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Facile Preparation of α-Nitroketones from Enol Silyl Ethers

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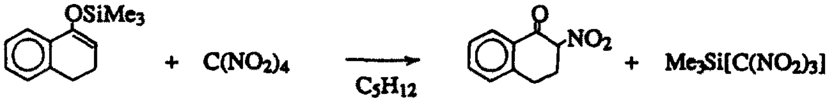
Abstract: Treatment of enol silyl ethers with the mild nitrating agent tetranitromethane gives good yields of α-nitroketones at room temperature and below.

Newer, general methods for the ready preparation of α-nitroketones are desirable owing to their wide utility as synthetic intermediates.[1] Unfortunately, the most direct methods involving the electrophilic nitration of ketones (with nitric acid) suffer from a variety of oxidative byproducts.[2] The alternative use of milder nitrating agents such as alkyl nitrates, nitryl chloride, acyl nitrates, etc., coupled with the conversion of ketones to their enolates,[3] enol acetates[4] and enol ethers,[5] does facilitate α-nitration but has generally met with limited success.[6] Accordingly, we directed our attention to one of the least oxidative nitrating agents, viz., tetranitromethane (TNM),[7] and examined the behavior of this substitutionally inert and neutral reagent[8] toward enol silyl ethers, which are among the most electron-rich derivatives of ketones.

When the enol trimethylsilyl (TMS) ether of α-tetralone dissolved in *n*-pentane was mixed with an equiv. of TNM (in pentane) at room temperature, the solution immediately took on a bright (dark) red coloration.[9] Upon standing shortly, the solution progressively bleached as yellow crystals of α-nitrotetralone separated in essentially quantitative yields (Table I). Aqueous workup of the reaction mixture within 15 min, followed by spectroscopic analysis, indicated the presence of one equiv. of trinitromethanide [$C(NO_2)_3^-$: λ_{max} = 350 nm, ε_{max} = 14,000 M^{-1} cm^{-1}].[10] The continuous monitoring of the nitration by HPLC analysis confirmed the 1 : 1 relationship between α-nitrotetralone and trinitromethanide, from which we inferred the following stoichiometry.



(1)

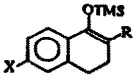
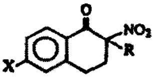
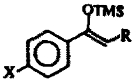
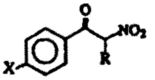
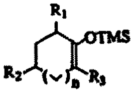
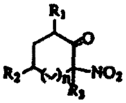
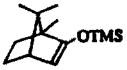
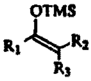
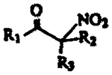
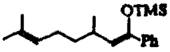
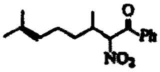
The trimethylsilyl complex of trinitromethanide[11] as presented in eq 1 was isolated as a labile yellow solid, but an attempt to obtain a single crystal suitable for X-ray crystallography resulted in a violent explosion (and further studies were suspended).

The wide variety of enol silyl ethers in Table I were nitrated at varying rates and efficiencies in either pentane or dichloromethane solution. Thus the TMS ethers of the tetralones (**1** - **3**) and the acetophenone analogues (**4** - **9**) afforded excellent yields of α-nitroketones in rapid reactions with TNM. Similarly, good yields of α-nitrocycloalkanones were isolated from the TNM treatment of the enol silyl ethers **10** - **15**, but the labile α-nitrocyclopentanone was subject to facile ring cleavage.[12] The effects of ring strain were shown in the TMS derivatives of norbornanone (**16**) and camphor (**17**), both of which reacted readily with TNM even at -30 °C. At the other extreme, the enol silyl ethers of acyclic ketones generally afforded only poor yields (~ 30%) of α-nitroketones in significantly slower nitrations with TNM. [Note the selective nitration of the enol silyl ether moiety in competition with the remote double bond in **21**.] However, the direct nitration of enol silyl ethers with TNM merits application even under such (limiting) conditions, since it can be simply implemented as follows.

> **General Procedure.** Tetranitromethane (2.2 g, 11 mmol) is added to a stirred solution of enol silyl ether (10 mmol) in pentane or dichloromethane. After standing (see Table I), the solution is treated with potassium fluoride and minimum amounts of water, stirred for 1/2 h, and diluted with dichloromethane (25 mL). The organic layer is separated, thoroughly washed with water to remove trinitromethanide[7], dried with magnesium sulfate, and evaporated *in vacuo* to afford crude α-nitroketone which is further purified by crystallization, distillation or chromatography.

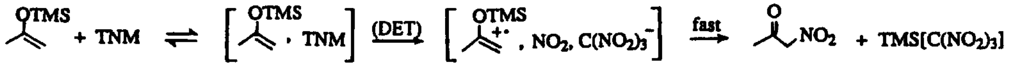
Although the nitration kinetics have not been measured, the conversions based on the time/yields listed in Table I provide a qualitative guide to the reactivities of various enol silyl ethers toward TNM. For example, the nucleophilic reactivity of enol silyl ethers is indicated by **3** requiring less time than **1**, and **5** requiring much longer time than **4**. On the other hand, steric effects are moderate, since **1** is not much different than **2**, despite the divergent primary and tertiary (α-carbon) centers. Moreover, the TNM nitration was not regiospecific, since the isomeric **12** and **13** yielded the same 2-methyl-2-nitrocyclohexanone, despite the absence of a spontaneous pathway for the rearrangement of the kinetic isomer of **13** to the thermodynamic isomer **12**. These reactivity patterns are not in general accord with the electrophilic transfer of a nitro group directly to the enol silyl ether.[13] Instead, they are reminiscent of the trend previously observed in the charge-transfer activation of electron-rich aromatic and olefinic donors by TNM.[14] As applied to enol silyl ethers (as donors), the charge-transfer mechanism formulates the nitration to result from a rate-limiting dissociative electron transfer (DET)

Table I. Nitration of Enol Silyl Ethers with Tetranitromethane (TNM).

No.	Enol Silyl Ether	α-Nitroketone	Time (h)	Yield (%)[a]	Ref.
					
1	X = H R = H		0.17	95	15
2	X = H R = Me		0.17	92	-
3	X = MeO R = H		0.01	93	15
					
4	X = H R = H		6	87	16
5	X = NO_2 R = H		16	85	16
6	X = H R = Me		6	90	16
7	X = H R = Et		6	92	16
8	X = H R = $(CH_2)_4Me$		6	93	-
9	X = H R = CH_2Ph		6	91	-
					
10	R_1 = H R_2 = H R_3 = H n = 1		6	70	4a
11	R_1 = H R_2 = t-Bu R_3 = H n = 1		6	70	4a
12	R_1 = H R_2 = H R_3 = Me n = 1		16	76	4a
13	R_1 = Me R_2 = H R_3 = H n = 1		16	68	4a
14	R_1 = H R_2 = H R_3 = H n = 2		6	70	17
15	R_1 = H R_2 = H R_3 = H n = 0		5	95[b]	18
16			0.5	60[c]	-
17			3	54[c]	5b
					
18	R_1 = n-Pr R_2 = Et R_3 = H		72	20	1a
19	R_1 = i-Pr R_2 = Me R_3 = Me		72	33	-
20	R_1 = t-Bu R_2 = H R_3 = H		168	25	1a
21			6	55[d]	-

[a] Isolated yields. [b] 2-Nitrocyclopentanone not isolated. [c] Reaction at -30 °C. [d] Mixture of stereoisomers.

followed by the homolytic coupling of the cation radical of the enol silyl ether with NO_2, e.g.



(2)

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