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N-Acyliminium ion cyclisation versus rearrangement. The synthesis of 13,13-dimethylberberines and 3,4-dimethylisoquinolin-1-ones

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Abstract

The regioselective reduction of a range of *N*-substituted-4,4-dimethylhomophthalimide derivatives gave the related carbinol amides that function as acyliminium ion precursors in the presence of Lewis or protic acids; the fate of the acyliminium ions is determined in part by the nucleophilicity of the β-arylethyl group on nitrogen, the electrophile used to generate the ion, and the precise reaction conditions and led either to cyclisation reactions or methyl migration.

Keywords: amido-alcohols; cyclisation; diastereoselection; nitrogen heterocycles.

The chemistry of acyliminium ions has been studied in considerable detail during the past two decades,[1] and the method continues to attract considerable attention.[2] A number of research groups have used the chemistry of acyliminium ions in routes to alkaloids or in the synthesis of compounds with potential biological activity.[3] Other targets have included isoquinolones by Friedel–Crafts amidoacylation reactions,[4a] and antagonists of platelet aggregation.[4b] Our interest in this area is concerned with both mechanistic and synthetic applications of acyliminium ions.[5] Our most recent work has been concerned with ring annelated tetrahydroisoquinolin-1[2*H*]-ones in which a key synthetic step involved 1,2-alkyl-shifts involving cations derived from 4,4-dialkyl-3-hydroxy-3,4-dihydroisoquinolin-1[2*H*]-one derivatives.[5c] A limited number of cyclisation reactions of *N*-β-arylacyliminium ions have been reported.[6] We now describe the use of a number of protic and Lewis acids in reactions of carbinolamides that result in the formation of 13,13-dimethylberberine derivatives and 3,4-dimethylisoquinolones.

The carbinolamides were prepared in three steps from commercially available homophthalic anhydride. Heating the anhydride with a variety of arylalkylamines at 200°C for 90–120 min gave the homophthalimide derivatives (**1a**–**e**) in yields ranging from 31 to 92%. The methylation of the compounds (**1a**–**e**) was carried out in aqueous ethanolic sodium hydroxide solution with an excess of

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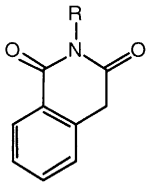
methyl iodide and gave the 4,4–dimethyl-3,4-isoquinolin-1[2*H*],3[4*H*]-dione derivatives (**2a**–**e**) in yields ranging from 74 to 95%.† The regioselective reduction of the compounds (**2a**–**e**) were carried out using an excess of $NaBH_4$ in ethanol at −7°C followed by extraction after the addition of sodium hydrogen carbonate and gave the carbinolamides (**3a**–**e**) in 21 to 85% yields. The homophthalimide (**1e**) and the carbinolamide (**3e**) were those associated with the lowest yields.



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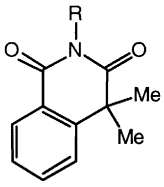
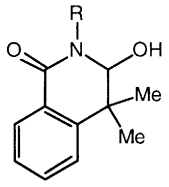


2

[**1a**,**2a**, **3a**, R = β-phenylethyl]
[**1b**, **2b**, **3b**, R = 3,4-dimethoxy-β-phenylethyl]
[**1c**, **2c**, **3c**, R = β-(3-indolyl)ethyl]
[**1d**, **2d**, **3d**, R = β-(3-methoxyphenoxy)ethyl]
[**1e**, **2e**, **3e**, R = α-ethoxycarbonyl-β-(3-indolyl)ethyl]



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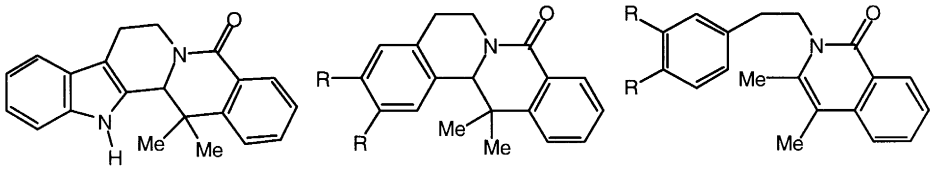
The iminium ion is formed particularly easily from the carbinolamide **3c** as evidenced by the partial conversion of a solution of **3c** in DMSO into **4** in 11% yield over a period of 10 days. When the carbinolamide **3c** was allowed to stand with aluminium chloride in THF at 0°C for 1 h it was converted into the β-carboline derivative **4** in 87% yield. On the other hand, the products formed in reactions of the carbinolamides **3a** and **3b** were found to depend on the reaction conditions used. When the carbinolamide **3a** was allowed to react with either aluminium chloride or bromide a mixture of the berberine derivative **5a**‡ and the isoquinolone **6a**§ was formed in ratios¶ that were dependent on the choice of reaction temperature and solvent. In view of the low solubility of aluminium chloride at low temperatures in either dichloromethane or *o*-dichlorobenzene we used aluminium bromide as the preferred Lewis acid. At low temperatures the compound **5a** was the major product while at high temperatures the compound **6a** predominated. Thus at −5°C in *o*-dichlorobenzene the ratio of **5a** to **6a** was 7:3 while in dichloromethane the ratio was 9.5:0.5. At ambient temperatures the ratios were almost 1:1 but at 180°C using either aluminium bromide or aluminium chloride as the Lewis acid the ratio of **5a** to **6a** was 0.6:9.4. Although the reactions leading to the two types of products are clearly irreversible the results suggest that the transition state leading to **5a** is early on the reaction coordinate while that leading to **6a** is a late transition state. Global energy calculations, conducted using SYBYL, showed that the minimum energies for **5a** and **6a** are 2.98 and 0.28 kJ/mol, respectively, thus supporting the view that although **5a** is kinetically accessible, **6a** is the thermodynamically preferred product.

