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2-Azabicyclo[2.2.1]hept-5-enes from 7-azabicyclo[2.2.1]heptadienes by tandem intermolecular radical addition—homoallylic radical rearrangement

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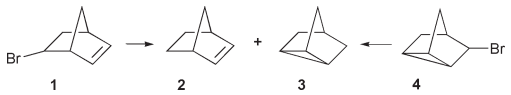
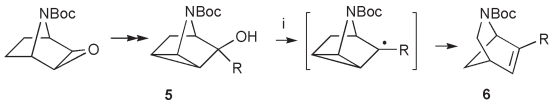
Addition of thiols to 7-azabicyclo[2.2.1]heptadienes such as 16 leads exclusively to 7-thio-substituted 2-azabicyclo[2.2.1]-hept-5-enes 17 in good yields *via* tandem intermolecular radical addition—homoallylic radical rearrangement.

Radical cyclisations and rearrangements are amongst the most powerful and versatile methods for the construction of mono and polycyclic systems.[1] Radical reduction of norbornenyl sbromide **1** or nortricyclyl bromide **4** is known to produce the same (~1:1) mixture of norbornene **2** and nortricyclene **3** (Scheme 1).[2] However, during the development of novel analgesics related to epibatidine by a strategy involving indirect skeletal interconversion of 7-aza to 2-azabicyclo[2.2.1]heptyl ring systems, we reported that radical deoxygenation of azanortricyclanol **5** delivers a single product **6**, even when R is potentially radical stabilising (*e.g.* Ar, Scheme 2).[3]

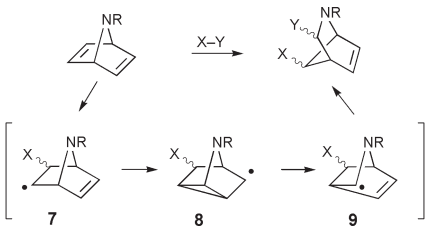


Scheme 1



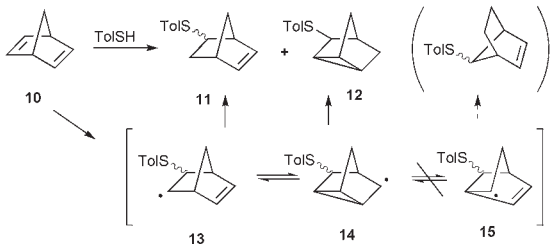
Scheme 2 *Reagents and conditions*: i, $ClCOCO_2Me$, DMAP, then Bu_3SnH, AIBN.

Following this demonstration of 'nitrogen-directed' radical rearrangement, we considered that a synthetically attractive direct skeletal interconversion might be possible by intermolecular radical addition–homoallylic radical rearrangement (Scheme 3). This would provide convergent access to synthetically important 2-azabicyclo[2.2.1]heptyl ring systems containing substitution not easily available by other methods.[4] Here we communicate our preliminary results concerning the realisation of this concept.



Scheme 3

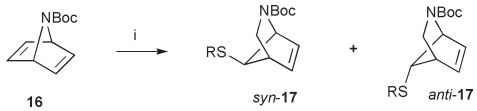
Radical additions to norbornadiene **10** (and substituted norbornadienes), using thiols for example, have been well-studied and usually result in substituted nortricyclanes as the major products.[5] Consistent with these earlier studies, we found that addition of *p*-thiocresol to norbornadiene **10** (both 2 mol dm^{-3} in toluene) at 25 °C led preferentially to nortricyclyl sulfide **12**, with bicyclic sulfide **11** (*exo*- : *endo*-, 5:1)[6] being the only other product detected (**11**:**12**, ~1:3, Scheme 4).



Scheme 4

Further experiments at increasing dilution indicated that the product ratio reached a constant level (**11**:**12**, ~ 1:6), once the concentration of each reactant was < 0.1 mol dm^{-3}. These latter results indicate attainment of equilibrium between the substituted norbornenyl and nortricyclyl radicals **13** and **14**. The presence of the sulfur substituent therefore leads to preferential cyclopropane opening in **14** back to **13** (rather than from **14** to **15**), with H-atom transfer to **14** to give nortricyclyl sulfide **12** being faster than H-atom transfer to **13** to give bicyclic sulfide **11**; hence the product profile observed does not reflect the **13**/**14** equilibrium position. This is in contrast to Scheme 1, where the rates of H-atom transfer to the norbornenyl and nortricyclyl radical intermediates leading to **2** and **3** are likely to be similar and therefore the product profile should reflect the ratio of radicals at equilibrium.

By comparison to the reactions of norbornadiene with thiols, the corresponding 7-aza systems such as **16** (available in two steps from the alkoxycarbonyl-protected pyrrole and tosyl ethyne)[7] behave in dramatically different fashion (Scheme 5, Table 1), but in accord with the earlier analysis (Scheme 3).



Scheme 5 *Reagents and conditions*: i, RSH (0.9 equiv.), benzene or toluene, 25 °C (R = aryl) or 80 °C (R = alkyl), 6–24 h.

