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USE OF ATOM-TRANSFER RADICAL CYCLIZATIONS AS AN EFFICIENT ENTRY INTO A NEW "SEROTONERGIC" AZANORADAMANTANE

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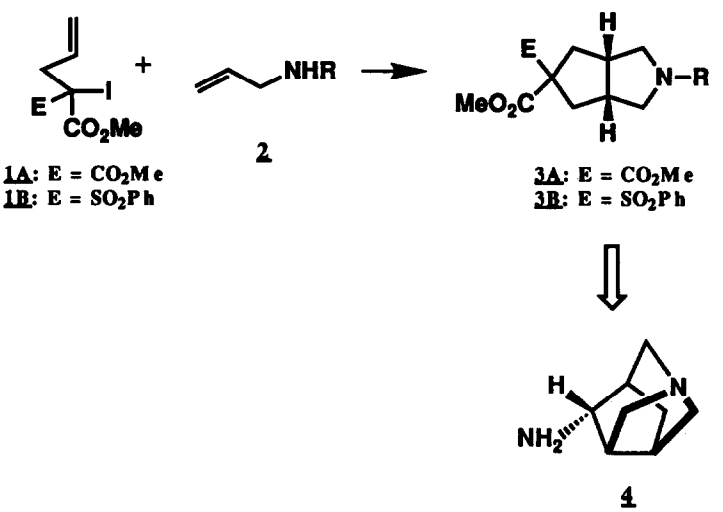
Abstract: A route to azanoradamantanes is described which makes use of an atom-transfer radical cyclization to afford 3-azabicyclo[3.3.0]octanes **3A** and **3B**. Subsequent elaboration of exo-allylamine functionality, followed by cyclization of the endo-hydroxymethyl intermediate **9**, affords the new azanoradamantanes **11** and **4**. This new azatricyclic system is useful for producing serotonin 5-HT3 antagonists and 5-HT4 agonists.

In previous reports we have described the use of 2-allyl-2-iodo malonate **1A**[1] or the corresponding phenylsulfonyl acetate **1B**[2] in a tandem reaction sequence wherein an iodine atom-transfer radical annulation with an allylamine **2** is followed by an ionic cyclization to produce 3-azabicyclo[3.3.0]octanes **3A/3B** efficiently in a one-pot operation. Besides providing these interesting azabicycles for the production of pharmacologically active substances, we envisioned that **3A/3B** might also provide a rapid entry into a new class of azanoradamantyl amines **4** (Scheme 1), targeted as azatricycles for the preparation of compounds having activity at serotonin 5-HT_4 and/or 5-HT_3 receptor subtypes.



1A: E = CO_2Me
1B: E = SO_2Ph

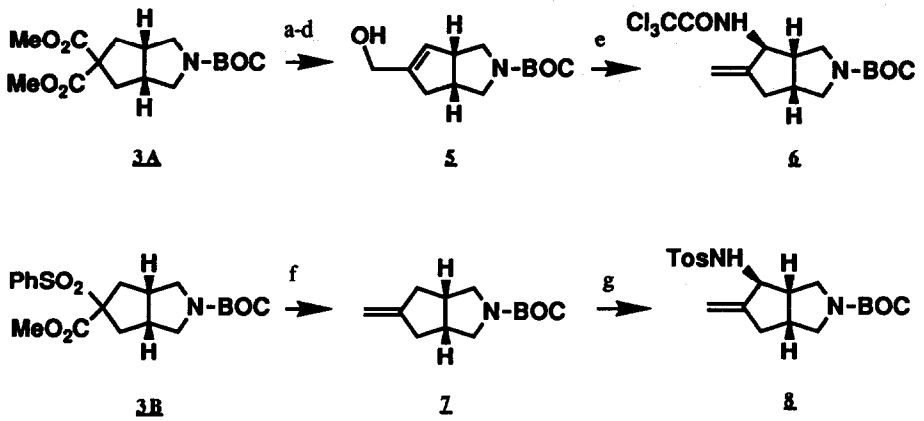
3A: E = CO_2Me
3B: E = SO_2Ph

4

Scheme 1

The azabicycles **3A/3B** possess the requisite azabicyclo[3.3.0]octane skeleton embedded in the structure of the azanoradamantane **4**. The geminal 7,7-substitution pattern (E-C-CO_2Me) present in **3A/3B** would serve as the functionality required to introduce the primary amine moiety as well as the methano-bridge found in **4**. We report herein the successful realization of this strategy.

Initially, we turned our attention to the geminal di-carbomethoxy azabicycle **3A**, produced in the tandem atom-transfer annulation/ionic cyclization reaction as previously described[1] in an optimized 65% isolated yield. As illustrated in Scheme 2, a Krapcho decarboxylation/ phenylselenation/oxidative elimination sequence produced the corresponding unsaturated ester which was reduced with DiBAH to afford the allylic alcohol **5** in 31% overall yield from **3A**. Application of Overman's hetero-Claisen rearrangement[3], via the intermediacy of the trichloroacetimidate of **5**, efficiently produced exclusively the unstable exo-trichloroacetamide **6** in 51% yield.



