Radical Deoxygenation of 3-Azatricyclo[2.2.1.0^{2,6}]heptan-5-ols to 1,2-Dihydropyridines

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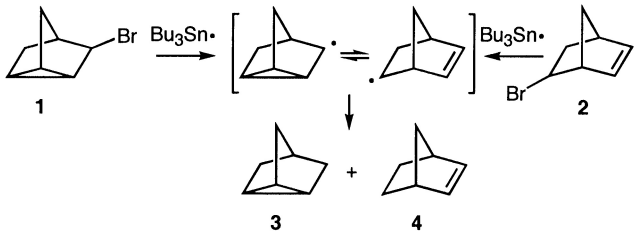
Received 1 October 2004

Abstract: Radical deoxygenations of 7-alkyl-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ols **9** (R = alkyl) give 7-alkyl-4-tosyl-2-azabicyclo[2.2.1]hept-5-enes **10**, whereas 7-aryl-1-tosyl-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ols **9** (R = aryl) give 2-aryl-5-tosyl-1,2-dihydropyridines **12**.

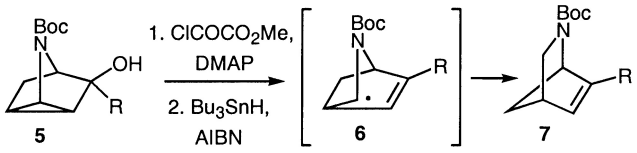
Key words: free radicals, deoxygenation, rearrangements, alcohols, dihydropyridines

Radical cyclisations and rearrangements constitute powerful methodology for the synthesis of ring systems.[1] Radical rearrangements in nortricyclyl (tricyclo[2.2.1.0^{2,6}]heptanyl) and norbornenyl (bicyclo[2.2.1]heptenyl) systems are well-known, usually leading to mixtures of tricyclic and bicyclic products. For example, radical-induced reductions of nortricyclyl bromide **1** and norbornenyl bromide **2** are known to give the same mixture of nortricyclene **3** and norbornene **4** (**3**:**4**, ca. 40:60; Scheme 1).[2]



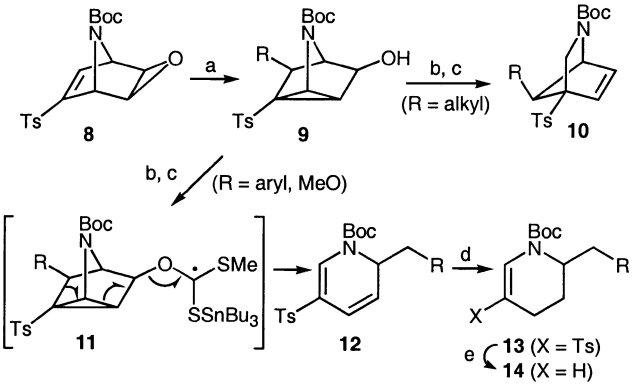
Scheme 1

Recently, during the development of novel analgesics related to epibatidine, we showed that radical deoxygenation of 7-azanortricyclanols **5** selectively gave 6-substituted 2-azabicyclo[2.2.1]hept-5-enes **7**, even when R is potentially radical stabilising (e.g. aryl, Scheme 2).[3] The origin of the selectivity in this rearrangement is probably the stabilisation afforded to the intermediate radical **6** by the α-nitrogen.[4] In the present communication we report on studies originally designed to broaden the scope of the above strategy to give differently substituted 2-azabicyclo[2.2.1]hept-5-enes, but which have also led to an extended radical rearrangement process to give 1,2-dihydropyridines.



