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Sulfur-mediated difunctionalization of internal and terminal alkynes for the synthesis of α-acetoxy ketones

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ABSTRACT

The sulfur-mediated difunctionalization of alkynes is reported to give α-acetoxy ketones in a one-pot operation under mild conditions with 19–92% yield. By using wet potassium acetate as both the aqueous base and nucleophilic reagent, both terminal alkynes and internal alkynes could be converted into the α-acetoxy ketone products.

Introduction

The alkyne motif is an important functional group in organic synthesis and the transformations of carbon-carbon triple bonds have been extensively researched [1]. Traditionally, the conversion of alkynes to α-acetoxy ketones requires several steps: mercury-catalyzed hydration of the carbon-carbon triple bonds, bromination of the resulting ketones, and then nucleophilic substitution of the α-bromo ketones. One-step methods for converting alkynes into α-acetoxy ketones are still rare in the literature [2]. In 2009, Hou and co-workers utilized $PhI(OAc)_2$ as an oxidant to prepare α-acetoxy ketones from terminal alkynes and acetic acid (Scheme 1a, condition A) [3]. Zhang group and Xiang group reported a similar transformation with gold catalysts and 8-methylquinoline *N*-oxide as the oxidant, respectively (Scheme 1a, condition B) [4]. We have recently reported a general method for the difunctionalization of internal alkynes, however, terminal alkynes failed to undergo the desired reaction pathway (Scheme 1b) [5]. Herein, we report a one-pot method for the oxidative hydration of both terminal alkynes and internal alkynes through a sulfur-mediated reaction using an activated sulfoxide reagent (Scheme 1c).

In recent years, activated sulfoxides [6–8] have been widely applied in reactions beyond the traditional Swern oxidation or Pummerer reactions [9], such as the functionalization of alkyne substrates. For example, the propargylic C—H alkylation and arylation of alkyl substituted alkynes have been reported by Procter's group and our group, respectively [10]. During our recent study on the difunctionalization of internal alkynes to prepare α-substituted ketones [5], we found that terminal alkynes did not give the desired products due to the strong basicity of sodium hydroxide, leading to alkynyl sulfonium salts as the elimination products [10]. It was thus reasoned that if we conducted the reaction under relatively weak basic reaction condition to avoid the elimination pathway, such as using potassium acetate to replace sodium hydroxide, phenyl substituted internal, as well as terminal alkynes could give the desired α-acetoxy ketones.

At the outset, alkyne **1a** was chosen as the model substrate to optimize the reaction conditions. A solution of 1 equivalent of alkyne and 1.2 equivalents of diphenyl sulfoxide was treated with 1.2 equivalents of triflic anhydride. When the wet potassium acetate (5 equivalents, calculated as anhydrous KOAc) was added to the solution and stirred at room temperature, the α-acetoxy ketone product **3a** was afforded in 40% yield (Table 1, entry 1). Upon increasing the reaction temperature to 40 °C, the yield increased to 71% (Entry 2). Other bases such as LiOAc and NaOAc were tested, but the yield was not improved (Entries 3–4). In order to increase the reaction temperature further, solvents with higher boiling points such as MeCN and DCE were used, but the yields decreased to 33% and 65%, respectively (Entries 5–6). When mixtures of MeCN or DCE with CH_2Cl_2 were used in step 2, the product **3a**

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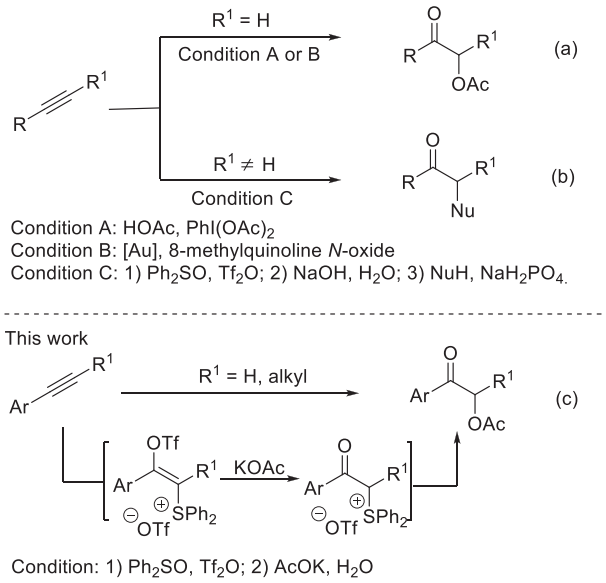
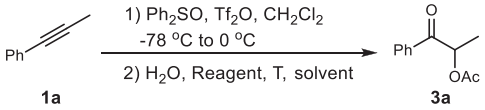


