Tetrahedron Letters,Vol.23,No.18,pp 1947-1950,1982 0040-4039/82/181947-04$03.00/0
Printed in Great Britain

AN IMPROVED SYNTHESIS OF [2.2.3]CYCLAZINES FROM 3H-PYRROLIZINES

By Volker Batroff, Wilhelm Flitsch* and Wilfried Lübisch

Organisch-Chemisches Institut der Universitat Münster, Orleans-Ring 23, D-4400 Münster (Western Germany)

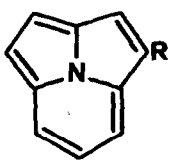
and

Derek Leaver* and David Skinner

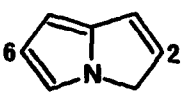
Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ (Scotland)

Abstract: *[2.2.3]Cyclazines are obtained in moderate yields by reaction of 3H-pyrrolizines bearing conjugative substituents (Ph or CO_2Me) with vinamidinium salts in the presence of strong bases. Syntheses of the previously unknown 2-phenyl-3H-pyrrolizine and 1-methoxycarbonylcyclopenta[h][2.2.4]cyclazine are also described.*

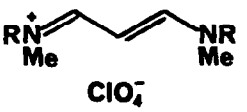
Despite considerable activity in the cyclazine field[1] during the past 24 years, the original indolizine-based syntheses of [2.2.3]cyclazines (1), developed by Boekelheide and his co-workers[2], remain among the most convenient of existing routes to these interesting [10]annulene derivatives. In principle, an approach to [2.2.3]cyclazines starting from 3H-pyrrolizine (2a)[3] and based on the three-carbon annellation procedure of Jutz and his co-workers[4] would seem to offer a shorter alternative route. In practice, however, the yield of the parent cyclazine (1a) obtained[5] from 3H-pyrrolizine and the vinamidinium salt (3a) was only 2.8%. Condensations[5,6] and cycloadditions[5,6,7] starting from 3-methylenepyrrolizines have been somewhat more successful, though less convenient.



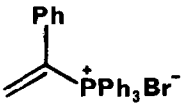
(1) a: R = H
b: R = Ph
c: R = CO_2Me



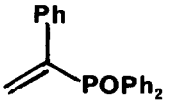
(2) a: parent
b: 2-Ph
c: 6-CO_2Me
d: 2-CO_2Me



(3) a: R = Me
b: R = Ph



(4)



(5)

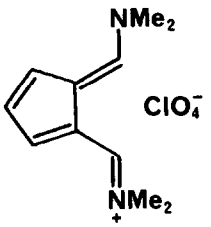
We now report that the Jutz procedure, and modifications of it, are applicable to 3H-pyrrolizines, (2b) and (2c), bearing conjugative substituents in the 2- or 6-position. These substituted pyrrolizines, unlike the parent compound, are quite stable in air and the yields of derived cyclazines, though not yet optimised, are moderately good. We believe, therefore, that this method will provide a valuable alternative means of entry to the [2.2.3]-cyclazine series.

2-Phenyl-3H-pyrrolizine (2b), which is unobtainable[8] by the original Schweizer procedure from pyrrole-2-carbaldehyde and the phosphonium salt (4) was readily prepared by a modification of this route: a toluene solution containing pyrrole-2-carbaldehyde and the phosphine oxide (5)[9] was stirred and heated under reflux with 5M aqueous potassium hydroxide in the presence of a phase-transfer catalyst (Bu_4N^+); work-up after 100 h yielded the pyrrolizine (2b)† [66%, m.p. 179°C (from CH_2Cl_2-light petroleum), δ($CDCl_3$) 4.94 (2H, m), 5.90 (1H, dd, J 3.5 and 1.0 Hz), 6.14 (1H, dd, J 3.5 and 2.7 Hz), 7.00 (1H, m), 7.08 (1H, m), and 7.15-7.60 (5H, m)].

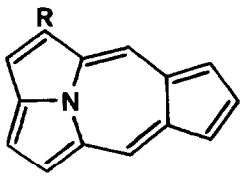
The pyrrolizine (2b) was converted into 1-phenyl[2.2.3]cyclazine (1b) by treatment with the vinamidinium salt (3b) and sodium methoxide in quinoline (0.5 h at 40°C and 3 h at 160°C) according to the general procedure of Jutz and his co-workers[4]. Evaporation of the solution, chromatography (SiO_2-CH_2Cl_2), and sublimation yielded the cyclazine (1b)† [36%, m.p. 61°C (from light petroleum), δ(CD_3COCD_3) 7.40 (1H, d, H-4), 7.64 (1H, d, H-3), 7.89 (1H, t, H-6), 7.98 (1H, s, H-2), 8.16 (1H, dd, H-5), 8.42 (1H, dd, H-7) and 7.34-8.00 (5H, Ph) $J_{3,4}$ 4.3 Hz, $J_{5,6} = J_{6,7}$ 7.8 Hz)].

