Tetrahedron Letters, Vol.22, No.25, pp 2349 - 2352, 1981
Printed in Great Britain

0040-4039/81/252349-04$02.00/0

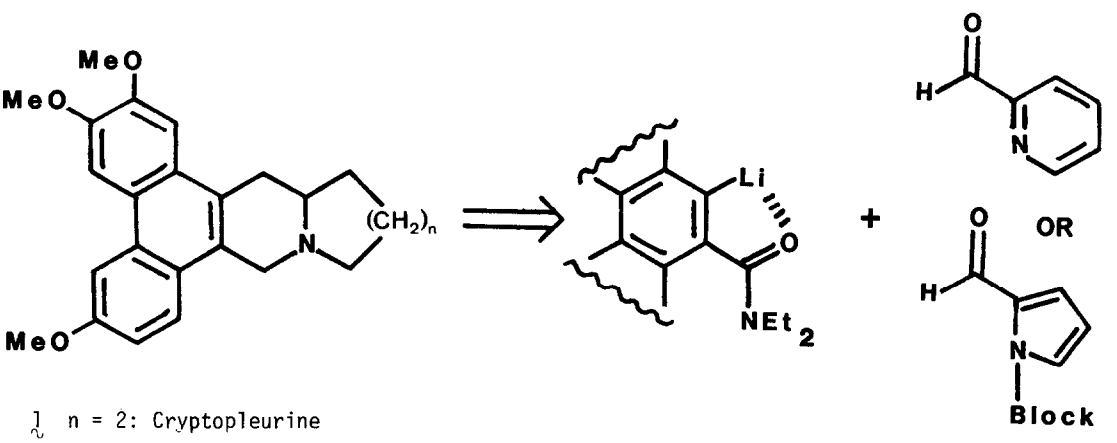
DIRECTED METALATION OF TERTIARY BENZAMIDES. ABBREVIATED SYNTHESES OF PHENANTHRO-QUINOLIZIDINE AND -INDOLIZIDINE ALKALOIDS

M. Iwao,[1] M. Watanabe,[1] S.O. de Silva, and V. Snieckus*

The Guelph-Waterloo Centre for Graduate Work in Chemistry, Waterloo Campus
Department of Chemistry, University of Waterloo, Waterloo, Canada N2L 3G1

Summary. Short syntheses of the alkaloids cryptopleurine (1) and antofine (2) via directed metalation of the common phenanthrene amide 3 are described.

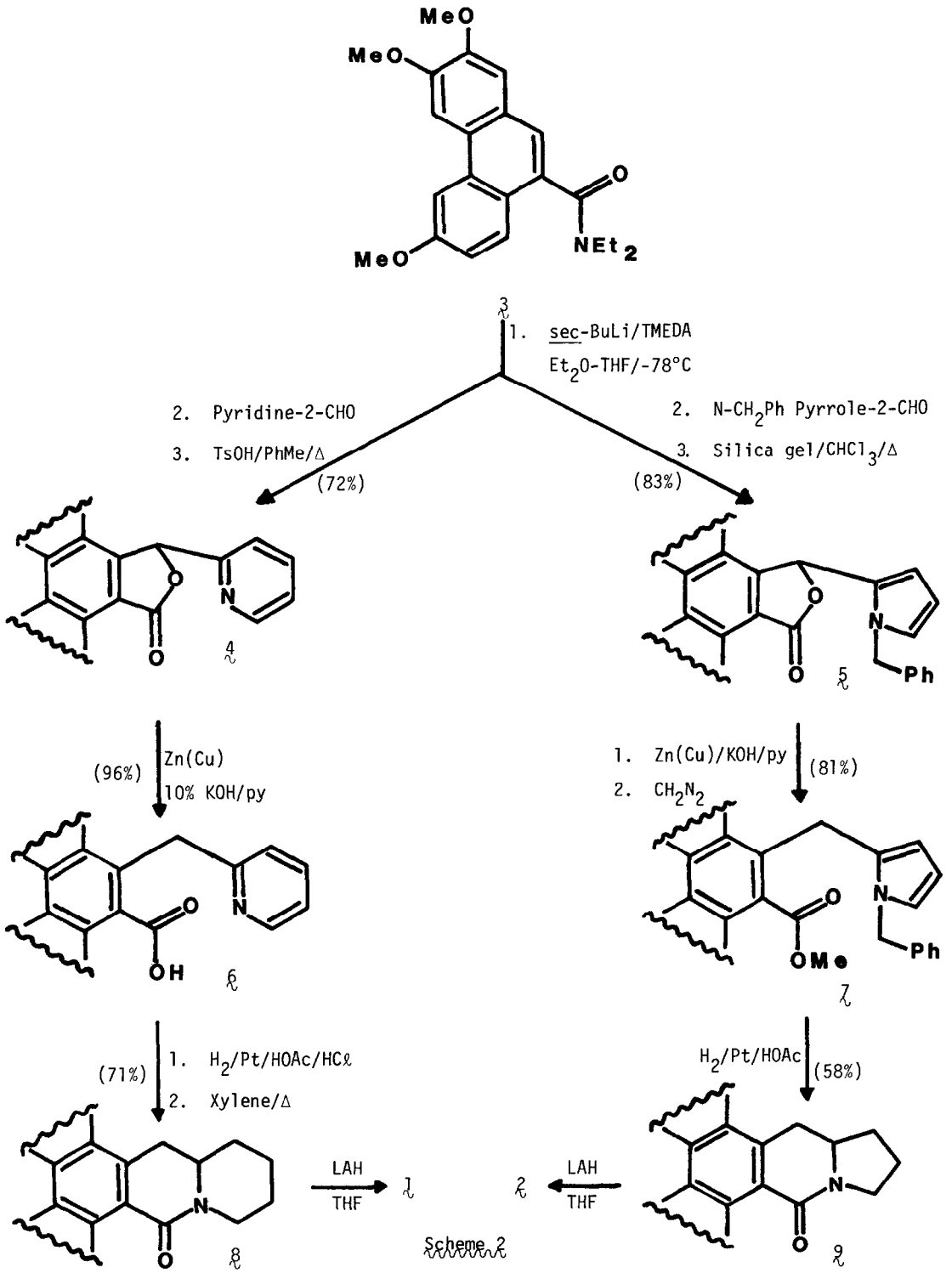
We wish to report convenient syntheses of cryptopleurine (1) and antofine (2), representative alkaloids of the phenanthroquinolizidine and -indolizidine types, by application of benzamide directed metalation strategy[2] (Scheme 1). As a result of their interesting biosynthesis[3] and their potential antitumor properties,[4] these classes of alkaloids have been the subject of vigorous synthetic activity.[5] Our approach demonstrates the viability of the directed metalation reaction for condensed aromatic substrates, extends its utility for the synthesis of diverse natural products,[2a] and illustrates a general method of heterocyclic ring annelation.



