Tetrahedron Letters, Vol. 34, No. 20, pp. 3331-3334, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

# [2,3] Sigmatropic Rearrangement of 1-Vinylic Tetrahydroisoquinoline *N*-Ylides and *N*-Oxides.

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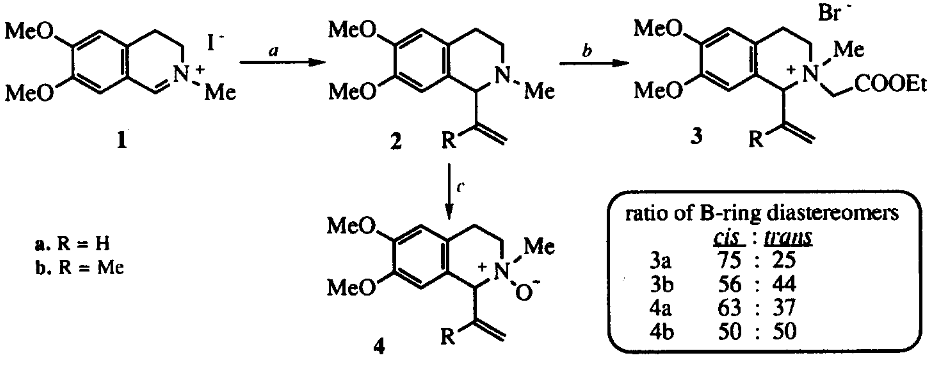
***Abstract:*** [2,3] Sigmatropic rearrangement of the *N*-ylides from the 1-vinyl and 1-(1-propenyl) tetrahydroisoquinolinium salts **3a** and **3b** at room temperature in acetonitrile gave high yields of the functionalised 3-benzazonine derivatives **6a** (90%: *E*/*Z* = 19) and **6b** (93%: *E*/*Z* = 2) respectively. The *N*-oxide analogues **4a** and **4b** gave the 2,3-benzoxazepines **8a** and **8b**, together with the first representative of the 4,3-benzoxazonine system, **9b**, from **4b**.

2-Vinylpyrrolidine[1a] and piperidine[1b] *N*-ylides are known to undergo [2,3] sigmatropic rearrangements with ring expansion[1c]. A [2,3] sigmatropic rearrangement was postulated as the initial step in the overall Stevens rearrangement of 1-phenyl tetrahydroisoquinoline *N*-ylide derivatives[1d]. In contrast 2-vinylpiperidine *N*-oxide[2a] underwent only the Meisenheimer rearrangement. More complex allylic *N*-oxide systems have, however, been reported to produce [2,3] rearrangement and ring expansion[2b,c,d]. We now wish to report the analogous rearrangements of 1-vinylic tetrahydroisoquinoline *N*-ylide **5** and *N*-oxide **4** derivatives. The rearrangements provide both a new and convenient route to functionalised 3-benzazonines[3] and also access to the previously undescribed 4,3-benzoxazonine system.

**Scheme 1.**

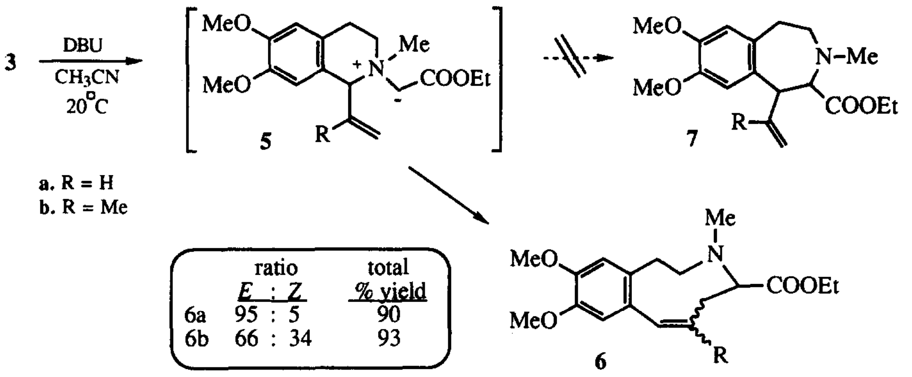


| ratio of B-ring diastereomers | *cis* | : | *trans* |
|---|---|---|---|
| 3a | 75 | : | 25 |
| 3b | 56 | : | 44 |
| 4a | 63 | : | 37 |
| 4b | 50 | : | 50 |

**Reagents:** *a)* $BrMgC(R)CH_2$ *b)* $BrCH_2COOEt$ *c)* m-CPBA

The precursors required for the rearrangements were prepared from the iminium salt **1**[4]. Addition of **1** to the appropriate alkenyl Grignard reagent in THF at -78°C, then stirring at RT for 15 hrs, gave the bases **2** in excellent yields (Scheme 1)[5]. The quaternary salts **3** were obtained by *N*-alkylation with neat ethyl bromoacetate, trituration of the crude product with ether and crystallisation from ethanol/THF. The *N*-oxides **4** were obtained by oxidation of **2** with *m*-CPBA in $CH_2Cl_2$ at 0-25°C and were utilised as crude oils. In both cases the products were observed by NMR to be mixtures of B ring diastereomers. By analogy with the piperidine system the major product was assumed to be the *cis* diastereomer, formed by axial attack on the nitrogen with the alkenyl substituent in the equatorial position.