6-Methoxycarbonyl-3H-pyrrolizine (2c), first prepared by Flitsch and Heidhues[10] in two stages from pyrrole-2-carbaldehyde and methyl acrylate, was obtained in better overall yield by a more recently described[11] three-stage procedure from the same starting materials. Although it is claimed[11] that the later synthesis gives 2-methoxycarbonyl-3H-pyrrolizine (2d), our product was identical with that of Flitsch and Heidhues who showed unambiguously by ^1H n.m.r. that the compound is the 6-methoxycarbonyl isomer. Treatment[5] of the pyrrolizine (2c) with the vinamidinium salt (3a)[12] and sodium hydride in

N,N-dimethylformamide (DMF) (1 h at 60°C and 35 h at reflux), dilution with water, ether extraction, and chromatography gave 1-methoxycarbonyl[2.2.3]-cyclazine (1c) [49%, m.p. 60°C (from pentane), (lit.[13] m.p. 59-61°C)]. The same product was obtained in lower yield (26%), but somewhat more conveniently, by heating the pyrrolizine (2c) for 6 h with 1,1,3,3-tetramethoxypropane in boiling acetic anhydride.



(6)



(7) a: R = H
b: R = CO_2Me

6-Methoxycarbonyl-3H-pyrrolizine was also used to prepare 1-methoxycarbonyl-cyclopenta[h][2.2.4]cyclazine (28%) by reaction with the fulvene iminium salt (6) and sodium hydride in DMF (0.25 h at room temp., 0.5 h at 70°C, and 20 h at reflux). Like the parent compound (7a)[14] and its methyl[14] and halogeno-derivatives[14,15], the cyclazine (7b)† was a green crystalline solid [m.p. 135-136°C (from light petroleum) δ($CDCl_3$) 3.98 (3H, s, OMe), 7.30 (1H, d, H-3), 7.49 (1H, d, H-4), 7.76 (1H, s, H-2), 7.84 (2H, m, H-6 and 8), 7.97 (1H, t, H-7), 8.54 (1H, s, H-5), and 9.58 (1H, s, H-9)].

We are currently investigating further applications and improvements of these reactions.

Acknowledgements We thank the Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen and the University of Edinburgh (for a Research Studentship to D.S.).

References and Footnote

† Satisfactory elemental analyses were obtained for all new compounds.

1. W. Flitsch and U. Krämer, Adv.Heterocyclic Chem., 1978, 22, 321.
2. V. Boekelheide and R.J. Windgassen, J.Am.Chem.Soc., 1958, 80, 2020; R.J. Windgassen, W.H. Saunders and V. Boekelheide, ibid., 1959, 81, 1459; A. Galbraith, T. Small and V. Boekelheide, J.Org.Chem., 1959, 24, 582; A. Galbraith, T. Small, R.A. Barnes and V. Boekelheide, J.Am.Chem.Soc., 1961, 83, 453.
3. E.E. Schweizer and K.K. Light, J.Am.Chem.Soc., 1964, 86, 2963; J.Org.Chem., 1966, 31, 870.

4. C. Jutz, R. Kirchlechner, and H.-J. Seidel, Chem.Ber., 1969, 102, 2301.
5. M.A. Jessep and D. Leaver, J.Chem.Soc., Perkin I, 1980, 1319.
6. W. Flitsch, J. Koszinowski, and P. Witthake, Chem.Ber., 1979, 112, 2465.
7. D. Johnson and G. Jones, J.Chem.Soc., Perkin I, 1972, 2517.
8. E.E. Schweizer, A.T. Wehman and D. Meedes Nycz, J.Org.Chem., 1973, 38, 1583.
9. S.O. Grim, R.P. Molenda, and J.D. Mitchell, J.Org.Chem., 1980, 45, 250; K.D. Berlin and G.B. Butler, ibid., 1961, 26, 2537; M.P. Savage and S. Trippett, J.Chem.Soc.(C), 1968, 591.
10. W. Flitsch and R. Heidhues, Chem.Ber., 1968, 101, 3843.
11. S. Mori, M. Watanabe, S. Kajigaeshi, and S. Kanemasa, Heterocycles, 1976, 4, 957.
12. H. McNab, J.Chem.Research, 1979, (S) 121, (M) 1448.
13. V. Boekelheide and T. Small, J.Am.Chem.Soc., 1961, 83, 462.
14. M.A. Jessep and D. Leaver, J.Chem.Soc., Perkin I, 1980, 1324.
15. W. Flitsch and E.R. Gesing, Tetrahedron Letters, 1979, 3405.

(Received in UK 8 March 1982)