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Highly efficient synthesis of 2,3,4-trisubstituted furans via silver-catalyzed sequential nucleophilic addition and cyclization reactions of haloalkynes ☆

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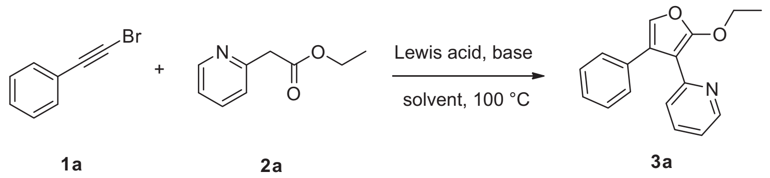
A regioselective synthesis of 2,3,4-trisubstituted furans using $AgNO_3$ catalyst from haloalkynes in a one-pot procedure has been reported. The transformation consists of a sequential silver-catalyzed nucleophilic addition and cyclization reaction of haloalkynes. A wide variety of haloalkynes can be used in this chemical process.

The haloalkynes are a pivotal class of compounds that have been used widely in organic synthesis.[1] Haloalkynes are generally regarded as a dual functionalized molecule in reactions, which may go through a metal–halogen exchange or be used as an electrophilic alkyne.[2] Due to these interesting characteristics of haloalkynes, many reactions of haloalkynes have been developed during

Table 1
Optimization of the reaction conditions[a]



Entry	Lewis acid	Base	Solvent	Yield[b] (%)
1	Ag_2O	Li_2CO_3	DMSO	45
2	$AgSbF_6$	Li_2CO_3	DMSO	50
3	CuI	Li_2CO_3	DMSO	30
4	$ZnCl_2$	Li_2CO_3	DMSO	21
5	$AgNO_3$	Li_2CO_3	DMSO	60

(*continued on next page*)

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Table 1 (*continued*)

Entry	Lewis acid	Base	Solvent	Yield[b] (%)
6	$In(OTf)_2$	Li_2CO_3	DMSO	41
7	**$AgNO_3$**	**DABCO**	**DMSO**	**88**
8	$AgNO_3$	Cs_2CO_3	DMSO	54
9	$AgNO_3$	DBU	DMSO	70
10	$AgNO_3$	*t*-BuOK	DMSO	50
11	$AgNO_3$	DABCO	DMF	71
12	$AgNO_3$	DABCO	1,4-Dioxane	21
13	$AgNO_3$	DABCO	Toluene	15
14	$AgNO_3$	DABCO	NMP	51
15[c]	$AgNO_3$	DABCO	DMSO	41
16[d]	$AgNO_3$	DABCO	DMSO	70

[a] Reactions were carried out using phenylethynyl bromide (1.0 mmol), ethyl 2-pyridylacetate (0.6 mmol), Lewis acid (0.2 equiv), base (1.0 equiv), 12 h.

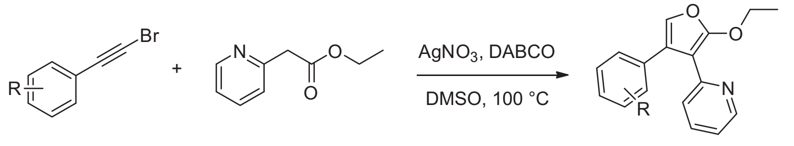
[b] Determined by GC.

[c] Reaction at 60 °C.

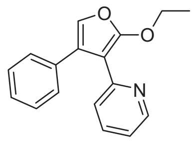
[d] Reaction at 120 °C.

Table 2

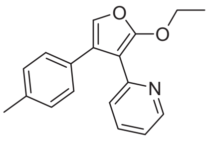
Substrate scope of 2,3,4-trisubstituted furans[a,b]



