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A STEREOSELECTIVE 3-ENDO-ALKYL-5,6-DEHYDROISOQUINUCLIDINE SYNTHESIS.

Grant R. Krow,* James T. Carey, Kevin C. Cannon and Kenneth J. Henz
Department of Chemistry, Temple University, Philadelphia, PA 19122

Summary: Cycloaddition of N-carbethoxy-2-alkyl-1,2-dihydropyridines 4 with phenylvinylsulfone 5 provides adducts 6, which upon desulfonylation afford stereoselectively N-carbethoxy-3-endo-alkyl-5,6-dehydroisoquinuclidines 1.

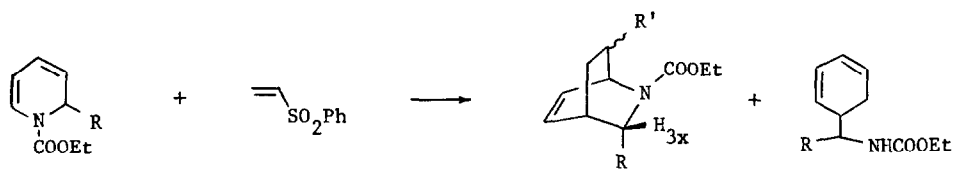
Isoquinuclidines 1-3, substituted at the 3-position and having 5,6-unsaturation, have potential utility as intermediates in piperidine natural product syntheses.[1] For example, 3-endo-alkyl analogs 1 with an R substituent syn to the C_1-C_6 bond can be transformed[2] into 2,6-cis-dialkyl substituted piperidines 3.[1a,2] We have earlier described a synthetic approach from aldimines to 3-substituted-5,6-dehydroisoquinuclidines having predominately R = exo substitution as in 2.[3] We here describe a highly stereoselective synthesis of the 3-endo-alkyl-5,6-dehydroisoquinuclidine synthons 1b-e and the parent 1a as shown in Scheme 1.[1,4]

1 R_{exo} = H; 2 R_{endo} = H 3

The appropriate N-carbethoxy-2-substituted-1,2-dihydropyridine 4[5] was refluxed with phenylvinylsulfone 5 in toluene to afford cycloadduct 6.[6] Desulfonylation of 6 with 6% sodium amalgam in disodium hydrogen phosphate buffered methanol[7] afforded the desired 5,6-dehydroisoquinuclidine 1 in 24-50% overall yield from dihydropyridine 4. Although desulfonylation yielded a minor amount of diene cleavage product 7, this was readily removed from the desired adduct 1 by refluxing the mixture of 1 and 7 with maleic anhydride in chloroform and extracting the cycloadduct of 7 with aqueous base. The success of the desulfonylation of 6 to afford 1 is gratifying, since β-acetoxysulfones, electronically similar to adducts 6, afford olefinic cleavage products under our conditions.[8]

As shown in Table 1, the 3-endo-R stereochemistry and the isomeric purity of the azabicycles 1 could be determined by utilizing as a probe the unique chemical shifts for protons H_{3x} of 1 and the shielded proton H_{3n} of the stereoisomeric 3-exo-R adducts 2.[9] Accordingly, ^{1}H-NMR integrals for protons H_3 in expanded 360 MHz spectra of the cycloadducts 1b-e were consistent with 3-endo-R stereoisomeric purities of at least 99.7%.[10] The 3-endo-R adducts 1b and 1d and the adduct 1a are expected to prove useful as natural product synthons.

Scheme 1. A Stereoselective Route to 3-endo-R-5,6-Dehydroisoquinuclidines 1.



4 5 6 R' = SO_2Ph; 1 R' = H 7

(a) R = H; (b) R = Me; (c) R = Et; (d) R = Propyl; (e) R = iso-Propyl

Table 1. Relevant Yield and Chemical Shift Data for Adducts 1.

Compound	R	Yield[a]	Chemical Shift (δ) H_{3x}[b]
1a	H_{3n}	28[c]	3.26 (dd)[d]
1b	Methyl	50	3.61 (dq)[e]
1c	Ethyl	24	3.40 (br)[f]
1d	Propyl	32	3.55 (dt)[g]
1e	iso-Propyl	37	3.43 (br)[h]

(a) Yields are based upon N-carbethoxy-1,2-dihydropyridine derivatives 4. (b) $CDCl_3$; (c) N-COOMe analog; (d) H_{3n}, δ2.94 (dt); (e) H_{3n} of 2b, δ3.32; (f) H_{3n} of 2c, δ3.08; (g) H_{3n} of 2d, δ3.18; (h) H_{3n} of 2e, δ3.03.

FOOTNOTES AND REFERENCES

1. (a) Baxter, A. J. G.; Holmes, A. B., J. Chem. Soc., Perkin Trans. 1, 1977, 2343; we and Professor Holmes since have noted that bridgehead oxygen insertion with isoquinuclidin-5-ones can be effected (unpublished). (b) Natsume, M.; Ogawa, M., Heterocycles, 1980, 14, 169, 615, and 1981, 16, 973; (c) Ott-Longoni, R.; Viswanathan, N.; Hesse, M., Helv. Chim. Acta, 1980, 63, 2119.
2. Krow, G. R.; Johnson, C.; Synthesis, 1979, 50.
3. (a) Krow, G.; Rodebaugh, R.; Carmosin, R.; Figures, W.; Pannella, H.; DeVicaris, G.; Grippi, M., J. Amer. Chem. Soc., 1973, 95, 5273; (b) Krow, G. R.; Johnson, C.; Boyle, M., Tetrahedron Lett., 1978, 1971; (c) Krow, G. R.; Pyun, C.; Rodebaugh, R.; Marakowski, J., Tetrahedron, 1974, 30, 2977.
4. Nader, B.; Franck, R. W.; Weinreb, S. M., J. Amer. Chem. Soc., 1980, 102, 1153, and reference 8 therein; 1d is a potential deshydroxy palustrine synthon.
5. Compound 4a was prepared according to Fowler, F. W., J. Org. Chem., 1972, 37, 1321; 4b-4e were prepared according to a general procedure of Fraenkel, G.; Cooper, J. W.; Fink, C. M.; Angew. Chem. internat. Edit., 1970, 9, 523.
6. Carr, R. V. C.; Paquette, L. A., J. Amer. Chem. Soc., 1980, 102, 853.
7. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R., Tetrahedron Lett., 1976, 3857.
8. Kocienski, P. J.; Lythgoe, B.; Waterhouse, I., J. Chem. Soc., Perkin 1, 1980, 1045.
9. An independent synthetic route to adducts 2 is to be published; see also reference 3a.
10. Satisfactory spectral and analytical data were obtained for all new compounds. Compounds 1a-e are each homogeneous by TLC and VPC. Aberrations in the 360 MHz ^{1}H-NMR spectra of 1b-e near the known chemical shift values for H_{3n} and H_4 of 3-exo-R adducts 2b-e were conservatively assigned to 2b-e.

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