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Title: Hydration and Intramolecular Cyclization of Homopropargyl Sulfonamide Derivatives Catalyzed by AgSbF6: Synthesis of Structurally Diverse 2,3-Dihydro-1H-Pyrroles

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COMMUNICATION

Hydration and Intramolecular Cyclization of Homopropargyl Sulfonamide Derivatives Catalyzed by Silver Hexafluoroantimonate(V): Synthesis of Structurally Diverse 2,3-Dihydro-1*H*-Pyrroles

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Abstract. We have developed an efficient, simple protocol for synthesis of structurally diverse functionalized 2,3-dihydro-1*H*-pyrroles by hydration and intramolecular cyclization of homopropargyl sulfonamide derivatives. Mechanistic experiments revealed that the sulfonamide nitrogen participated in the hydration reaction by chelating the Ag atom of the catalyst to assist in the formation of the hydration intermediate. The protocol accommodated a wide range of substrates and was used for a formal synthesis of (*S*)-nicotine.

Keywords: Cyclization; Heterocycle; Hydration; Silver; Sulfonamides

Heterocyclic compounds are widely distributed in nature and have shown great potential as inspirations for the design of new molecules with interesting properties and biological activities.[1] Five-membered N-heterocycles such as pyrroles and pyrrolidines are found in many bioactive natural products, as well as pharmaceuticals and pesticides.[2] Examples include nicotine, which has insecticidal activity;[3] crispine A, which was isolated from *Carduus crispus* Linn. and has significant cytotoxic activity;[4] and the polycyclic insecticide chlorfenapyr (Figure 1).

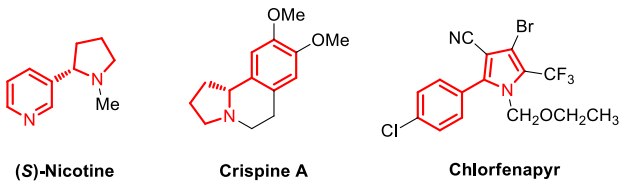
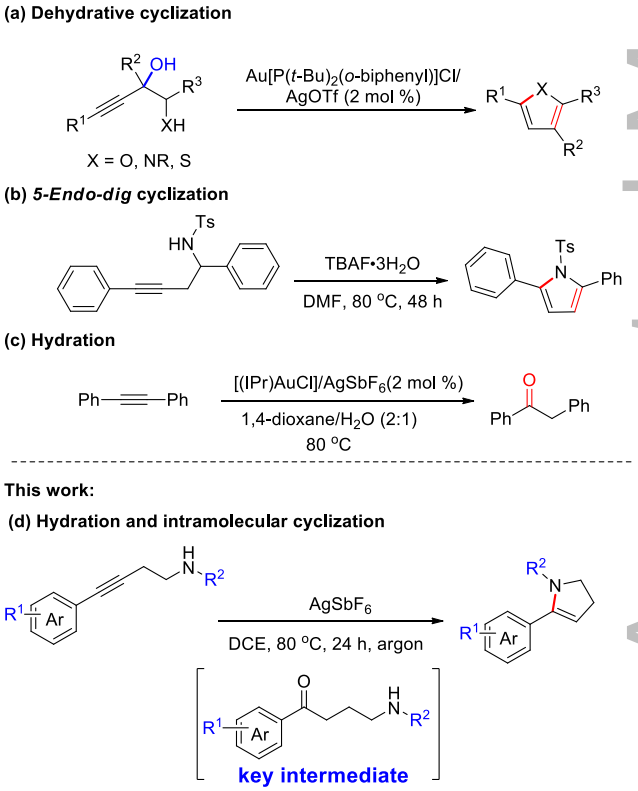


Figure 1. Natural Products and Agrochemicals with Pyrrole or Pyrrolidine Ring Systems.

The pyrrole moiety has attracted considerable interest because of its many applications,[5] and much research effort has been devoted to the development of new approaches to the synthesis of this moiety.[6,7] Representative methods include Au/Ag-catalyzed dehydrative cyclization of propargyl alcohols (Scheme 1a)[8] and 5-*endo-dig* cyclization of homopropargyl sulfonamides promoted by tetra-*n*-butylammonium fluoride (Scheme 1b).[9] However, the existing methods generally require complex substrates, use expensive catalysts, or have a limited substrate scope. Accordingly, the development of new, efficient methods that address these drawbacks is highly desirable.



Scheme 1. Catalytic Cyclization and Hydration Reactions of Alkynes.