† New compounds have been fully characterised by elemental analysis or by accurate mass measurement of the molecular ion by high resolution mass spectrometry and by spectroscopic methods including appropriate ^1H and ^{13}C NMR studies on homogeneous material and by infrared measurements.

‡ M^+ 277.1468, $C_{19}H_{19}NO$ requires 277.1467: ν_{max}: 2955, 1647, and 1602 cm^{-1}: δ_H 250 MHz ($CDCl_3$) 0.90 (s, 3H, Me), 1.40 (s, 3H, Me), 2.72–3.0 (m, 3H), 4.81 (s, 1H), 4.97–5.04 (m, 1H), 7.17–7.48 (m, 7H), and 8.12–8.16 (m, 1H) ppm: δ_C 62.8 MHz ($CDCl_3$) 23.07 (Me), 23.79 (Me), 29.97 (CH_2), 39.56 (CH_2), 40.70 (C), 64.88 (CH), 123.35 (CH), 125.23 (CH), 126.84 (CH), 127.27 (CH), 128.24 (C), 128.47 (CH), 128.98 (CH), 130.13 (CH), 131.76 (C), 132.01 (CH), 138.61 (C), 147.68 (C), and 164.38 (C=O) ppm. DEPT, COSY 45, and ^1H–^{13}C HETCOR experiments support the assignments.

§ M^+ 277.1458, $C_{19}H_{19}NO$ requires 277.1467: ν_{max}: 3050,1645, and 1614 cm^{-1}: δ_H 250 MHz ($CDCl_3$) 2.32 (s, 3H, Me), 2.40 (s, 3H, Me), 3.01–3.07 (m, 2H), 4.33–4.40 (m, 2H), 7.27–7.69 (m, 8H), and 8.49–8.52 (m, 1H) ppm: δ_C 100.5 MHz ($CDCl_3$) 13.75 (Me), 16.22 (Me), 34.79 (CH_2), 46.34 (CH_2), 109.01 (C), 122.41 (CH), 124.39 (C), 125.52 (CH), 126.37 (CH), 127.81(CH), 128.33 (2×CH), 128.41 (2×CH), 131.90 (CH), 134.82 (C), 136.95 (C), 138.48 (C), and 162.18 (C=O) ppm. DEPT, COSY 45, and ^1H–^{13}C HETCOR experiments support the assignments.

¶ The ratios of mixtures of products were estimated from ^1H NMR spectra of crude reaction mixtures.



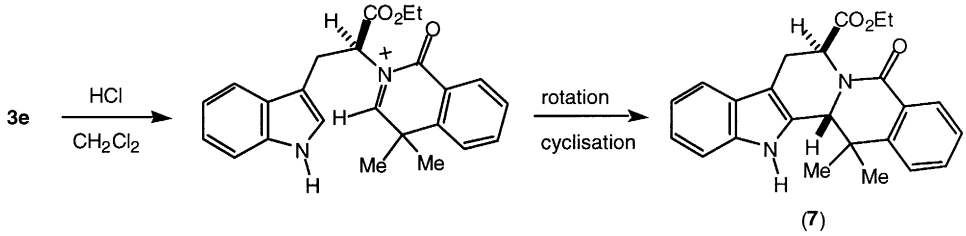
4 **5a**, R = H; **5b**, R = OMe; **6a**, R = H; **6b**, R = OMe

