Tetrahedron Letters,Vol.23,No.14,pp 1419-1422,1982
Printed in Great Britain
0040-4039/82/141419-04$03.00/0

AN ANOMALOUS MANNICH REACTION OF A TRIMETHYLSILYL ENOL ETHER

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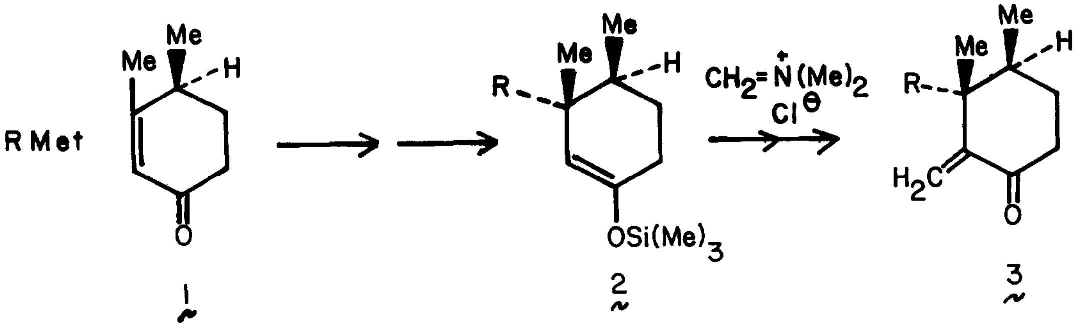
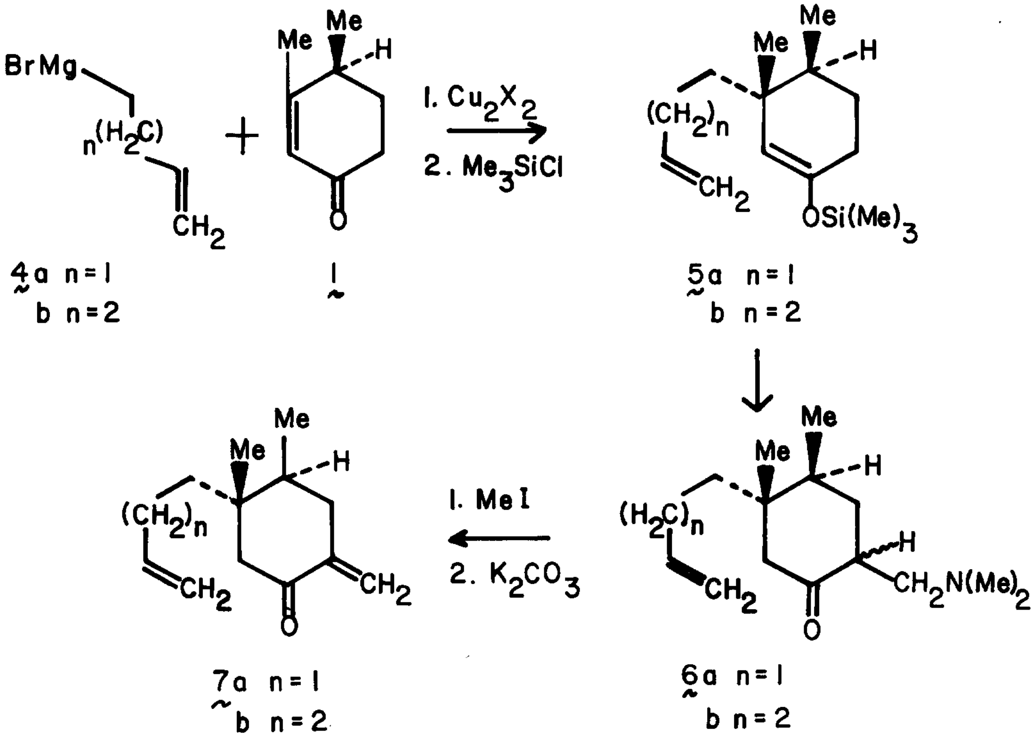
Abstract: Mannich reaction between dimethyl (methylene) ammonium chloride and a silyl enol ether gives a regiochemical result opposite to that obtained from the derived lithium enolate and the same salt.

In connection with a proposed total synthesis of the novel indolic terpenoid, aflavanine,[1] we had need to generate system 3. A simple possibility presented itself. Conjugate addition of an organometallic system to enone 1[2] would be expected to generate a metalloenolate specie which upon silylation would be expected to afford 2. At this stage it was expected that we could take advantage of the reaction of silyl enol ethers with preformed Mannich salts.[3a,b] We had previously shown the Mannich step to occur directly on a silyl enol ether in a regiospecific way.[3b] In this paper we describe a hitherto unsuspected complication in this reaction as well as a successful solution to the problem.