Pleasingly, both aromatic and aliphatic thiols were found to react cleanly with only a slight excess (1.1 equiv.) of azadiene **16** in benzene or toluene (0.1 mol dm^{-3}) to give rearranged sulfides **17** in 6–72 h, depending on the reactivity of the thiol. In the case of the less reactive aliphatic thiols, heat was required for completion of the reaction in a satisfactory time. Aliphatic thiols are considerably poorer H-atom transfer agents than their aromatic counterparts.[8] This may explain the lower yields in these cases, as polymerisation could compete with atom

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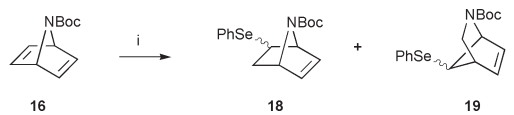
Table 1 Thiol additions to 7-azabicyclo[2.2.1]heptadiene **16**

Thiol	T/°C	*t*/h	Yield (%)	*syn*-**17**:*anti*-**17**
TolSH[a]	20	24	92	3:1
PhSH	20	24	92	4:1
2,6-diMeC_6H_3SH	20	24	90	4:1
4-$NO_2C_6H_4SH$	20	72	50	7:1
Bu^nSH	80	6	59	2:1
Bu^tSH	80	24	48	5:1
$HO(CH_2)_3SH$	80	14	56	4:1

[a] TolSH with **16** (Boc = CO_2Me) at 20 °C for 4 h gave **17** (R = Tol, Boc = CO_2Me) in 66% yield (*syn*- : *anti*-, 4:1).

transfer. The major diastereoisomer in the reaction with *p*-thiocresol was shown by NOE analysis to be the *syn*-isomer arising from initial *exo*-attack of thiyl radical on azadiene **16**, and the predominant isomer obtained with the other thiols is assigned as *syn* by analogy. Evidence that the product sulfides **17** possess the rearranged 2-azabicyclo[2.2.1]hept-5-ene framework is, for example, that oxidation of **17** (R = Tol) using buffered peracetic acid (6 equiv., 25 °C, 18 h) gave in 91% yield the epimeric sulfones **17** (RS = Ts) with spectral data distinctly different from the 2-Ts-7-Boc-7-azabicyclo[2.2.1]hept-5-enes[9] that would be obtained from oxidation of the product of simple addition across one double bond in azadiene **16**. Subsequent desulfonylation of sulfones **17** (RS = Ts) with 6% sodium–amalgam (MeOH, 25 °C, 12 h) gave the known 2-azabicyclic alkene **6** (R = H)[3,10] in 33% yield as the only identifiable product.

Benzeneselenol shows similar behaviour with unsaturated systems to aromatic thiols, but is an order of magnitude superior as an H-atom transfer agent.[8] Under otherwise identical conditions to the earlier reactions of aromatic thiols (Table 1), it was found that benzeneselenol with azadiene **16** gives a small proportion (12%) of the selenide **18** arising from simple addition across one double bond, as well as the expected rearranged selenide **19** (81%, Scheme 6).



16 18 19

Scheme 6 *Reagents and conditions*: i, PhSeH (0.9 equiv.), benzene, 25 °C, 24 h.

This result allows an estimation of the rate constant for the rearrangement **7** → **9** (Scheme 3). Given that no products other than the 2-azabicyclic epimers **17** are observed in the addition of aromatic thiols, it seems probable that the rate constant for the rearrangement is between 1 and 2 orders of magnitude greater than the initial rate of H-atom transfer from the thiol. A thiol concentration of 0.1 mol dm^{-3} (typical in our studies) and an approximate second order rate constant for H-atom transfer of 10^8 mol^{-1} dm^3 s^{-1} (ref. 8), suggests a rate constant of $\approx 10^8$—10^9 s^{-1} for the rearrangement at 25 °C.

The absence of tricyclic products in any of the reactions with azadiene **16** suggests that the lifetime of the azatricyclic intermediate **8** is much shorter than that for either of the bicyclic intermediates **7** and **9** (Scheme 3). In kinetic studies of the nortricyclyl–norbornenyl radical rearrangement [**13** (Tos = H) and **14** (Tos = H), Scheme 4], the rates of ring opening and ring closure have been shown to be similar: $\approx 10^7$ s^{-1} at 25 °C.[11] In the azabicyclic system, however, it seems probable that the ring opening step (**8** → **9**) is significantly faster, with the transition state being lowered in energy by the stabilisation of the developing radical α- to nitrogen.[12] Rate constants for the ring opening of cyclopropyl methyl radicals to but-3-enyl radicals are known to be strongly influenced by substitution.[13]

In summary, we describe the first examples of free radical additions to 7-azanorbornadienes. The process demonstrates a new approach to the 2-azabicyclo[2.2.1]heptyl ring system by homoallylic radical rearrangement, which uses a nitrogen atom to promote and guide cyclopropane ring opening.[3,14] Extensions of the principle to other addition reactions, different ring systems and manipulation of the adducts towards targets of biological interest, are under investigation.

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