

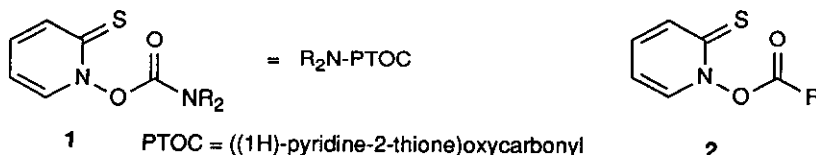
N-HYDROXYPYRIDINE-2-THIONE CARBAMATES AS AMINIUM RADICAL CATION
 PRECURSORS. TRANSANNULAR RADICAL CYCLIZATIONS FORMING TROPANES[§]

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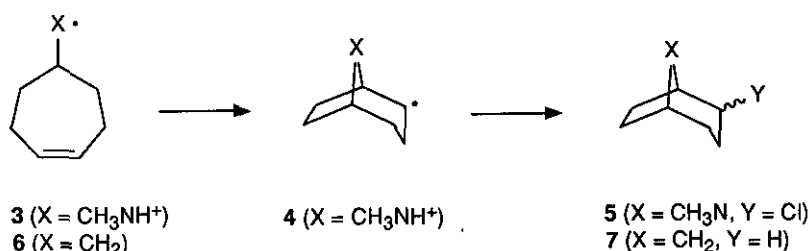
Abstract *N*-Methylcyclohept-4-enaminium cation radical, produced from the corresponding *N*-hydroxypyridine-2-thione carbamate, cyclizes to give, ultimately, tropane and substituted tropanes in high yield.

Free radical cyclization reactions are becoming increasingly popular in organic synthesis. Most commonly these cyclizations involve the formation of a five-membered ring in a C-C bond forming step. However, cyclizations of nitrogen-centered radicals onto δ,ϵ -unsaturated sites are also known.¹ Both neutral aminyl and charged aminium cation radicals can add intramolecularly to an unsaturated site, but the aminium cation radicals appear to be more useful.¹ Recently, we demonstrated that aminyl radicals could be produced in radical chain reactions from *N*-hydroxypyridine-2-thione carbamates (1)² which are related to the *N*-hydroxypyridine-2-thione esters (2) developed by Barton's group.³ In the presence of a weak organic acid, the aminyl radicals thus formed were protonated to give aminium cation radicals that, when substituted with a δ,ϵ -double bond, cyclized to give, ultimately, pyrrolidine products.² This chemistry is similar to that seen with other aminium cation radical precursors,¹ but the procedures are milder. In this communication we report an extension of our methodology for formation of tropanes by transannular aminium cation radical cyclizations.



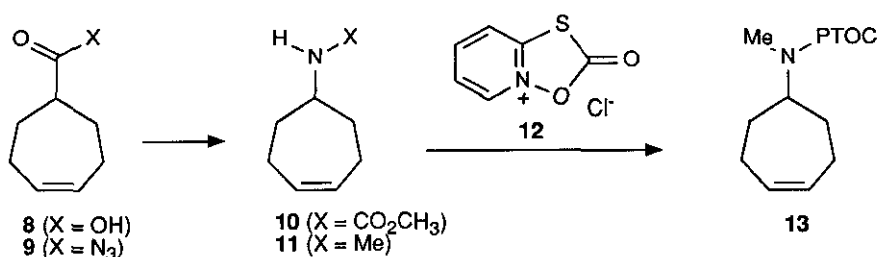
Bastable, Hobson and Riddell (BHR) have demonstrated that the *N*-methylcyclohept-4-enaminium cation radical (3) can cyclize in a transannular fashion to give radical 4, however, when the precursor to 3 was an *N*-chloroamine, the ultimate product of the reaction sequence, 2-chlorotropane (5), was obtained in only 7.5% yield.⁴ The corresponding carbon radical cyclization of cyclohept-4-enylmethyl (6), however, gives bicyclo[3.2.1]octane (7) in yields as high as 75% when the reaction is conducted in the presence of Bu_3SnH ,⁵ so it was possible that the low yields of 5 obtained by BHR resulted not from an inherently poor radical cyclization step but rather from the instability of 5, a nitrogen mustard that could decompose via an aziridinium salt.⁶ Thus, the *N*-hydroxypyridine-2-thione carbamate approach appeared to be promising.

