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REGIOSPECIFIC UREIDOALKYLATION OF SILYL ENOL ETHERS

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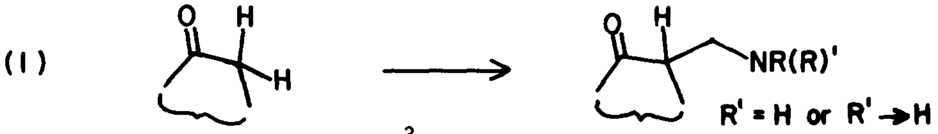
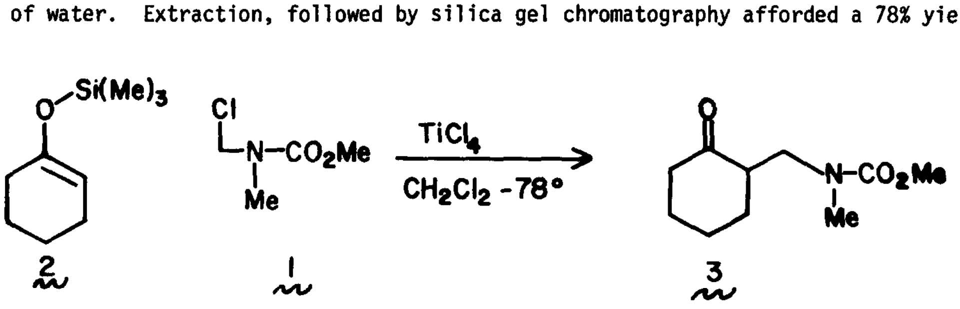
Summary: Site-specific ureidoalkylation of silyl enol ethers can be achieved by their reactions with chloromethylcarbamates at -78° under the influence of titanium tetrachloride.

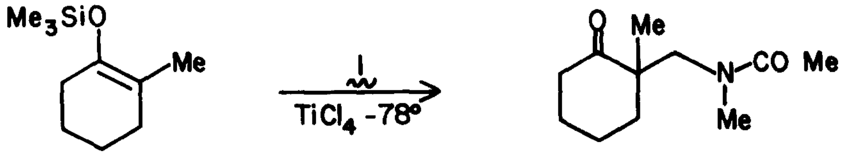
The Mannich reaction accomplishes the introduction of the unit CH_2NR_2 α- to a carbonyl system.[1] For various synthetic programs, we have been concerned with the transformation summarized in eq (1) wherein, in overall terms, the unit CH_2NRH is inserted α- to a ketone. A general solution involving ureidoalkylation[2a] seemed attractive since a secondary amine can be readily retrieved from a carbamate. To our knowledge, the feasibility of regiospecific amido- or ureidoalkylation of difficultly enolizable ketones such as cyclohexanones (as opposed to readily enolizable β-dicarbonyl compounds[2b]) has not been described.



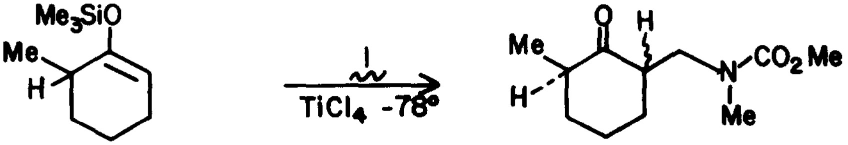
In the light of our previous findings[3], and in view of the elegant investigations of Mukaiyama[4a,b], we examined the reactions of silyl enol ethers with carbamate 1[5] under the influence of titanium tetrachloride. The silyl enol ether 2 (1.03 mmole/1 ml of methylene chloride) was added to 2 ml of methylene chloride (-78°) containing 1.03 mmole each of $TiCl_4$ and carbamate, 1. After being maintained for 1 hr at -78°, the reaction mixture was quenched with 2 ml of water. Extraction, followed by silica gel chromatography afforded a 78% yield of 3.[6]



We next investigated the positional integrity of this reaction, starting with compounds **4** and **5**, using strictly stoichiometric equivalents of each reagent. From reaction of compound **4**[7] with **1**, there was obtained a 65% yield of **6**.[6] Similar reaction of compound **5**[7] with **1**, afforded an 80% yield of **7**[6], as a mixture of stereoisomers. No erosion of regiospecificity was observed under these very mild reaction conditions.



4 **6**



5 **7**

Comparable yields were obtained using the silyl enol ethers **8** and **9** derived from cyclopentanone and acetophenone, respectively. With these substrates, we used the carbamate **10** in addition to **1**. The adducts **12** and **14**, available via **10**, may be deblocked by reductive means.

Finally, we also studied the reaction of silyldienolate **15** with **1** under the same conditions used for the previously described cases. As was found[3] in the corresponding reaction of **15** with $CH_2{=}\overset{\oplus}{N}(Me)_2I^{\ominus}$, the sole products observed were those arising from γ-alkylation. There was obtained a mixture of ureidoalkylation products at C_6 in the ratio and yield shown. Spectral analysis of these epimers does not rigorously define their configurations. The assignments are based on the observation that the ratio of the kinetic products (ca. 3:1) can be shifted to 9:1 by stirring the crude reaction mixture with pyridine/acetic anhydride at rt for 15 hrs. On this basis, it may be assumed that the major product is the one containing the equatorial ureidomethyl function at C_6, arising from alkylation of **15** from its less hindered face.

