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Regioselective Preparation of α,β–Unsaturated Ketones *via* the Direct Dehydrogenation of Triisopropylsilyl Enol Ethers

P. Andrew Evans,* James M. Longmire and Dilip P. Modi

Lammot du Pont Laboratory, Department of Chemistry and Biochemistry,
University of Delaware, Newark, DE 19716.

Abstract: *Treatment of the triisopropylsilyl enol ethers 1a-h with ceric ammonium nitrate in dimethylformamide at 0 °C afforded the α,β-unsaturated ketones 2a-h in 63-98% yield.*

The regioselective dehydrogenation of ketones to α,β-unsaturated ketones represents an important transformation in synthetic chemistry.[1] Current methodologies may be categorized in terms of dehydrohalogenation, *syn*-elimination of selenoxides and sulfoxides, β-elimination of β-azido silyl enol ethers[2] and the direct dehydrogenation of ketones and enol ethers.[1,3] Dehydrogenation of enol ethers provides one of the most direct and versatile methods, and has been the focus of a number of studies.[3] Many of these protocols employ either catalytic or stoichiometric amounts of palladium to effect the dehydrogenation, making them fairly expensive for preparative scale synthesis. Furthermore, many of these methods utilize trimethylsilyl ethers which are particularly sensitive to acid-catalyzed hydrolysis. Triisopropylsilyl enol ethers have been shown to be significantly more stable, making them more convenient to use as synthetic intermediates.[4,5] In this letter, we report a practical method for the regioselective dehydrogenation of a range of triisopropylsilyl enol ethers 1 to the corresponding α,β-unsaturated ketones 2 (**Scheme 1**).

Scheme 1

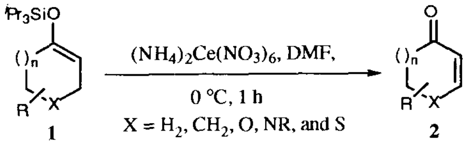


Table 1 summarizes our preliminary studies on the optimization of this reaction. Treatment of the triisopropylsilyl enol ether **1d** (X = O) with ceric ammonium nitrate at 0 °C furnished the α,β-unsaturated ketone **2d** in 6% yield (Entry 1). The low yield was attributed to the insolubility of the ceric ammonium nitrate in dichloromethane. Treatment of the silyl enol ether **1d** (X = O) under analogous conditions in acetonitrile, which completely dissolves the ceric ammonium nitrate, afforded the α,β-unsaturated ketone **2d** in an improved 30% yield (Entry 2). When the reaction was carried out in dimethylformamide the α,β-unsaturated ketone **2d** was obtained in a much improved 83% yield (Entry

3). Preliminary studies indicated that the stoichiometry was important, and that 2.25 equivalents of ceric ammonium nitrate were optimum for the complete conversion of starting material. However, attempts at making the process catalytic in ceric ammonium nitrate using a co-oxidant were unsuccessful (Entry 4). Treatment of the silyl enol ether **1d** (X = O) with a catalytic amount of ceric ammonium nitrate in the presence of the co-oxidant sodium bromate[6] furnished the α,β-unsaturated ketone **2d** in a disappointing 25% yield . Therefore, the dehydrogenation reactions outlined in **Table 2** were carried out under the optimum conditions described above (**Table 1**, Entry 3).

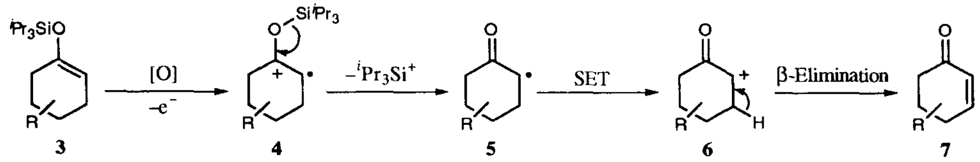
Table 1: Optimization of the Dehydrogenation with the Triisopropylsilyl Enol Ether **1d** (X = O)

Entry	*Ceric Ammonium Nitrate (eq.)*	*Solvent*	*Sodium Bromate (eq.)*	*Reaction Conditions*[a]	*Yield of 2d (%)*[b]
1	2.25	DCM	None	0 °C to RT, 20 h	6[c]
2	"	MeCN	"	0 °C, 1.75 h	30
3	"	DMF	"	"	83
4	0.20	"	2.25	0° C to RT, 69 h	25

[a] All the reactions were carried out on a 0.5 mmol scale. [b] Isolated yields. [c] The silyl enol ether **1d** was recovered (32%) in addition to the ketone derived from desilylation.