[§] Dedicated to Sir Derek H. R. Barton on the occasion of his 70th birthday.



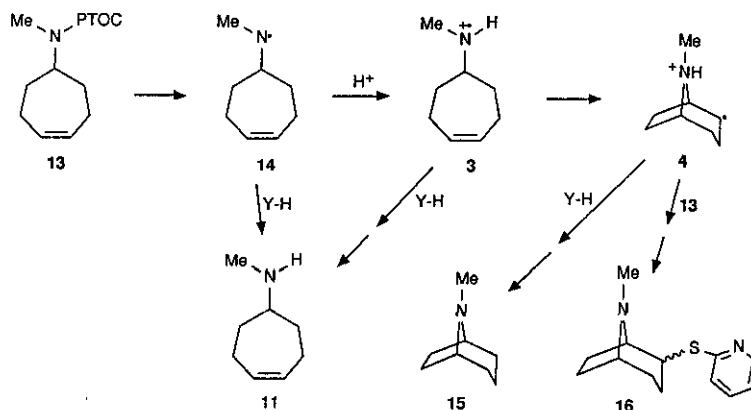
The preparation of the appropriate carbamate precursor was accomplished by the procedure shown in Scheme 1. 4-Cycloheptene-1-carboxylic acid (**8**), prepared by a modification^{7a} of the enamine route reported by Stork,^{7b} was converted to *N*-methylcyclohept-4-enamine (**11**) via azide **9** and carbamate **10** in a slight modification of the procedure reported by BHR.⁴ Treatment of amine **11** with salt **12**⁸ in the presence of Et_3N gave carbamate **13** in 81% yield from amine **11** after recrystallization.^{9,10}

Scheme 1

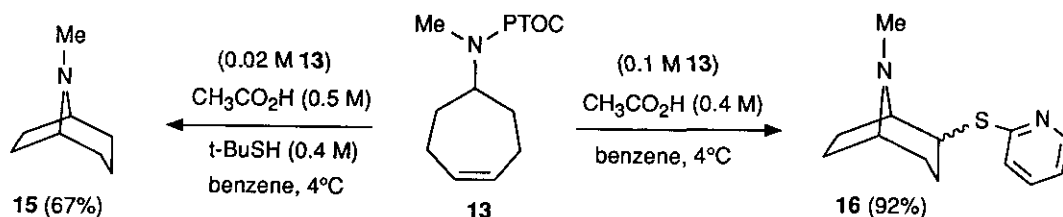


The efficacy of the aminium radical cyclization was studied by allowing carbamate **13** to react in the presence of weak organic acids and various hydrogen atom donors (Y-H). In a radical chain sequence (Scheme 2), carbamate **13** gives aminyl radical **14** that, apparently, is protonated by the weak acid² to give aminium cation radical **3**. The aminium radical (or radical **14**) can react with the hydrogen atom donor to give, ultimately, amine **11**, or radical **3** can cyclize to the bicyclic radical **4**. Carbon radical **4** can react with the hydrogen donor to give tropane (**15**) or with precursor **13** to give *endo*- and *exo*-2-(2-pyridylthio)tropane (**16**).

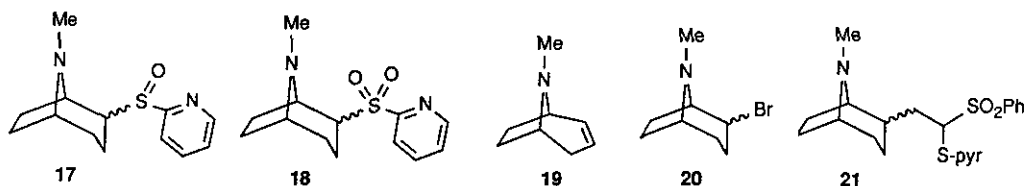
Scheme 2



Acetic acid proved to be adequate for protonation of **14** and *tert*-BuSH was an efficient and selective hydrogen atom trapping agent. In visible light initiated reactions similar to those previously described,² tropane^{10,11} was isolated in 67% yield when *tert*-BuSH was present and sulfides **16**¹⁰ were isolated in 92% yield in the absence of *tert*-BuSH (*exo*-**16** : *endo*-**16** = 15 : 1).



