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Synthesis of Bicyclic Aza-enones *via* a Lewis Acid Catalysed Michael-type Addition with Silyl Enol Ethers bearing a Nitrogen Atom.

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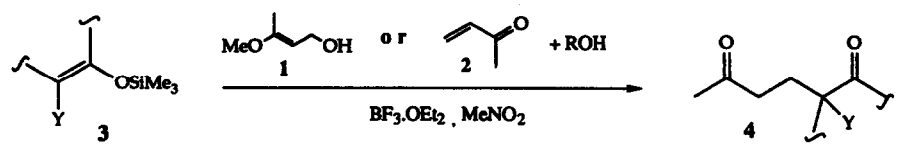
Abstract: Silyl enol ethers bearing a nitrogen atom protected by an electron-withdrawing group give in high yield a Michael-type addition with hemiacetal vinylog or a mixture of methyl vinyl ketone and an alcohol in the presence of boron trifluoride etherate as a catalyst. The aza-1,5-diketones so prepared can be cyclised leading to aza-enones precursors of some biologically active structures.

Bicyclic aza-enones have been proved to be useful starting material for the synthesis of many alkaloids but their preparation by Michael addition was not so obvious.

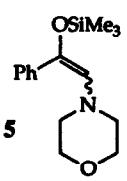
We have previously shown[1] that the reaction of a hemiacetal vinylog **1** or the mixture of methyl vinyl ketone **2** and a hydroxylic compound in the presence of a catalytic amount of boron trifluoride etherate led with silyl enol ethers **3** (Y = H, alkyl, aryl) to a Michael-type addition. The postulated carbocationic species (produced either from **1** or the mixture of methyl vinyl ketone **2** with ROH in the presence of $BF_3.OEt_2$) was reacted with enol ether **3** leading to 1,5-dicarbonyl compounds **4** in high yield even with a hindered reaction site. The same result was obtained with heterosubstituted silyl enol ethers **3** (Y = Cl, Br, OMe, SR)[2] (scheme 1).



Y = H, alkyl, aryl, Cl, Br, OMe, SR

Scheme 1

In the present paper are described the results relative to the reaction of compound **1** or the mixture methyl vinyl ketone **2**-ROH with silyl enol ethers bearing a nitrogen atom.[3] We first tried with the dialkylamino silyl enol ethers **5**-**7** prepared from the corresponding aminoketones[4] for testing the Michael addition.



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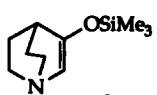

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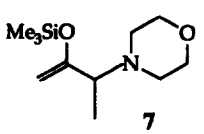

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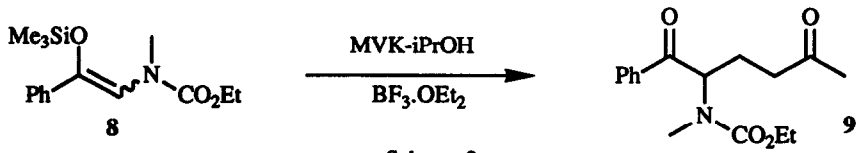
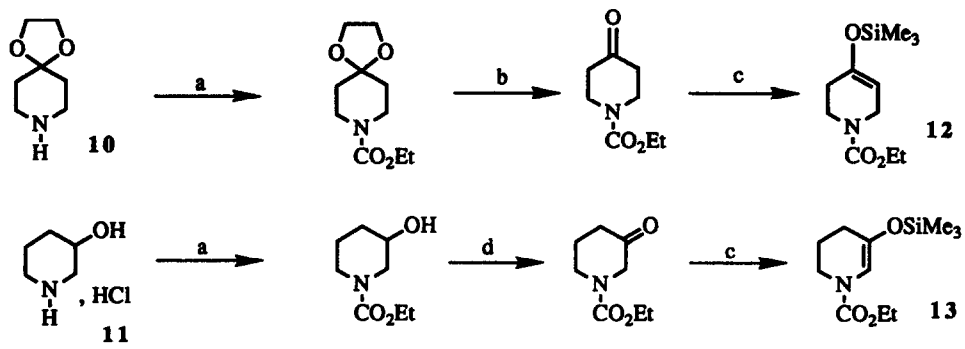
In all cases, the silyl enol ethers **5,6** (nitrogen in vinylic position) or **7** (nitrogen in allylic position) when reacted with hemiacetal vinylog **1** or with methyl vinyl ketone **2**-ROH, yield after aqueous work-up, the corresponding aminoketones. Probably the more basic lone pair of nitrogen reacts with the Lewis acid leading to an enammonium compound unreactive and very sensitive to hydrolysis.[6] So, we decided to protect the nitrogen with an electron-withdrawing group and we chose an urethane as the protecting group.