Reactions involving the carbinolamide **3b** showed a different trend. The electron releasing methoxy group at the 3-position in the carbinolamide **3b** clearly promotes the cyclisation pathway both at ambient and elevated temperatures when only one equivalent of aluminium bromide was used. The yields of **5b** and **6b** were 72% and 20%, respectively, at ambient temperature in dichloromethane and 78% and 22%, respectively, when the reaction was carried out at 180°C in *o*-dichlorobenzene. On the other hand reactions carried out at −5°C with either 1 or 3 mol equivalents of aluminium bromide or with 3 mol equivalents of aluminium bromide at ambient temperatures strongly favour the migration route to the isoquinolone derivative **6b**. A reaction carried out at −5°C was incomplete after 2 h but the isoquinolone derivative **6b** was the only product formed in 42% yield whereas at ambient temperature the compound **6b** was formed in a quantitative yield after 2 h. These results clearly reflect the ability of aluminium bromide to complex with the oxygen atoms that are present in the 3,4-dimethoxyphenyl residue and thereby reduce the nucleophilicity of the aryl residue. Similar effects have been noted in connection with Friedel–Crafts acylation reactions of a range of benzene derivatives that carry *ortho*-oxygen substituents.[7]

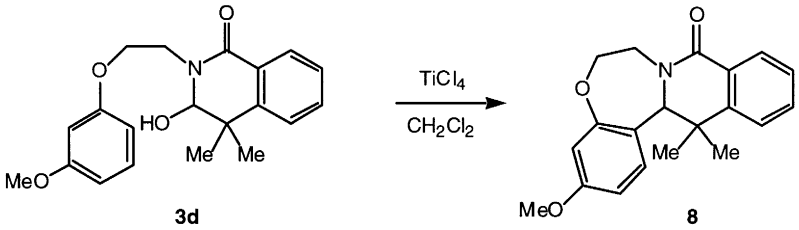
We were also interested to investigate possible diastereoselectivity effects in the cyclisation reactions and selected for that purpose the carbinolamide **3e** that was prepared starting from the ethyl ester of tryptophan. The β-carboline derivative **7** was isolated in 77% yield as a single diastereomer when a solution in CH_2Cl_2 was treated with a catalytic amount of hydrogen chloride. The gross structure was confirmed[††] using the usual spectroscopic methods and the configuration at the newly formed ring-junction was established by a consideration of the ^1H–^1H spin–spin coupling constants and ^1H–^1H NOESY experiments. We assume that the *cis*-relationship of the ethoxycarbonyl group and the hydrogen at the newly formed ring-junction is formed with high diastereoselectivity as a result of rotation about the bond between the β-indolyl residue and the remainder of the acyliminium ion fragment. Cyclisation is presumed to be strongly favoured when rotation proceeds in a direction away from the ethoxycarbonyl group that places the two hydrogen atoms *trans* to each other and the ethoxycarbonyl moiety in a pseudo-axial position (Scheme 1).

Cyclisation reactions were not restricted to the formation of six-membered ring products. The conversion of the carbinolamide **3d** into the oxazepinoisoquinolone derivative **8** was achieved in modest yield (32%) in a reaction carried out using titanium tetrachloride in dichloromethane, by starting at −78°C and allowing the reaction mixture to warm slowly to ambient temperature (Scheme 2).

[††] M^+ 388.1784, $C_{24}H_{24}N_2O_3$ requires 388.1787: ν_{max}: 3302 (br), 2978, 1734, 1638, and 1602 cm^{-1}: δ_H 400 MHz ($CDCl_3$) 0.82 (t, 3H, *J*=7.1 Hz), 0.94 (s, 3H, Me), 1.56 (s, 3H, Me), 3.00 (d×d, 1H, B of ABX, J_{AB}=15.2 Hz, J_{BX}=5.4 Hz), 3.45 (d×d, 1H, A of ABX, J_{AB}=15.2 Hz, J_{AX}=1.8 Hz), 3.77–3.86 (m, 2H), 5.02 (s, 1H), 5.85 (dxd, X of ABX, J_{AX}=1.8 Hz, J_{BX}=5.4 Hz), 7.02–7.47 (m, 7H), 8.12–8.14 (m, 1H), and 8.18 (br s, 1H, N–H) ppm: δ_C 62.8 MHz ($CDCl_3$) 14.00 (Me), 23.14 (Me), 23.26 (Me), 23.67 (CH_2), 40.35 (C), 52.32 (CH), 61.10 (CH), 61.21 (CH_2), 110.35 (C), 111.03 (CH), 118.15 (CH), 119.78 (CH), 122.41 (CH), 123.43 (CH), 126.35 (C), 127.09 (CH), 127.47 (C), 129.54 (CH), 129.85 (C), 132.68 (CH), 136.34 (C), 147.09 (C), 165.65 (C=O), and 171.22 (C=O) ppm. DEPT, COSY 45, and ^1H–^{13}C HETCOR experiments support the assignments. The relative orientations of the ethoxycarbonyl group and the vicinal methylene and bridgehead methine hydrogen atoms were established by 400 MHz ^1H–^1H NOESY experiments carried out in $CDCl_3$ at 298 K over a mixing time of 0.7 sec.



Scheme 1.



Scheme 2.

Acknowledgements

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