In addition to these cyclization reactions, alkynes undergo numerous other potentially useful

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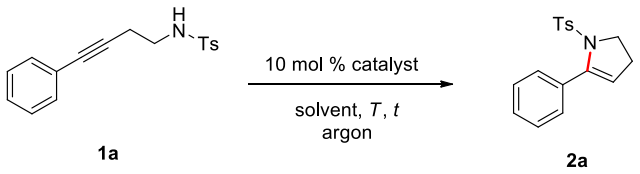
transformations. For example, recent rapid progress in the area of transition-metal-catalyzed reactions of alkynes has resulted in methods for easy access to an incredible variety of functionalized carbonyl derivatives (Scheme 1c).[10] Alkyne hydration to form carbonyl derivatives is of particular interest, owing to the wide availability of alkynyl substrates and the fundamental importance of the carbonyl motif in modern organic synthesis.[11] As part of our ongoing work on the construction of alkaloid skeletons, we herein report the synthesis of 2,3-dihydro-1*H*-pyrroles via hydration and subsequent intramolecular cyclization of homopropargyl sulfonamide derivatives (Scheme 1d).

Table 1. Optimization of Reaction Conditions.[a]

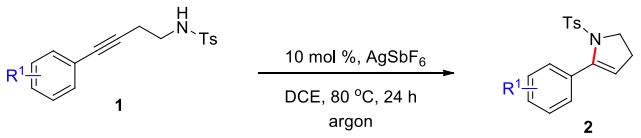


Entry	Catalyst	Solvent	*T* (°C)	*t* (h)	**2a** Yield (%)[b]
1	$Sc(OTf)_3$	DCE	80	24	0
2	$In(OTf)_3$	DCE	80	24	0
3	$Cu(OAc)_2$	DCE	80	24	0
4	**$AgSbF_6$**	**DCE**	**80**	**24**	**92**
5	$AgSbF_6$	DCE	60	24	65
6	$AgSbF_6$	DCE	80	10	71
7	$AgSbF_6$	$CHCl_3$	60	24	57
8	$AgSbF_6$	acetonitrile	80	24	trace
9	$AgSbF_6$	1,4-dioxane	80	24	trace
10	$AgSbF_6$	toluene	80	24	trace
11	AgOTf	DCE	80	24	69
12	AgOAc	DCE	80	24	36
13	$AgBF_4$	DCE	80	24	47
14	—	DCE	80	24	0

[a]Reactions were conducted with **1a** (1 equiv) in the presence of catalyst (10 mol %) under argon in 1,2-dichloroethane (DCE) for 24 h at 80 °C, unless otherwise stated. Ts = 4-methylphenylsulfonyl. [b]Isolated yields are provided.

We began by investigating the reaction of 4-methyl-*N*-(4-phenylbut-3-ynyl)benzenesulfonamide (**1a**) with transition-metal catalysts (10 mol %) in 1,2-dichloroethane (DCE) under argon for 24 h at 80 °C (Table 1, entries 1–4). To our delight, the reaction efficiently afforded desired 2,3-dihydro-1*H*-pyrrole **2a** in 92% yield when $AgSbF_6$ was used as the catalyst (entry 4). Neither lowering the reaction temperature to 60 °C (entry 5) nor shortening the reaction time to 10 h (entry 6) provided any benefit. The nature of the solvent greatly influenced the reaction outcome (entries 7–10). Specifically, only a trace of **2a** was obtained when the solvent was acetonitrile, 1,4-dioxane, or toluene, and the yield was only 57% in $CHCl_3$. Other Ag(I) catalysts gave no better results than $AgSbF_6$ (entries 11–13), and the reaction did not proceed in the absence of a silver salt (entry 14). Extensive screening of various other reaction parameters revealed that the optimal reaction conditions were 10 mol % $AgSbF_6$ in 1,2-dichloroethane at 80 °C for 24 h (entry 4).

Table 2. Effect of Phenyl-Group Substituent on Reaction Outcome.[a]



Entry	Sulfonamide	R^1	Product	Yield (%)
1	**1a**	H	**2a**	92
2	**1b**	3-Me	**2b**	72
3	**1c**	4-Me	**2c**	65
4	**1d**	4-MeO	**2d**	68
5	**1e**	4-*t*-Bu	**2e**	67
6	**1f**	4-F	**2f**	81
7	**1g**	4-Cl	**2g**	92
8	**1h**	4-Br	**2h**	50
9	**1i**	4-CF_3O	**2i**	40
10	**1j**	4-CH_3CO	**2j**	72
11	**1k**	4-MeOCO	**2k**	45
12	**1l**	4-NO_2	**2l**	40
13	**1m**	3,4-Me	**2m**	52
14	**1n**	3,4-F	**2n**	62
15	**1o**	3,5-Cl	**2o**	50

[a]Reaction conditions: **1** (1 equiv) and $AgSbF_6$ (10 mol %) in DCE (5 mL) at 80 °C under argon for 24 h. Isolated yields are provided.

