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A mild and efficient $AgSbF_6$-catalyzed synthesis of fully substituted pyrroles through a sequential propargylation/amination/cycloisomerization reaction

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ABSTRACT

Development of an efficient synthesis of fully substituted pyrroles via a sequential propargylation/amination/cycloisomerization was accomplished using $AgSbF_6$ as a catalyst. The one-pot three-component reaction of propargylic alcohols, 1,3-dicarbonyl compounds, and primary amines proceeds at a mild temperature, which prevents the formation of furan by-product. The reaction was also successfully applied to the more basic aliphatic amines with the addition of 1.1 equiv of acetic acid.

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1. Introduction

There is a great interest in developing efficient synthetic routes to structurally diverse heterocycles from readily available simple starting materials, especially in pharmaceutical chemistry where heterocycles are predominant building blocks.[1] Pyrrole, one of the major heterocycles, is embedded in many biologically active compounds of both natural and synthetic origin, and is also present in many organic materials.[2,3] Compounds with pyrrole ring as a key structural motif display an impressive range of biological properties,[3] such as antibacterial,[4] antifungal,[5] anti-inflammatory,[6] antitubulin,[7] anticonvulsant,[8] and hypnotic[9] activities. Consequently, considerable efforts have been made in developing methods for construction of the pyrrole ring.[10] The most efficient and versatile strategy for the assembly of pyrroles is via multicomponent reactions in which three or more starting materials undergo a series of chemical reactions in a single-pot without separation and purification of intermediates.[3,10a,h,11] One prominent example of this strategy is the synthesis of fully substituted pyrroles **4** through a sequential propargylation/amination/cycloisomerization reaction of propargylic alcohols **1**, 1,3-dicarbonyl compounds **2**, and primary amines **3** (Scheme 1).[12–14] Three methods have been reported for this type of one-pot process, including a cooperative [$Ru(\eta^3$-2-$C_3H_4Me)(CO)(dppf)][SbF_6]$/trifluoroacetic acid (TFA) catalytic system,[12] a single metal catalyst $InCl_3$,[13] and more recently, a hetero-bimetallic catalyst $[Ir(COD)(SnCl_3)Cl(\mu\text{-}Cl)]_2$ (Ir^{III}–Sn^{IV}).[14] A noticeable limitation of the first method is the high cost of catalyst and the propargylic alcohols used in the method appear to be limited to the ones with a terminal alkyne group (R^2=H, Scheme 1). The Ir^{III}–Sn^{IV} method only works on aromatic primary amines.[14] The $InCl_3$ method appears to be the most attractive because of the low cost of catalyst and the wide substrate compatibility, but a relatively high temperature (reflux in toluene) is required.[13] Therefore, it is still desirable to further develop mild, highly efficient, and inexpensive reaction systems for this one-pot transformation.

A number of Brønsted and Lewis acid catalysts have been reported for the nucleophilic substitution of propargylic alcohols **1** with 1,3-dicarbonyl compounds **2** to form compounds **5** (Scheme 1).[15] Some of these catalysts have been shown to facilitate the subsequent amination/cycloisomerization for the conversion of **5** to pyrroles **4**, although in poor yields.[13] In relation to our recent efforts on the synthetic application of propargylic alcohols,[16] we expanded the list of catalytic systems for the conversion of 1,3-diphenyl propargylic alcohol **1a** and ethyl acetoacetate **2a** to compound **5a** (Table 1). Further exploration of these catalysts on the subsequent amination/cycloisomerization with aniline **3a** led to the discovery of a novel $AgSbF_6$-catalyzed, efficient and mild one-pot synthesis of fully substituted pyrroles that we report herein.