In summary, it would appear that this methodology allows for the α-ureidoalkylation of cycloalkanones in a site-specific way. The generalization of these findings and their implications for the synthesis of various alkaloids are the objects of ongoing investigations.

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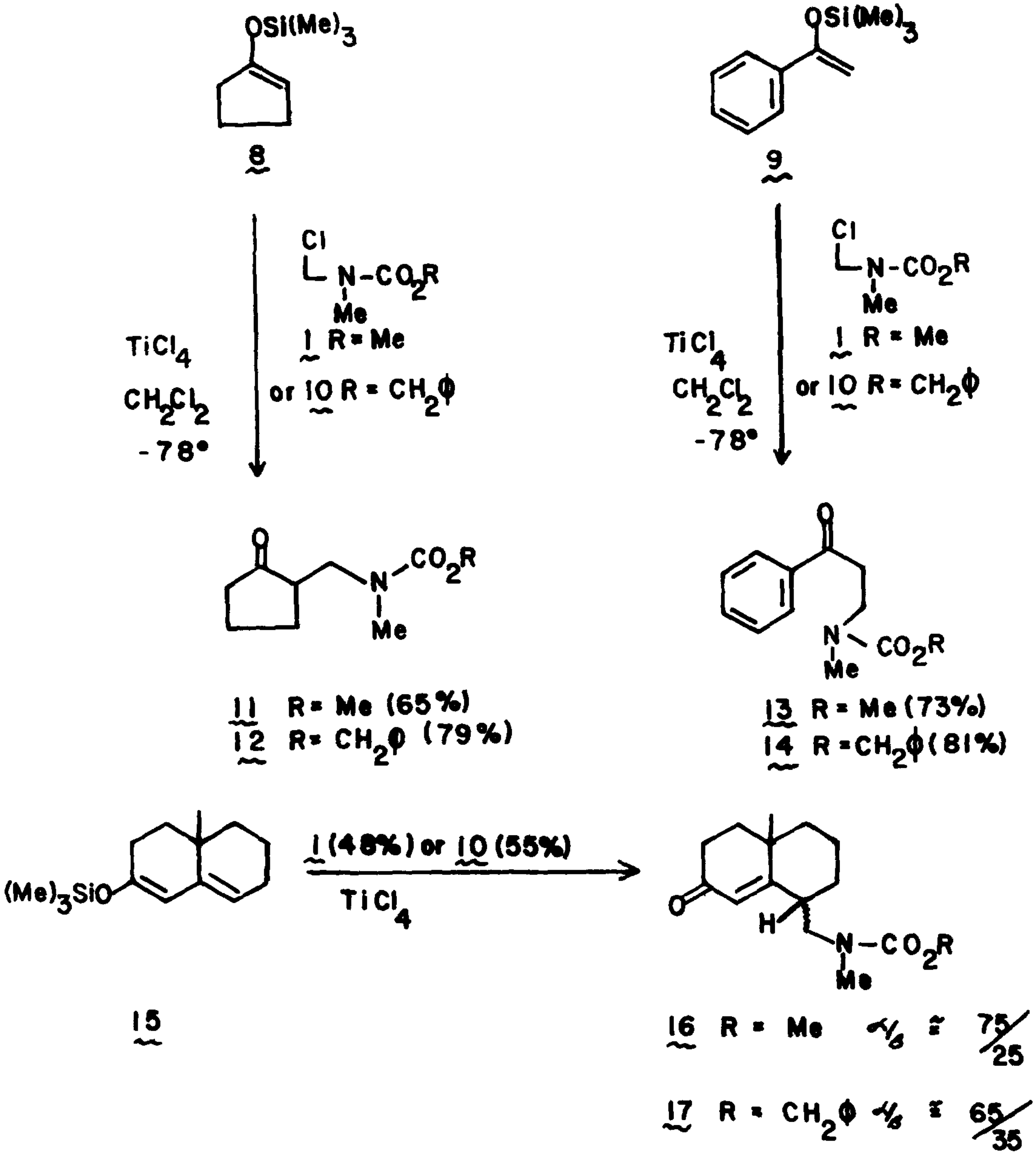
OSi(Me)3
8
TiCl4
CH2Cl2
-78°
Cl
N-CO2R
Me
1 R = Me
or 10 R = CH2Φ
O
N
CO2R
Me
11 R = Me (65%)
12 R = CH2Φ (79%)
OSi(Me)3
9
TiCl4
CH2Cl2
-78°
Cl
N-CO2R
Me
1 R = Me
or 10 R = CH2Φ
O
N
CO2R
Me
13 R = Me (73%)
14 R = CH2Φ (81%)
(Me)3SiO
15
1 (48%) or 10 (55%)
TiCl4
O
H
N-CO2R
Me
16 R = Me α/β ≅ 75/25
17 R = CH2Φ α/β ≅ 65/35

References

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2. (a) For a review see: H. E. Zaugg, ibid., **49** (1970); (b) For acid catalyzed amidoalkylation of β-dicarbonyl compounds see: D. Ben-Ishai, J. Altman, Z. Bernstein and N. Peled, Tetrahedron, **34**, 467 (1978).

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6. The structure of this compound is in accord with its infrared, nmr and mass spectra.

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