Scheme 2

Epoxide **8** (readily available in two steps from *N*-Boc pyrrole)[5] underwent *exo*-selective attack at the α,β-unsaturated sulfone functionality with a variety of Grignard reagents, organolithiums, and MeOLi[6] to give the corresponding substituted 7-azanortricyclanols **9** in good yields (72–96%, Scheme 3). In the case of 7-azanortricyclanol **9** (R = 4-MeOC$_6$H$_4$) the structural assignment was supported by X-ray crystallographic analysis.[7] Subsequent radical deoxygenation[8] of alkyl-substituted 7-azanortricyclanols **9** (R = Me, *i*-Pr) using Bu$_3$SnH (2 equiv) gave the anticipated 2-azabicyclo[2.2.1]heptenes **10**.[9]



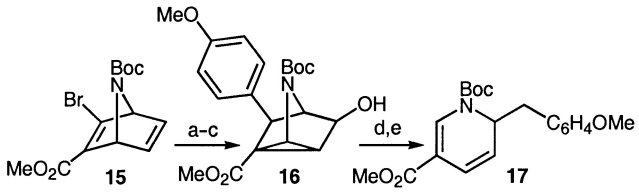
Scheme 3 (a) RMgBr, THF [R = Me (96%), *i*-Pr (90%), 4-MeOC$_6$H$_4$ (72%), Ph (82%)], or 6-methoxypyridin-3-ylLi,[3] THF (78%), or pyridin-3-ylLi, TMEDA, THF (74%), or MeOLi, MeOH (90%); (b) KH, CS_2, MeI, THF [R = Me (78%), 4-MeOC$_6$H$_4$ (84%), Ph (95%), 6-methoxypyridin-3-yl (80%), pyridin-3-yl (77%), MeO (77%)], or 1,1′-thiocarbonyldiimidazole, CH_2Cl_2 [R = *i*-Pr (92%)]; (c) Bu$_3$SnH, AIBN, toluene, reflux [R = Me (65%), *i*-Pr (52%), 4-MeOC$_6$H$_4$ (62%), Ph (65%), 6-methoxypyridin-3-yl (78%), pyridin-3-yl (52%), MeO (37%)]; (d) (R = 6-methoxypyridin-3-yl), H_2, 10% Pd/C, toluene (87%); (e) 6% Na-Hg, MeOH (55%).

SYNLETT 2005, No. 2, pp 0325–0327
Advanced online publication: 10.12.2004
DOI: 10.1055/s-2004-836066; Art ID: D30204ST

In attempting to apply the above chemistry towards new epibatidine analogs, deoxygenation of the xanthate of 7-azanortricyclanol **9** (R = 6-methoxypyridin-3-yl, 0.02 mol dm^{-3} in toluene) by addition of Bu_3SnH (2 equiv) was examined. However, none of the expected 2-azabicyclo[2.2.1]hept-5-ene **10** (R = 6-methoxypyridin-3-yl) was detected, but rather the reaction proceeded cleanly to give 1,2-dihydropyridine **12** (R = 6-methoxypyridin-3-yl, 78%, Scheme 3). All spectral data (including ^1H–^1H and ^1H–^{13}C correlation spectra) were fully in accord with the structural assignment. Use of Bu_3SnD instead of Bu_3SnH in the deoxygenation resulted in deuterium incorporation in the methylene group of 1,2-dihydropyridine **12** (R = 6-methoxypyridin-3-yl). This is what would be expected from the fragmentation pathway suggested in intermediate **11**. Further supporting evidence for the product of deoxygenation was obtained by partial hydrogenation and desulfonylation; the resulting tetrahydropyridines **13** and **14** both exhibited analytical data consistent with the proposed structures.[10]

