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Silver-Promoted Benzannulations of Siloxyalkynes with Pyridinium and Isoquinolinium Salts

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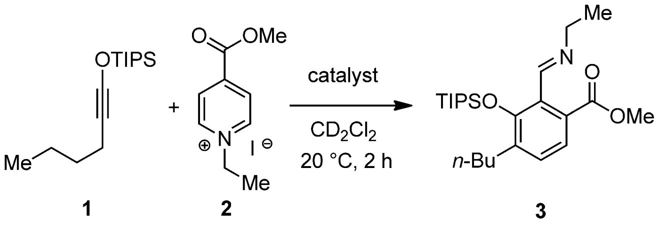
Abstract: We describe the development of efficient benzannulations of siloxyalkynes with pyridinium and isoquinolinium salts. Such reactions are successfully promoted by a stoichiometric amount of silver(I) benzolate under mild reaction conditions. This process proceeds *via* a formal inverse-electron demand Diels–Alder reaction, followed by fragmentation of the initially produced bicyclic adducts to deliver a range of synthetically useful phenols and naphthols.

Keywords: alkynes; benzannulation; cycloaddition; silver

Benzannulation is a highly modular way of assembling aromatic compounds starting from two or more components.[1] Structural variation of the reaction partners enables rapid diversification of the resulting aromatic products. Alkynes have been employed successfully to develop a number of synthetically useful benzannulations.[2] Indeed, our recent study demonstrated that siloxyalkynes underwent benzannulations with pyrones and isoquinoline *N*-oxides in the presence of a catalytic amount of Au(I) phosphine complex.[3] However, pyridine *N*-oxides were found to be unreactive under such conditions. We now describe a solution to this limitation and demonstrate that reactions between *N*-alkylpyridinium iodides and siloxyalkynes efficiently proceed in the presence of stoichiometric amounts of Ag(I) salts to afford a range of substituted phenols. The process occurs presumably *via* a formal inverse-electron demand Diels–Alder reaction, followed by fragmentation of the initially produced cycloadducts. The newly developed benzannulation has a broad substrate scope and also works with a variety of *N*-alkylisoquinolinium iodides.

We initially examined a reaction between 1-siloxy-1-hexyne (**1**) and 1-ethyl-4-(methoxycarbonyl)pyridinium iodide (**2**). No significant reaction between **1** and **2** occurred either in the absence of additives or in the presence of catalytic amounts of several Ag(I) and Au(I) complexes (Table 1, entries 1–3). However, treatment of a solution of **1** and **2** with stoichiometric amounts of several silver salts, which gave suspensions in the employed solvent, was found to promote formation of imine **3**. While $AgCO_2CH_3$ and $AgCO_2CF_3$ were only moderately effective (Table 1, entries 4 and 5), the use of $AgCO_2Ph$ resulted essentially in quantitative conversion to **3** within 2 h at 20 °C (Table 1,

Table 1. Initial reaction optimization.



Entry	Catalyst	Catalyst loading	Conversion [%][b]
1	$LAu(MeCN)SbF_6$[a]	5 mol%	9.1
2	$AuCl_3$	5 mol%	11.5
3	$AgNTf_2$	5 mol%	8.2
4	$AgCO_2CH_3$	100 mol%	55
5	$AgCO_2CF_3$	100 mol%	50
6	$AgCO_2Ph$	100 mol%	99
7	Ag_2CO_3	100 mol%	48
8	Ag_2SO_4	100 mol%	60
9	AgF	100 mol%	<5
10	$AgNO_2$	100 mol%	<5
11	$AgCO_2Ph$	10 mol%	10

[a] L = Johnphos.

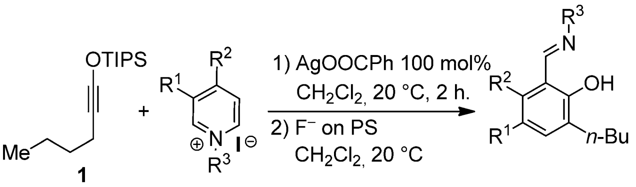
[b] Conversion was measured by 500 MHz ^1H NMR analysis of the crude reaction mixtures.

