deactivation, many researchers have resorted to either incorporating additional protection and deprotection steps of *N*-aryl and *N*-alkyl derivatives prior to and after the coupling reaction, or seeking more effective ligands and catalysts. The novel scandium-catalyzed hydrazination of propargyl alcohols followed by cyclization of either the tosyl-substituted or tosyl-free products provides an alternative route to pyrazoles with significant potential applications. For example, sulfonylated 3,4-bis(aryl)pyrazoles, are known to undergo desulfanylation when treated with Raney Ni to afford the polyarylpyrazoles.[15]

In conclusion, we report the first convenient method for the preparation of propargyl hydrazides from the corresponding alcohols through scandium-catalyzed hydrazination in $MeNO_2/H_2O$. Moreover, gold/silver-catalyzed reactions and base-promoted cyclizations of the hydrazides lead to the formation of *N*-tosyl pyrazoles and *N*-H pyrazoles, respectively. Furthermore, both gold and a combination of scandium and gold catalysts facilitate the one-step transformation of propargyl alcohols into pyrazoles. Therefore, this protocol provides access to a wide variety of aryl-substituted pyrazoles through either stepwise or one-step protocols.

Experimental Section

Typical procedure for preparation of propargyl hydrazides: To a nitromethane/H_2O (10:1, 22 mL) solution of 1,3-diphenyl-2-propyn-1-ol (**1a**; 1.0 g, 4.8 mmol), *p*-toluenesulfonyl hydrazide (2.7 g, 14.5 mmol), and tetrabutylammonium hydrogensulfate (0.16 g, 0.48 mmol) at room temperature was added scandium triflate (0.24 g, 0.48 mmol). The reaction mixture was stirred for 10 h at 40 °C and then poured into saturated aqueous sodium hydrogen carbonate (100 mL). The organic layer was separated and the aqueous layer was extracted with AcOEt. The organic layer and the extracts were combined and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$/*n*-hexane (5:1) to give 1-(*p*-tosylhydrazino)-3-phenyl-2-propyn-1-ylbenzene (**2a**; 1.38 g, 76%) as a white powder. M.p. 140–142 °C.

Typical procedure for the AuCl/$AgClO_4$-catalyzed cyclization leading to 3,5-disubstituted pyrazoles: To a dichloromethane/H_2O (10:1, 15.4 mL) solution of 1-(phenylsulfanylethynyl)-1-(*p*-toluenesulfonylhydrazino)cyclohexane (**2m**; 0.20 g, 0.50 mmol) and tetrabutylammonium hydrogensulfate (17 mg, 0.05 mmol) were added silver perchlorate (21 mg, 0.10 mmol) and then gold(I) chloride (5.8 mg, 0.0025 mmol). The reaction mixture was stirred at reflux for 2 h. The cooled mixture was poured into a saturated aqueous sodium hydrogencarbonate (50 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel eluting with $CHCl_3$ to give spirocyclohexane-5-(phenylsulfanyl)-*3H*-pyrazole (**4m**; 71 mg, 58%) as a pale yellow oil.

Typical procedure for the direct hydrazination/cyclization of propargyl alcohols: To a nitromethane/H_2O (10:1, 1.1 mL) solution of 1-thienyl-3-(phenylsulfanyl)propargyl alcohol (**1g**) (50 mg, 0.20 mmol), *p*-toluenesulfonyl hydrazide (45 mg, 0.24 mmol), and tetrabutylammonium hydrogensulfate (14 mg, 0.04 mmol) at room temperature were added scandium triflate (14 mg, 0.04 mmol) and gold(I) chloride (2.4 mg, 0.01 mmol). The reaction mixture was stirred for 5 min at reflux and then poured into water (50 mL). Workup as detailed in the procedure above for the preparation of **4m** was followed to give **3g** (39 mg, 74%).

Keywords: C–N bond formation · cycloisomerization · heterocycles · hydrazides · hydroamination · propargylic amines · pyrazoles

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Received: August 7, 2012
Revised: October 5, 2012
Published online: November 9, 2012

