Regio- and Diastereoselective Synthesis of Unsymmetrical 1,4-Diketone-Derived (Z)-Monosilyl Enol Ethers via Siloxyallylpotassium Intermediates

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This paper describes the regio- and diastereoselective synthesis of unsymmetrical 1,4-diketone-derived (Z)-monosilyl enol ethers from 1-aryllallyloxysilanes and Weinreb amides using (trimethylsilyl)methylpotassium as a base. The metatation of 1-aryllallyloxysilanes to generate siloxyallylpotassium is the key step in this transformation. The products can be transformed into diverse α-monofunctionalized unsymmetrical 1,4-diketones.

1,4-Diketones are important structural motifs found in many natural products and bioactive compounds. They are also valuable building blocks for the construction of cyclopentenones and heteroaromatic compounds such as furans, pyroles, and thiophenes. Accordingly, numerous synthetic methods have been developed to access these compounds, including the reaction of enolates with α-haloalkanes,¹ oxidative coupling of enolates,² acylation of homoenoates,³ and conjugate addition of acyl anions to enones.⁴ Despite such progress, the introduction of various functional groups at the α-position of unsymmetrical 1,4-diketones remains challenging because of the poor regioselectivity. In this context, we focused on the preparation of monosilyl enol ethers of unsymmetrical 1,4-diketones because they can participate in diverse regiospecific reactions to provide target molecules (Scheme 1). However, classical silylation of 1,4-diketones using a base and silyl halide is not practical due to the lack of regioselectivity; thus, efficient methods for the regiocontrolled synthesis of 1,4-diketone-derived monosilyl enol ethers are being sought. In 2016, Kartika et al. reported a Brønsted acid-catalyzed cross-coupling of β-siloxyallyl alcohol with silyl enol ethers.⁵ The reaction proceeded through the regioselective attack of a silyl enol ether on a siloxyallyl cation intermediate, generated by the Brønsted acid-catalyzed C–O bond activation of a β-siloxyallylic alcohol. Although this approach enables the synthesis of highly functionalized 1,4-diketone-derived monosilyl enol ethers, there are two limitations: (i) only cyclic siloxyallylic alcohols can be employed in this reaction, and (ii) double bond of the product is located outside the 1,4-diketone unit. We recently reported the (trimethylsilyl)methylpotassium (TMSCH₂K)-mediated synthesis of α,β-difunctionalized ketones⁶a and 3-functionalized silyl enol ethers⁶b from readily available 1-aryllallylic alcohols via dipotassium α,β-dianion intermediates. During the course of this study, we found that TMSCH₂K could effectively deprotonate Cl–H of 1-aryllallyloxysilanes to generate siloxyallyl anions, which were previously inaccessible with classical strong bases.⁷ We anticipated that the reaction of siloxyallylpotassium with Weinreb amides would yield the desired monosilyl enol ethers regioselectively. The products were expected to be versatile synthetic precursors that could undergo diverse regiospecific reactions to afford monofunctionalized unsymmetrical 1,4-diketones, which could be further converted into trisubstituted five-membered heteroaromatic compounds.

Scheme 1. Synthesis of unsymmetrical 1,4-diketone-derived (Z)-monosilyl enol ethers.

To probe the feasibility of our proposed strategy, 1-phenylallyloxysilane 1a was treated with various bases in THF at −78 °C, and the in situ-generated siloxyallyl anion was trapped by Weinreb amide 2a (Table 1). Considering the strong basicity of TMSCH₂K,⁶ as observed in our previous study,⁶ we initially used this base in the model reaction. To our delight, the desired silyl enol ether 3aa was isolated in 82% yield (entry 1). The performances of ‘BuLi and ‘BuLi were also tested using hexamethylphosphoramide (HMPA), which are commonly used for the lithiation of 1-unsaturated allyloxysilanes.⁷,⁹,¹⁰ Using ‘BuLi and HMPA, 3aa was obtained in only 15% yield (entry 2). A longer reaction time (1 h) for the deprotonation step did not improve the yield of 3aa (entry 3). When the deprotonation was carried out at a higher temperature (−40 °C), byproduct 5a was formed instead of 3aa via retro-[1,4]...
Brook rearrangement\textsuperscript{10} (entry 4). No desired product 3aa was observed when the ‘BuLi/HMPA system was used (entry 5). When (trimethylsilyl)methylsodium (TMSCH\textsubscript{3}Na) was used, 3aa was obtained in a moderate yield (entry 6). Thus, it was concluded that potassium carbanions were essential for the smooth metatation of 1a. The effect of silyl group on the reactivity was also evaluated. Complete conversion to 3aa’ (64% yield) was achieved when triethylsilyl (TES) derivative 1a’ was used (entry 7). In contrast, incomplete conversion was observed when trisopropylsilyl (TIPS) derivative 1aa’ was used (entry 8).

