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# 2-Azabenzonorbornanes from 7-Azabenzonorbornanols by a Nitrogen-Directed Neophyl-Type Radical Rearrangement

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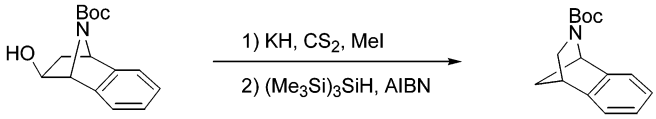
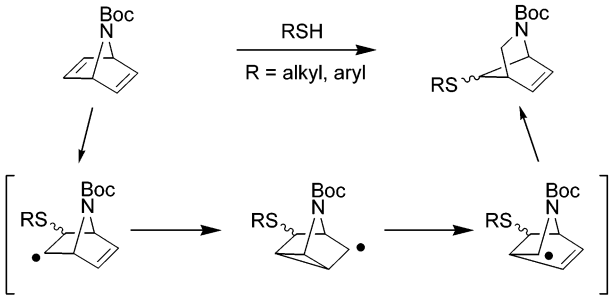
## ABSTRACT




**Barton deoxygenation of 7-azabenzonorbornanols leads to a synthetically useful neophyl-like rearrangement to give 2-azabenzonorbornane derivatives in 64–90% yields.**

Azabicyclic systems are ubiquitous in natural products and pharmaceutical agents. New methods for their construction are therefore important synthetic goals.[1] Radical cyclizations and rearrangements constitute some of the most powerful methods for the construction of such polycycles.[2] Radical rearrangements are well-known in norbornenyl (bicyclo[2.2.1]heptenyl) systems, usually leading to mixtures of bi- and tricyclic products.[3] However, during the course of our studies in free radical rearrangements of related azabicyclic systems, we recently demonstrated that clean radical rearrangements can occur.[4] These latter processes are likely driven by the stabilizing feature of generating a radical α to nitrogen.[5] For example, radical addition of thiols to 7-azanorbornadienes gave rise to homoallylic rearrangement and 2-azabicyclic sulfides as the sole products (Scheme 1).[6]

**Scheme 1.** Radical Addition of Thiols to 7-Azanorbornadienes[6]




Compared with radical rearrangements in norbornenyl systems, (partial) neophyl-type rearrangements (1,2-shift of

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(1) For a review of 2-azabicyclo[2.2.1]heptanes, see: Blondet, D.; Morin, C. *Heterocycles* **1982**, *19*, 2155−2182.

(2) (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, pp 161−310. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React (N.Y.)* **1996**, *48*, 301−856. (c) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001.

(3) (a) Warner, C. R.; Strunk, R. J.; Kuivila, H. G. *J. Org. Chem.* **1966**, *31*, 3381−3384. (b) Davies, D. I. *Chem. Soc. Spec. Publ*. **1970**, *24*, 201−237. (c) Wilt, J. W. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, pp 333−502.

(4) (a) Hodgson, D. M.; Maxwell, C. R.; Matthews, I. R. *Synlett* **1998**, 1349−1350. (b) Hodgson, D. M.; Maxwell, C. R.; Wisedale, R.; Matthews, I. R.; Carpenter, K. J.; Dickenson, A. H.; Wonnacott, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3150−3158.

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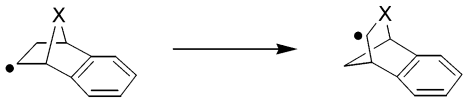
**Scheme 2.** Neophyl-Type Radical Rearrangement