With the optimized conditions in hand, we investigated the substrate scope of the reaction (Table 2). First, we carried out reactions of homopropargyl sulfonamides with various substituents on the phenyl group. Most of the tested substrates gave the corresponding 2,3-dihydro-1*H*-pyrroles in good to excellent yields (**2a–2o**), indicating that neither the electronic properties nor the position of the phenyl substituent influenced the reaction outcome. Specifically, substrates with an electron-donating substituent (**1b–1e**), a weakly electron-withdrawing substituent (**1f–1h**), or no substituent at all (**1a**) afforded the desired compounds in good yields. Substrates with a strongly electron-withdrawing group, such as trifluoromethyl, nitro, carbonyl, or methoxycarbonyl, could also be converted to the desired products (**2i–2l**), albeit in slightly lower yields. Disubstituted products **2m–2o** could be obtained in moderate yields (>50%).

Next, we evaluated substrates bearing various other aryl groups (Table 3). Products containing a biphenyl ring (**2p**, 60%), thiophene ring (**2q**, 45%), or pyridyl ring (**2r**, 65%) could be obtained under the optimized conditions. In addition, we prepared substrates **1s–1v** to investigate the influence of the

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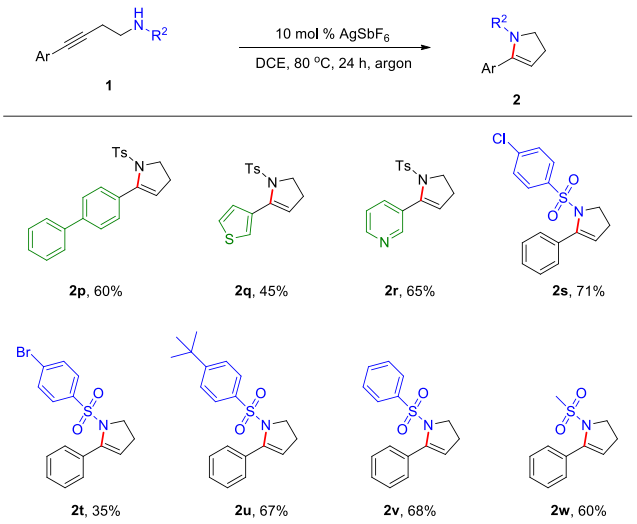
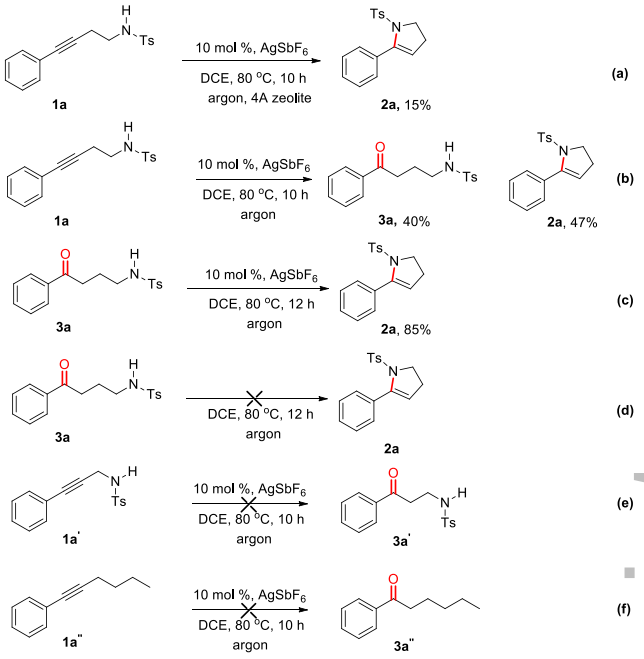
nature of the protecting group on the cyclization reaction. The electronic properties of the substituent on the benzenesulfonyl group had some influence on the reaction outcome: compounds with a chloro substituent (**1s**), a *t*-Bu substituent (**1u**), or no substituent (**1v**) gave the expected products in about 70% yield, whereas bromo-substituted compound **1t** gave a lower yield. The reaction also worked well when we changed the benzenesulfonyl group to a methyl sulfonyl group: compound **2w** was obtained in 60% isolated yield. No hydrolysis or cyclization product was obtained when *n*-propyl-substituted homopropargyl sulfonamide **1x** was employed as the substrate (see Supporting Information).