We first prepared the silyl enol ether **8**, (from N-methyl-2-amino-1-phenyl-ethanol as described below). The double bond of this compound is as substituted as that of the silyl enol ether **5** but the nitrogen atom is less basic. In the same reaction conditions[7] the dicarbonyl compound **9** (scheme 2) was obtained in 55% yield[8] after flash chromatography.



Scheme 2

Owing to our interest in the field of alkaloid chemistry, we decided to continue our study with heterocyclic structures. Silyl enol ethers **12** and **13** with a nitrogen atom in vinylic or allylic position were synthesised from commercially available compounds **10** and **11** as described in scheme 3 in respectively 53 % and 56 % overall yield.



a) $ClCO_2Et$,NEt_3, H_2O/acétone (1/1) or CH_2Cl_2; b) HCl, 3N; c)TMSCl, NEt_3, DMF, 80°C (ref 9); d) Jones reagent, 0°C.

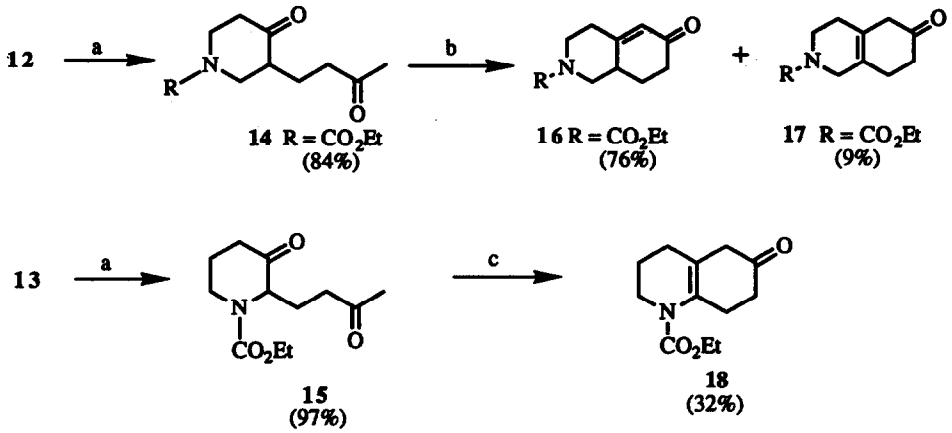
Scheme 3

The preparation of the silyl enol ether **13** from the corresponding aminoketone needs 48 hours at 80°C to obtain this compound as a single regio-isomer; with a shorter reaction time the two regio-isomers are present.[10]

The silyl enol ether **12** was reacted with the hemiacetal vinylog **1** in the presence of boron trifluoride etherate (0.36 eq) to lead to the aza-diketone **14**[8] in 37% yield. With the mixture methyl

vinyl ketone 2 and menthol, the aza-diketone **14** was obtained in higher yield (84%), as expected.[1b,d]

With the hemicetal vinylog 1 and the silyl enol ether 13 in the same reaction conditions, the aza-diketone **15**[8] was obtained in 53% yield but the use of the mixture methyl vinyl ketone 2 and *i*-propanol leads to the aza-diketone **15** in quasi-quantitative yield (scheme 4).



a) MVK, ROH, $BF_3.OEt_2$, -20°C; b) MeONa, MeOH, 40°C; c) pyrrolidine, dimethylformamide, 80°C.

Scheme 4

Compound **14** can be cyclized into the corresponding enone by treatment with sodium methoxide in methanol (1h, 40°C) yielding essentially the enone **16** (R = CO_2Et) accompanied by a little of the non-conjugated enone **17** which can be separated by flash chromatography with 76% and 9% yields respectively (scheme 4). In the same reaction conditions, diketone **15** does not yield the cyclic enone. The non-conjugated enone **18** can be obtained in modest yield (32%) by heating diketone **15** in the presence of pyrrolidine (scheme 4).

