Synthesis of 3-spiroannulated hexahydro-6,8a-epoxyisoquinolines

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The title compounds were synthesised by the intramolecular [4+2]-cycloaddition of 1-*N*-furfurylamino-1-allylcyclanes in the presence of acetic anhydride.

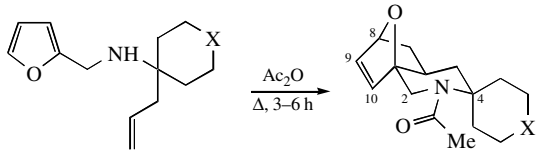
The intramolecular [4+2]-cycloaddition of 1-*N*-alkenylfurfurylamines is widely used for building hexahydro-3a,6-epoxyindole and hexahydro-3a,6-isoindole systems. The intramolecular Diels–Alder reaction in the furan series is more rarely used to synthesise hexahydro-6,8a-epoxyquinolines[1–3] and hexahydro-6,8a-isoquinolines[3–7] because the parent compounds are inaccessible and the cycloaddition occurs ambiguously. The synthesis of analogous spiroannulated structures was not described previously.[8]

Here, we propose a facile synthetic route to 3-spiroannulated 6,8a-epoxyisoquinolines **2a–e** based on the intramolecular [4+2]-cycloaddition of 1-allyl-1-*N*-furfurylaminocycloalkanes **1a–e**. Starting homoallylamines **1** are formed in high yields in the reaction of the appropriate Schiff bases with allylmagnesium bromide.[9,10] Compound **1e** (X = CHBu^t) is formed as a mixture of two isomers with different arrangements of the *tert*-butyl and allyl groups, the major isomer being a diequatorial derivative. According to the ^{1}H NMR data, the ratio between *e*-1-allyl-*e*-4-*tert*-butyl and *a*-1-allyl-*e*-4-*tert*-butyl is approximately 1.5:1.

The refluxing of amines **1** in an excess of acetic anhydride† is accompanied by easy intramolecular *exo*-[4+2]-cyclization of intermediate *N*-acetyl derivatives. In this case, 3-spiroannulated hexahydro-6,8a-epoxyisoquinolines **2a–e** are formed in moderate yields. These compounds are colourless crystalline substances stable in storage. The reaction of an isomeric mixture of **1e** with an excess of acetic anhydride leads to the formation of isomeric bicyclic compounds **2e**, the fractional crystallization of which gave major diequatorial derivative **2e** (maj).

Note that a mixture of isomeric *tert*-butyl-substituted allylamines **1e** slowly undergoes cyclization even at room temperature to form an isomer mixture of **2f**. Both isomers were chromatographically separated in moderate yields. Their structure will be reported elsewhere.

The structures of synthesised epoxyisoquinolines **2a–f** were found from spectroscopic data.‡ The mass spectra exhibited the peaks of molecular ions in accordance with the empirical formulae. The pyrilium ion (*m*/*z* 81), which is formed by the retrodiene decomposition of an oxabicyclo[2.2.1]heptene unit, exhibited maximum peak intensities in the mass spectra of all of the compounds. The IR spectra exhibited characteristic bands



2	X	Yield (%)
a	—	48
b	CH_2	68
c	$(CH_2)_2$	66
d	NEt	48
e (maj)	CHBu^t	44
f[a]	CHBu^t	25

[a]The overall yield of the isomer mixture.

† *Typical procedure for the synthesis of 4-annulated 11-oxa-3-azatricyclo[6.2.1.0^{1,6}]undec-9-enes* **2a–e**: 0.1 mol of homoallylamine **1** with a 20-fold molar excess of acetic anhydride was refluxed for 3–6 h. An excess of the anhydride was distilled in a vacuum. The residue was added to 200 ml of water, and the solution was alkalified with sodium carbonate to pH 9–10. The mixture was extracted with ethyl acetate (3×70 ml), and the extract was dried with $MgSO_4$. The residue after the distillation of the solvent was recrystallised from hexane–ethyl acetate. Bicyclic compounds **2** were obtained as colourless crystals.

‡ **2a**: mp 88–89 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.36 (dd, 1H, *J* 6.0 and 1.3 Hz), 6.09 (d, 1H, *J* 6.0 Hz), 4.91 (dd, 1H, *J* 4.0 and 1.3 Hz), 4.03 (d, 1H, *J* 15.4 Hz), 3.94 (d, 1H, *J* 15.4 Hz), 2.10 (s, 3H, Me), 2.22–1.95 and 1.79–1.42 (m, 13H). IR (KBr, ν/cm^{-1}): 1630 (C=O and C=C). MS (EI, 70 eV), *m*/*z* (%): 247 (M$^+$, 18), 206 (10), 204 (6), 164 (6), 126 (15), 122 (9), 82 (7), 81 (100), 53 (6), 43 (11), 41 (5). Found (%): C, 72.62; H, 8.24; N, 5.81. Calc. for $C_{15}H_{21}NO_2$ (%): C, 72.87; H, 8.50; N, 5.67.

