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LETTERS

The Bis(homoallylic) Stabilisation of an Acyliminium Ion and Reactions with Nucleophiles

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Abstract: The bis(alkylation) of N-benzylhomophthalimide by allyl bromide in the presence of aqueous ethanolic sodium hydroxide and regioselective reduction gave the bis(homoallylic) stabilised acyliminium ion precursor and hence the ion that was studied by ^{13}C nmr spectroscopy: the subsequent fate of the ion, in a number of cases leading to the formation of a new five-membered ring, was shown to depend on the Lewis acid used to generate the ion and on the nucleophiles that were present in the reaction medium. © 1998 Elsevier Science Ltd. All rights reserved.

The chemistry of acyliminium ions has been studied in considerable detail during the past two decades.[1] Our interest in this area is concerned with both mechanistic and synthetic applications of acyliminium ions.[2] Cyclisation reactions of acyliminium ions that have an alkene residue tethered either on nitrogen or at another position have been reported. In a number of cases the formation of single isomers of six-membered ring products arise from unsymmetrical bicyclic π-complexes.[3] Only in examples where alkenes were electronically biased were five-membered rings formed.[4] In the case of reactions of allyl-silanes and -stannanes the reactions were highly stereoselective.[4c,d] Vinylsilane cyclisation has also been used in the formation of the six-membered ring in (+)-streptazoline starting from tartaric acid.[5] The method continues to attract considerable attention.[6] Our most recent work has been concerned with ring annelated tetrahydroisoquinolin-1[2H]-ones in which a key synthetic step involved 1,2-alkyl-shifts involving cations derived from 4,4-dialkyl-3-hydroxy-3,4-dihydroiso-quinolin-1[2H]-one derivatives.[7]

The alkylation of *N*-benzylhomophthalimide[7] with allyl bromide in aqueous ethanolic sodium hydroxide solution gave the 4,4-diallyl-3,4-isoquinolin-1[2H],3[4H]-dione in 91% yield. Regioselective reduction was effected with sodium borohydride and gave the 4,4-diallyl-3-hydroxy-3,4-dihydroisoquinolin-1[2H]-one (**1**) in 46% yield. Treatment of a solution of the carbinolamide (**1**) in deuteriochloroform with boron trifluoride etherate at 298 K resulted in the generation of the bis(homoallyl)-stabilised acyliminium ion (**2**) and allowed the collection of the ^{13}C nmr spectrum, the chemical shifts of which are shown against the structure. *N*-Acyliminium ions generated from α-alkoxycarbamates have been detected previously using ^{13}C nmr spectroscopy.[8] Our data demonstrate the result of the greater electron withdrawing effect of the amide carbonyl group as compared to the effect of an alkoxycarbonyl residue in a carbamate. In addition the data show that both allyl residues are identical and that each carbon atom is deshielded with respect to the shifts of the starting material, as a result of π-electron interactions with the carbenium ion centre. We may note that the ion had reasonable stability but after *ca.* 1h the ^{13}C nmr spectrum showed the presence of a new compound. In a separate experiment the reaction mixture was allowed to stand at room temperature for 2.5h and gave after work-up the compound (**3**)[9] in 60% yield. The cation evidently had been captured by fluoride ion with high stereo-selectivity. The structure of the compound (3) follows from spectroscopic data, in particular from the ^{1}H decoupled ^{13}C nmr spectrum (chemical shifts shown against the structure) and $^{1}H,^{1}H$-