3A **5** **6**

3B **7** **8**

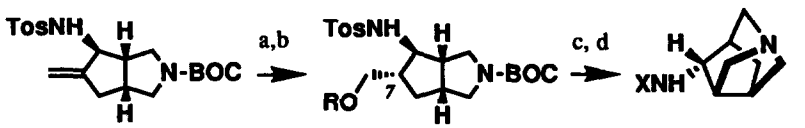
a) NaCN/DMSO, 160 °C (63%); b) LDA, THF/HMPA, -78° C, then $(PhSe)_2$, 0° C (65%);
c) MCPBA, CH_2Cl_2, -78° C, then CCl_4, reflux (83%); d) DIBAH, CH_2Cl_2, -78° C (91%);
e) NaH, Cl_3CCN, then toluene reflux (51%); f) See reference 2; g) TosN=S=N-Tos/CH_2Cl_2/0° C to RT, then aq. K_2CO_3 (82%)

Scheme 2

While the sequence **3A** --> **6** did afford the requisite exo-allylamine needed for elaboration to the target azanoradamantane **4**, the number of operational steps and the sensitivity in handling **6** led us to consider a more direct route based on the phenylsulfonyl-substituted azabicycle **3B**. **3B** is readily obtained (51% yield) via the tandem atom-transfer annulation/ionic cyclization sequence shown in Scheme 1. As reported in the preceding communication[2], **3B** is converted to the exo-methylene substituted-azabicycle **7** via a Julia olefination sequence. At this stage, use of

Sharpless' sulfodiimide procedure[4] allowed the exo-allylic tosylamide **8** to be produced in one step in an excellent 81% yield (Scheme 2). This sequence resulted in a marked improvement in efficiency over that used to convert **3A** to **6**. Moreover, the tosylamide **8** was quite stable on storage. Single crystal X-ray analysis revealed that **8** is the exo-allylic tosylamide as shown.

Having the allylamine function introduced, we subjected **8** to hydroboration in order to provide the endo-hydroxymethyl cyclization precursor **9** (Scheme 3). Use of borane was disappointing, giving **9** (endo-hydroxymethyl) and its 7-epimer **epi-9** (exo-hydroxymethyl) in a ratio of 1:1.2. Thexylborane improved the ratio somewhat (1.25:1.0), while rhodium-catalyzed hydroboration afforded exclusively the undesired **epi-9**. These results are in keeping with a frontier orbital model of hydroboration proposed by Burgess.[5] In any case, the undesired **epi-9** could be easily separated from **9** and submitted to an oxidation/epimerization/reduction sequence to allow formation of **9** in 67% yield.



8

9: R =H
10: R = Tos

11: X = Tos
4: X = H

a) Thexylborane/THF, then aq. H_2O_2 (67%); b) TosCl/pyr (99%);
c) TFA, then *i*-Pr_2NEt/CH_3CN (92%); d) Na/NH_3 (99%)

Scheme 3

O-Tosylation of **9** provided **10** in quantitative yield, which was not purified but used in crude form. Removal of the N-BOC group, followed by Hünig's base-promoted cyclization, produced the desired azanoradamantane tosylamide **11**[6] in 98% isolated yield from **9**. Reductive removal of the tosyl group afforded the target azanoradamantyl amine **4**. This tricycle has been synthesized in five operational steps and 45% overall yield starting from the readily available 3-azabicyclo[3.3.0]octane **3B**, which is itself prepared in one operational step from methyl 2-iodo-2-(phenylsulfonyl)-4-pentenoate and N-BOC-allylamine[2].

Azanoradamantyl amine **4** has been used to prepare a number of agents which act as agonists at the newly identified serotonin 5-HT_4 receptor, or as antagonists at the serotonin 5-HT_3 receptor. The biological details of these findings will be reported elsewhere.

References

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4) Sharpless, K. B.; Hori, T.; *J. Org. Chem.* **1976**, *41*, 176.

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6) Tosylamide substituted azanoradamantane **11**:
mp 199-200° C (dec); IR (KBr) 3440 (br), 3030, 1600, 1340, 1324, 1167, 1095 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) d 7.76 (2 H, d, J = 8.1 Hz), 7.32 (2 H, d, J = 8.1 Hz), 4.43 (1 H, d, J = 6 Hz, exchanges with D_2O) 3.56 (1 H, d, J = 6 Hz, s with D_2O), 2.97-2.84 (3 H, m), 2.81-2.69 (3 H, m) 2.44 (3 H, s), 2.42-2.37 (2 H, m), 2.00 (1H, m) 1.93 (1 H, s), 1.77 (1 H, d, J = 12.0 Hz). ^{13}C NMR (75MHz, $CDCl_3$) d 143.4, 138.0, 129.7, 126.9, 66.3, 65.5, 65.1, 57.3, 45.8, 42.8, 38.5, 37.5, 21.5. MS m/e calcd for $C_{15}H_{20}N_2O_2S$: 292.1245 Found: 292.1245. Anal calcd for $C_{15}H_{20}N_2O_2S$: C, 61.62; H, 6.89; N, 9.58; S, 10.96. Found: C, 61.65; H, 6.96; N, 9.53; S, 11.29.

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