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INTRAMOLECULAR REACTIONS OF ACYCLIC N-ACYLIMINIUM IONS I

PROPARGYL SILANES AS NUCLEOPHILES

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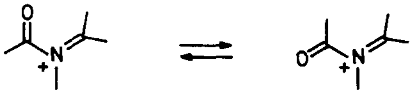
Abstract: Intramolecular reactions of acyclic N-acyliminium ions with propargyl silanes, induced by protic or Lewis acid, lead to α-allenic amides or carbamates, i.e. derivatives of 3-vinylidene-pyrrolidine, 3-vinylidene-piperidine or 1-amino-2--vinylidenecyclopentane.

N-acyliminium ions (1, 2) have proven to be valuable intermediates in organic synthesis[1]. In particular, their intramolecular electrophilic anti addition to olefinic double bonds has shown to be very useful for the synthesis of alkaloids[2]. In elaborate applications cyclic species of type 2 have mainly been utilized, partly due to their ready accessibility from cyclic imides[2,3]. Intramolecular reactions of acyclic species 1 with olefins are scarce[4] and with acetylenes are unknown as far as we know. In this context it is interesting to note that in intermolecular reactions 1 acts as a heterodiene in a Diels-Alder fashion[1c,5]. Of course, such reactivity is impossible for 2 because of its s-trans heterodienic structure.



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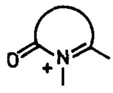

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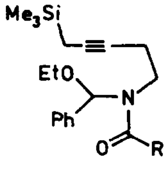
Recently, we reported intramolecular reactions of N-acyliminium ions of type 2 with allyl and propargyl silanes[6], and found that these silicon containing π-nucleophiles are more reactive and sometimes show even better regiocontrol than ordinary olefins and acetylenes. It occurred to us that propargyl and allyl silanes might also engender successful intramolecular reactions with acyclic N-acyliminium ions 1. This paper describes our experiments with propargyl silanes, while the accompanying paper reports allyl silane reactions[4].

As precursors for N-acyliminium ions we synthesized the α-ethoxyamides 3d and 4d and the α-ethoxycarbamates 3d' and 5d. The alcohols 3a-5a[6,7] served as starting materials. Pentynol 3a and hexynol 4a were converted into primary amines 3b and 4b (overall yield for both cases 88%) via the sequence: a) mesylation ($MeSO_2Cl$, Et_3N, CH_2Cl_2, 0→20°C); b) substitution with azide (NaN_3 (8 eq, DMF, 110°C, 1.5 h) and c) reduction[8] (PPh_3, THF, 2h; then H_2O, 16 h). Imines 3c and 4c were obtained in quantitative yield by treatment of 3b and 4b with a small excess of benzaldehyde in toluene at r.t., and azeotropic removal of the water in vacuo. Imine 5c was obtained from 5a via the sequence: a) oxidation to aldehyde 5b (CrO_3, C_5H_5N, CH_2Cl_2)[9] and b) imine formation ($PhCH_2NH_2$ (neat), then KOH pellets)[10]. Ethoxyamides 3d and 4d were synthesized in a one pot

$$Me_3SiCH_2C \equiv C(CH_2)_nX$$

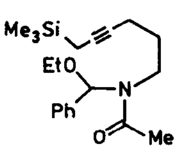
	3a	3b	3c	4a	4b	4c	5a	5b	5c
X	OH	NH_2	N=CHPh	OH	NH_2	N=CHPh	OH	CHO	$CH=NCH_2Ph$
n	2	2	2	3	3	3	4	3	3

procedure[11] by treating 3c and 4c, successively, with 1.2 eq of acetylchloride (r.t., CH_2Cl_2, 30 min), 1.5 eq of triethylamine (2 min, r.t.) and 5 eq of anhydrous ethanol (1 h, r.t.). The pure products were obtained as colourless oils after flash chromatography in 77% (3d) and 57% (4d) overall yield from the primary amines. Their ^1H NMR spectra[12] were rather complex as a result of hindered rotation around the amide bond. Both amides were a 2.5:1 mixture of rotamers, determined by integration of the singlets from the benzylic protons (6.97 ppm for the major and 5.95 ppm for the minor rotamer in both 3d and 4d). A much simpler reaction to arrive at N-acyliminium ion precursors appeared to be the addition of commercially available diethyl pyrocarbonate (6) to imines with expulsion of CO_2[13]. Reaction of 3c with 1.2 eq of 6 for 24 h at 60°C in a small amount of ethanol furnished 3d' in 87% yield (overall from amine 3b) after flash chromatography. The ^1H NMR spectrum[12] of 3d' now showed a broad singlet at 6.5 ppm for the benzylic proton. The reaction of imine 5c with 6 was much faster, and was complete after 2 h at r.t. The product 5d was rather sensitive and was used in crude state for the cyclization reaction. It showed its methine proton in the ^1H NMR spectrum as a triplet (7 Hz) at 6.60 ppm.

