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Sulfanyl Radical Addition to Alkynyl Azides: an Insight into Vinyl Radical Cyclization onto the Azido Function

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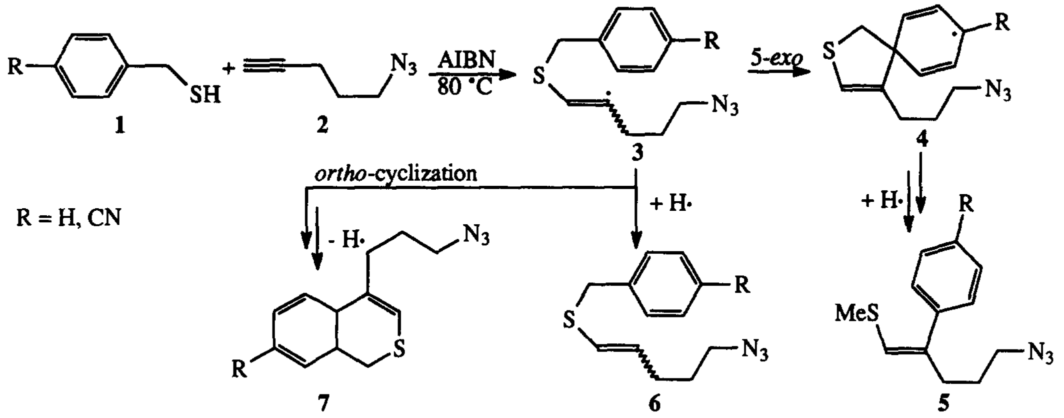
Abstract. 5-*Exo*-Cyclization of 2-sulfanylvinyl radicals **16** and **21** is a fast process which prevents intramolecular addition to the sulfanyl aromatic ring and hydrogen abstraction. In contrast, the 2-sulfanylvinyl radicals **3** and **9** are reluctant to add to their aliphatic azido substituent either in a π-(*endo*) or in a π-(*exo*) mode. These radicals exclusively undergo cyclization onto the adjacent aromatic ring and H-transfer from the thiol present. © 1997 Elsevier Science Ltd.

In recent years radical cyclizations involving carbon-carbon bond formation have been widely employed in the planning of synthetic strategies,[1] but those forming carbon-nitrogen bonds have instead received much lesser attention. Examples have been reported of aminyl radical cyclizations onto C=C and C=O double bonds[2] as well as of iminyl radical cyclizations onto aromatic rings and alkene double bonds.[3] Moreover, a few examples of C-N bond formation through carbon radical addition to nitrogen radical acceptors have been reported, all of these using addition to the azido group. We first showed that aryl[4] and thiocarbonyl[5] radicals can smoothly cyclize onto aromatic azides and, very recently, Kim[6] and Murphy[7] found that alkyl radical cyclization onto aliphatic azides provides a useful entry to N- heterocycles.

Our interest in vinyl radical rearrangements and cyclizations[8] led us to undertake a study of possible vinyl radical cyclizations onto nitrogen-containing radicophilic moieties. Herein we report our preliminary results of the fate of vinyl radicals containing either an aliphatic or an aromatic azido group as radical acceptor. Vinyl radicals were produced under thermal conditions by addition of sulfanyl radicals to suitable alkynyl azides. Reactions were carried out in boiling benzene by treating equimolar amounts of the appropriate thiol and alkynyl azide in the presence of AIBN (0.2 equiv) for 3 h. The product mixtures were directly analyzed by ^{1}H NMR and then chromatographed on silica gel column. Structural assignment to reaction products arose from ^{1}H NMR, MS and HRMS spectral analyses.