2b: mp 134–135 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.35 (dd, 2H, *J* 1.8 and 5.8 Hz), 4.92 (dd, 1H, *J* 4.3 and 1.8 Hz), 3.97 (d, 1H, *J* 15.3 Hz), 3.80 (d, 1H, *J* 15.3 Hz), 2.17 (s, 3H, Me), 1.42 (m, 1H), 1.92 (dd, 1H, *J* 12.8 and 4.6 Hz), 1.6–1.2 (m, 13H). IR (KBr, ν/cm^{-1}): 1630 (C=O and C=C). MS (EI, 70 eV), *m*/*z* (%): 261 (M$^+$, 63), 220 (19), 218 (13), 204 (34), 176 (12), 140 (40), 122 (14), 121 (29), 81 (100), 43 (25), 40 (26). Found (%): C, 73.36; H, 8.79; N, 5.24. Calc. for $C_{16}H_{23}NO_2$ (%): C, 73.56; H, 8.81; N, 5.36.

2c: mp 135–136 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.32 (s, 2H), 4.90 (d, 1H, *J* 4.3 Hz), 4.04 (d, 1H, *J* 15.0 Hz), 3.47 (d, 1H, *J* 15.0 Hz), 2.14 (s, 3H, Me), 1.96 (dd, 1H, *J* 11.3 and 3.1 Hz), 1.41 (dt, 1H, *J* 11.3 and 4.3 Hz), 1.2–2.0 (m, 15H). IR (KBr, ν/cm^{-1}): 1623 (C=O and C=C). MS (EI, 70 eV), *m*/*z* (%): 275 (M$^+$, 45), 234 (12), 204 (24), 176 (11), 154 (41), 135 (18), 122 (11), 81 (100), 53 (10), 43 (18), 41 (11). Found (%): C, 74.27; H, 9.15; N, 5.26. Calc. for $C_{17}H_{25}NO_2$ (%): C, 74.18; H, 9.10; N, 5.10.

2d: mp 113–114 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.38 (dd, 1H, *J* 1.5 and 5.8 Hz), 6.08 (d, 1H, *J* 5.8 Hz), 4.93 (d, 1H, *J* 1.5 and 3.7 Hz), 4.04 (d, 1H, *J* 15.0 Hz), 3.89 (d, 1H, *J* 15.0 Hz), 2.16 (s, 3H, Me), 2.65–2.22 and 1.9–1.34 (m, 14H), 1.43 (dt, 1H, *J* 11.3, 3.7 and 8.2 Hz), 1.08 (t, 3H). IR (KBr, ν/cm^{-1}): 1674 (C=O). MS (EI, 70 eV), *m*/*z* (%): 290 (M$^+$, 27), 275 (10), 248 (14), 247 (100), 152 (42), 150 (18), 124 (14), 123 (13), 122 (21), 110 (64), 108 (14), 85 (14), 84 (25), 58 (12), 56 (11), 43 (17), 41 (8). Found (%): C, 70.52; H, 8.78; N, 9.55. Calc. for $C_{17}H_{26}N_2O_2$ (%): C, 70.31; H, 9.02; N, 9.65.

2e: mp 154–154.5 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.38 (dd, 1H, *J* 1.5 and 5.8 Hz), 6.05 (d, 1H, *J* 5.8 Hz), 4.91 (dd, 1H, *J* 1.5 and 4.6 Hz), 4.10 (d, 1H, *J* 15.9 Hz), 3.52 (d, 1H, *J* 15.9 Hz), 2.16 (s, 3H), 2.5–2.2 and 1.95–0.95 (m, 13H), 0.85 (s, 9H). IR (KBr, ν/cm^{-1}): 1637 (C=O and C=C). MS (EI, 70 eV), *m*/*z* (%): 317 (M$^+$, 5), 260 (11), 218 (10), 196 (13), 177 (12), 176 (16), 122 (10), 107 (10), 91 (12), 81 (100), 79 (13), 57 (56), 54 (15), 43 (50), 41 (34). Found (%): C, 75.58; H, 9.83; N, 4.26. Calc. for $C_{20}H_{31}NO_2$ (%): C, 75.70; H, 9.78; N, 4.41.

2f (maj): mp 127–129 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.37 (dd, 1H, *J* 5.8 and 1.8 Hz), 5.97 (d, 1H, *J* 5.8 Hz), 4.92 (dd, 1H, *J* 1.8 and 4.6 Hz), 3.52 (d, 1H, *J* 15.3 Hz), 3.32 (d, 1H, *J* 15.3 Hz), 2.3–2.15 and 1.8–1.0 (m, 14H), 0.86 (s, 9H). IR (KBr, ν/cm^{-1}): 3320 (NH), 1610 (C=C). MS (EI, 70 eV), *m*/*z* (%): 275 (M$^+$, 8), 176 (47), 154 (16), 83 (13), 81 (100), 79 (10), 77 (10), 57 (47), 53 (23), 41 (54), 39 (12). Found (%): C, 78.72; H, 10.70; N, 5.21. Calc. for $C_{18}H_{29}NO$ (%): C, 78.49; H, 10.61; N, 5.09.

due to the stretching vibrations of the amide C=O group at 1623–1674 cm^{-1}. The ^1H NMR spectra of compounds **2a–f** contained no signals of allylic protons (4.8–5.3 ppm), which are present in the spectra of starting amines **1a–e**. At the same time, the spectra exhibited the proton systems H-8 (dd) and H-9 (dd), and H-10 (dd) at 4.90–4.93 and 5.97–6.32 ppm, respectively, with the vicinal constants $J_{8,9}$ 1.3–1.8 and $J_{9,10}$ 5.8–6.0 Hz, respectively. These systems are typical of 7-oxabicyclo[2.2.1]heptenes.[3] The *exo*-configuration of adducts **2a–e** was established on the basis of $J_{7\text{-}exo,6\text{-}endo}$ 2.8–3.2 Hz values compared with published data.[3,11]

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