Presuming that dihydropyridine formation might be favoured by R in **9** being an electron donating and/or aryl substituent, we examined additional 7-azanortricyclanols **9** bearing such functionality (Scheme 3). However, the xanthate of 7-azanortricyclanol **9** (R = 4-$MeOC_6H_4$) initially gave a disappointing yield (31%) of the corresponding dihydropyridine **12** (R = 4-$MeOC_6H_4$). This might be due to stannyl radical attack on the product, since subjecting dihydropyridine **12** (R = 4-$MeOC_6H_4$) to the reaction conditions resulted in 60% decomposition, whereas simply boiling dihydropyridine **12** (R = 4-$MeOC_6H_4$) in toluene for two hours resulted in no discernible decomposition (^1H NMR analysis). With these observations in mind, we reduced the quantity of Bu_3SnH to 1.1 equivalents and increased the time over which it was added from 20 minutes to 2.25 hours. These latter conditions gave the desired dihydropyridine **12** (R = 4-$MeOC_6H_4$) in satisfactory and reproducible yields (62%).[11,12] Similar yields of 2,3-dihydropyridines **12** were observed with phenyl and pyridin-3-yl substituents. With a methoxy substituent the yield was considerably reduced (25%), however, the 2,3-dihydropyridine **12** (R = MeO) remained the only isolable product.

Preliminary studies of the deoxygenation of xanthate of 7-azanortricyclanol **9** (R = 4-$MeOC_6H_4$) but lacking the tosyl substituent[13] indicate that rearrangement only occurs to a 2-azabicyclo[2.2.1]hept-5-ene **10** (R = 4-$MeOC_6H_4$, Ts = H). The effect of an alternative electron withdrawing group to the sulfone substituent was therefore investigated, with ester-substituted 7-azanortricyclanol **16** (Scheme 4). This alcohol was prepared by debromination[14] of the known diene **15**,[15] followed by epoxidation and subsequent addition of 4-$MeOC_6H_4MgBr$. Reaction of the corresponding thiocarbonylimidazole with Bu_3SnH gave 1,2-dihydropyridine **17** as the only isolable product (41%).



Scheme 4 (a) Zn/Ag, HOAc (80%); (b) MCPBA, $NaHCO_3$ (44%); (c) 4-$MeOC_6H_4MgBr$, THF (46%); (d) 1,1′-thiocarbonyldiimidazole, CH_2Cl_2 (quant.); (e) Bu_3SnH, AIBN, toluene, reflux (41%).

Dihydropyridines are important as biologically active agents, and therefore new methods for their construction are of significance.[16] One common method to prepare dihydropyridines is by nucleophilic addition of organometallics to *N*-acylpyridinium salts, although the regioselectivity of addition (C-2/C-4) can sometimes be problematic. For example, regioisomeric mixtures were obtained in the addition of Grignard reagents to the *N*-benzoylpyridinium salt of a pyridin-3-yl sulfonamide.[17] In the present study, reductive deoxygenation of 3-azatricyclo[2.2.1.$0^{2,6}$]heptan-5-ols **9** [bearing an aryl or methoxy substituent in the 7-position and an electron withdrawing group (sulfone or ester) at C-1] is shown to provide a regiospecific route to 2,5-disubstituted 1,2-dihydropyridines **12**. As the precursor to epoxide **8** (the cycloadduct of *N*-Boc pyrrole and tosyl ethyne) is available as either enantiomer,[18] then the potential for accessing enantiopure 1,2-dihydropyridines **12** also exists.

Acknowledgment

We thank the EPSRC for a Research Grant (GR/M55541), and the EPSRC, Evotec OAI and Syngenta for CASE awards (to M.L.J. and C.R.M.). We also thank the EPSRC National Mass Spectrometry Service Center for mass spectra.

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(9) No 1,2-dihydropyridines **12** were observed as by-products from these reactions.

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(11) Variation of the thiocarbonyl moiety (thiocarbonylimidazole, or CSOPh) gave 1,2-dihydropyridine **12** (R = 4-$MeOC_6H_4$) in 43% and 59% yields, respectively.