1 n = 2: Cryptopleurine

2 n = 1: Antofine

Scheme 1


MeO
MeO
MeO
O
NEt2
3
1. sec-BuLi/TMEDA
Et2O-THF/-78°C
2. Pyridine-2-CHO
3. TsOH/PhMe/Δ
(72%)
2. N-CH2Ph Pyrrole-2-CHO
3. Silica gel/CHCl3/Δ
(83%)
4
5
Ph
(96%)
Zn(Cu)
10% KOH/py
1. Zn(Cu)/KOH/py
2. CH2N2
(81%)
OH
6
OMe
7
Ph
(71%)
1. H2/Pt/HOAc/HCl
2. Xylene/Δ
H2/Pt/HOAc
(58%)
LAH
THF
1
2
LAH
THF
8
9

Scheme 2

Metalation of the readily available phenanthrene amide 3[6] under standard conditions[2a] followed by treatment with freshly-distilled pyridine-2-aldehyde gave the intermediate amide alcohol which, without isolation, was converted into the pyridino phthalide 4[7] by TsOH catalyzed cyclization. Hydrogenolysis with copper sulfate-activated zinc[8] afforded the carboxylic acid 6[7] which upon catalytic reduction and thermolysis provided the known[9] lactam 8.[7] Metal hydride reduction yielded cryptopleurine 1 which was shown to be identical (mp, t&c, IR, NMR) with an authentic sample.[10]

Metalated phenanthrene amide 3 was similarly converted into the pyrrolo phthalide 5[7] except that the second step was effected by a slurry of silica gel in chloroform. Zinc (copper sulfate) reduction followed by esterification gave compound 7[7] which, after considerable experimentation,[11] was transformed into lactam 9 by hydrogenation. Lithium aluminum hydride reduction provided antofine (2) whose physical and spectral properties were shown to be identical with an authentic sample.[5e,12]

Especially in view of the ready accessibility of substituted phenanthrene carboxylic acids,[13] these brief syntheses serve as protreptic examples for the application of the directed metalation strategy to the synthesis of other phenanthro-quinolizidine and -indolizidine alkaloids and their analogues.[5,14]

References and Footnotes

1. On leave of absence from Nagasaki University, Nagasaki, Japan: M.I. (1980-81), M.W. (1977-79).

2. a) Review-lecture of work from these laboratories: V. Snieckus, Heterocycles, 1980, 14, 1649; b) Comprehensive review on heteroatom-assisted metalation: H.W. Gschwend and H.R. Rodriguez, Org. Reactions, 1979, 26, 1.

3. R.B. Herbert and F.B. Jackson, J.C.S. Chem. Comm., 1977, 955; E. Leete in Biosynthesis (Specialist Periodical Reports), The Chemical Society, London, 1977, 5, 148.

