

REGIOSELECTIVE MANNICH REACTIONS VIA TRIMETHYLSILYL ENOL ETHERS

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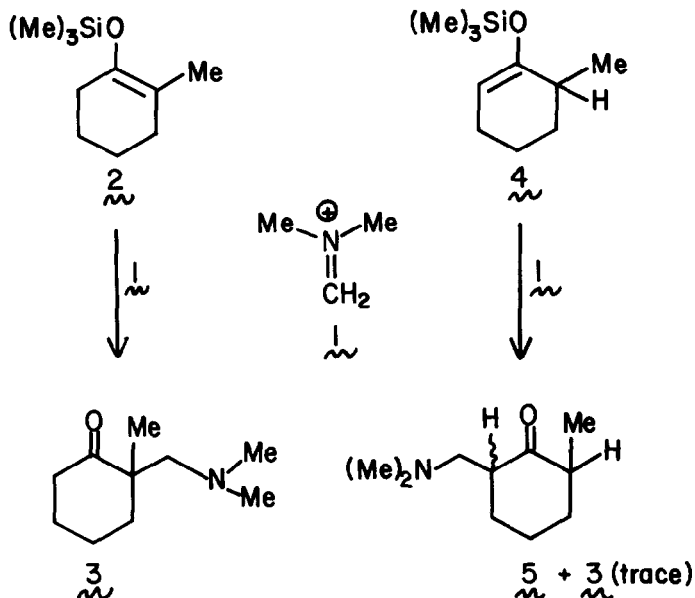
Summary: Site-specific reactions of trimethylsilyl enolates and trimethylsilyldienolates are described.

Recently some reactions of the Eschenmoser salt, 1 , with enolates^{2,3,4}, Grignard^{5a} and lithium^{5b} reagents were described. This methodology was used to some advantage in a synthesis of vernolepin.⁶ A more detailed study was provided by Holy.⁷

In our preliminary experiments² we also noted that compound 1 is sufficiently electrophilic to react with trimethylsilyl enol ethers. This process was used in the synthesis of a known precursor of dl-progesterone. We now describe a fuller examination of the reactions of 1 with trimethylsilyl enol ethers. In particular we were attracted by the possibility of exploiting such methodology to address the longstanding problem of regioselectivity in the Mannich Reaction.^{8a} While some solutions to this problem have been advanced in the literature^{8b}, the possibility of obtaining positionally defined Mannich bases via positionally defined silyl enol ethers⁹ seemed most attractive.

Treatment of 1-trimethylsilyloxy-2-methylcyclohexene (2) with the iodide, 1 , at room temperature for 45 min followed by acidic workup and basification afforded a 65% yield of a Mannich base. Singlet resonances for the quaternary bound methyl group $\delta 1.1$ (s, 3) and for the NCH₂ protons $\delta 2.54$ (s, 2) served to define the structure of the Mannich base as 3 .¹⁰

