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A SIMPLE APPROACH TO NORTROPANE AND NORTROP-6-ENE DERIVATIVES

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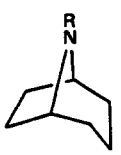
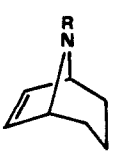
Abstract: Intramolecular cyclisation of trans-1-(benzylamino)-4-chlorocycloheptane and hept-2-ene gives the corresponding 8-azabicyclo[3.2.1]octane (nortropane) and -oct-6-ene (nortrop-6-ene) derivatives respectively. Under appropriate conditions, cyclohepta-1,3-diene is converted into nortropane in 75% overall yield.

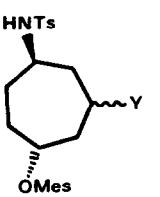
We have sought a simple, high-yield synthesis of nortropane (1a), nortrop-6-ene (2a) and derivatives in order to extend our studies[1] of nitrogen inversion of bridged bicyclic amines, stereoelectronic control in their reactions and, in the case of (2), to provide model compounds for study of facial selectivity in reactions of the double bond. We are prompted to record our initial studies in this area by a very recent report[2] of the application of the intramolecular cyclisation of (3a) to produce tropan-3-ol derivatives.[3a] This report also described a preparation of (1d) (a protected derivative of (1a)) from (3b) and an unsuccessful attempt to prepare (2d). We report here a synthesis of (1a) in high overall yield together with the first synthesis of a derivative of (2) using an intramolecular displacement reaction. The key intermediate (4b) is the precursor to both systems.



1 a R = H
b R = Bz (CH_2Ph)
c R = Me
d R = Ts

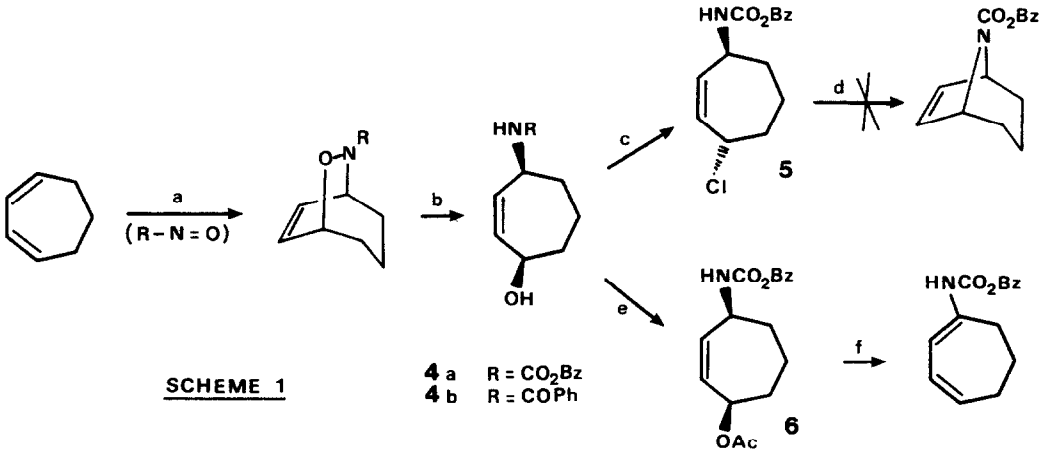


2 a R = H
b R = Bz
c R = Me
d R = Ts



3 a Y = OBz
b Y = H

Whilst attracted by the cycloaddition of nitroso-compounds[4] to cyclohepta-1,3-dienes to provide the initial cis-stereochemistry in the 1,4-difunctionalised cyclohept-2-ene precursors, we were mindful of the failure of an earlier approach to produce nortropane[4] and wished to avoid reported difficulties in the production and cyclisation of N-acyl- and N-acyloxy-1-amino-4-chlorocyclohept-2-enes.[4] Our own early attempts to achieve cyclisation of (5a) and the corresponding bromo-compound were unsuccessful even using potassium t-butoxide in hexamethylphosphoric triamide/benzene (Scheme 1); attempted cyclisation of the cis-acetoxy compound (6) using palladium catalysis[5] also failed, giving only diene by elimination.[3b]