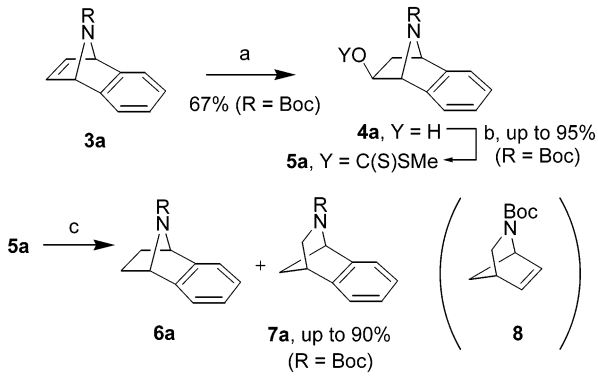



an aryl group, Scheme 2, X = $CH_2$) in the corresponding benzofused systems are much more rare. This applies both to free radical additions to benzonorbornadiene and to H-atom abstraction from benzonorbornane.[7] Indeed, many additions to benzonorbornadiene were found to proceed without any rearrangement. This is presumably due to the comparatively unfavorable disruption of aromaticity.[3c] These early observations, together with our recent studies, suggested that extending the "aza homoallylic rearrangement" process to 7-azabenzonorbornyl systems (Scheme 2, X = NR) would be challenging, but could provide an attractive entry to 2-azabenzonorbornanes.[8] The latter systems are of interest, for example, as conformationally defined adrenergic agents.[9]

7-Azabenzonorbornadienes (e.g. **3a**, Scheme 3) were considered to be excellent substrates to examine the chemistry in Scheme 2 (X = NR), since they are readily available via aryne cycloadditions with pyrroles.[10] However, radical addition of thiols (cf. Scheme 1) to **3a** (R = Boc)[11] gave only simple addition to the double bond, without any rearrangement. Therefore, hydroboration of **3a** followed by oxidation to the alcohol and then Barton deoxygenation was thought an attractive alternative method for radical generation, since hydroboration is known to proceed with good facial and regioselectivity in substituted alkenes,[12] and the rate of H-atom transfer would be slowed relative to that of a thiol.[13]

Hydroboration−oxidation of **3a** (R = Boc) gave alcohol **4a** as a single isomer (Scheme 3) in satisfactory yield (67%), assigned as the *exo*-product in accordance with previous work.[14] Formation of xanthate **5a** then proceeded smoothly in excellent (95%) yield. We were pleased to find that treatment of xanthate **5a** with tris(trimethylsilyl)silane (TTMSS) (1.5 equiv) in boiling toluene with AIBN as initiator for 2 h gave a 1:1 mixture of **6a**,[15] the product of direct

**Scheme 3.** Synthesis and Deoxygenation of 7-Azabenzonorbornanol[a]




[a] Conditions: (a) 9-BBN (1.5 equiv) ,THF, 25 °C, 24 h, then 35% aq $H_2O_2$ (15 equiv), 2 M NaOH (4 equiv), THF/$H_2O$ (5:1), 25 °C, 5 h; (b) KH (4 equiv), $CS_2$ (4 equiv), MeI (4 equiv), THF, 0−25 °C, 90 min; (c) TTMSS (1.5 equiv), AIBN (0.5 equiv), toluene, reflux, 2 h.

reduction, and **7a**, which was identified as the desired rearranged product by NMR studies and by comparison with known alkene **8** (Scheme 3).[16,17] We supposed that increasing the lifetime of the first-formed radical would lead to a higher proportion of the rearranged product **7a**.[18] By increasing the dilution by a factor of 3, and adding a mixture of TTMSS and AIBN to a preheated solution of xanthate **7a** over 100 min, the ratio increased to ∼20:1, and gave a 90% isolated yield of **7a**.

Encouraged by the above results, we undertook a more detailed study of the effect on the rearrangement of bicyclic core substitution and also of variation of electronics in the aromatic ring. Benzyne cycloadditions[11] with Boc-protected[19] 3-ethylpyrrole and 2,4-dimethylpyrrole[20] gave adducts **3b** and **3c** in 56% and 52% yields, respectively (Scheme 4). Hydroboration then occurred with complete facial and regioselectivity to produce alcohols **4b** and **4c** as single diastereomers.

Radical deoxygenation of the xanthates **5b** and **5c** in the manner previously described for **5a** gave good yields of the rearranged products (Scheme 4). Only traces of directly reduced products were observed in the crude $^1$H NMR spectra.[21] Noteworthy is that NOESY experiments revealed