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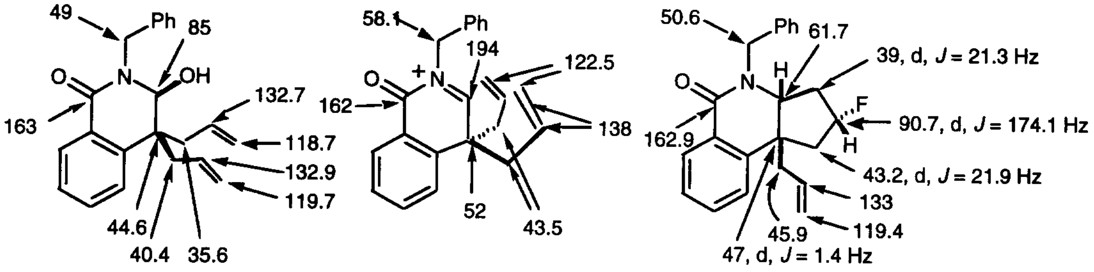
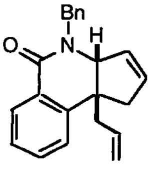
NOESY experiments at 400 MHz over two mixing times: 0.55 and 0.70 s, which confirmed the *cis*-ring junction and the *trans*- relationship of the fluorine atom and the allyl-group. It is unlikely that the compound (3) was formed completely from adventitious hydrogen fluoride and we presume that the fluorine atom arises, at least in part, from the $[HOBF_3]^-$ ion which then attacks the stabilised cation from an unhindered face.



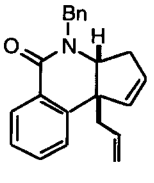
(1) (2) (3)

^{13}C Nuclear Magnetic Resonance data

Reactions were also carried out in the presence of other nucleophiles. The acyliminium ion is more stable, or more likely is formed more slowly, in diethyl ether than in the more polar chloroform. The compound (1) was allowed to react with boron trifluoride etherate in diethyl ether at room temperature for 3h 20 min. and an aliquot taken and quenched with aqueous sodium hydrogen carbonate. Analysis using thin layer chromatog-raphy showed only the presence of starting material. The reaction was therefore allowed to proceed for 24h and we then obtained, in addition to recovered starting material (2%) and the compound (3) (24%), a mixture of the alkenes (4) (minor) and (5) (major) [ratio 2:3] in a combined yield of 9% which were not separated, together with the ether (6) (7%). Reactions involving the presence of either bromide or chloride ions resulted in the loss of an allyl residue. Thus a reaction in which the carbinolamide (1) in dichloromethane was treated with $TiCl_4$ gave, after 4.5h, the product (7) in 92% yield whereas a similar reaction using $AlBr_3$ as the Lewis acid gave the product (7) in 42% yield together with recovered starting material (34%).



(4)



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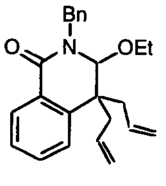

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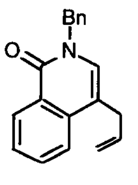

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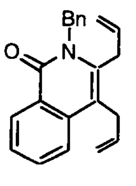
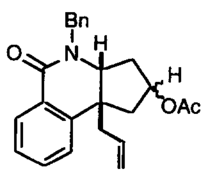


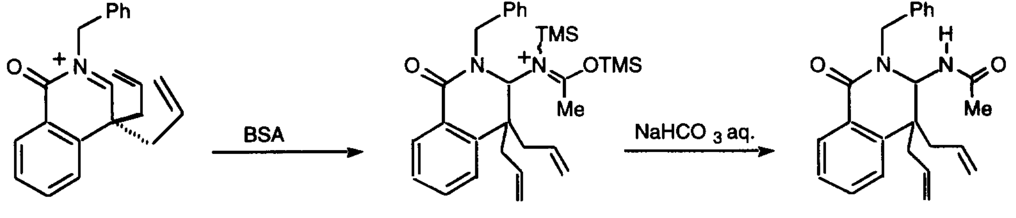
(9)



(10)

We were disappointed that we had not observed the product of the 1,2-allyl migration which would have provided a substrate for olefin metathesis. So we also carried out a series of reactions in which we generated the acyliminium ion by using trimethylsilyl triflate (TMSOTf). Although we were aware that reactions have been reported where acyliminium ions have been captured by *N*,*O*-bis(trimethylsilyl)acetamide (BSA)[10a] we wished to avoid the presence of triflic acid and so we used BSA as a proton scavenger.[10b,c] We also carried out one reaction using *N*-trimethylsilylacetamide as a potential nucleophile.

A solution of the carbinolamide (1) in dichloromethane was treated with BSA (3 equivalents) at –78 °C and then with a catalytic amount of TMSOTf before being allowed to come to room temperature. After a further 4h the reaction mixture was quenched with aqueous sodium hydrogencarbonate and worked up to give unchanged starting material (55%) and the acetamide derivative (**8**)[11], isolated in 44% yield, which we conclude was formed by hydrolysis of the silyliminium ion as shown in the **Scheme**.