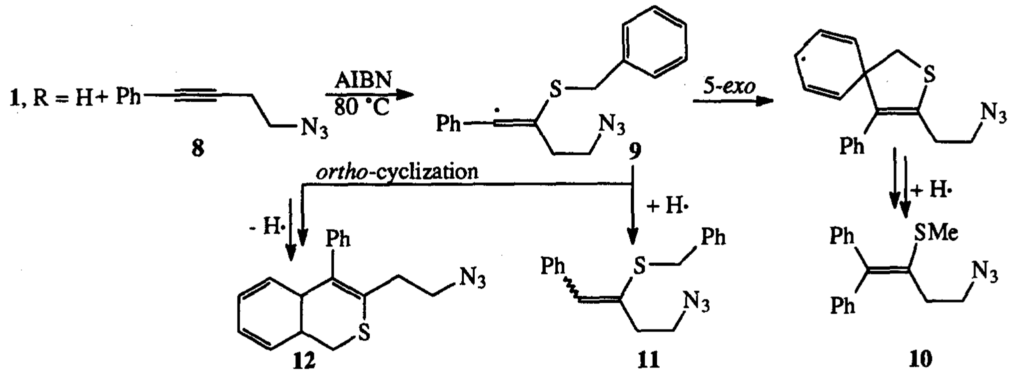
Reaction of 4-cyanobenzyl mercaptan **1**, R = CN with the pentynyl azide **2**[9] furnished the rearranged methyl vinyl sulfide **5**, R = CN (65%), the expected product of intramolecular 5-(π-*endo*)*exo* cyclization of the intermediate vinyl radical **3**, R = CN onto the aromatic ring,[8b,g] in addition to minor amounts of the benzyl vinyl sulfide adduct **6**, R = CN (15%), in turn ascribable to hydrogen abstraction reaction of the above radical (Scheme 1). Analogous reaction of parent thiol **1**, R = H with the azide **2** similarly gave the corresponding vinyl radical products **5**, R = H and **6**, R = H, but to an opposite relative extent (20 and 60% respectively). In such case the modest occurrence of **5**, R = H in favor of **6**, R = H was a result of lesser stabilization of the spirocyclohexadienyl intermediate **4** on passing from R = CN to R = H.[8b] Besides the compounds **5**, R = H and **6**, R = H, the latter reaction furnished small amounts of thiopyran **7**, R = H (**5**/**7** ratio = ca. 2.5 as determined by ^{1}H NMR analysis) which was derived from radical **3**, R = H through 6-membered aromatic *ortho*-cyclization (Scheme 1). From both thiol reactions we obtained no evidence at all for any product that might have arisen from the bent 1-alkyl vinyl radicals **3**, R = CN, H through possible 5-(π-*exo*) cyclization onto the azido function.

Scheme 1



This finding is in sharp contrast with the behavior exhibited by alkyl radicals, previously shown to be highly prone to undergo 5-membered cyclization onto aliphatic azides.[6,7] Since the 5-(π-*exo*) cyclization of radicals **3**, R = CN, H might have been discouraged by unfavorable stereoelectronic factors, we passed to examine the behavior of the 1-phenyl vinyl radical **9** which in principle might exhibit cyclization onto the azido group in a 5-(π-*endo*) mode. It is known that cyclizations of π-*endo* and π-*exo* type may be sensitive to different stereoelectronic factors.[8d,g] Moreover, the linear 1-phenyl vinyl radicals have been reported to cyclize onto both double bonds[8e] and aromatic rings[10] more rapidly than the bent 1-alkyl congeners. However, the radical **9** displayed a chemical behavior strictly comparable to that of the 1-alkyl analog **1**, R = H. In fact, reaction of thiol **1**, R = H with 1-phenylbutynyl azide **8**[9] gave the rearranged sulfide **10** (40%) and the adduct **11** (20%), along with the thiopyran **12** (3%), as the only identifiable products (Scheme 2).