(5) Wayner, D. D. M.; Clark, K. B.; Rauk, A.; Yu, D.; Armstrong, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 8925−8932.
(6) Hodgson, D. M.; Bebbington, M. W. P.; Willis, P. *Chem. Commun.* **2001**, 889−890.
(7) (a) Cristol, S. J.; Nachtigall, G. W. *J. Org. Chem.* **1967**, *32*, 3727−3737. (b) Cristol, S. J.; Sullivan, J. M. *J. Am. Chem. Soc.* **1971**, *93*, 1967−1970. (c) Sonawane, H. R.; Najundiah, B. S.; Kelkar, R. G. *Tetrahedron* **1986**, *42*, 6673−6682. (d) For a recent review of radical aryl migrations, see: Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649−9667.
(8) For an alternative method, see: Pedrosa, A.; Andrés, C.; Iglesias, J. M.; Pérez-Encabo, A. *J. Am. Chem. Soc.* **2001**, *123*, 1817−1821.
(9) Grunewald, G. L.; Sall, D. J.; Monn, J. A. *J. Med. Chem.* **1988**, *31*, 433−444.
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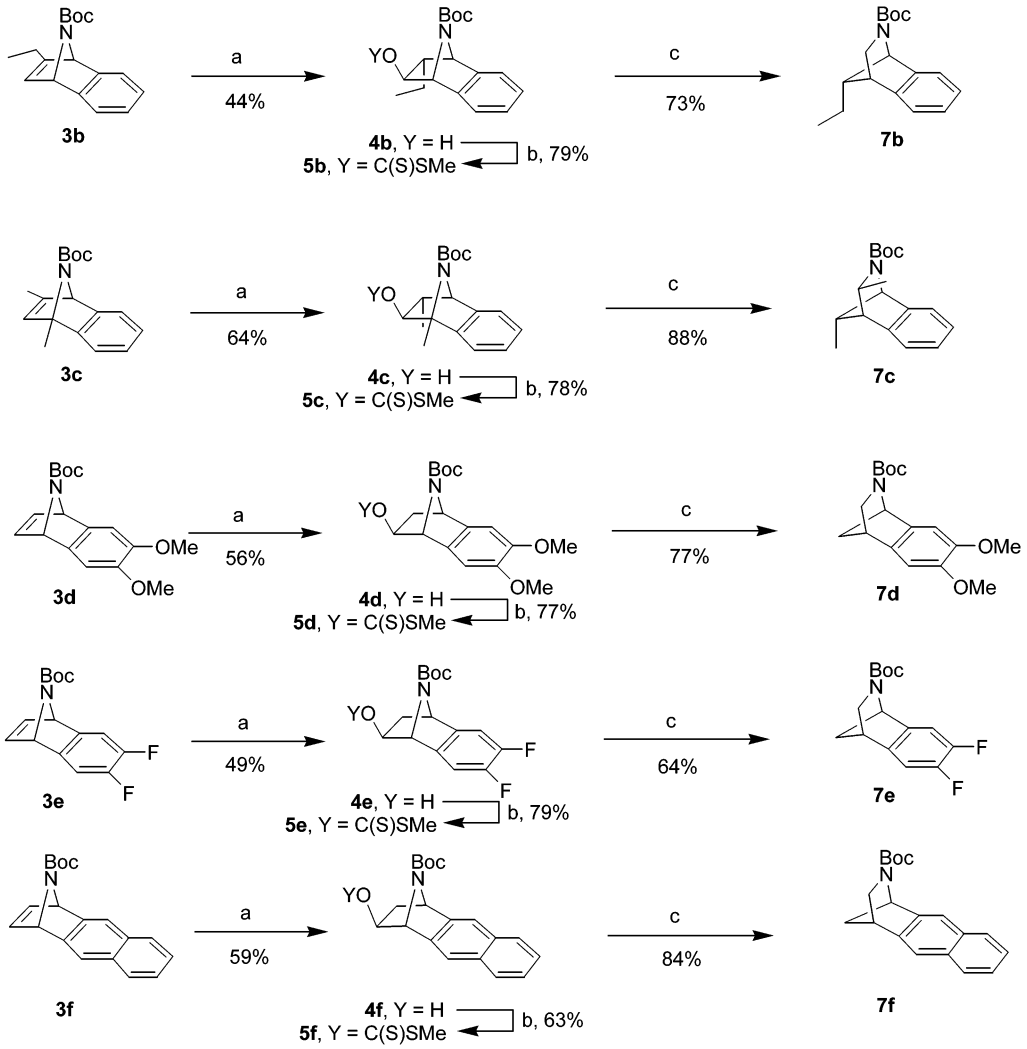
(12) Brown, H. C.; Prasad, J. V. N. V. *Heterocycles* **1987**, *25*, 641−657.
(13) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176.
(14) Anderson, P. S. *Tetrahedron Lett.* **1976**, *17*, 1141−1144.
(15) Ohwada, T.; Miura, M.; Tanaka, H.; Sakamoto, S.; Yamaguchi, K.; Ikeda, H.; Inagaki, S. *J. Am. Chem. Soc.* **2001**, *123*, 10164−10172.
(16) Kasyan, A.; Wagner, C.; Maier, M. E. *Tetrahedron* **1998**, *54*, 8047−8054.
(17) Further support that the rearrangement proceeds in the manner indicated is provided by rearrangement of **5a** (R = $CO_2$Me) and base hydrolysis (KOH) of the resulting **7a** (R = $CO_2$Me) to give the free amine **7a** (R = H), which had spectroscopic data matching those given in ref 9 for **7a** (R = H).
(18) Studies on the kinetics of the process are currently underway in our laboratories.
(19) Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 296−301.
(20) Ethylpyrrole was prepared by hydrolysis (KOH) of the known 3-ethyl-1-phenylsulfonylpyrrole, see: Ketcha, D. M.; Carpenter, K. P.; Atkinson, S. T.; Rajagopolan, H. R. *Synth. Commun.* **1990**, 1647−1655. 2,4-Dimethylpyrrole is commercially available (Aldrich).
(21) Authentic samples of the directly reduced products were prepared by hydrogenation[15] of the benzyne cycloadducts.