(2) **(8)**

Scheme

In another experiment the carbinolamide (**1**) in dichloromethane was treated with TMSOTf (2 equiv.) at – 78 °C and then after warming to room temperature BSA (4 equiv.) was added after 1h 20min. Work up after a further 10h gave a complex mixture of products that was separated by flash chromatography. In order of increasing polarity we obtained the allyl migration product (**9**) in 15% yield, the alkene (**5**)[12] in 28% yield, the acetate (**10**)[13] as a mixture of diastereomers, in 24% yield, and the acetamide derivative (**8**) in 31% yield. Both of the compounds (**8**) and (**10**) were formed in a reaction using *N*-tri-methylsilylacetamide in place of BSA. The unexpected formation of the acetates (**10**) presumably result from capture of *N*-trimethylsilylacetamide and subsequent hydrolysis of the reaction product: this reagent may also be responsible for the formation of some of the acetamide derivative (**8**).

The results reported in this letter show that attack by a wide range of nucleophiles, either at the original site of the acyliminium ion or at a carbon atom of a tethered allyl group, occurs more readily than the 1,2-allyl shift to give after loss of a proton the compound (**9**). It is anticipated that an improved yield of the desired olefin metathesis substrate could be obtained by not having BSA in the reaction medium and by reducing the nucleophilicity of counter ions that may be present when the acyliminium ion is generated.