(12) (a) **Typical Procedure for the Preparation of a 1,2-Dihydropyridine:**
A solution of 7-azanortricyclanol **9** (R = 4-$MeOC_6H_4$) (350 mg, 0.74 mmol) in THF (4 mL) was added dropwise to a slurry of KH (30% dispersion in mineral oil; 148 mg, 1.11 mmol) in THF (4 mL) at 0 °C. After 20 min, CS_2 (55 μL, 0.91 mmol) was added and the mixture stirred for a further 15 min before addition of MeI (55 μL, 0.88 mmol). The solution was then warmed to r.t. over 20 min, after which time H_2O (20 mL) was added dropwise. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (40% Et_2O in petrol ether) gave a white solid foam, xanthate (350 mg, 84%); R_f = 0.5 (50% Et_2O in petrol ether). Selected diagnostic data: ^{1}H NMR (400 MHz, $CDCl_3$, rotamers observed): δ = 5.51 (0.4 H, t, *J* = 1.3 Hz, CHO), 5.50 (0.6 H, t, *J* = 1.3 Hz, CHO), 2.53 (1.8 H, s, SMe) and 2.52 (1.2 H, s, SMe). A solution of Bu_3SnH (211 μL, 0.78 mmol, 1.1 equiv) and AIBN (23 mg, 0.14 mmol, 0.2 equiv) in toluene (5 mL) was added via syringe pump over 2.25 h to a solution of the above xanthate (400 mg, 0.71 mmol) in toluene (25 mL) at reflux. The mixture was then stirred for an additional 45 min before being cooled and worked-up according to the method of Curran and Chang.[12b] Purification of the residue by column chromatography (30–50% Et_2O in petrol ether) gave a colourless oil, 1,2-dihydropyridine **12** (R = 4-$MeOC_6H_4$) (202 mg, 62%); R_f = 0.5 (60% Et_2O in petrol ether). IR (film): 2979 (m), 2933 (m), 1723 (s), 1633 (m), 1596 (m), 1513 (s), 1393 (m), 1370 (m), 1288 (s), 1250 (s), 1176 (m), 1144 (s), 1088 (s), 814 (m), 732 (m), 715 (m), 662 (s), 579 (s) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01–7.75 (1 H, m, =CHN), 7.70 (2 H, d, *J* = 8.0 Hz, 2 × CH of Ts), 7.30 (2 H, d, *J* = 8.0 Hz, 2 × CH of Ts), 6.97 (2 H, d, *J* = 8.2 Hz, 2 × CH of MeO*Ar*), 6.76 (2 H, d, *J* = 8.2 Hz, 2 × CH of MeO*Ar*), 6.10–5.90 (1 H, m, CC*H*=), 5.41 (1 H, dd, *J* = 9.8, 5.5 Hz, CHC*H*=), 5.01–4.89 (1 H, m, CHN), 3.77 (3 H, s, OMe), 2.69 (1 H, dd, *J* = 13.1, 8.2 Hz, H of CH_2), 2.59 (1 H, dd, *J* = 13.1, 5.2 Hz, H of CH_2), 2.43 (3 H, s, Me of Ts), 1.48 (9 H, s, *t*-Bu). ^{13}C NMR (100 MHz, DMSO, 373K): δ = 159.3 (C_{quat} of MeOAr), 152.0 (C=O), 144.5 (C_{quat} of Ts), 139.4 (C_{quat} of Ts), 134.1 (=CHN), 131.3 (2 × CH of Ts), 130.7 (2 × CH of MeOAr), 128.7 (C_{quat} of MeOAr), 127.6 (2 × CH of Ts), 124.3 (CH*C*H=), 119.9 (TsC_{quat}), 118.0 (C*C*H=, br), 114.9 (2 × CH of MeOAr), 84.3 (*C*Me_3), 56.1 (OMe), 54.9 (CHN, br), 40.2 (Ar*C*H_2), 28.4 (3 × Me of Boc) and 21.7 (Me of Ts). MS (CI, NH_3): *m/z* (%) = 473 (100) [M + NH_4^+] and 354 (30). $C_{25}H_{33}O_5N_2S$ requires [M]: 473.2110; found [M + NH_4]: 473.2098. (b) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

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