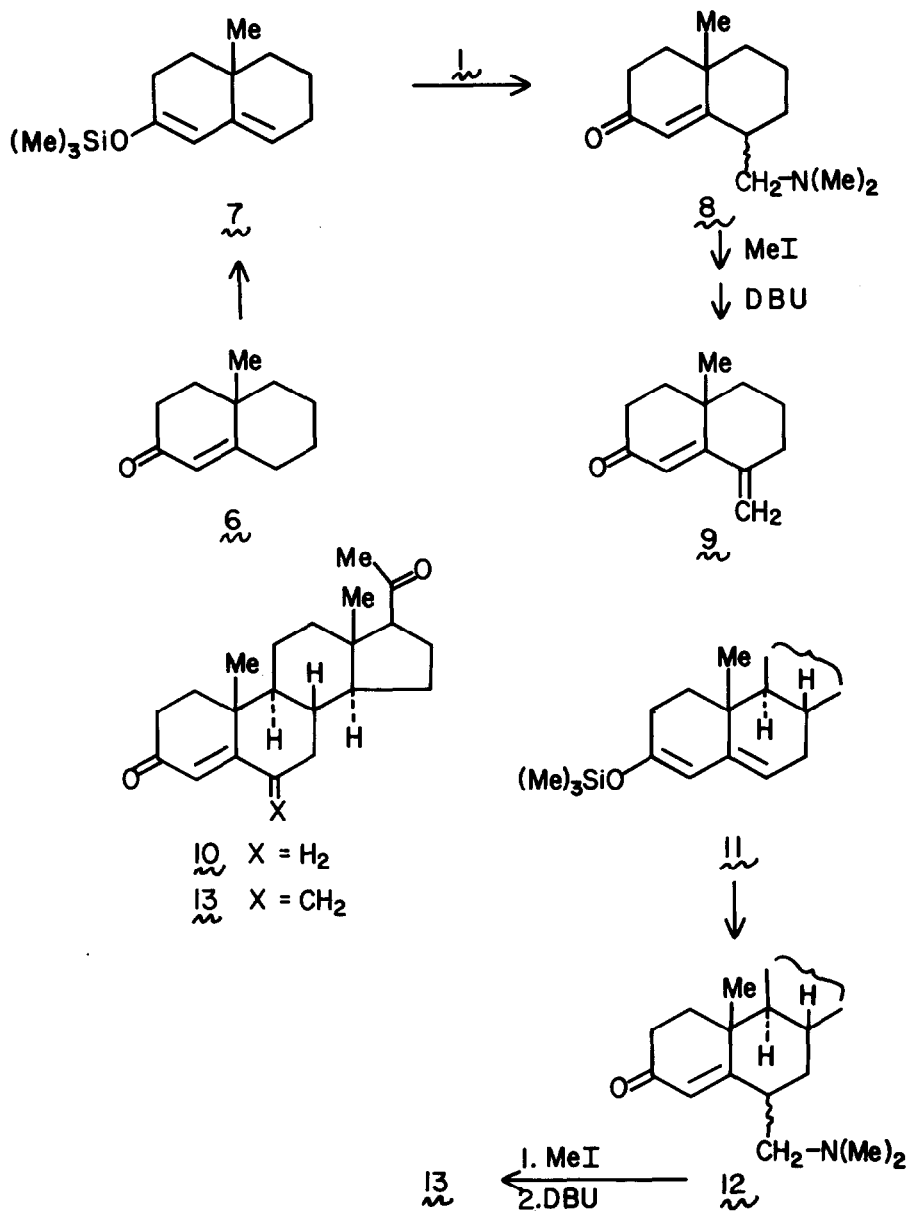
Similarly, reaction of 4 with 1 afforded a 79% yield of 5 as a 2:1 mixture of stereoisomers. With both 3 and 5 in hand, it was possible to probe the regioselectivity of the reactions of 2 and 4 with 1 in greater detail. Within the limits of nmr detection at 250 MHz, we could find no indication that any component of isomer mixture 5 had risen in the reaction of $1 + 2$. However, there could be detected ca 4% of 3 in the reaction of $1 + 4$. Since starting silyl enol ether 4 was free of detectable amounts of its isomer, 2 there appears to be a very slight loss of specificity in the latter case.



We next investigated the reactions of conjugated silyldienolates¹¹ with compound 1. The hope, that such a process would provide a means for the introduction of carbon functionality at the γ -position of an enone, was realized in practice. Reaction of siloxydiene 7 (prepared from the readily available 6 in the usual way) with 1 (chloroform; reflux; 30 min) afforded a 65% yield of 8 (single epimer; configuration at C₆ not rigorously determined). Conversion of 8 to the γ -methylene ketone, 9¹⁰, was accomplished in 73% yield as shown. The overall method for introduction of a γ -methylene group onto 6 appears to be much simpler than that recently described by Yoshikoski.¹²

The process was readily extended to the steroid series. Thus, without protection of the C₂₀ ketone, progesterone (10) was converted to the silyldienolate 11¹⁰, mp 80-81°. Reaction of 11 with 1, as above, afforded oily 12 (apparently a single isomer, stereochemistry at C₆ not determined), which was converted to 13¹⁰, mp 105-106°, in 58% yield in the same fashion.

In summary, it would appear that the reactions of silylenolates and silyldienolates with 1 provide excellent regioselectivity for Mannich reactions. The use of this methodology in the context of larger synthetic programs is a matter under investigation.



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References

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