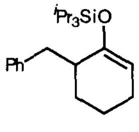
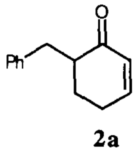
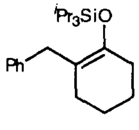
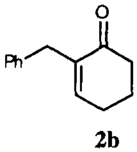
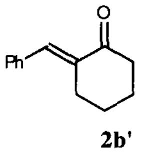
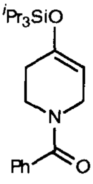
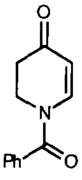
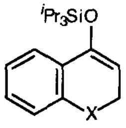
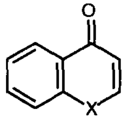
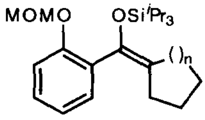
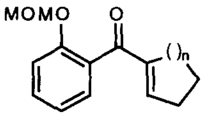
Table 2 lists the triisopropylsilyl enol ethers investigated and the isolated yields for their conversion to the corresponding α,β-unsaturated ketones. The reaction was usually complete after *ca.* 2 hours at 0 °C with the α,β-unsaturated ketones being formed in good to excellent yields. The reaction was regioselective as illustrated by the transformation of the enol ether **1a** to the α,β-unsaturated ketone **2a**, and the dehydrogenation of the isomeric enol ether **1b** which afforded a 10 : 1 mixture of endocyclic and exocyclic α,β-unsaturated ketones **2b/b'** respectively. This transformation was also applicable to oxygen, nitrogen and sulfur containing heterocycles **1c-e**, making it particularly attractive for target directed synthesis (Entries 3 and 4). Furthermore, the reaction also appears to be particularly useful for preparative work as demonstrated by the dehydrogenation of **1d** (X = O) which proceeds to afford the α,β-unsaturated ketones **2d** in 90% yield on a 5 mmol reaction scale (Entry 4).[9] The effect of having an acyclic ketone[7] and ring size was also examined (Entry 5). These examples demonstrate how particularly sensitive functionality, like a methoxymethyl ether, may be tolerated by the dehydrogenation reaction.

Scheme 2



The proposed mechanism for this transformation is outlined in **Scheme 2**. Oxidation of the silyl enol ether **3** to the radical cation **4**,[8] followed by desilylation would give the radical intermediate **5**. This can then undergo a single electron transfer (SET) to afford the carbocation intermediate **6**, which explains the observed stoichiometry of the reaction. β-Elimination of **6** would then afford the α,β-unsaturated ketone **7**.

Table 2: Direct Dehydrogenation of the Triisopropylsilyl Enol Ethers **1a-h**

Entry	*Tips Enol Ether*[a]	*Product*[b]	*Yield (%)*[c]
1	 **1a**	 **2a**	83
2	 **1b**	 **2b**  **2b'**	63
3	 **1c**	 **2c**	81[d]
4	 **1d-e**	 **2d-e**	**2d**; X = O; 90[e] **2e**; X = S; 98
5	 **1f-h**	 **2f-h**	**1f**; n = 1; 85 **1g**; n = 2; 65 **1h**; n = 3; 67

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[a] All the reactions were carried out as outlined in **Table 1** (Entry 3) on a 0.5 mmol scale, except where indicated to the contrary. [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] Reaction required 4.25 equivalents of ceric ammonium nitrate. [e] Reaction carried out on a 5 mmol scale.[9]

In conclusion, we have developed a new method for the direct and regioselective dehydrogenation of triisopropylsilyl enol ethers which is likely to find significant synthetic utility. We are continuing to explore other applications of this important synthetic transformation.

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9. Typical procedure: The 4-triisopropylsilyl(oxy)-(2*H*)-1-benzopyran **1d** (1.512 g, 5.0 mmol) was dissolved in anhydrous dimethylformamide (50 ml) and cooled with stirring 0 °C under an atmosphere of nitrogen. Ceric ammonium nitrate (6.126 g, 11.2 mmol) was then added portionwise over 45 minutes, and the reaction allowed to stir for a further 1 hour at 0 °C (t.l.c. control). The reaction mixture was then poured into saturated $NaHCO_3$ solution (200 ml) and extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with 10% hydrochloric acid solution (3 x 100 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a crude oil. Residual dimethylformamide and triisopropylsilyl alcohol were removed using a kugelrohr at 60 °C under high vacuum. Purification by flash chromatography on silica gel (eluting with 1 : 4; 3 : 7 ethyl acetate/hexane) furnished 1-benzopyran-4(4*H*)-one **2d** (0.651 g, 90%) as a light yellow crystalline solid.

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