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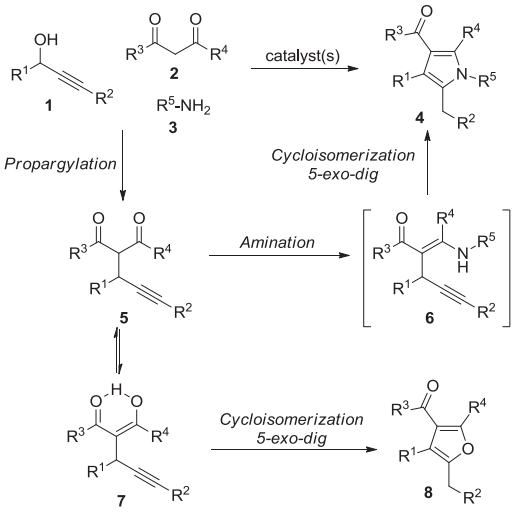
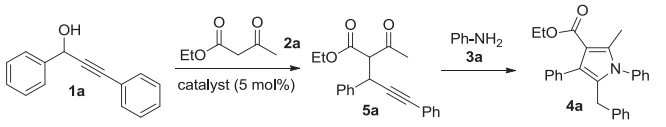


Scheme 1. One-pot synthesis of fully substituted pyrroles and the competing furan formation.

Table 1
Screening of reaction conditions for the formation of fully substituted pyrroles



Entry[a]	Catalyst	Solvent	Temp[b] (°C)	Time[c] (h)	Temp[d] (°C)	Time[e] (h)	Yield[f] (%)
1	Amberlite IR-120H[g]	CH_3CN	Reflux	2	Reflux	12	0
2	$Zn(OTf)_2$	Toluene	60	1	Reflux	12	37
3	$Sc(OTf)_3$	Toluene	60	1	Reflux	14	0
4	$Yb(OTf)_3$	BMIM-PF_6	60	0.5	100	10	0
5	$Bi(NO3)_3$	Toluene	60	2	Reflux	12	35
6	$Bi(OTf)_3$	Toluene	60	2	Reflux	14	54
7	$AgPF_6$	Toluene	60	2	Reflux	14	25
8	$AgBF_4$	Toluene	60	3	Reflux	14	18
9	*$AgSbF_6$*	*Toluene*	*60*	*0.5*	*60*	*6*	*82*
10	$AgSbF_6$	CH_3CN	rt	1	Reflux	12	0
11	$AgSbF_6$	1,2-DCE	60	0.5	Reflux	12	76
12	$AgSbF_6$	CH_3NO_2	rt	1	60	12	31

[a] Reaction conditions: **1a**/**2a**/catalyst=0.5:0.55:0.025 in 2 mL solvent; **3a** (0.55 mmol) added after **1a** fully consumed; reaction temperature and time as indicated.
[b] Reaction temperature for **5a** formation.
[c] Reaction time for **5a** formation.
[d] Reaction temperature for amination/cycloisomerization.
[e] Reaction time for amination/cycloisomerization.
[f] Isolated yields of **4a**.
[g] Catalyst (150 mg) was used.