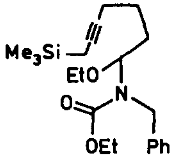


3d R = Me

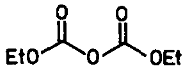
3d' R = OEt



4d



5d



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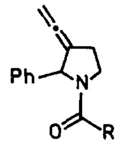
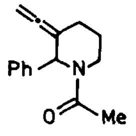
For the cyclizations we first tried simple stirring in neat formic acid, conditions that in the past had worked best for ring closures via intermediates of type 2[6b]. In this manner 3d and 4d were converted after 17 h at r.t. into allenes 3e[14] and 4e[15] in yields of 68% and 74%, respectively, after flash chromatography. According to ^{1}H NMR[12] 3e was a 2:1 mixture of amide rotamers with characteristic absorptions at 4.86 (m) for the allene protons and at 5.36 (br s, major rotamer) and 5.68 (br s, minor rotamer) for the benzylic proton. Amide 4e was a 1:1 mixture with allene protons at 4.88 (m) and the benzylic proton at 5.58 (s) and 6.52 (s). Yields of cyclization products were moderate due to competing hydrolysis, followed by protodesilylation giving benzaldehyde and 3f or 4f. This side reaction was even more a problem in the cyclization of 3d' leading to a 1:1 mixture of 3e' and 3f'. The side reaction was completely suppressed by performing the cyclization in CH_2Cl_2 at 0°C with Et_2AlCl (3 eq) as Lewis acid. In this way 3e'[16] was obtained in 55% yield after flash chromatography. The ^{1}H NMR spectrum[12] showed the allene protons at 4.84 (m) and the benzylic proton at 5.44 (br s).

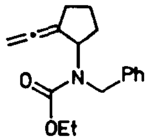


3e R = Me

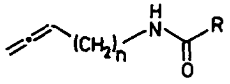
3e' R = OEt



4e



5e



3f n = 2 , R = Me

3f' n = 2 , R = OEt

4f n = 3 , R = Me

Cyclizations discussed so far were of the exo-dig-endo-trig type[17]. Ring closure of 5e would be of the 5-exo-dig-exo-trig type[17], and proceeded well by stirring 5d in formic acid for 1 h at r.t. to give 5e[18] in about 50% overall from 5a. Characteristic signals in the ^{1}H NMR spectrum come from the allene protons (AB system, J=5 Hz, centered at 4.75 ppm), the benzylic protons (AB system, J= 16 Hz, 4.66 and 4.26 ppm) and the methine proton (br, 5.16 ppm).

In summary, we have shown that acyclic N-acyliminium ions of type 1 react well as electrophiles in intramolecular reactions with propargyl silanes. The products are hetero- or carbocyclic α-allenic amides or carbamates, which may be of interest for two reasons. First, allenes of increasing utility in synthesis[19]. Second, the allenes described here are precursors to α-allenic amines, which in certain cases exhibit physiological activity as mechanism based enzyme inhibitors[20].

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15 IR (neat liq): 1965, 1635 cm^{-1}; ^{13}C NMR (62.9 MHz, $CDCl_3$, major rotamer): δ 205.2 (s), 170.1 (s), 137.7 (s), 129.0 (2C, d) 126.9 (d), 126.2 (2C, d), 98.0 (s), 75.2 (t), 61.2 (d), 37.6 (t), 26.1 (t), 25.8 (t), 21.7 (q); exact mass: calcd for $C_{15}H_{17}NO$ 227.1310, found 227.1297.

16 IR (neat liq): 1970, 1695 cm^{-1}; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 202.4 (s), 128.2 (2C, d), 127.0 (d), 125.7 (2C, d), 78.9 (t), 62.6 (d), 61.1 (t), 46.3 (t), 28.4 (br t), 14.3 (q); remaining carbons were not observed due to hindered rotation causing very broad signals; exact mass: calcd for $C_{15}H_{17}NO_2$ 243.1259, found 243.1256.

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