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Sulfanyl radical mediated cyclization of aminyl radicals

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Abstract

1-(2-Aminophenyl)pent-1-yne **1** reacted with benzenethiol at 150 °C under radical conditions to give the thiol/alkyne adduct **2**, the benzothiophene **4** and the indole **5**. Reaction of **1** with benzenesulfanyl radicals produced from diphenyl disulfide in the absence of hydrogen donors gave only the indole **5** in high yields. Formation of indole **5** was explained in terms of sulfanyl radical mediated aminyl radical cyclization onto the alkyne triple bond.

Keywords: Radicals and Radical Reactions. Cyclisation. Alkynes. Amines.

In our interest in vinyl radical chemistry[1-3] we have recently considered the fate of β-(phenylthio)vinyl radicals for investigating the factors which govern the 5-(π-endo)ortho cyclization of vinyl radicals onto the benzene ring[4]. β-(Phenylthio)vinyl radicals were generated by reacting a number of mono- and di-substituted alkynes with benzenesulfanyl radicals, in turn produced from benzenethiol (PhSH) and azobis*iso*butyronitrile (AIBN) (Scheme 1). Reactions were carried out by adding, over 3 h, a bromobenzene solution of benzenethiol (3 mmol) and AIBN (2 mmol) to a boiling bromobenzene solution (20 mL) of the appropriate alkyne (2 mmol). The resulting reaction mixture was refluxed for an additional 1h, then the solvent was evaporated and the organic residue chromatographed on a silica gel column. During this study we considered the behavior of 1-(2-aminophenyl)pent-1-yne **1**. This alkyne gave, after column chromatography, a mixture of the thiol/alkyne adduct **2** (30%; 2:1 E/Z mixture), the regioisomeric adduct **3** (16%; 3:1 E/Z mixture), the 3-arylbenzothiophene **4** (20%) and the indole derivative **5** (20%) (Scheme 1). Diphenyl disulfide (PhSSPh) was also recovered. Products **2** and **4** were derived from vinyl radical intermediate **6** through hydrogen abstraction and cyclization onto the adjacent phenyl ring, respectively. The regioisomeric adduct **3** was probably formed from the adduct **2** through an isomerization promoted by 2-cyano*iso*propyl radicals, likely through intermediacy of the allyl radical **7**. In an independent experiment we found that the adduct **2** was converted to **3** upon heating in boiling bromobenzene in the presence of 1.5 equivalents of AIBN (35% conversion).

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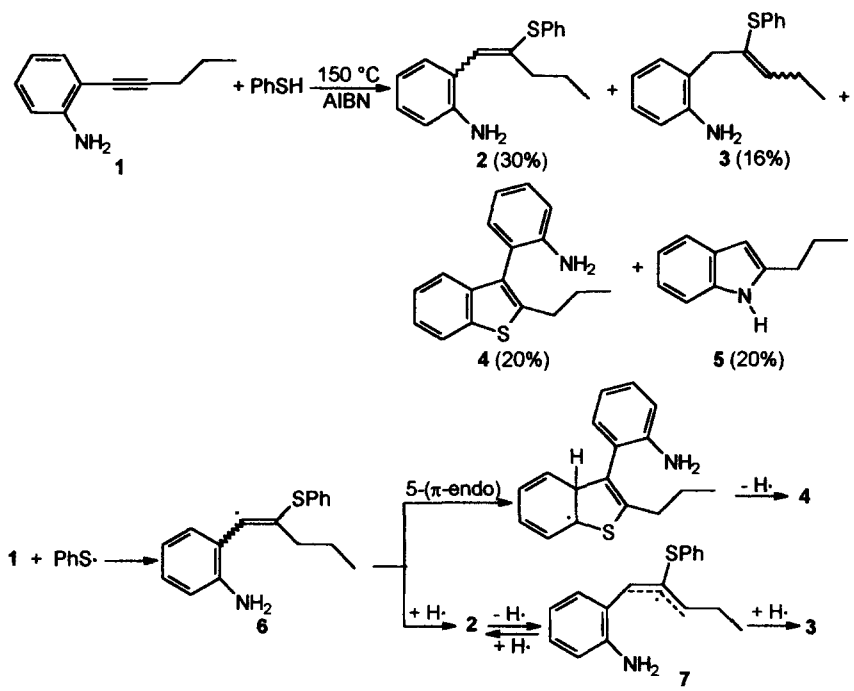
In contrast, the formation of indole **5** was totally unexpected and this finding prompted us to investigate its source. In principle, the indole might derive from **1** through thermal electrocyclic closure or from **2** through nucleophilic addition to the CC double bond followed by elimination of benzenethiol. However, both these possibilities were easily ruled out because starting alkyne **1** and the adduct **2** were found to be thermally stable up to 200 °C. In the same way, an ionic route involving benzenethiol and alkyne **1** was excluded on the basis of results provided by a repeated reaction carried out in the absence of AIBN. Under these non-radical conditions no benzothiophene **4** nor indole **5** was formed, as evidenced by GC-MS analysis. Surprisingly, this reaction gave the adduct **2** in nearly quantitative yields (70% conversion). Possibly, this product could be derived from nucleophilic sulfur addition to the CC triple bond via preliminary (or concomitant) proton transfer from thiol to the amino nitrogen atom (Scheme 2). In agreement, we found that the presence of the 2-amino group is essential to promote the non-radical thiol addition to the alkyne triple bond. In fact, the parent phenylpentyne was recovered unchanged (^{1}H NMR and GC-MS analysis) after heating in boiling bromobenzene for 3 h in the presence of 1.5 equivalents of benzenethiol.