**Scheme 2**

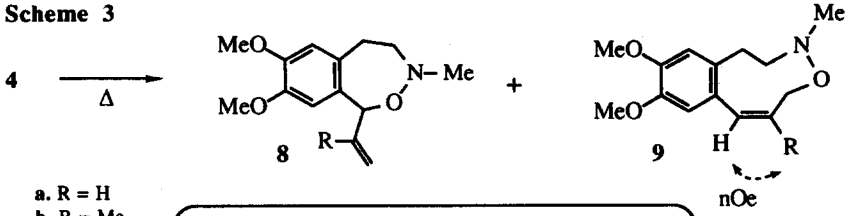


| | ratio *E* : *Z* | total % yield |
|---|---|---|
| 6a | 95 : 5 | 90 |
| 6b | 66 : 34 | 93 |

The ylide rearrangements were found to produce only the 3-benzazonines **6** via the [2,3] sigmatropic mechanism, with none of the alternative Stevens rearrangement products **7** observed (Scheme 2). The ylides were generated by deprotonation of **3** with DBU. A rearranged fraction, as indicated by $^1H$ and $^{13}C$ NMR, was obtained by chromatography on alumina with DCM/20% L.P.(60-80°). The diastereomeric products were then separated by reverse phase HPLC on a C18 column with MeCN/20% $H_2O$. Attempts to purify the mixture by PLC on silica resulted in loss of the *E*-benzazonines. The unsaturated 3-benzazonines were characterised[6] by olefinic $^{13}CH$ peaks at 128-135 δ, H7 at 6.3-6.7 δ and H4 at 3.4-3.6 δ. The observed selectivity towards the *E* isomer is consistent with the behaviour of the piperidine *N*-ylide system[1b] and proposed [2,3] rearragement transition states[1c].

In contrast, the *N*-oxides **4** upon thermolysis demonstrated either [1,2] and/or [2,3] rearrangements, with the selectivity greatly dependent on the reaction conditions and substituents present (Scheme 3). Thus thermolysis of **4a** in refluxing MeCN gave only the benzoxazepine **8a**[7], the product of Meisenheimer rearrangement. Heating **4b** under the same conditions produced two inseparable products consistent with the benzoxazepine **8b** and benzoxazonine **9b**. Thermolysis in refluxing DCM, however, gave **9b** (41%)[8] selectively, most probably via a stereoselective [2,3] sigmatropic rearrangement of *cis*-4b, as *trans*-4b was recovered unchanged. The structure of **9b** was confirmed only after low temperature NMR experiments[8] with the broad peaks observed at 25°C resolved to two distinct forms, of equal population, at -30°C. The *Z* stereochemistry of **9b** was confirmed by nOe experiments. Compound **9b** isomerised almost completely to **8b** (8b/9b = 19) upon refluxing in xylene for 1 h., indicating the less strained benzoxazepine ring is thermodynamically favoured. Refluxing **9b** in MeCN for 1 h. produced only slight isomerisation (≤ 7%) to **8b**.

**Scheme 3**



**a.** R = H
**b.** R = Me

| *N*-oxide | Conditions | ratio<br>8 : 9 | total<br>% yield |
|---|---|---|---|
| 4a | Δ MeCN, 50 m. | 100 : 0 | 61 |
| 4b | Δ MeCN, 50 m. | 42 : 58 | - |
| 4b | Δ DCM, 34 h. | 0 : 100 | 41 |

Studies are continuing on factors affecting the competition between [2,3] and [1,2] rearrangements in appropriately substituted tetrahydroisoquinoline *N*-oxide and *N*-ylide derivatives and on the usefulness of these rearrangements in synthesis.

**Acknowledgements:** Support of this work by a grant from the Australian Research Council and by the Universities of Tasmania and Wollongong, together with an Australian Postgraduate Research Award to T.S.B., is gratefully acknowledged.

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4. Spath, E.; Epstein, H. *Chem. Ber.* **1926**, *59*, 2791-2800.
5. All new compounds gave spectral data consistent with the proposed structures.

