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5-Membered Heterocyclic Allylsilanes in Synthesis : Generation *via* Aza-ene Reaction and Application to the Synthesis of a Bicyclic 1,2-Dinitrogen Analogue of Naturally Occurring Pyrrolizidines

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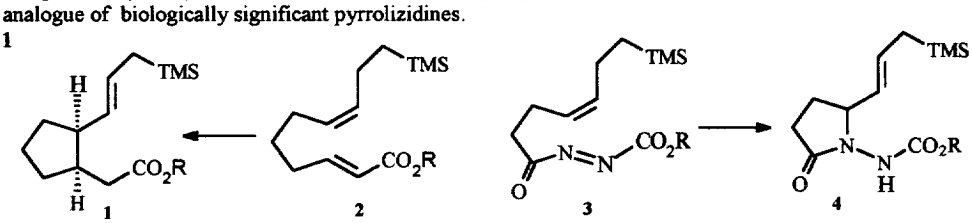
Dedicated to Prof. S. K. Talapatra on the occasion of his 65th Birthday

Abstract: A cyclic hydrazide containing an allylsilane functionality obtainable by an aza-ene reaction provides ready access to a bicyclic 1, 2- dinitrogen compound related to naturally occurring pyrrolizidines.

Keywords: Aza-ene Reaction, Heterocyclic Allylsilanes, Fused Tetrahydropyrazole

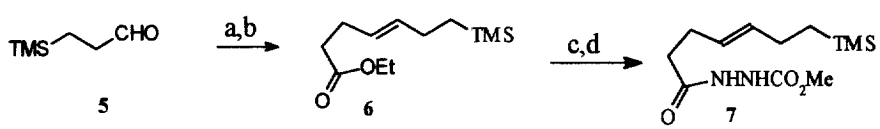
In a series of papers, we have recently described the utility of cyclopentanoid allylsilanes **1** as versatile building blocks for the synthesis of a diverse group of cyclopentane containing natural products (Scheme 1).[1,2] These intermediates are available in near quantitative yields by 5-(3,4) ene cyclization of activated 1,6–dienes **2** containing a homoallylsilane unit as ene donor. This work prompted us to examine a related aza-ene reaction[3] of **3** featuring a reactive azodicarbonyl moiety as enophile to the cyclic hydrazide **4**. The resulting species can then be elaborated *via* reductive cleavage of the N-N bond[3,4] and exploitation of the allylsilane side-chain to azabicyclo[3.3.0]octane, the nucleus of a group of pyrrolizidine alkaloids which continues to receive intense attention by synthetic chemists.[5] In this letter, we report on the feasibility of the aza-ene route to **4** and allylsilane induced stereoselective cyclization of the corresponding methoxymethyl derivative **9** to a fused tetrahydropyrazole **10** which may be looked upon as a mono-nitrogen analogue of biologically significant pyrrolizidines.

Scheme 1



The ene educt **7** (mp. 76° C), a crystalline acylhydrazocarboxylate, was made from 3-(trimethylsilyl)propanal (**5**)[6] in an overall yield of 51% as described in Scheme 2.

Scheme 2



a) CH_2=CHMgBr, THF, 80%. b) $CH_3C(OEt)_3$, H^+, tol, 82%. c) KOH, MeOH, 94%. d) (i) NaH, bz, then $(COCl)_2$; (ii) H_2NNHCO_2Me, Et_3N, CH_2Cl_2, 84%.