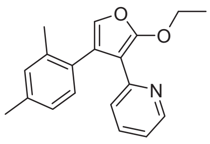
1 **2a** **3**



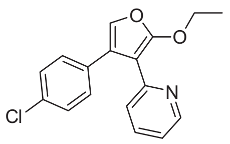
3a, 88%



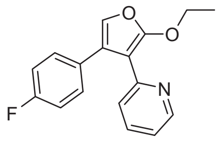
3b, 85%



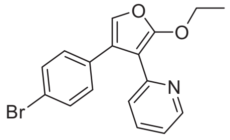
3c, 84%



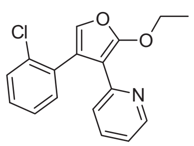
3d, 75%



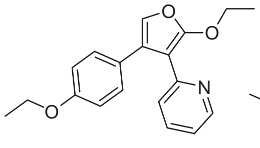
3e, 78%



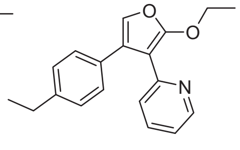
3f, 80%



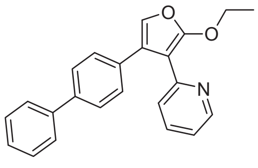
3g, 75%



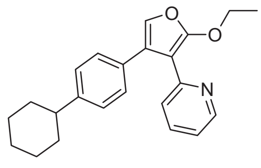
3h, 76%



3i, 85%



3j, 70%



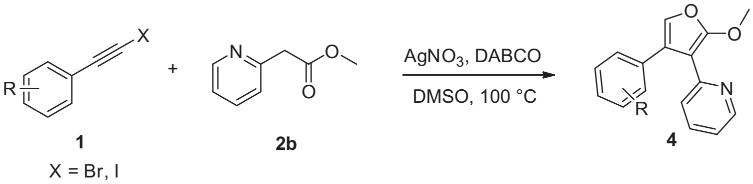
3k, 73%

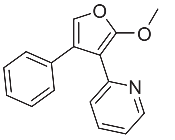
[a] Reactions were carried out using haloalkynes (1.0 mmol), ethyl 2-pyridylacetate (0.6 mmol), $AgNO_3$ (0.2 equiv), DABCO (1.0 equiv), 100 °C, 12 h.

[b] Isolated yields.

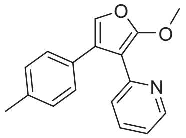
recent years, such as cycloaddition reactions,[3] carbon–hydrogen functionalization reactions,[4] and nucleophilic addition reactions.[5] The vinyl halides generated by nucleophilic addition of haloalkynes are very important intermediates that can undergo numerous chemical transformations[6] and also a very useful precursor to the synthesis of heterocycles.[7] Thus, the development of new reaction systems to achieve efficient and selective nucleophilic addition for heterocycle construction is still highly desirable.

Table 3
Substrate scope of 2,3,4-trisubstituted furans[a,b]

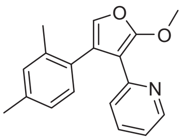




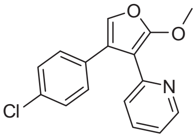
4a, X=Br 88%
X=I 70%



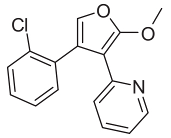
4b, X=Br 86%
X=I 65%



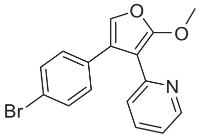
4c, X=Br 80%
X=I 64%



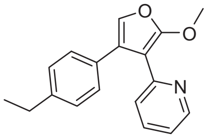
4d, X=Br 78%
X=I 61%



4e, X=Br 77%
X=I 62%



4f, X=Br 73%
X=I 55%



4g, X=Br 79%
X=I 60%

[a] Reactions were carried out using haloalkynes (1.0 mmol), methyl 2-pyridylacetate (0.6 mmol), AgNO$_3$ (0.2 equiv), DABCO (1.0 equiv), 100 °C, 12 h.

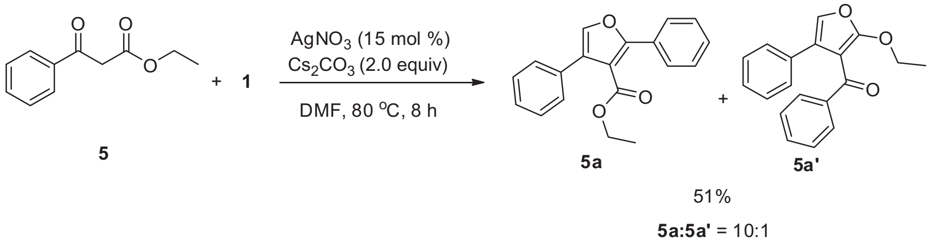
[b] Isolated yields.