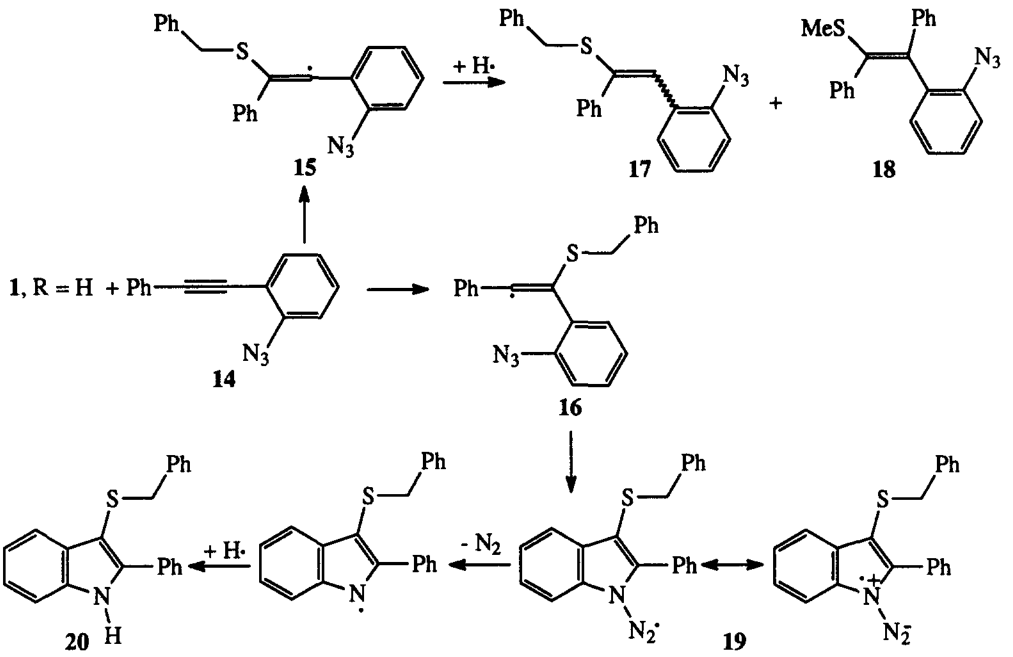
Scheme 2



Instead, sound evidence for smooth cyclization of vinyl radical onto aromatic azide was provided by reactions of 2-azidodiphenylacetylene **14**[11] with benzyl mercaptan **1**, R = H and benzenethiol (PhSH). In the presence of thiol **1**, R = H the alkyne **14** led to the vinyl sulfides **17** (20 %) and **18** (9 %) together with major amounts (48 %) of the indole **20** (Scheme 3). Conceivably, non-regioselective (and non-reversible)[8g] addition of benzylsulfanyl radicals to the alkyne **14** initially produced a comparable mixture of the isomeric vinyl radicals

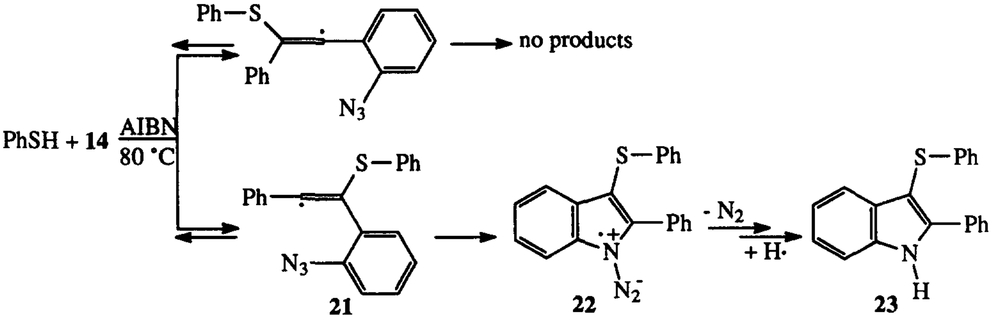
15 and **16**. The former radical led to the expected hydrogen abstraction and rearrangement products, **17** and **18**, whereas the latter exclusively furnished the indole **20** through 5-cyclization onto the azido moiety followed by nitrogen loss from the triazenyl radical intermediate **19** and eventual H-abstraction by derived aminyl radical (Scheme 3).

Scheme 3



Moreover, the alkyne **14** reacted with benzenethiol to give only the corresponding indole **23** in 85% yield. The exclusive formation of the indole product clearly suggests that non-regioselective (but reversible)[8g,12] addition of benzenesulfanyl radicals to the triple bond of **14** resulted in easy cyclization of the vinyl radical **21** onto the aromatic azide (Scheme 4).[13]

Scheme 4



In conclusion, 2-sulfanylvinyl radicals **16** and **21** were shown to be highly prone to undergo 5-membered cyclization onto the aromatic azido moiety, whereas the vinylic analogs **3**, R = H, CN and **9** were reluctant to exhibit a similar intramolecular addition to the aliphatic one. The fair reactivity of radicals **16** and **21** might be explained in terms of resonance stabilization of the ensuing triazenyl radicals **19** and **22** due to unpaired electron delocalization onto the indole ring. The observed inertness of radicals **3**, R = H, CN and **9** is somewhat curious especially in view of the reported findings that alkyl radicals can efficiently add to alkyl azides. It might be possible that the more electrophilic vinyl radicals can be discouraged to attack an aliphatic azido group owing to unfavorable polar effects occurring in the transition state of the addition process. Comparative studies of the intramolecular reactivity of vinyl and alkyl radicals towards both aromatic and aliphatic azides are now in progress to clarify the actual role of stabilization and polar effects in these cyclization processes.

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