2. Results and discussion

We selected **1a**, **2a**, and aniline **3a** as the model starting materials to survey catalysts and reaction conditions for the one-pot propargylation/amination/cycloisomerization reaction. In addition to Amberlite IR-120H in acetonitrile (CH_3CN) (Table 1, entry 1),[16] we found a number of catalytic systems, including $Zn(OTf)_2$ in toluene, $Sc(OTf)_3$ in toluene, $Yb(OTf)_3$ in BMIM-PF_6, $Bi(NO_3)_3$ in toluene, $Bi(OTf)_3$ in toluene, $AgPF_6$ in toluene, $AgBF_4$ in toluene, and $AgSbF_6$ in toluene, were also capable of facilitating the nucleophilic substitution of **1a** with **2a** to form intermediate **5a** under mild heating (60 °C) (Table 1, entries 2–9). Upon completion of the conversion from **1a** to **5a** (0.5–3 h, monitored by TLC and GC–MS), aniline **3a** was added to the reaction mixture to carry out the subsequent amination/cycloisomerization reaction. We were delighted to find that the fully substituted pyrrole **4a** was formed in the presence of $Zn(OTf)_2$, $Yb(OTf)_3$, $Bi(NO_3)_3$, $Bi(OTf)_3$, $AgPF_6$, $AgBF_4$, and $AgSbF_6$ (Table 1, entries 2, 5–9), among which $AgSbF_6$ gave the best results with 82% isolated yield (Table 1, entry 9). With $AgSbF_6$, the amination/cycloisomerization reaction proceeded smoothly at 60 °C, no by-products were observed from TLC and GC–MS analysis. The reaction took place without exclusion of air or moisture from the reaction mixture. However, when other catalysts were used, reflux temperature of toluene (110 °C) was required for the conversion of **5a** to **4a**. Due to the high temperature used in these reactions, a significant amount of **5a** was converted into furan **8a** (Scheme 1, where R^1=R^2=Ph, R^3=OEt, R^4=Me), which was partially co-eluted with **4a** on a silica gel column, leading to low yields of **4a** and tedious purification process. The side reaction was somewhat predictable since several Lewis acids, including $InCl_3$,[15e] $FeCl_3$,[17] and $Cu(OTf)_2$,[15g] have previously been shown to efficiently catalyze furan formation at high temperature (from 1 and 2 to 8 via 5, Scheme 1). Although not explicitly discussed, we suspect that the furan formation could have occurred in the previously reported $InCl_3$-catalyzed pyrrole formation reaction due to the high temperature.[13,18] Interestingly, we observed that in the absence of catalysts, intermediate **5a** could also be converted into the corresponding furan in toluene under reflux, albeit in low rate.[19] Thus, reaction temperature played a key role in the formation of furan by-product. The superior results obtained under $AgSbF_6$ are likely due to its ability of facilitating the amination/cycloisomerization reaction at a temperature not high enough for the furan formation.

The reaction also tested in CH_3CN, 1,2-dichloroethane (1,2-DCE), and nitromethane (CH_3NO_3) (Table 1, entries 10–12). The results indicated that the propargylation reaction could tolerate different solvents; **5a** was rapidly formed at 60 °C when 1,2-DCE was used as solvent or at room temperature when CH_3CN or CH_3NO_3 was used as solvent. However, the amination/cycloisomerization reaction was remarkably sensitive to solvents. Toluene was found to be the most effective for the conversion of **5a** to **4a**. Compared to toluene, a longer reaction time was required with 1,2-DCE as solvent (Table 1, entry 11), while CH_3CN did not promote the formation of **4a** and the yield of **4a** was poor when CH_3NO_3 was used as solvent.

The mechanism for the present $AgSbF_6$-catalyzed one-pot pyrrole formation is likely to be similar to previously proposed $InCl_3$-catalyzed reaction.[13]

The scope and limitations of this novel $AgSbF_6$-catalyzed one-pot pyrrole synthesis was then explored under the standard conditions (Table 1, entry 9). We initially applied the reaction procedure to **1a** and **2a** with a series of substituted anilines (Table 2, entries 2–6). The reactions proceeded smoothly, yielding the corresponding pyrroles in good isolated yields. It is interesting to note that every reaction gave a single product peak on GC–MS and practically identical isolated yields were obtained with different anilines, although electron-donating group (entry 5, methoxy) substituted aniline appeared to react slightly faster when compared to electron-withdrawing group (entries 2–4, and 6, halogens and methyl ester) substituted anilines.

The scope of the application was then extended to various benzylic phenyl ring-substituted 1,3-diphenyl propargylic alcohols (Table 2, entries 7–13). Both electron-donating group (entries 8 and 13) substituted and electron-withdrawing group (entries 7, 9–11, halogens) substituted 1,3-diphenyl propargylic alcohols participated well in the reaction. However, no propargylation of **2a** with 4-cyano substituted 1,3-diphenyl propargylic alcohol **1f** was observed in toluene even at reflux temperature. This can be explained by the destabilization effect of the strong electron-withdrawing cyano group on the putative carbocation intermediate from propargylic alcohol. It appeared the destabilization effect could be compensated by an increase in solvent polarity; when toluene was

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