Table 3. Effects of Other Aryl and Protecting Groups on Reaction Outcome.[a]



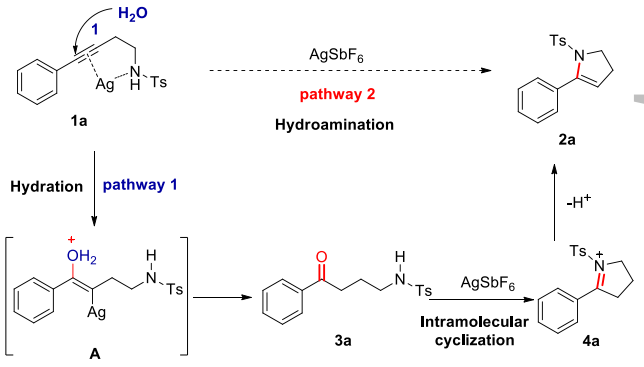
[a]Reaction conditions: **1** (1 equiv) and $AgSbF_6$ (10 mol %) in DCE (5 mL) at 80 °C under argon for 24 h. Isolated yields are provided.

To study the reaction mechanism, we performed some control experiments. When zeolites (4Å) were present in the reaction mixture, the yield of **2a** dropped to 15% (Scheme 2a); this result suggests that water played an important role in the reaction. When **1a** was subjected to the standard conditions for a shorter duration (10 h), we obtained hydrolysis product **3a** (40%) in addition to **2a** (47%) (Scheme 2b). Subjecting **3a** to the same conditions for 12 h smoothly afforded **2a** (Scheme 2c), but **3a** could not be transformed to **2a** in the absence of a silver salt (Scheme 2d), suggesting that $AgSbF_6$ promoted the intramolecular cyclization reaction. We also evaluated the reactivity of alkyne **1a'** under the optimized conditions and found that hydrolysis product **3a'** did not form after 10 h (Scheme 2e). Alkyne **1a″** did not provide the corresponding hydration product (**3a″**) either (Scheme 2f). These results suggest that the presence of the tethered nucleophile and its location relative to the triple bond were crucial to the success of the reaction.[12]



Scheme 2. Control Experiments.

Two possible pathways for this intramolecular cyclization reaction are depicted in Scheme 3. Pathway 1 involves initial coordination of Ag(I) to the triple bond of **1a** with assistance from the tethered nucleophile (HNTs), followed by regioselective hydration to afford **3a** via key intermediate **A**. Then intramolecular cyclization of **3a** affords cation **4a**, which loses a proton to generate **2a**. Pathway 2. which involves intramolecular hydroamination catalyzed by $AgSbF_6$, cannot be ruled out.



Scheme 3. Proposed Reaction Pathways.

Because 2,3-dihydro-1*H*-pyrrole **2r** is a key intermediate in a reported synthesis of (*S*)-nicotine,[11,12] the protocol described herein allowed for a rapid formal synthesis of this natural product starting from 3-iodopyridine and Ts-protected but-3-yn-1-amine **1r**, as shown in Scheme 4.

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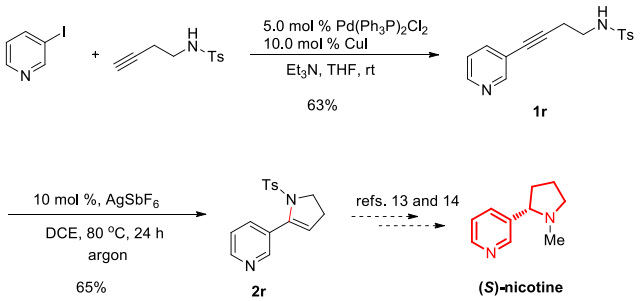

Scheme 4. Formal Synthesis of (*S*)-Nicotine.

In summary, we have developed an efficient, simple protocol for the synthesis of a range of functionalized of 2,3-dihydro-1*H*-pyrroles, including an intermediate in the reported synthesis of (*S*)-nicotine.

Experimental Section

A homopropargyl sulfonamide **1** (1 equiv), $AgSbF_6$ (10 mol %), and DCE (5.0 mL) were added sequentially to a Schlenk tube. The reaction mixture was stirred at 80 °C under argon. When TLC indicated complete consumption of the starting material, DCM and H_2O were added to the reaction mixture. After separation of the organic layer, the water layer was extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and filtered, the filtrate was evaporated, and the residue was purified via column chromatography on silica gel with petroleum ether/ethyl acetate as the eluent to afford the desired product.

Acknowledgments

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COMMUNICATION

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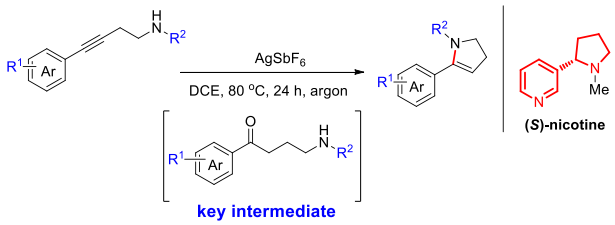

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