Substituted furans are ubiquitous in biologically active molecules[8] and have also been used as building blocks for both heterocyclic and acyclic compounds.[9] Consequently, the synthesis of furans has attracted extensive interest.[10] In particular, transition metal-catalyzed nucleophilic addition of carbon–carbon triple bond has proved to be a versatile method for the construction of substituted heterocycles.[11] In which, the transition metals usually function as a Lewis acid to activate the carbon–carbon multiple bonds via π-binding, thus facilitating the nucleophilic addition process.[12] As our continuing research programs on haloalkyne chemistry and furan synthesis,[5a,5b,13,14] herein, we report an efficient method for the construction of 2,3,4-trisubstituted furans via a sequential Ag-catalyzed nucleophilic addition and cyclization reaction of haloalkynes.

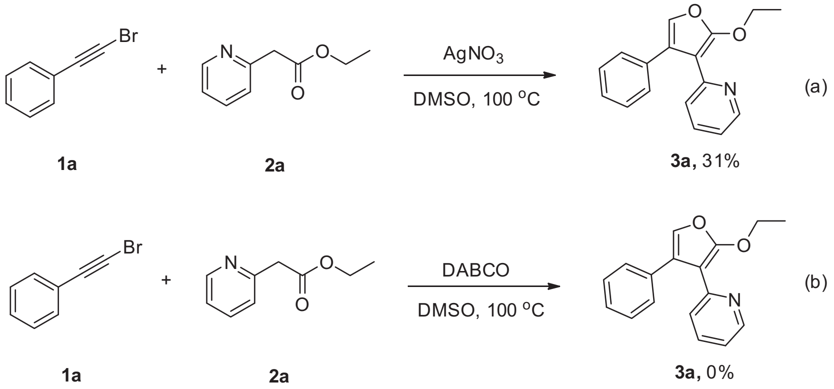
We first studied the reaction of phenylethynyl bromide (**1a**) and ethyl 2-pyridylacetate (**2a**) in DMSO using Ag$_2$O as the Lewis acid and Li$_2$CO$_3$ as the base. To our delight, the desired furan **3a** was obtained in 45% GC yield (Table 1, entry 1). This result prompted us to screen suitable reaction conditions (Table 1). After Lewis acid evaluation, we found that AgNO$_3$ was the best choice and afforded **3a** in 60% GC yield (entry 5), while other Lewis acids just led to moderate or low yields (entries 1–6). Further investigation revealed that the base played a critical role for this transformation (entries 7–10). Cs$_2$CO$_3$ and *t*-BuOK were less effective, and DBU just gave moderate yields, while DABCO was the best choice. The effects of different solvents were also studied (entries 11–14). Compared with the above results, DMSO was found to be the most suitable solvent. The temperature was then examined, and 100 °C was optimal for this reaction (entries 15 and 16).

With the optimized conditions in hand [phenylethynyl bromide (1.5 mmol), ethyl 2-pyridylacetate (1.0 mmol), AgNO$_3$ (0.2 equiv), and DABCO (1.0 equiv), 100 °C, 12 h], we then explored the substrate scope of different arylethynyl bromides (Table 2). Aromatic alkynylbromides with either electron-donating or electron-withdrawing groups on the benzene ring were able to generate the corresponding products in excellent yields. The reaction conditions were compatible with alkyl, alkoxy, and halogen groups on the benzene ring, providing the corresponding products in good yields (**3a**–**3i**). Fortunately, aryl- and cyclohexyl-substituted alkynyl bromides were also suitable substrates for this transformation and gave the desired furans **3j** and **3k** in 70% and 73% yields, respectively.