SCHEME 1

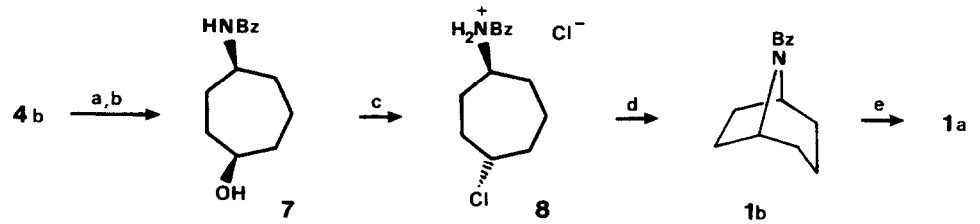
4 a R = CO_2Bz
4 b R = COPh

R=CO_2Bz: a. BzOCONHOH/$Me_4\overset{+}{N}\ \bar{I}O_4/CH_2Cl_2$, 91% b. (i) HBr/HOAc, 72% (ii) Zn/HOAc, 64% (iii) NaH/BzOCOCl/Et_2O, 99%[6]

R=COPh: a. PhCONHOH/$Me_4\overset{+}{N}\ \bar{I}O_4/CHCl_3$/dmf, 99% b. Al/Hg/thf/$H_2O$, 92%

c. $SOCl_2$/pyridine/$CHCl_3$, 70% d. $Bu^tO^-\overset{+}{K}$/hmpa/benzene e. CH_3COCl/pyridine CH_2Cl_2, 94%
f. $Pd(PPh_3)_4/NEt_3$/thf

We resolved to retain the advantages of the nitroso-cycloaddition route[3c] but to modify the nitrogen substituents subsequently. The choice of benzoyl allowed for an effective initial nitroso-cycloaddition[4] and N-O cleavage to the cis-1,4-amino alcohol[6]; subsequent reduction to benzyl was intended to modify the nitrogen to provide (i) a nucleophilic nitrogen to facilitate the intramolecular nucleophilic displacement to give the azabicyclic system (in contrast to the amide or carbamate nitrogen) and (ii) a removable substituent on nitrogen at the conclusion of the synthesis.[7] The successful application of this approach is summarised in Scheme 2.



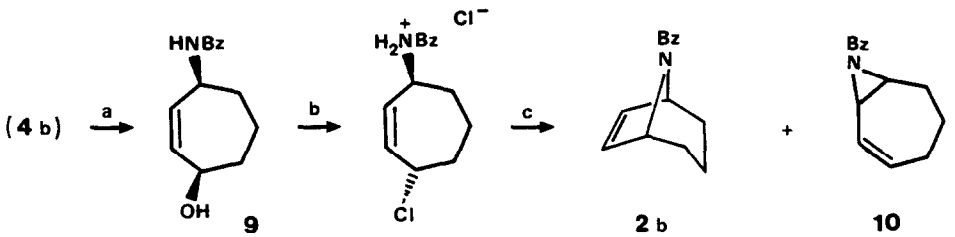
SCHEME 2

a. H_2/Pd/C/MeOH, 99% b. $LiAlH_4/Et_2O$, 99% c. $SOCl_2/CHCl_3$ d. pyridine, 88% overall
e. H_2/Pd/C/MeOH, 95%

Cyclohepta-1,3-diene was converted into (4b) in 91% yield. Following reduction of the CO and CC double bonds, the cis-amino-alcohol (7) was converted efficiently into the trans-chloroamine using thionyl chloride. Initial difficulties[3d] were overcome by the use of 1 mole equivalent of $SOCl_2$ but no added base. Under these conditions, the amino nitrogen displayed an additional virtue, acting as an effective intramolecular base which mopped up the HCl formed in the reaction and ensured that choride ion achieved the substitution with clean inversion of configuration. The salt (8) was not purified further but, on basification with pyridine, gave the free amine which cyclised smoothly at ambient temperature to yield (1b). Debenzylation gave (1a) in 82% yield from (4b). Further functionalisation of (1a) (chlorination, alkylation) and nitrogen inversion studies will be reported elsewhere.

We believe that this represents the most practical route to nortropane (1a) to date. It uses common reagents and simple procedures in an overall yield from cyclohepta-1,3-diene of 75%.[3e]

Significantly, the same approach also gave the unsaturated system (2) from the key intermediate (4b) via hydride reduction to (9) as shown in Scheme 3. The use of $SOCl_2$/LiCl in $CHCl_3$ followed by addition of a heterogeneous base (K_2CO_3) under the influence of ultrasound led to the isolation of the 1,4-cyclisation product (2b)[8] in 65% yield, accompanied by 10% of the aziridine (10) which arose from 1,2-cyclisation. The overall yield of (2b) from cycloheptadiene was 57% after chromatographic separation on silica.



