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Regioselective Preparation of α-Nitro Cyclohexyl Triisopropylsilyl Enol Ethers

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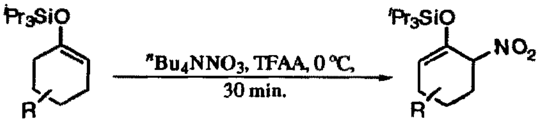
Abstract: *Treatment of the triisopropylsilyl enol ethers **1a-h** with tetra-*n*-butyl ammonium nitrate and trifluoroacetic anhydride at 0 °C afforded the α-nitro triisopropylsilyl enol ethers **2a-h** in 40-72% yield.*

The electrophilic amination of enolates and enol ethers is an important area of interest, particularly with respect to the synthesis of α-amino acids.[1] However, despite extensive work in this area, the search continues for more general synthetic methods.[2] The α-nitration of a variety of enol ethers has been examined by a number of groups,[3,4] and provides an excellent route to α-nitro ketones. The α-nitro ketones have considerable utility as versatile synthetic intermediates for target directed synthesis.[5,6] Magnus and coworkers recently reported the direct electrophilic amination of triisopropylsilyl enol ethers[7] with the Sharpless reagent $(TsN)_2Se$[8] in which the enol ether functionality was retained for further functionalization. Triisopropylsilyl enol ethers are known to have increased steric hindrance at silicon which reduces desilylation, and thus provides functionality not accessible *via* classical enolate or enol ether chemistry.[7] We decided to investigate the direct α-nitration of triisopropylsilyl enol ethers, and thus avoid the necessary intermediacy of the unstable α-nitro ketones.

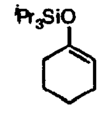
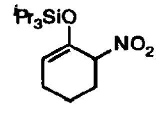
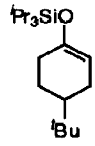
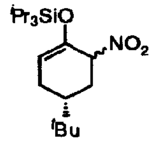
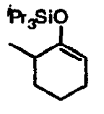
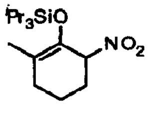
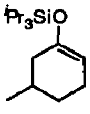
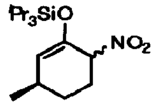
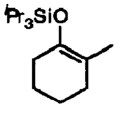
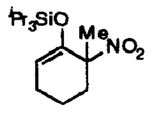
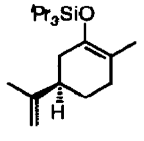
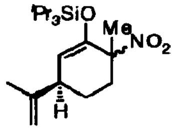
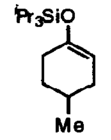
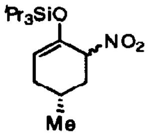
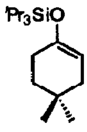
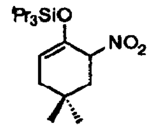
Scheme 1



1a-h **2a-h**

In this letter, we report the first example of the nitration of a triisopropylsilyl enol ether where the enol ether functionality is retained, thus providing a new functional group to organic chemistry. Treatment of the triisopropylsilyl enol ether **1a** with tetra-*n*-butylammonium nitrate and trifluoroacetic anhydride at 0 °C furnished the α-nitro enol ether **2a** in 49% yield (**Scheme 1**). Our initial studies indicated tetra-*n*-butylammonium nitrate to be the superior source of nitrate ion ($^nBu_4NO_3 > NH_4NO_3 > KNO_3$) owing to its increased solubility in organic solvents.[9] The electronic nature of the activating agent was also found to be fairly important with the more electron deficient anhydrides proving to be superior $(CF_3CO)_2O > (CCl_3CO)_2O > (CH_3CO)_2O$.[10] Solvent polarity had little effect on the reaction rate or the overall efficiency of the transformation. The moderate yield of the α-nitro enol ether **2a** was initially attributed to the desilylation of silyl enol ether **1a**, by trifluoroacetic acid formed from the hydrolysis of nitronium trifluoroacetate **3**, the proposed electrophilic nitrogen source.[4,10] However, all attempts at buffering the reaction (K_2CO_3, Na_2HPO_4 and 2,6-DTBMP), including the introduction of 4Å molecular sieves, proved futile. The α-nitro enol ether **2a** appears to be fairly stable under the reaction conditions as very little α-nitro ketone was formed.[11]