6. Compound *E*-**6a**. $^{1}$H NMR* δ: 6.77 (s, H8), 6.62 (s, H11), 6.43 (d, *J* 16.1 Hz, H7), 5.48 (m, H6), 4.17-4.04 (m, $CH_2$ of Et), 3.87 (s, $OCH_3$), 3.84 (s, $OCH_3$), 3.54 (dd, *J* 1.7 Hz, *J* 6.3 Hz, H4), 2.84-2.60 (m, 4H), 2.70 (s, $NCH_3$), 2.38-2.28 (m, 2H), 1.25 (t, $CH_3$ of Et); $^{13}$C NMR* δ: 173.25 (COO), 147.30 ($C9^{A}$), 147.09 ($C10^{A}$), 134.69 (C7), 133.87 ($C7a^{B}$), 132.09 ($C11a^{B}$), 130.64 (C6), 113.77 (C11), 110.66 (C8), 67.19 (C4), 60.58 ($CH_2$ of Et), 56.40 ($2OCH_3$), 56.00 (C2), 45.24 ($NCH_3$), 38.03 (C1), 36.32 (C5), 14.92 ($CH_3$ of Et); MS m/z: 319 ($M^+$, 8%; Calcd. for $C_{18}H_{25}NO_4$ 319.1783, found 319.178), 246 (100), 215 (7), 204 (7), 189 (12).

   *NMR were run in $CDCl_3$ at 300MHz ($^{1}$H) and 75.5MHz ($^{13}$C).

   Compound *Z*-**6a**. $^{1}$H NMR δ: 6.67 (d, *J* 10.7 Hz, H7), 6.58 (s, ArH), 6.54 (s, ArH), 5.90-5.81 (m, H6), 4.10 (q, $CH_2$ of Et), 3.87 (s, $OCH_3$), 3.84 (s, $OCH_3$), 3.49-3.44 (m, H4), 3.14-3.07 (m, 1H2), 2.90-2.70 (m, 2H), 2.62-2.56 (m, 1H), 2.58 (s, $NCH_3$), 2.22-2.12 (m, 2H5), 1.23 (t, $CH_3$ of Et); $^{13}$C NMR δ: 173.60 (COO), 148.34 ($C9^{A}$), 147.53 ($C10^{A}$), 134.24 ($C7a^{B}$), 132.42 ($C6^{C}$), 131.60 ($C7^{C}$), 129.53 ($C11a^{B}$), 113.84 ($C8^{D}$), 111.89 ($C11^{D}$), 66.94 (C4), 60.88 ($CH_2$ of Et), 56.51 ($2OCH_3$), 53.07 (C2), 45.48 ($NCH_3$), 37.86 (C5), 32.63 (C1), 15.00 ($CH_3$ of Et); MS m/z: 319 ($M^+$, 14%; Calcd. for $C_{18}H_{25}NO_4$ 319.1783, found 319.1778), 246 (100), 215 (2), 203 (3), 189 (6).

   Compound *E*-**6b**. $^{1}$H NMR δ: 6.71 (s, ArH), 6.67 (s, ArH), 6.28 (s, H7), 4.12 (q, $CH_2$ of Et), 3.87 (s, $OCH_3$), 3.85 (s, $OCH_3$), 3.54 (d, *J* 6.3 Hz, H4), 2.88-2.70 (m, 3H), 2.65 (s, $NCH_3$), 2.59-2.53 (m, 1H), 1.45 (s, $CH_3$), 1.26 (t, $CH_3$ of Et); $^{13}$C NMR δ: 174.34 (COO), 147.29 ($C9^{A}$), 147.03 ($C10^{A}$), 133.87 ($C7a^{B}$), 132.48 ($C11a^{B}$), 131.64 ($C6^{B}$), 129.66 (C7), 113.84 ($C8^{C}$), 111.89 ($C11^{C}$), 65.92 (C4), 60.82 ($CH_2$ of Et), 56.67 ($OCH_3$), 56.51 ($OCH_3$), 55.22 (C2), 45.64 ($NCH_3$), 41.56 (C5), 39.00 (C1), 18.91 ($CH_3$), 14.99 ($CH_3$ of Et); MS m/z: 333 ($M^+$, 23%; Calcd. for $C_{19}H_{27}NO_4$ 333.1940, found 333.1922), 276 (10), 260 (100), 217 (5), 203 (10).

