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Silver-catalysed hydroamination: synthesis of functionalised pyrroles

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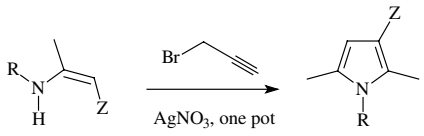
Abstract—It has been shown that functionalised pyrroles can be efficiently prepared using a two-step sequence. This sequence involves the propargylation of secondary enaminones using *n*-BuLi and propargyl bromide, followed by intramolecular hydroamination catalysed by silver nitrate. The hydroamination can be carried out at room temperature (overnight) or in a domestic microwave oven (60 s).

Hydroamination of unactivated carbon–carbon multiple bonds is an active area of research in catalysis and organic synthesis and, as a result, has been reviewed extensively in the literature in recent times.[1] The vast majority of work is concerned with the preparation of highly efficient transition metal catalysts that are used to convert simple amines to imines, enamines and alkylated amines. These compounds constitute important bulk and fine chemicals.[1] Hydroamination has also been used as a key step in several total syntheses although to a lesser extent.[2]

Hydroamination can be accomplished by amine or carbon–carbon multiple bond activation. Both strategies employ metals to affect the activation.[1] The most commonly used metals for this purpose are lanthanides, actinides and those belonging to groups 4 and 10.[1] Silver, and other group 11 metals, have received far less attention and only a handful of methods have been published using silver as a hydroamination catalyst.[3]

We have recently reported a novel one-pot synthesis of functionalised pyrroles **2** via the silver-mediated reaction of secondary vinylogous amides or carbamates **1** with propargyl bromide (Scheme 1).[4] This reaction, although facile, does not generate high enough yields (~25%) to be synthetically useful. In addition, insufficient understanding of the mechanism in operation has led to little success in optimising these yields.



1 **2**

Z = COMe, CO_2Et
R = Me, Bu, Cy, Bn, Ph

Scheme 1.

After further investigation, the following mechanism is proposed for this transformation (Scheme 2). Co-ordination between the silver ion and the carbon–carbon triple bond of propargyl bromide facilitates hydroamination and gives rise to enamine **4**. Enamine **4**, a tertiary enaminone, undergoes cyclisation in typical fashion[5] to give cyclic enamine **5**. Rearrangement of cyclic enamine **5** affords the thermodynamically more stable pyrrole **2**. Based on this proposed mechanism, it is suspected that the reason for the low yields observed for this reaction is that there are many potential reaction pathways subsequent to the initial hydroamination.

It was believed that performing a *C*-propargylation of vinylogous amides and carbamates **1**, followed by silver-mediated hydroamination, would provide an improvement in overall yields (Scheme 3).

Keywords: Amination; Pyrroles; Silver and compounds; Microwave heating.
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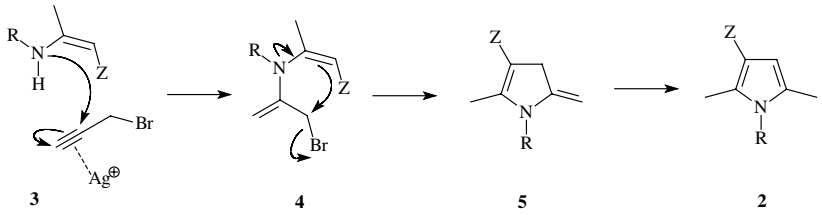
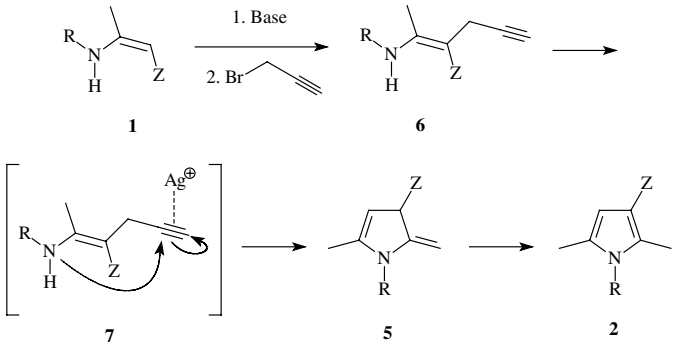


Scheme 2.