Table 1: α-Nitration of Cyclohexyl Triisopropylsilyl Enol Ethers **1a-h**

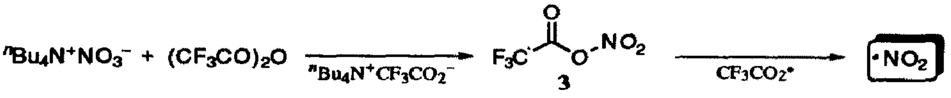
Entry	*Tips Enol Ether*[a]	*Product*[b]	*Yield (%)*[c]	*Entry*	*Tips Enol Ether*[a]	*Product*[b]	*Yield (%)*[c]
1	 **1a**	 **2a**	49	*5*	 **1e**	 **2e**	43[d]
2	 **1b**	 **2b**	40	*6*	 **1f**	 **2f**	47[d]
3	 **1c**	 **2c**	61	*7*	 **1g**	 **2g**	72[d]
4	 **1d**	 **2d**	46[d]	*8*	 **1h**	 **2h**	47

[a] All the reactions were carried out on a 0.5 mmol scale. [b] All new compounds exhibited spectroscopic (IR, ^1H and ^{13}C NMR) and analytical (HRMS) data in accord with the assigned structure. [c] Isolated yields. [d] 1:1 mixture of diastereoisomers by ^1H NMR.

Table 1 lists the triisopropylsilyl enol ethers investigated and the yields for their conversion to the α-nitro triisopropylsilyl enol ethers. In most cases, the reaction was complete after *ca.* 30 minutes at 0 °C with the α-nitro product being formed in moderate to good yields. The reaction was regiospecific in all cases investigated, and was significantly more efficient for *tetra*-substituted silyl enol ethers (Entries 3 and 7). However, the reaction was not stereoselective since the α-nitro silyl enol ethers were formed as mixtures of diastereoisomers (Entries 4, 5, 6 and 7). This result was somewhat surprising as the 4-methyl triisopropylsilyl enol ether **1d** was known to undergo stereoselective electrophilic functionalization *via* a variety of ene-type reactions.[7a] Possible equilibration under the reaction conditions was discounted as a possible explanation since the quaternary substituted α-nitro adduct **2g** cannot enolize.

The mechanism for this type of transformation was originally thought to involve an ene-reaction of the enol ether with **3**, which is formed *in situ* from trifluoroacetic anhydride with tetra-*n*-butylammonium nitrate (**Scheme 2**).[4,10] However, it is plausible that the reaction proceeds *via* a radical pathway, since **3** can in principle undergo homolytic cleavage to afford the nitronium radical which is known to add to olefins.[12] Furthermore, this would explain the need for highly electron withdrawing anhydrides that inductively weaken the N-O bond of the nitronium species, allowing facile homolysis. The stable free radical Tempo would be expected to intercept radical intermediates formed during the course of the reaction. When the reaction was carried out in the presence of excess Tempo, only a trace amount of the α-nitro adduct was observed. Control experiments indicated that Tempo and the silyl enol ether do not react with each other, except under the reaction conditions. Therefore, based on the results it seems reasonable that the reaction may proceed *via* the nitronium radical rather than **3**.

Scheme 2



In conclusion, we have demonstrated the first example of the α–nitration of a silyl enol ether where the enol ether functionality is retained for further functionalization. We are continuing to explore both the mechanism and synthetic potential of this novel reaction.[13]

Acknowledgments

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11. Authentic 2-nitrocyclohexanone was prepared from the enol acetate for comparison.[3]
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13. In a typical procedure a solution of tetra-*n*-butylammonium nitrate (1.942 g, 6.4 mmol) and 1-triisopropylsilyl(oxy)-cyclohexene **1a** (1.264 g, 5.0 mmol) in dichloromethane (50 ml) was stirred under nitrogen at 0 °C, and then trifluoroacetic anhydride (0.8 ml, 5.5 mmol) was added. The resulting light green colored solution was then stirred at 0 °C for 1 hour (reaction complete by tlc). The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (50 ml) shaken and separated. The aqueous layer was then back-extracted with dichloromethane (3 x 25 ml) and the combined organic layers dried over anhydrous Na_2SO_4, filtered, and the solvent removed *in vacuo* to afford a yellow oil. Purification by flash chromatography on silica gel (eluting with hexane and then 1:19 diethyl ether/hexane) furnished the *α-nitro triisopropylsilyl enol ether* **2a** (0.696 g, 47%) as a lime colored oil.

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