These cyclization products can be considered as the precursors of some alkaloids since the ellipticin skeleton was prepared from the N-benzoyl enone **16** (R = COPh).[11] Similarly, enone **18** can be considered as the precursor of a dopamine agonist since the same structure (but N-propyl) was used in the synthesis of quimprol.[12]

In conclusion, we have shown that the Michael addition catalysed by boron trifluoride etherate can also be applied to silyl enol ethers bearing a nitrogen atom if the nitrogen is protected by an electron withdrawing group. This reaction leads to the corresponding aza-diketones. These diketones can be cyclized into bicyclic aza-enones which are precursors of biologically active compounds. Application of this succession of reactions to the synthesis of spirocyclic aza-enones is under investigation.

Acknowledgment. A. D. thanks the Mauritanian Ministère de l'Education Nationale for a grant.

References and notes

1) a) Duhamel, P.; Poirier, J.M.; Tavel, G. *Tetrahedron Lett.*, **1984**, *25*, 43.
b) Duhamel, P.; Hennequin, L.; Poirier, N.; Poirier, J.M.*Tetrahedron Lett.*, **1985**, *26*, 6201.c) Duhamel, P.; Hennequin, L.; Poirier, J.M.; Tavel, G.; Vottero, C. *Tetrahedron*, **1986**, *42*, 477.
d) Duhamel, P.; Dujardin, G.; Hennequin, L.; Poirier, J.M. *J. Chem. Soc. Perkin I*, **1992**, 387.

2) a) Duhamel, P.; Poirier, J.M.; Hennequin, L. *Tetrahedron Lett.*, **1984**, *25*, 1471.
b) Fomani, M.; Hennequin, L.; Poirier, J.M. *Bull. Soc. Chim. Fr.*, **1985**, 436.

3) Taken in part from the PhD thesis of A. Deyine, University of Rouen, february 1993.

4) The enol ethers **5-7** were prepared using the procedure desribed by Cazeau *et al.*[5]

5) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O; Dunogues, J. *Tetrahedron*, **1987**, *43*, 2075 and 2089.

6) The use of 1.25 eq of $BF_3.OEt_2$ gave the same result.

7) To 4 mmol of silyl enol ether in 3 mL of nitromethane, 3 mmol of methyl vinyl ketone **2** (210 mg) in 3 mL of nitromethane were added at -20°C. Then a mixture of 3 mmol of the secondary alcohol (i-propanol for compounds **8** and **13**, menthol for silyl enol ether **12**) and 145 µL of boron trifluoride etherate was added, *via* syringe, at -20°C. The reaction was monitored by CCM (until the spot of enol ether disapeared, 30 to 60 min). The reaction mixture was warmed up to 0°C and treated with 3 mL of an aqueous saturated solution of sodium hydrogenocarbonate. The organic phase was extracted with dichloromethane (5 x 15 mL), dried ($MgSO_4$) and evaporated. The diketone was purified by flash chromatography (eluant: ether / petroleum ether, 20 to 50 / 100).
With hemiacetal vinylog **1** the preceding procedure was used but the secondary alcohol was omitted and a mixture of $BF_3.OEt_2$ (145 µL) and anhydrous diethylether (volumic ratio $BF_3.OEt_2$ / Et_2O = 4/1) was added at -20°C.

8) All new compounds (**9**, **14-18**) exhibit spectral data and analyses fully compatible with the proposed structures.

9) a) House, H.O.; Czuba, L.I.; Gall, M.; Olmstead, H.D. *J. Org. Chem.*, **1969**, *34*, 2324.
b) Garst, M.E.; Bonfiglio, J.N.; Grudoski, D.A.; Marks, J. *J. Org. Chem.*, **1980**, *45*, 2307.

10) The regio-isomerisation of enol ethers will be published elsewhere

11) a) Rastogi, S.N.; Bindra, J.S.; Rai, S.N.; Anand, N. *Indian J. Chem.*, **1972**, *10*, 673.
b) Freter, K.; Fuchs, V.; Pitner, T.P. *J. Org. Chem.*, **1983**, *48*, 4593.

12) a) Schaus, J.M.; Huser, D.L.; Titus, R.D. Synth. Commun., **1990**, *20*, 3553.
Mehta, P.; Kumar, Y.; Saxena, A.; Gulati, A.K.; Singh, H.K.; Anand, N. *Indian J. Chem.*, **1991**, *30B*, 673.

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