It was envisaged that oxidants[7] capable of converting hydrazides into azo compounds would convert **7** into **8** (Scheme 3) *via* ene reaction of the *in situ* generated azodicarbonyl intermediate (*cf.* **3**). It was also deemed necessary to make use of neutral or slightly basic oxidants to ensure survival of the acid labile allylsilane **8**. Two different oxidants *e.g.*, Ag_2CO_3–impregnated celite[8] and activated MnO_2[9] were initially selected for optimum results. Sonicating **7** with 25-30 eq of activated MnO_2[3,9] in 1,2-dichloroethane at 15°C for 3h gave a white crystalline solid which upon recrystallization from ether-petroleum ether (40-60° C) gave *E*-**8** (m.p. 89° C) containing traces (*ca.* 5%) of the *Z*-isomer

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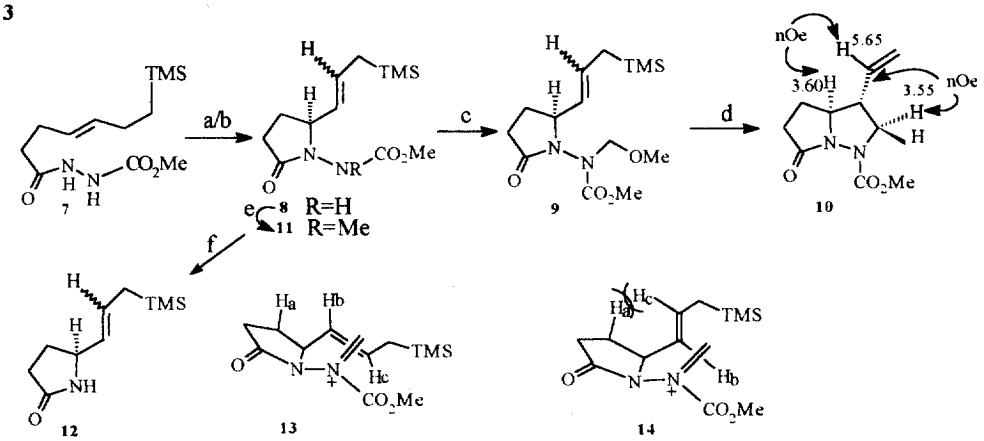
in an yield of 49%. The structural and stereochemical confirmation of **8**[13] followed from analysis of its ^{1}H-and ^{13}C-NMR spectra. Sonicating **7** with 10 eq of Ag_2CO_3/celite[8] reagent in hot benzene for 7h followed by preparative layer chromatography of the crude product also gave a semisolid material (38%) as a mixture (the isomers do not resolve on TLC) of ***E*-8** and ***Z*-8** in a ratio of 4.5:1, respectively. It is our experience that MnO_2 oxidations generally give a purer ene product **8** in consistently good yields.

Scheme 3



a)MnO_2,$ClCH_2CH_2Cl$,15^{0}C,49%. b)Ag_2CO_3-Celite,bz,38%. c)NaH,MOMCl,THF,90%. d)$BF_3.OEt_2$(2.5eq),CH_2Cl_2,0^{0}C,51%. e)KOBu^t,MeI,THF,0^{0}C,90%. f)Li/NH_3,70%.

In order to demonstrate the utility of the allylsilane side-chain, **8** was next converted to the methoxymethyl derivative **9** and exposure of the latter to $BF_3.Et_2O$[10,11] (2.5 eq) in dichloromethane gave the fused tetrahydropyrazole **10** in 51% yield. The structure and relative stereochemistry of **10**[13] rest on high-field ^{1}H- & ^{13}C-NMR as well as nOe studies. The high stereoselectivity in the reaction **9**→**10** is readily explicable in terms of the synclinal[12] transition structure **13** of the N-acylhydrazonium intermediate which for steric reasons is largely favoured over **14**. Finally, **8** was converted to **11** and reductive cleavage of the latter with Li/NH_3 yielded **12**, the building block for pyrrolizidine alkaloids.

In conclusion, a route to 5-membered heterocycles **8** and **12**, each with a built-in allylsilane terminator has been developed and the use of the former in the synthesis of a fused tetrahydropyrazole demonstrated. Further work to utilize **12** for the synthesis of azabicyclo[3.3.0]octane skeleta related to pyrrolizidines is under active investigation in this laboratory.

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References & Notes

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