The reaction scope with respect to allyloxilanes was explored under the optimized conditions (Scheme 2). Allyloxilanes 1b–1f bearing electron-neutral and electron-rich aryl groups were smoothly transformed into the corresponding silyl enol ethers 3ba–3fa in 71–83% yields. When 1g containing a dimethylamino group was used, a higher temperature (–60 °C) was required for the generation of siloxyallylpotassium. In this case, product 3ga was desilylated during column chromatography, because of which amino-functionalized silica gel was employed for purification. The reaction was amenable to heteroaromatic substrates, with 3ha–3ja obtained in moderate to high yields.\textsuperscript{11} It should be noted that excellent Z/E selectivities (Z/E ≥ 96:4) were observed for all products, as judged by \textsuperscript{1}H NMR analysis of the crude reaction mixture.

The scope of Weinreb amides was then investigated (Scheme 3). A variety of Weinreb amides can be trapped by the silyloxyallylpotassium intermediate to produce the corresponding silyl enol ethers 3 in good to excellent yields. While a \textit{para}-methyl group on the aryl ring was well tolerated (3ab), \textit{ortho}-substitution led to a slight decrease in the yield (3ac). The reaction could tolerate a range of functional groups such as the methoxy, fluoro, chloro, bromo, cyano, and trifluoromethyl groups (3ad–3ai). Electron-rich furanyl amide 2j was also compatible, producing an 83% yield of 3aj. In addition to \textit{aryl}-substituted Weinreb amides, alkyl derivatives are suitable for this transformation. The reactions of methyl and isopropyl derivatives afforded products 3ak and 3al in 58% and 72% yields, respectively, regardless of the presence of acidic α-protons. Bulky tert-butyl Weinreb amide 2m was also compatible with this reaction, demonstrating the broad substrate scope of this protocol. The configuration of 3am was determined to be Z by NOESY analysis,\textsuperscript{12} and all products were assigned by analogy.
The silyl enol ethers obtained in this reaction are versatile synthetic precursors; various carbon- and heteroatom-based electrophiles can be regiospecifically introduced, affording monofunctionalized unsymmetrical 1,4-diketones (Scheme 4). For example, silyl enol ether 3da reacted with Selectfluor to afford $\alpha$-fluorinated 1,4-diketone 6 in 73% yield. $\alpha$-Oxygenated 1,4-diketone 7 was obtained in 89% yield via Rubottom oxidation. Cu-catalyzed $\alpha$-arylation of 3da was also accomplished using a diphenyldiodonium salt, giving 8 in 82% yield. Compound 8 could be further converted into the corresponding trisubstituted furan 9 and pyrrole 10 by a Paal–Knorr reaction.

In conclusion, we achieved the regio- and diastereoselective synthesis of unsymmetrical 1,4-diketone-derived (Z)-monosilyl enol ethers from readily available 1-arylallyloxysilanes. The smooth deprotonation of 1-arylallyloxysilanes by TMSCH$_2$K to generate the siloxyallyl anion is the key step in this transformation, in which classical bases such as $\text{BuLi}$ and $\text{BuLi}$ are not effective. Siloxyallylpotassium is highly nucleophilic and reacts with various aryl- and alkyl-substituted Weinreb amides even at cryogenic temperatures, avoiding undesired side reactions involving retro Brook rearrangements. The products are synthetically versatile compounds that can undergo diverse regiospecific reactions to afford monofunctionalized 1,4-diketones, which can be further converted to trisubstituted five-membered heteroarenes.

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Conflicts of interest

There are no conflicts to declare.

Notes and references
