Tetrahedron Letters, Vol. 33, No. 45, pp. 6883-6884, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

AN INTRAMOLECULAR ARYNE CYCLOADDITION APPROACH TO PHENANTHRENE ALKALOIDS

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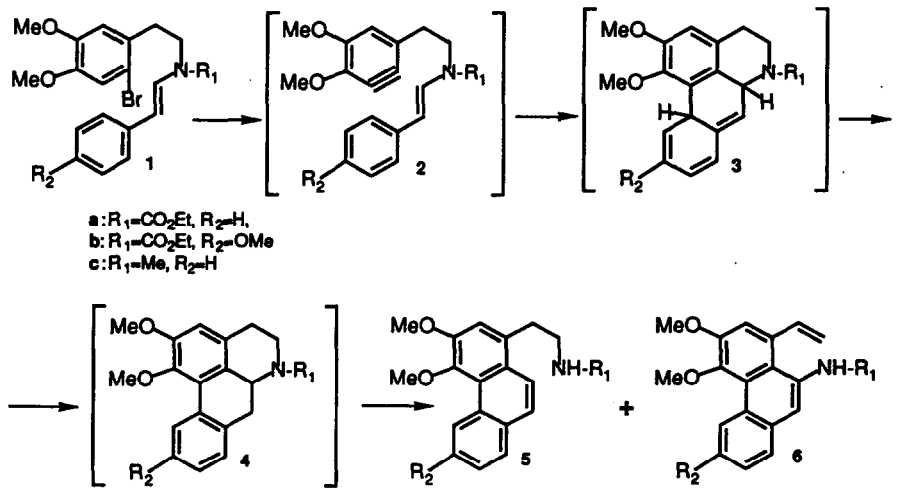
SUMMARY. A new synthesis of phenanthrene alkaloids which is based on the intramolecular Diels-Alder reaction between a styrene and an aryne is described.

Continuing with our studies on the viability of the intramolecular aryne cycloaddition approach to the synthesis of various types of alkaloid,[1,2,3] we have now attempted to extend this method to the preparation of aporphine and phenanthrene alkaloids. Previous synthesis of these pharmacologically important isoquinoline alkaloids are usually laborious and not always satisfactory.[4]

When the synthesis of aporphines was attempted from amine **1c**, an isoindole derivative was obtained.[5] Our experience in this field[1,2,3] suggested the need to protect the nitrogen as an amide. Accordingly, urethanes **1a** and **1b** were considered as precursors.



The *N*-styrylurethane **1a**[6] was easily obtained in very good yield by condensation of commercially available phenylacetaldehydedimethylacetal and *N*-carbethoxy-2-bromo-4,5-dimethoxyphenylethylamine, the latter having been prepared by bromination of 3,4-dimethoxybenzaldehyde, condensation of the resulting *o*-bromoveratraldehyde with nitromethane, reduction of the nitrostyrene so generated with Zn/HCl and treatment of the product, *o*-bromophenylethylamine, with ethyl chloroformate. When **1a** was treated with LDA in dry THF at 0°C,[1] the expected *N*-carbethoxyaporphine **4a** was not obtained. The main product of the reaction was the phenanthrene **5a**[7] (60% yield), which, by reduction with LAH, was transformed into *N*-noratherosperminine (**5c**).[8] Compound **5a** can also be easily transformed into atherosperminine.[7] A minor product of the reaction was identified as the phenanthrene **6a**.[6]

Similar results were obtained with *N*-styrylurethane **1b**,[6] which was easily prepared analogously to **1a** by condensation of *N*-carbethoxy-2-bromo-4,5-dimethoxyphenylethylamine with *p*-methoxyphenylacetaldehydedimethylacetal, the latter having been prepared from 4-methoxybenzaldehyde.[9] Treatment of **1b** with LDA, as above, produced a mixture of phenanthrene **5b**[6] (60%) with a small amount of phenanthrene **6b**.[6]

These results show that the desired intramolecular cycloaddition reaction occurs more readily than in the case of aristolactams.[1] We belive that the initial adducts **3** may in fact give the *N*-carbethoxyaporphines **4** which we originally expected, and that under the basic conditions of the reaction compounds **4** undergo eliminations to give the phenanthrene compounds **5a** or **5b**, and **6a** or **6b**. The elimination leading to **5a** or **5b** must be more favoured because of the gain of aromaticity of the phenanthrene system.

This new method of synthesis of phenanthrene alkaloids is more simple and efficient than previous ones.[10] We are currently investigating its modification to allow synthesis of aporphines as originally intended.

ACKNOWLEDGEMENTS

We thank the DGICYT and the Xunta de Galicia for financial support and the latter for a grant to Juan C. Estévez.

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6. All new compounds gave satisfactory spectroscopic and analytical data. **6a**: ^{1}H-NMR (δ, ppm, $CDCl_3$): 1.34 (t, J=7.1 Hz, 3H, $-CH_3$), 3.88 (s, 3H, $-OCH_3$), 4.05 (s, 3H, $-OCH_3$), 4.27 (q, J=7.1 Hz, 2H, $-CH_2$-), 5.47 (d, J=10.7 Hz, 1H,-CH=C*H*H), 5.61 (d, J=17.2 Hz, 1H, -CH=CH*H*), 7.05-7.95 (m, 7H, 5xAr-H, -C*H*=CH_2 and -N-H) and 9.56 (d, J=9.4 Hz, 1H, Ar-H). MS (m/z, %): 351 (M^+, 2), 262 (60) and 44 (100). **5c**: ^{1}H-NMR (δ, ppm, $CDCl_3$): 1.21-1.38 (m, 3H, $-CH_3$), 3.29-3.38 (m, 2H, $-CH_2$-), 3.50-3.63 (m, 2H, $-CH_2$-), 3.94 (s, 3H, $-OCH_3$), 4.00 (s, 3H, $-OCH_3$), 4.08 (s, 3H, $-OCH_3$), 4.18 (q, J=7.1 Hz, 2H, $-CH_2$-), 4.84 (m, 1H, -N-H), 7.21-7.32 (m, 2H, 2xAr-H), 7.61 (d, J=9.0 Hz, 1H, Ar-H), 7.74-7.78 (m, 2H, 2xAr-H) and 9.27 (d, J=2.3 Hz, 1H, Ar-H). MS (m/z, %): 383 (M^+, 46), 337 (9), 291 (100) and 267 (11). **6b**: ^{1}H-NMR (δ, ppm, $CDCl_3$): 1.33 (t, J=7.0 Hz, 3H, $-CH_3$), 3.89 (s, 3H, $-OCH_3$), 3.96 (s, 3H, $-OCH_3$), 4.04 (s, 3H, $-OCH_3$), 4.26 (q, J=7.0 Hz, 2H, $-CH_2$-), 5.43 (d, J=10.8 Hz, 1H, -CH=C*H*H), 5.56 (d, J=17.1 Hz, 1H,-CH=CH*H*), 7.00 (bs, 1H, Ar-H), 7.19-7.26 (m, 2H, 2xAr-H), 7.47 (dd, J= 17.1 and J=10.8 Hz, 1H, -C*H*=CH_2), 7.69 (d, J=8.7 Hz, 1H, Ar-H), 7.79 (bs, 1H, -NH) and 9.17 (d, J=2.2 Hz, 1H, Ar-H). MS (m/z, %): 381 (M^+, 100), 229 (41) and 269 (19).
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(Received in UK 27 July 1992)