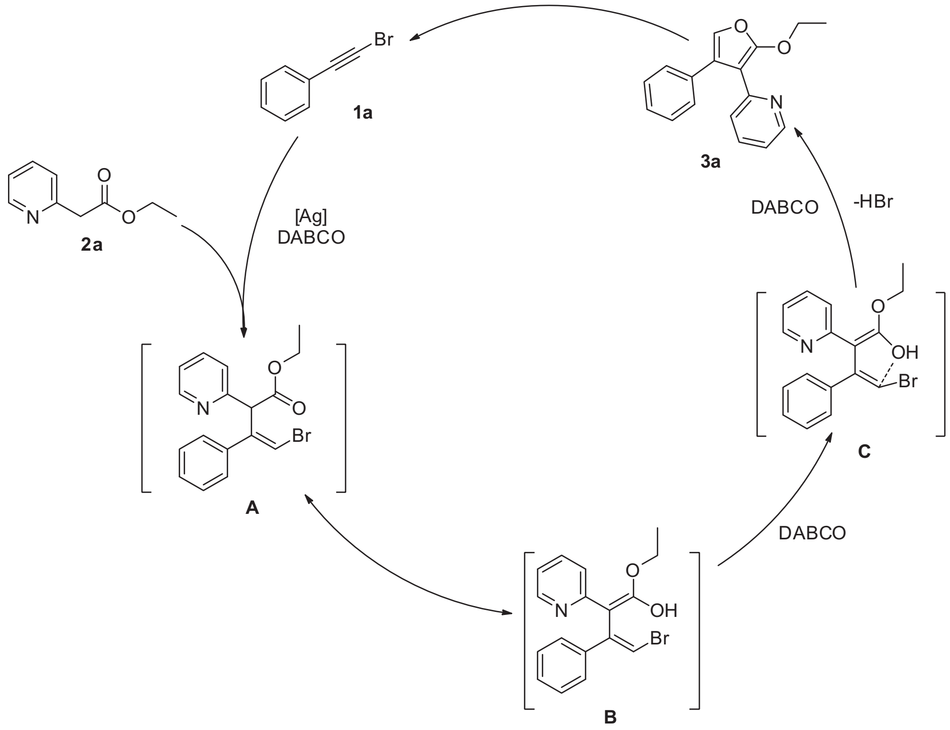
To demonstrate the efficiency and generality of this process, we have examined the transformation with haloalkynes (bromoalkynes and iodoalkynes) and methyl 2-pyridylacetate (**2b**) under the optimized reaction conditions. As shown in Table 3, with **2b** as the starting material, aromatic alkynyl bromides and iodides with either an electron-donating or electron-withdrawing group on the benzene ring were able to transform into the corresponding products in moderate to good yields (55–88%). Generally, the alkynyl bromides gave better results than those of alkynyl iodides, which was due to the reason that the alkynyl iodides were likely to



Scheme 1. Reaction of ethyl benzoylacetate.



Scheme 2. Control experiments.



Scheme 3. Proposed mechanism.

undergo the head-to-head dimerization coupling and generate the 1,4-diphenylbuta-1,3-diyne side products.[15]

We also examined the reaction of ethyl benzoylacetate with phenylethynyl bromide, and the furan products **5a** and **5a**′ could be obtained in 51% isolated yield. The ratio of **5a**:**5a**′ is 10:1 (estimated by the integral of ^{1}H NMR, see Supplementary data for details). We suspected that the side product **5a**′ might be generated through the enol–ketone equilibrium in the ester carbonyl group (Scheme 1).

To further gain a mechanistic insight into the process of this reaction, several competition experiments were conducted. As shown in Scheme 2, the reaction was less effective in the absence of DABCO (Scheme 2a), and no product could be detected without $AgNO_3$ (Scheme 2b).

On the basis of our experimental data and previous reports,[11d], [16] a plausible reaction mechanism for the synthesis of furans is illustrated in Scheme 3. First, the vinyl bromide intermediate **A** was generated via an intermolecular nucleophilic addition of ethyl 2-pyridylacetate to phenylethynyl bromide, promoted by DABCO and $AgNO_3$. Subsequently, **B** would undergo the enol–ketone equilibrium to provide intermediate **C**. Finally, the carbon–oxygen bond formation occurred with the loss of HBr to afford the corresponding product **3a**.

In summary, we have developed a highly efficient approach for the synthesis of 2,3,4-trisubstituted furans via a sequential nucleophilic addition and cyclization reaction of 2-pyridylacetic acid esters and haloalkynes. This method exhibits a good aryl group tolerance and provides the corresponding products in high yields and regioselectivity. Furthermore, the readily available starting materials and mild reaction conditions are some of the additional features of this protocol.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.140.

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