Further derivatization of the sulfides **16** was possible. Oxidation of the mixture with one equivalent of mcpba gave sulfoxide **17** in 80% yield.^{10,12} More extensive mcpba oxidation afforded sulfone **18** in 100% yield.^{10,13} Various attempts to deprotonate **17** or **18** followed by addition of an electrophile did not afford substitution products, however sulfoxide **17** suffered elimination upon treatment with DBU to give tropidine (**19**) in 74% isolated yield.^{10,14}



Reactions of carbamate **13** in the presence of various known carbon radical trapping reagents were also studied. In the presence of CBr_4 , 2-bromotropane (**20**) was obtained in 60% yield;^{10,15} the crude reaction mixture contained a trace of sulfides **16** (ca. 6% yield). When phenyl vinyl sulfone was present in the reaction of **13**, product **21**, from addition of carbon radical **4** to the vinyl sulfone followed by reaction with precursor **13**, was obtained in 36% yield along with 54% of sulfides **16**.^{10,16} The low yield of **21** relative to **16** was unexpected since, in the case of simple carbon radicals, addition to phenyl vinyl sulfone is known to be much faster than self-trapping by the *N*-hydroxypyridine-2-thione ester precursor **2**.¹⁷

The high yields of tropane products obtained in this work indicate that the cyclization of aminium cation radical **3** is quite efficient. This result might not have been predicted given the low yield of 2-chlorotropane obtained by BHR when radical **3** was formed from the *N*-chloroamine⁴ and an expectation that the preferred conformation of radical **3** would be chair-like with the aminium center in an equatorial position. However, as noted, MacCorquodale and Walton obtained good yields of bicyclo[3.2.1]octane (**7**) from the cyclohept-4-enylmethyl radical (**6**);⁵ further, ESR spectroscopic studies of **6** showed that more than one conformation must be well populated at ambient temperature.⁵ Apparently, radical **3** also contains a reasonable population of at least one reactive conformation.

The *N*-hydroxypyridine-2-thione carbamate route to alkaloid skeletons appears to be useful as evidenced by the high yields of the simple tropanes isolated in this work. Consistent with earlier results,² the use of carbamates 1 for formation of aminium cation radicals affords milder conditions for production and subsequent reactions of these intermediates than do other routes. This is especially apparent in the reaction forming 2-bromotropane in 60% yield which can be compared to the 7.5% yield of 2-chlorotropane obtained in the corresponding *N*-chloroamine reaction.⁴

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8. Salt 12 (mp 148-148.5 °C) is prepared in 85-90% yield by treatment of 2-mercaptopyridine-*N*-oxide with 1 equiv. of phosgene in toluene at 0 °C.
9. Recrystallized from benzene/cyclohexane; mp 80-82 °C (dec).
10. Characterized by ¹H and ¹³C nmr spectroscopy.
11. The ¹H and ¹³C nmr spectra matched those reported: H. Iida, Y. Watanabe, and C. Kibayashi, *J. Org. Chem.*, 1985, **50**, 1818.
12. Solvent CH₂Cl₂, 1.0 equiv. mcpba, 1.0 equiv. camphorsulfonic acid, 0 °C, 2 h.
13. Solvent CH₂Cl₂, 2.2 equiv. mcpba, 1.0 equiv. camphorsulfonic acid, 25 °C, 6 h.
14. Solvent toluene, 3 equiv. DBU, 110 °C, 12 h.
15. Solvent benzene, 0.025 M 13, 0.13 M CH₃CO₂H, 0.33 M CBr₄.
16. Solvent benzene, 0.1 M 13, 0.3 M CH₃CO₂H, 0.3 M phenyl vinyl sulfone.
17. Barton's group obtained high yields of adducts to phenyl vinyl sulfone in reactions of 2.¹⁸ We have found that cyclohexyl radical, formed from the corresponding ester 2 precursor (0.12 M), reacted with phenyl vinyl sulfone (0.5 M) in preference to the self-trapping reaction with a selectivity of at least 40:1.
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