Scheme 1. Synthesis of α-acetoxy ketones from alkynes.

Table 1
Optimization of the reaction conditions.



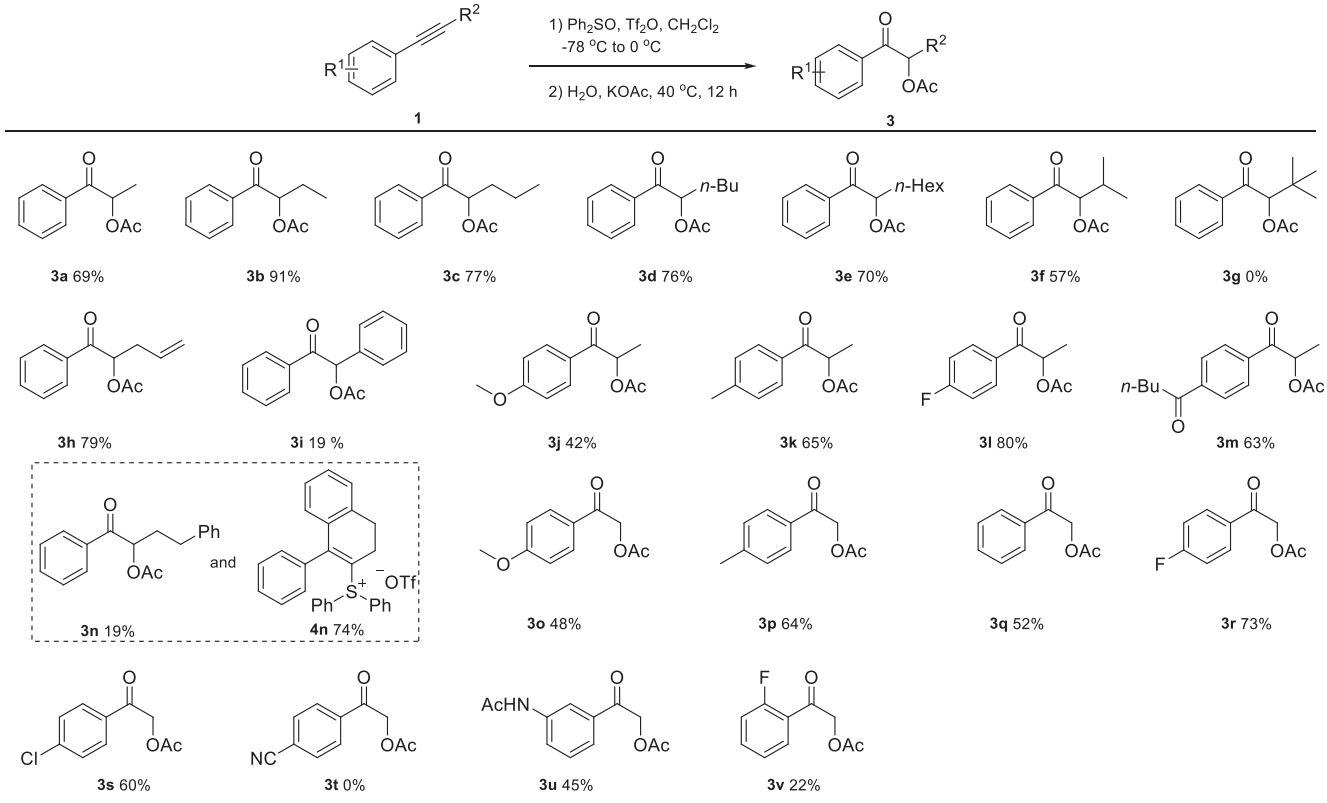
1a 3a

Entry	Solvent	Reagent	T (°C)	Yield 3a (%)[a]
1	CH_2Cl_2	KOAc	r.t	40[b]
2	CH_2Cl_2	KOAc	40	71(69[b])
3	CH_2Cl_2	$LiOAc{\cdot}2H_2O$	40	11
4	CH_2Cl_2	$NaOAc{\cdot}3H_2O$	40	52
5	MeCN	KOAc	82	33
6	DCE	KOAc	84	65
7	CH_2Cl_2/DCE	KOAc	60	55
8	CH_2Cl_2/MeCN	KOAc	60	29
9[c]	CH_2Cl_2	KOAc	40	58
10[d]	CH_2Cl_2	KOAc	40	60
11[e]	CH_2Cl_2	KOAc	40	62[b]
12[f]	CH_2Cl_2	KOAc	40	13[b]

[a] NMR yield.
[b] Isolated yield.
[c] An additional 2.5 equiv·H_2O was added in step 2.
[d] An additional 5 equiv·H_2O was added in step 2.
[e] PhS(O)Me was added instead of Ph_2SO.
[f] DMSO was added instead of Ph_2SO.

was obtained in moderate yields (Entries 7–8). We also tried to add additional water in step 2, but the yield was not improved (Entries 9–10). When DMSO or methyl phenyl sulfoxide were used to replace diphenyl sulfoxide, the yield decreased to 62% or 13%, respectively (Entries 11–12).

With the optimized reaction conditions in hand, we then investigated the scope of the internal alkynes. As shown in Scheme 2, the alkyl phenyl alkynes gave the corresponding products in good to moderate yields (**3a**-**3f**). When alkyne **1g** was used as the substrate, the expected product **3g** was not detected presumably due to steric hindrance of the *tert*-butyl group. Alkyne **1h** gave the product in 79% yield, which indicated that the reactivity of a terminal alkene is worse than a phenyl conjugated alkyne. Diphenyl substituted alkyne **1i** gave the product **3i** in 19% yield. When alkyne **1n** was used as the substrate, the product **3n** was afforded in 19% yield