Scheme 3.

This new strategy has been investigated and has given some interesting results. It is possible to *C*-propargylate vinylogous amides (**1**, Z = COMe) using propargyl bromide and either sodium hydride or *n*-butyllithium as base. As expected, the Z-configuration of the vinylogous amide starting materials is preserved during this reaction. This is evident from the downfield shifts of the N–H protons in the ^{1}H NMR spectra of these compounds, suggesting hydrogen bonding, and has been confirmed by NOE experiments. The propargyl compounds **6** are stable enough to be purified by column chromatography but must be used shortly thereafter. Yields for this conversion are modest (Table 1) but it is anticipated that improvements can be made in future as a large portion of starting material is recovered. It is possible that this is due to abstraction of the relatively acidic terminal acetylenic proton (p$K_a \sim 25$) of propargyl bromide by the initially formed vinylogous amide anion. Vinylogous carbamates (**1**, Z = CO_2Et), on the other hand, do not undergo *C*-propargylation in the same manner. A variety of bases (NaH, *n*-BuLi, LDA, LHMDS) and solvents (THF, diethyl ether) have been employed with little success.

Table 1. Synthesis of pyrroles **2** from vinylogous amides **1** via hydroamination

Entry	R	Yield **1** (%)[6]	Base	Yield **6** (%)	Yield **2** (%)
a	Me	80	*n*-BuLi	55	93
b	Me	80	NaH	46	93
c	*n*-Bu	76	*n*-BuLi	51	95
d	Cy	88	*n*-BuLi	52	87
e	*t*-Bu	6	—	—	—
f	Ph	94	*n*-BuLi	21	75
g	Bn	95	*n*-BuLi	—	43[a]

[a] **2g** was obtained directly from **1g**.

Propargyl compounds **6** (Z = COMe) are, indeed, converted to pyrroles **2** by a catalytic amount (0.2 equiv) of silver nitrate in acetonitrile. The mechanism in operation is assumed to involve activation of the triple bond by the silver ion **7**, affecting hydroamination and affording cyclic intermediate **5**. This initial step is followed by rearrangement to afford pyrrole **2**. This mechanism is consistent with the generally accepted mechanism of nucleophilic addition to metal-activated carbon–carbon multiple bonds.[7] It should be noted that this procedure is analogous to the gold-catalysed preparation of similar pyrroles reported by Arcadi et al.[8]

An interesting observation is the direct conversion of **1g** to **2g** without isolation of the intermediate propargyl compound **6g**. This is presumed to be the result of hydroamination catalysed by the small excess of *n*-butyllithium (activation of the amine).[9] The reason for this to be restricted to the benzyl group is not clear. The remainder of the results reveal that slightly better yields of **6** are achieved using *n*-butyllithium instead of sodium hydride. Yields of **6** and **2** are unaffected by the steric bulk of the alkyl groups attached to nitrogen, however, yields are markedly lower for the aromatic analogue. This observation is unsurprising.

A further investigation was carried out to determine the effects of microwave irradiation on the hydroamination reaction (Table 2). The reaction mixtures were subjected to microwave irradiation in a sealed tube using a domestic microwave oven (700 W). Yields are typically of the same order as those obtained at room temperature, however, reaction times are dramatically reduced from 16–20 h to 1 min.

In conclusion, we have developed a mild, efficient means of preparing functionalised pyrroles, from readily avail-

Table 2. Microwave enhanced hydroamination

Entry	R	Yield **2** (%)
a	Me	93
c	*n*-Bu	91
d	Cy	96
f	Ph	78

able starting materials, using an inexpensive catalyst system. The practical value of this method is increased by the fact that the reaction time can be significantly reduced using microwave irradiation. We are currently investigating the potential of employing this procedure to prepare *N*-bridgehead pyrroles and applying this methodology to the total synthesis of pyrrolizidine and indolizidine alkaloids.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.07.019.

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