**Scheme 4.** Synthesis and Rearrangement of Substituted 7-Azabenzonorbornanol Xanthates[a]




[a] Conditions: (a)−(c) as in Scheme 3.

that H-atom transfer to form **7c** occurs exclusively from the *exo* face, leading to a single diastereomer. These studies also showed that the 7-alkyl substituent in **7b** and **7c** resides *anti* to nitrogen, confirming that the earlier hydroborations were completely *exo*-selective.

To determine the effect of arene ring electronics on the neophyl-like migration, we prepared adducts **3d**−**f** (Scheme 4) by diazotization of the appropriate aromatic amino acid derivatives in the presence of *N*-Boc pyrrole.[22] Deoxygenation of the derived xanthates **5d**−**f** gave the expected products **7d**−**f** in good yields. Dimethoxy substitution in **5d** was found to have a retarding effect on the rearrangement, as shown by a 6:1 ratio of rearranged:directly reduced products.[23] This is consistent with the initial formation of a nucleophilic secondary alkyl radical and a slower cyclization onto the more electron-rich aromatic ring than in the unsubstituted system. This ratio in the reaction of the difluorinated xanthate **5e** did not appear to differ greatly from that of **7a**:**6a**, which suggests only a mild overall electron-withdrawing effect due to the fluorine substituents. None of the directly reduced product was detected in the reaction of **5f**, which is in agreement with rate enhancements observed (compared to phenyl) in studies of other naphthyl group radical migrations.[7d]

In summary, a synthetically useful and conceptually interesting neophyl-type radical rearrangement process has been established, leading to azabicycles that are not readily accessible by other means.[8,9] Extensions of the process to provide enantioenriched 2-azabenzonorbornanes as well as manipulation of the products to targets of biological interest are under investigation.

**Acknowledgment.** We thank the EPSRC and AstraZeneca for an Industrial CASE award (to M.W.P.B.) and the EPSRC National Mass Spectrometry Service Centre for mass

(22) See Supporting Information for the preparation of **3d** and **3e**. Adduct **3f** was prepared according to the procedure of Bornstein, see: Remy, D. E.; Bissett, F. H.; Bornstein, J. *J. Org. Chem.* **1978**, *43*, 4469−4472.

(23) % of directly reduced product was isolated from the reaction of **5d**.

spectra. We also thank Dr. B. Odell for expert assistance with structure determination using NMR.

**Supporting Information Available:** Experimental procedures, full characterization data, and $^{13}C$ NMR spectra for **3b**−**e**, **4a**−**f**, and **7a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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