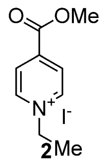
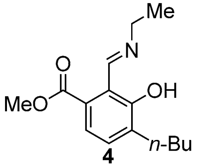
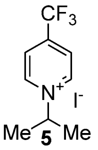
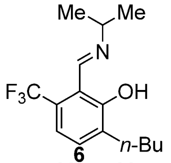
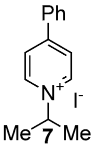
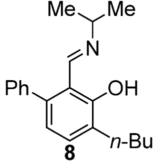
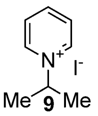
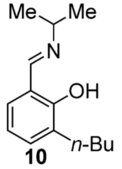
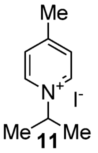
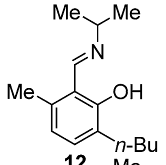
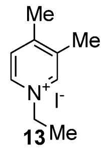
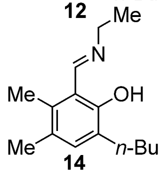
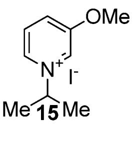
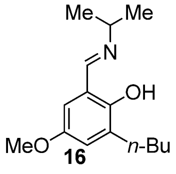
entry 6). Changing the nature of the Ag(I) salt counterion seemed to have substantial effect on the efficiency of this reaction. For example, the use of Ag_2CO_3 and Ag_2SO_4 resulted only in moderate conversion levels (Table 1, entries 7 and 8). In addition, AgF and $AgNO_2$ were unsuccessful in promoting this reaction (Table 1, entries 9 and 10). Substoichiometric amounts of $AgCO_2Ph$ did not catalyze this reaction effectively, showing that a full equivalent of such a promoter is required (Table 1, entry 11). The use of other Brønsted bases including K_2CO_3, Cs_2CO_3, $NaCO_2CH_3$ and *t*-BuOK proved to be inefficient in catalyzing this transformation.

Having identified $AgCO_2Ph$ as the best promoter for this reaction, we then studied the effect of the counterion and the *N*-alkyl group of the pyridinium salt on the reaction efficiency. Various counterions were investigated including Cl^-, Br^-, I^-, BF_4^- and PF_6^-. Halogen counterions proved to be the most effective, with I^- leading to the highest conversion levels. On the contrary, use of BF_4^- and PF_6^- counterions was much less effective leading to complex mixtures of products or no reactivity. Also, examination of *N*-*n*-butyl-, *N*-ethyl-, and *N*-isopropylpyridinium salts revealed that *N*-ethyl- and *N*-isopropylpyridinium salts were equally reactive towards siloxyalkynes.

Having identified an optimum set of conditions for benzannulation of siloxyalkyne **1** with *N*-ethylpyridinium iodide **2**, we next investigated the scope of this transformation in respect to the pyridinium salt. This study is summarized in Table 2. Pyridinium salts bearing electron-deficient substituents such as **2** ($R^2 = CO_2CH_3$) and **5** ($R^2 = CF_3$) successfully reacted with siloxyhexyne **1**. Subsequent desilylation using a polymer-supported fluoride source gave the corresponding phenols **4** and **6** in 70 and 85% yields, respectively (Table 2, entries 1 and 2). Since the presence of electron-withdrawing groups may activate the pyridium moiety towards the initial cycloaddition with siloxyalkyne, we examined a range of other pyridinium salts that would not have such an activating substituent. Subjection of aryl-containing pyridinium salt **7** to the standard reaction conditions delivered the corresponding phenol **8** in 85% yield (Table 2, entry 3). Furthermore, fully unsubstituted pyridinium iodide **9** successfully reacted with alkyne **1** to give phenol **10** (Table 2, entry 4). Substitution of the pyridinium ring with either one or two methyl groups was also well tolerated (Table 2, entries 5 and 6). As expected, further increase in the electron-donating ability of pyridinium substituents rendered such substrates substantially less reactive. Indeed, introduction of a methoxy group at the 4-position of the pyridinium ring resulted in no reaction. However, 3-substituted pyridinium salt **15** delivered the corresponding benzannulation product **16** (Table 2, entry 7).

Table 2. Ag-promoted benzannulations of siloxyalkynes with *N*-alkylpyridinium iodides.

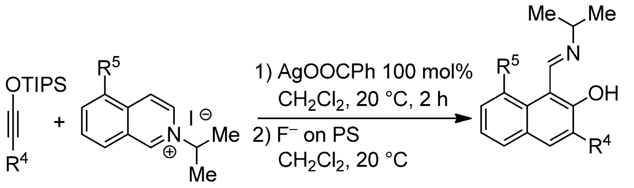


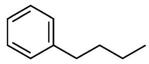
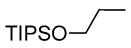
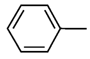
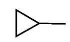
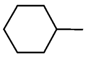
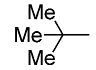
Entry	Pyridinium salt	Product	Yield [%][a]
1	 **2**	 **4**	70
2	 **5**	 **6**	85
3	 **7**	 **8**	85
4	 **9**	 **10**	70
5	 **11**	 **12**	66
6	 **13**	 **14**	55
7	 **15**	 **16**	61

[a] Isolated yields after standard chromatographic purification.

We also examined the propensity of quinolinium and isoquinolinium salts to participate in the same transformation. While the use of several quinolinium salts resulted in the formation of complex mixtures of products, isoquinolinium iodides proved to be highly

Table 3. Ag-promoted benzannulations of siloxyalkynes with *N*-alkylisoquinolinium iodides.