Grignard reagents 4 were prepared from the commercially available bromolefins. These reacted with enone 1 in the presence of 10% cuprous iodide and a 1:1 dimethyl sulfide-ether mixture from 0° → room temperature. Reaction of the resultant magnesium enolate with trimethylchlorosilane afforded (*ca.* 85%) the silyl enol ethers 5.[4]

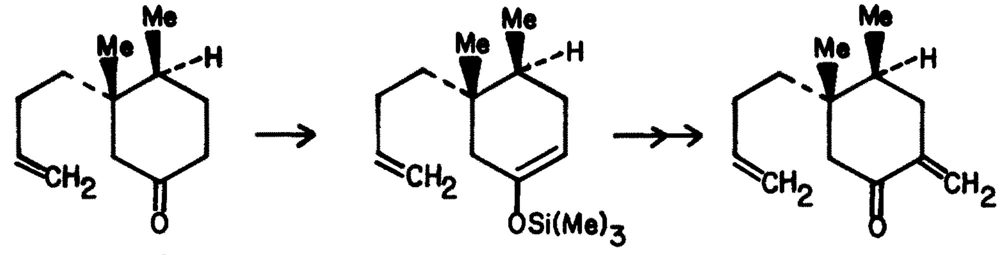
Reaction of 5 with dimethyl (methylene) ammonium chloride[5] afforded a Mannich base which upon quaternization and elimination afforded (∿50%) quite surprisingly the α-methyleneketones **7a** and **b**.[4,6]



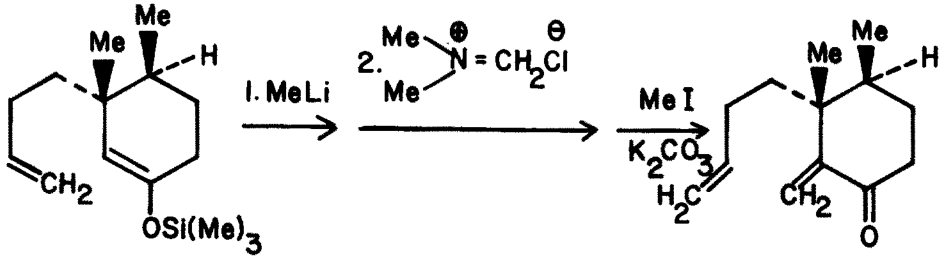
We investigated the phenomenon in greater detail for the potentially relevant butenyl series. Ketone **8** was obtained from the reaction of **4a** with **1** under the same conditions as above. Reaction of **8** with lithium di-isopropylamide in THF at -78° under conditions appropriate for kinetic enolate formation[7] followed by silylation afforded the isomeric **9** whose spectral properties[4] are clearly different from **5a**. Indeed, when **9** was submitted to the Mannich reaction with dimethyl (methylene) ammonium chloride followed by quaternization and elimination as above, the same methyleneketone, **7** was obtained.

We were able to prepare the desired methyleneketone, **10**. This was accomplished by generating the required lithium enolate via the reaction of **5a** with methyllithium according to Stork and Hudrlik.[8] The enolate reacted with the same Mannich salt[5] following procedures which we had developed.[3a] Quaternization and elimination as before afforded the desired **10**[4] in 49% yield.

Apparently the hindrance of attack by the Mannich cation on the silyl enol ether is more serious in the case of **5a**, bearing β, β, γ-trisubstitution, than for 2-methyl trimethylsilyloxycyclohexene where essentially no specificity is lost.[3b] The mechanism by which enoxysilanes 5 give rise to Mannich bases 6 remains to be explored in detail. For the moment it is important to take note of the loss of regiointegrity in the Mannich reaction of the neutral silyl enol ether. Happily, kinetic control can be retained through the derived lithium enolate.



4a + 1 ⟶ 8 9 7



5a 10

Acknowledgements: This research was supported by P.H.S. Grant HL 48136-02. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University which was supported by the N.S.F. Chemistry Division Grant CHE 7916210.

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4. 5a NMR, 'H, $CDCl_3$, δ (0.03, s, 9 H; 0.83, s, 3 H; 0.87, d, 3 H, J = 6 Hz; 1.3-2.05, m, 9 H; 4.56, s, 1 H; 4.96, m, 2 H; 5.80, m, 1 H). IR, $CHCl_3$, cm^{-1} (1670). 7a NMR, δ (0.85, s, 3 H; 0.94, d, 3 H, J = 6 Hz; 1.3, 2.52, m, 7 H; 2.28, s, 2 H; 4.78-6.0, m, 5 H). IR,

$CHCl_3$, *cm^{-1}* (1685, 1640). **9** NMR, δ (0.10, s, 9 H; 0.88, s, 3 H; 0.90, d, 3 H, J = 6 Hz; 1.3-2.2, m, 9 H; 4.68-6.12 m, 4 H). *IR*, *$CHCl_3$*, *cm^{-1}* (1675). **10** NMR, δ (1.06, d, 3 H; 1.10, s, 3 H; 1.3-2.56, m, 9 H; 4.82-6.0, m, 5 H). *IR*, *$CHCl_3$*, *cm^{-1}* (1680, 1635).

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6. We believe that the presence of more than 5% of **7** in **10**, or *vice versa*, could have been detected.
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8. G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, *90*, 4462 and 4464, **1968**.

(Received in USA 16 November 1982)