Scheme 2. Scope of alkynes. Reagents and conditions: 1) **1a** (0.4 mmol), Ph_2SO (0.48 mmol), Tf_2O (0.48 mmol), CH_2Cl_2 (2 mL), −78 °C to 0 °C; 2) wet potassium acetate (196 mg), 40 °C, 12 h. Isolated yield after column chromatography.

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while the electrophilic cyclization product **4n** was afforded in 74% yield [7e]. Electron-donating groups, such as methoxy and methyl on the phenyl ring gave the α-acetoxy ketones **3j** and **3k** in 48% and 64% yield, respectively. Fluoro and acyl substituted phenyl alkynes gave the α-acetoxy ketones **3l** and **3m** in 80% and 63% yield, respectively.

We also examined the reaction scope of some terminal alkynes. Methoxy and methyl substituted terminal alkynes **1o** and **1p** gave the products **3o** and **3p** in 48% and 64% yield, respectively. Halogen substituted alkynes **1r** and **1s** gave the corresponding products in good yields. When the phenyl ring contained the strong electron-withdrawing cyano group, the desired product **3t** was not detected. *meta*-Acetylamino substituted alkyne afforded product **3u** in 45% yield. The yield of *ortho*-fluoro substituted product **3v** decreased to 22% due to the stronger inductive effect.

In summary, we have expanded the reaction scope for the sulfur-mediated difunctionalization of alkynes. By using potassium acetate as the base and nucleophile, both internal and terminal phenyl alkynes could react smoothly to give α-acetoxy ketones. This one-pot/two-step reaction operation is simpler than our previously reported [5] one-pot/three-step protocol.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151707. These data include MOL files and InChiKeys of the most important compounds described in this article.

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