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9. New compounds have been fully characterised by high resolution mass spectrometry and a variety of spectroscopic techniques. $M^{+\cdot}$ found: 335.1685 $C_{22}H_{22}FNO$ $M^{+\cdot}$ requires: 335.1685: ν_{max}: 2977, 1648, 1601 cm^{-1}: δ_H 400 MHz ($CDCl_3$) 1.67-1.74 (m, 1H), 2.12-2.32 (m, 4H), 2.77-2.84 (m, 1H), 3.82 (dxd, 1H, J = 11.4 and 7.0 Hz), 4.47 (d, 1H, J = 14.4 Hz), 4.71 (dxd, 1H, J = 17.0, 1.8 Hz), 4.83-4.86 and 4.97-4.99 (m, 1H), 4.92 (dxd, 1H, J = 10.0, 1.8 Hz), 5.12 (d, 1H, J = 14.4 Hz), 5.37-5.44, (m, 1H), 7.27-7.53 (m, 8H), and 8.24-8.26 (m, 1H) ppm: δ_C 100.5 MHz ($CDCl_3$) 39.0 (d, CH_2, J = 21.3 Hz), 43.2 (d, CH_2, J = 21.9 Hz), 45.9 (CH_2), 47.0 (d, C, J = 1.4 Hz), 50.6 (CH_2), 61.7 (CH), 90.7 (d, CH, J = 174.1 Hz), 119.5 (CH_2), 126.5 (CH), 127.6 (CH), 128.1 (C), 128.2 (CH), 129.1 (CH x 2), 129.2 (CH), 129.3 (CH x 2), 132.7 (CH), 133.0 (CH), 137.8 (C), 143.0 (C), and 162.9 (C=O) ppm. Also supported by COSY 45 and ^1H-^{13}C HETCOR experiments.
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11. $M^{+\cdot}$ found: 374.1994 $C_{24}H_{26}N_2O_2$ $M^{+\cdot}$ requires: 374.1994: n_{max}: 3288, 1652, 1645, 1602 cm^{-1}: d_H 400 M Hz ($CDCl_3$) 1.82-1.86 (m, 1H), 1.87 (s, 3H), 2.01-2.04 (m, 1H), 2.33 (dxd, 1H, J = 14.8, 5.0 Hz), 2.73 (dxd, 1H, J = 14.8, 8.3 Hz), 4.14 (d, A of AB, J = 14.0 Hz), 4.65-4.69 (m,1H), 4.89-4.92 (m, 1H), 5.10-5.20 (m, 3H), 5.42 (d, B of AB, J = 14.0 Hz), 5.47 (d, 1H, J = 10.2 Hz), 5.5-5.7 (m, 1H), 5.89 (d, 1H, J = 10.2 Hz), 7.22-7.54 (m, 8H), and 8.19-8.21 (m, 1H) ppm: d_C 62.8 M Hz ($CDCl_3$) 23.3 (CH_3), 36.1 (CH_2), 41.1 (CH_2), 43.5 (C), 48.3 (CH_2), 65.8 (CH), 119.1 (CH_2), 119.7 (CH_2), 126.2 (CH), 127.6(8) (CH), 127.7(3) (CH), 127.8 (C), 128.6 (CH x 2), 129.2(5) (CH), 129.6 (CH x 2), 131.9(5) (CH), 132.1 (CH), 132.2 (CH), 136.8 (C), 140.7 (C), 162.9 (C=O), and 170.0 (C=O) ppm. Supported by ^1H-^{13}C HETCOR experiments.
12. $M^{+\cdot}$ found: 315.1624 $C_{22}H_{21}NO$ $M^{+\cdot}$ requires: 315.1623: ν_{max}: 2919, 1647, 1602 cm^{-1}: δ_H 400 MHz ($CDCl_3$) 2.02-2.07 (m, 1H). 2.12 (dxd, 1H, J = 13.9, 8.5 Hz), 2.27 (dxd, 1H, J = 13.9, 6.3 Hz), 2.45-2.51 (m, 1H), 3.69 (dxd, 1H, J = 9.3, 7.6 Hz), 4.26 (d, A of AB, J = 14.4 Hz), 4.41 (dxd, 1H, J = 17.0, 1.5 Hz), 4.74 (dxd, 1H, J = 10.1, 1.5 Hz), 5.15 (d, B of AB, J = 14.4 Hz), 5.35-5.43 (m, 1H), 5.68-5.70 (m, 1H), 5.97 (dxd, 1H, J = 6.2, 2.2 Hz), 7.05 (dxd, 1H, J = 8.7, 0.7 Hz), 7.20-7.39 (m, 7H), and 8.11-8.15 (m, 1H) ppm: δ_C 100.5 MHz ($CDCl_3$) 38.7 (CH_2), 45.2 (CH_2), 50.1 (CH_2), 51.0 (C), 62.3 (CH), 119.1 (CH_2), 127.0 (CH), 127.2 (CH), 127.3 (C), 128.1 (CH), 128.4 (CH), 129.0 (2xCH), 129.3 (2xCH), 130.5 (CH), 132.7 (CH), 133.3 (CH), 136.2 (CH), 138.1 (C), 142.2 (C), and 163.3 (C=O) ppm.
13. $M^{+\cdot}$ found: 375.1836 $C_{24}H_{25}NO_3$ $M^{+\cdot}$ requires: 375.1834: major diastereomer, n_{max}: 2978, 1736, 1645, 1602 cm^{-1}: δ_H 400 MHz ($CDCl_3$) 1.5-1.62 (m, 1H), 1.70 (s, 3H), 2.04-2.14 (m, 2H), 2.17-2.21 (m, 1H), 2.36-2.52 (m, 2H), 3.44 (dxd, 1H, J = 10.5, 7.9 Hz), 4.39 (d, 1H, J = 14.4 Hz), 4.64-4.73 (m,1H), 4.88-4.94 (m, 2H), 5.09 (d, 1H, J = 14.1 Hz), 5.3-5.41 (m, 1H), 7.22-7.51 (m, 8H), and 8.19-8.25 (m, 1H) ppm: δ_C 100.5 MHz ($CDCl_3$) 21.3 (CH_3), 38.5 (CH_2), 41.3 (CH_2), 45.6 (CH_2), 46.7 (C), 50.4 (CH_2), 62.2 (CH), 71.6 (CH), 119.5 (CH_2), 127.0 (CH), 127.3 (CH), 127.8 (C), 128.2 (CH), 129.1 (CH x 2), 129.2 (CH x 3), 132.7 (CH), 133.0 (CH), 137.8 (C), 143.0 (C), 163.2 (C=O), and 171.1 (C=O) ppm. Supported by COSY 45, ^1H-^{13}C HETCOR, and ^1H,^1H NOESY experiments.