   Compound *Z*-**6b**. $^{1}$H NMR δ: 6.56 (s, ArH), 6.53 (s, ArH), 6.38 (s, H7), 4.09 (q, $CH_2$ of Et), 3.86 (s, $OCH_3$), 3.83 (s, $OCH_3$), 3.59 (dd, *J* 4.0 Hz, *J* 12.6 Hz, H4), 3.06-2.99 (m, 1H), 2.90-2.82 (m, 1H), 2.71-2.57 (m, 2H), 2.60 (s, $NCH_3$), 2.27 (dd, *J* 13.3 Hz, *J* 13.3 Hz, 1H5), 2.03 (dd, *J* 3.9 Hz, *J* 14.0 Hz, 1H5), 1.90 (s, $CH_3$), 1.23 (t, $CH_3$ of Et); $^{13}$C NMR δ: 174.31 (COO), 148.07 ($C9^{A}$), 147.20 ($C10^{A}$), 138.59 ($C7a^{B}$), 135.04 ($C11a^{B}$), 130.70 ($C6^{B}$), 127.53 (C7), 113.63 ($C8^{C}$), 112.10 ($C11^{C}$), 65.04 (C4), 60.65 ($CH_2$ of Et), 56.43 ($2OCH_3$), 52.95 (C2), 45.57 ($NCH_3$), 38.35 (C5), 36.65 (C1), 22.31 ($CH_3$), 15.01 ($CH_3$ of Et); MS m/z: 333 ($M^+$, 21%; Calcd. for $C_{19}H_{27}NO_4$ 333.1940, found 333.1951), 260 (100), 229 (4), 203 (107), 130 (4).

7. Compound **8a**. $^{1}$H NMR δ: 6.67 (s, ArH), 6.58 (s, ArH), 6.01-6.10 (m, H1'), 5.45 (d, *J* 6.8 Hz, H1), 5.31-5.22 (m, 2H2'), 3.86 (s, $OCH_3$), 3.83 (bs, $OCH_3$ and 1H), 3.28-24 (m, 1H), 3.10-3.02 (m, 1H), 2.92-2.85 (m, 1H), 2.72 (s, $NCH_3$); $^{13}$C NMR δ: 148.03 ($C7^{A}$), 147.89 ($C8^{A}$), 137.17 (C1'), 132.81 ($C5a^{B}$), 129.63 ($C9a^{B}$), 117.78 (C2'), 114.39 ($C6^{C}$), 111.16 ($C9^{C}$), 87.12 (C1), 60.69 (C4), 56.57 ($2OCH_3$), 47.39 ($NCH_3$), 33.25 (C5); MS m/z: 249 ($M^+$, 22%; Calcd. for $C_{14}H_{19}NO_3$ 249.1363, found 249.135), 232 (10), 203 (11), 190 (100), 175 (44), 159 (22), 147 (17).

8. Compound **9b**. $^{1}$H NMR (25°C) δ: 6.67 (s, ArH), 6.52 (s, ArH), 6.46 (s, H7), 4.06 (bs, 2H5), 3.86 (s, $OCH_3$), 3.82 (s, $OCH_3$), 2.88 (bs, 2H), 2.57 (s, $NCH_3$), 1.90 (s, $CH_3$), 2H of $CH_2CH_2$ not detected; $^{13}$C NMR (25°C) δ: 148.25 ($C9^{A}$), 147.13 ($C10^{A}$), 138.68 ($C7a^{B}$), 133.58 ($C11a^{B}$), 131.10 (C6), 127.93 (bs, C7), 111.58 ($C8^{C}$), 111.16 ($C11^{C}$), 74.77 (bs, C5), 62.81 (C2), 56.28 ($OCH_3$), 56.20 ($OCH_3$), 47.41 (bs, $NCH_3$), 33.24 (bs, C1), 24.36 ($CH_3$); MS m/z: 263 ($M^+$, 12%; Calcd. for $C_{15}H_{21}NO_3$ 263.1521, found 263.1532), 246 (5), 204 (100), 189 (37), 175 (11).

   $^{1}$H NMR (-30°C) doubling of most peaks δ: 6.78, 6.65, 6.56 and 6.54 (s, 2ArH), 6.49 (s, H7), 4.25-3.95 ( 4 doublets, 2 superimposed, from 2H5), 3.92 and 3.89 (s, $OCH_3$), 3.85 (s, $OCH_3$), 3.2-2.9 (m, 2H), 2.9-2.7 (m, 1H), 2.7-2.5 (m, 1H, obscured by NMe), 2.67 and 2.57 (s, $NCH_3$), 1.98 and 1.87 (s, $CH_3$); $^{13}$C NMR (-30°C) doubling of most peaks δ: 147.95, 146.98, 146.59 and 146.13 (C9 and C10), 139.25 and 137.30 ($C7a^{B}$), 133.65 and 132.08 ($C11a^{B}$), 130.48 (C6), 129.37 and 126.18 (C7), 110.66 and 110.49 ($C8^{C}$), 110.11 and 109.85 ($C11^{C}$), 77.25 and 72.46 (C5), 62.80 and 62.20 (C2), 55.99 ($2OCH_3$), 48.64 and 46.29 ($NCH_3$), 34.44 and 31.35 (C1), 24.64 and 24.24 ($CH_3$).

(Received in UK 16 February 1993)