4. J.L. Hartwell and B.J. Abbott, Advan. Pharmacol. Chemother., 1969, 7, 117; E. Schlitter, The Alkaloids (Specialist Periodical Reports), 1971, 1, 489; G.R. Donalson, M.R. Atkinson, and A.W. Murray, Biochem. Biophys. Res. Commun., 1968, 31, 104.

5. Review: a) T.R. Govindachari and N. Viswanathan, Heterocycles, 1978, 11, 587. Syntheses: Phenanthroquinolizidines: b) G.G. Trigo, E. Galvez, M.M. Sollhuber, J. Heterocyclic Chem., 1980, 17, 69; c) R.B. Herbert, J.C.S. Chem. Comm., 1978, 794. Phenanthro-indolizidines: d) S.M. Weinreb, N.A. Khatri, and J. Shringarpure, J. Am. Chem. Soc., 1979, 101, 5073 and refs. therein; e) G. Dannhardt and W. Wiegrebe, Arch. Pharm., 1977, 310, 802; f) B. Chauncy and E. Gellert, Austr. J. Chem., 1970, 23, 2503.

6. Mp 152-153°C (CH_2Cl_2/Et_2O/hexane), prepared by normal methods from the corresponding carboxylic acid which, in turn is available by the Pschorr reaction (C.K. Bradsher and H. Berger, J. Am. Chem. Soc., 1958, 80, 930) or more tediously and in low yield according to the photocyclization method used by R.B. Herbert and C.J. Moody, J.C.S. Chem. Comm., 1970, 121 for an analogous system.

7. All compounds showed analytical and spectral data consistent with their structures. Salient physical and spectral data for all new compounds follow. 4: mp 239-241°C (PhMe); IR (Nujol) 1760 cm^{-1}; NMR ($CDCl_3$) δ 3.93, 4.04, 4.10 (3 x s, 9 H), 6.79 (s, 1 H) 8.67 (m, 1 H), 9.09 (d, 1 H, J = 9 Hz). 6: mp 278-280°C (EtOH); IR (Nujol) 1620 cm^{-1}; NMR ($CDCl_3$) δ 4.00, 4.03, 4.06 (3 x s, 9 H), 4.60 (s, 2 H). 8: mp 198-199°C (EtOH) [lit[9] mp 194-195°C]; IR (Nujol) 1635 cm^{-1}; NMR ($CDCl_3$) δ 4.01, 4.06, 4.12 (3 x s, 9 H), 4.75 (br d, 1H), 9.60 (d, 1 H, J = 9.5 Hz). 1: mp 197-200°C (Acetone) lit[5b] mp 196.5-198°C. 5: mp 248-250°C (CH_2Cl_2-Et_2O); IR (Nujol) 1740 cm^{-1}; NMR ($CDCl_3$) δ 3.71, 4.03, 4.11 (3 x s, 9 H), 5.22 (q, 2 H), 5.88 (dd, 1 H), 6.09 (t, 1 H), 6.84 (dd, 1 H), 9.03 (d, 1 H, J = 9 Hz). 7: mp 171-172°C (CH_2Cl_2-Et_2O); IR (Nujol) 1720 cm^{-1}; NMR ($CDCl_3$) δ 3.66, 3.83, 4.01, 4.08 (4 x s, 12 H), 4.22, 5.13 (2 x s, 4 H). 9: mp 254-255°C (CH_2Cl_2-Et_2O); IR (Nujol) 1635 cm^{-1}; NMR ($CDCl_3$) δ 4.01, 4.03, 4.12 (3 x s, 9 H), 9.31 (d, 1 H, J = 9 Hz). 2: mp 212-213°C (Acetone), lit[5f] 213-215°C.

8. M.S. Newman, V. Sankaran, and D.R. Olson, J. Am. Chem. Soc., 1976, 98, 3237.

9. E. Kotani, M. Kitazawa, and S. Tobinga, Tetrahedron, 1974, 30, 3027.

10. We are grateful to Dr. J. Douros, Natural Products Branch, Division of Cancer Treatment, NCI for a sample of cryptopleurine.

11. The N-CH_2OMe derivative corresponding to 7 suffered reduction to the N-Me pyrrolidine thus precluding its use in the synthesis.

12. Dr. E. Gellert[5f], University of Wollongong, Australia, and Dr. R.B. Herbert (R.B. Herbert and C.J. Moody, Phytochemistry, 1972, 11, 1184), University of Leeds, England graciously provided comparison samples and IR and NMR spectra of antofine.

13. A.J. Floyd, S.F. Dyke, and S.E. Ward, Chem. Rev., 1976, 76, 509.

14. We thank the Natural Sciences and Engineering Research Council of Canada for financial support.

(Received in USA 27 February 1981)