SCHEME 3

a. $LiAlH_4/Et_2O$, 97% b. $SOCl_2/LiCl/CHCl_3$ c. K_2CO_3/ultrasound

As far as we are aware, this is the first report of a synthesis of a simple derivative of the parent nortrop-6-ene skeleton which has been achieved in a significant yield; it demonstrates the viability of the intramolecular displacement approach, given an appropriately nucleophilic nitrogen. Further modification of the substituent at nitrogen at a late or early stage in the pathway is under further study as is the introduction of additional

functionality at other points in the bicyclic skeleton, especially at 'non-natural' sites. We intend to investigate further the functionalisation of the carbon-carbon double bond to give natural product analogues (e.g. epoxides) and the influence of the nature, stereochemistry and size of the substituents at nitrogen and the electronic effects of nitrogen itself[9] in controlling facial selectivity in attack on the π-bond in (2). Application of the general strategy to higher and lower homologues (9-azabicyclo[4.2.1]nonanes/enes and 7-azabicyclo[2.2.1]heptanes/enes) is also under way.

We thank the SERC for the award of a studentship to AB.

References and Notes

1. E.g. J.W. Davies, J.R. Malpass, J. Fawcett, L.J.S. Prouse, R. Lindsay and D.R. Russell, J. Chem. Soc. Chem. Commun., 1986, 1135; J.W. Davies, J.R. Malpass, and R.E. Moss, Tetrahedron Lett., 1986, 27, 4071; 1985, 26, 4533, and references cited therein.

2. J.E. Bäckvall, Z.D. Renko and S.E. Byström, Tetrahedron Lett., 1987, 28, 4199.

3. (a) See reference 2 for a summary of other synthetic approaches to tropane alkaloids, most of which have oxygen functionality at C-3.
   (b) The failure of a similar palladium-catalysed cyclisation of a closely related compound was reported in reference 2; elimination was also observed in this case and we see little future in this approach.
   (c) In reference 2, cycloheptadiene was functionalised using palladium-catalysed chloroacetoxylation followed by introduction of an N-tosyl group. An appropriate leaving group was then introduced with inversion or retention of configuration.
   (d) See footnote 10 in reference 2 and also reference 4 for difficulties encountered in earlier work.
   (e) The overall yield of (1e) in reference 2 was 33% from cycloheptadiene; the necessary final detosylation was not reported but would be expected to occur in ca. 80% yield.

4. (a) H. Iida, Y. Watanabe and C. Kibayashi, J. Org. Chem., 1985, 50, 1818.

5. B.M. Trost and J.P. Genêt, J. Amer. Chem. Soc., 1976, 98, 8516.

6. Direct reduction of the bicyclic oxazine to (4a) with Na/Hg proceeded in very low yield in our hands (7%) and the three-step conversion in Scheme 1 became necessary for (4a). In the case of (4b), Al/Hg was found to be the most effective reagent.

7. E.g. R.A. Olofson, R.C. Schnur, L. Bunes and J.P. Pepe, Tetrahedron Lett., 1977, 1567.

8. 8-Benzyl-8-azabicyclo[3.2.1]oct-6-ene (2b): ^{1}H NMR (300 MHz), $CDCl_3$, ambient temp.: δ 1.24-1.76 (complex, 6H), 3.45 (brs, 2H), 3.49 (s, 2H), 5.91 (s, 2H), 7.18-7.37 (m, 5H). ^{13}C NMR (75 MHz), $CDCl_3$, -100°C: equatorial benzyl, (96%) δ 16.6 (t), 25.6 (t), 57.8 (t), 65.4 (d), 126.5 (d), 128.0 (d), 128.6 (d), 129.2 (d), 140.3 (s); axial benzyl (4%), δ 15.4 (t), 25.9 (t), 59.0 (t), 66.2 (d), 126.9 (d), 127.2 (d), 130.4 (d), 130.8 (d), 140.1 (s). $^{m}/z$: 199.1353 (calc. for $C_{14}H_{17}N$, 199.1361).

9. E.g. the observation of anomalous hydride reduction of a CC double bond in a different nitrogen-bridged system, A.P. Marchand and R.W. Allen, Tetrahedron Lett., 1975, 67.

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