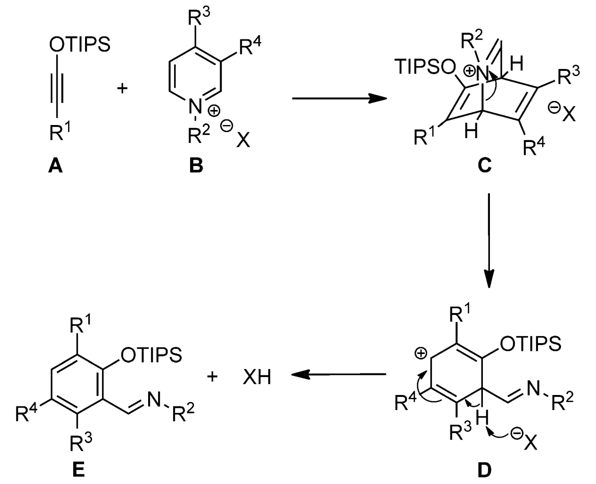


Entry	R^4	R^5	Product	Yield [%][a]
1	*n*-Bu	NO_2 **(17)**	**18**	70
2	*n*-Bu	H **(19)**	**20**	88
3	*n*-Bu	Br **(21)**	**22**	90
4	*n*-Bu	OBn **(23)**	**24**	80
5		Br	**25**	96
6		Br	**26**	96
7		Br	**27**	90
8		Br	**28**	93
9		Br	**29**	98
10		Br	**30**	93

[a] Isolated yields after standard chromatographic purification.

effective substrates (Table 3). Electron-deficient isoquinolinium salt **17** ($R^5 = NO_2$) afforded the expected naphthol **18** in 70% yield (Table 3, entry 1). Subjection of the unsubstituted isoquinolinium salt **19** (R^5 = H) to the general benzannulation protocol furnished the desired product **20** in 88% yield. Furthermore, the use of halogenated isoquinolinium salt **21** (R^5 = Br) successfully gave the corresponding naphthol **22** (Table 3, entry 3). Electron-donating groups were also well tolerated. Reaction of siloxyalkyne **1** with isoquinolinium salt **23** (R^5 = OBn) successfully furnished the expected product in 80% yield (Table 3, entry 4). This study also demonstrated that a broad substitution pattern of siloxyalkynes can be well tolerated (Table 3, entries 5–10). It is also interesting to note that ynamines are known to react with quinolinium and isoquinolinium salts to produce structurally different products under thermal conditions,[4] which points to a unique role of silver(I) salt in promoting the formation of the observed aromatic products.

Formation of benzannulation products can be rationalized using a mechanistic hypothesis depicted in Scheme 1. [4+2] Cycloaddition between siloxyalkynes **A** and pyridinium salts **B** leads to the bicyclic intermediate **C** that subsequently undergoes C–N bond cleavage to afford intermediate cation **D**. Subsequent loss of a proton produces the final aromatic product **E**. Currently, the role of Ag(I) salt in promoting this reaction is not entirely clear since this additive can facilitate the reaction by either activating the siloxyalkyne or promoting pyridinium anion exchange. Therefore, the observed regioselectivity of this transformation is difficult to rationalize at the current stage. However, further mechanistic studies are currently in progress.



Scheme 1. Proposed reaction mechanism.

In closing, we have developed a mild, silver-promoted benzannulation of siloxyalkynes with *N*-alkylpyridinium iodides. Investigation of the substrate scope revealed that this transformation tolerated a broad range of pyridinium salts and siloxyalkynes. Furthermore, high levels of efficiency were also observed for a variety of *N*-alkylisoquinolinium. This new benzannulation reaction enables a rapid access to a range of synthetically useful, highly functionalized phenols and naphthols.

Experimental Section

General Procedure

N-Alkylpyridinium or *N*-alkylisoquinolinium iodide (0.15 mmol) and $AgCO_2Ph$ (0.15 mmol) were suspended in CH_2Cl_2 (1.5 mL). The resulting mixture was treated with siloxyalkyne (0.165 mmol) and stirred at 20 °C for 2 h under a nitrogen atmosphere. The precipitate was removed by filtration and the solvent was evaporated under reduced pressure. The crude reaction mixture was then dissolved in CH_2Cl_2 (1 mL) and treated with fluoride on a polymer support (100 mg). After desilylation was complete, as verified by TLC, the reaction mixture was filtered. Following removal of solvent under reduced pressure, the product was purified by flash chromatography on silica gel using hexane containing 1% Et_3N (for *N*-alkylpyridinium substrates) and 3% Et_3N (for *N*-alkylisoquinolinium substrates) as eluent.

Acknowledgements

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