These findings let us to believe that formation of indole **5** occurs through a radical pathway involving the intermediacy of anilinyl radicals **8**. So, we attempted to react the alkyne **1** with AIBN at 150 °C. However, the alkyne **1** was recovered unchanged, this indicating that, even if radicals **8** were reaction intermediates, 2-cyano*iso*propyl radicals are incapable of forming them.

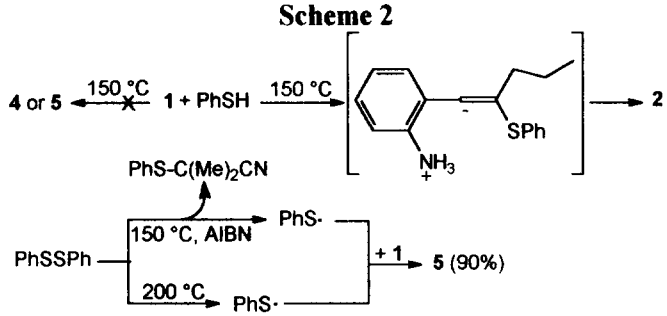
Scheme 1



Also, we found that the alkyne **1** is stable in boiling bromobenzene in the presence of 1 equivalent of diphenyl disulfide (PhSSPh). Indeed, when this latter reaction was carried out in a sealed tube at 200 °C for 7 h the alkyne **1** was converted to indole **5** (90% yield; 60%

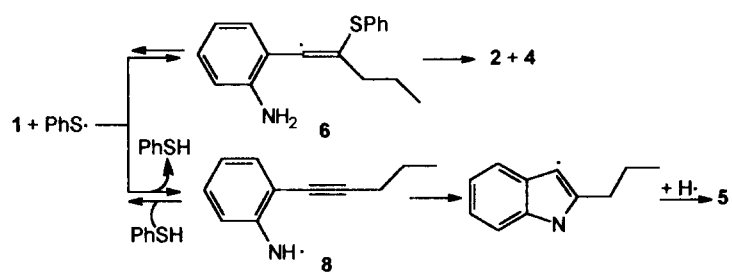
conversion). Analogously, **5** was obtained (90% yield; 45% conversion) by reacting the alkyne **1** with diphenyl disulfide at 150 °C in the presence of 1 molar equiv. of AIBN. In this case we found also noticeable amounts of phenyl 2-cyanopropyl sulfide [PhS-C(Me)$_2$CN](yields not determined). So, we can confidently assume that the formation of indole **5** was promoted by sulfanyl radicals, which under these reaction conditions were formed from diphenyl disulfide either by homolytic cleavage of the sulfur-sulfur bond at 200 °C or by 2-cyanopropyl radical substitution at the sulfur atom (Scheme 2).

Scheme 2



It is worth noting that in both reactions only trace amounts of benzothiophene **4** could be detected by GC-MS analysis. Since it was well precedented[4] that the formation of benzothiophene **4** was promoted by sulfanyl radicals, we must conclude that both **4** and **5** were formed through two competing radical pathways involving sulfanyl radicals, but benzothiophene **4** was formed only in the presence of benzenethiol, that is in the presence of a good hydrogen donor.

Scheme 3



All these findings point to the reaction mechanism outlined in Scheme 3: sulfanyl radicals could undergo both reversible addition to the CC triple bond of **1** leading to vinyl radicals **6** (and then to benzothiophene **4** and, at least in part, to the adduct **2**) and reversible hydrogen abstraction from the amino group to give aminyl radicals **8**. These latter could afford the indole **5** through 5-exo cyclization onto the CC triple bond.

In this scheme vinyl radicals **6** and aminyl radicals **8** are in equilibrium each other and this equilibrium will be shifted towards vinyl radicals **6**, and then benzothiophene **4**, by increasing the thiol hydrogen donor concentration.

These results appear to be of relevant interest because generation and cyclization of nitrogen-centered radicals is currently a main goal in radical chemistry. Formation of carbon-nitrogen

bonds through N-alkylaminyl radical addition to carbon radical acceptors, including CC and CO double bonds, has recently received much attention[5-8]. However, to our knowledge no previous example has been reported in the literature about N-arylaminyl radical cyclization or aminyl radical cyclization onto the alkyne triple bond.

From a mechanistic standpoint it appears that the possibility of sulfanyl radicals generating anilinyl radicals is noteworthy. Notwithstanding that sulfanyl radicals should not be expected to abstract hydrogen from aromatic amines, as this reaction is endothermic by about 10 Kcal/mol, our results appear to parallel those recently reported by Roberts[9,10] about generation of carbonyl radicals from aldehydes through hydrogen abstraction by sulfanyl radicals. This author suggested that an electrophilic radical can easily abstract a hydrogen atom when a nucleophilic radical is displaced, or vice versa. In his terminology this is reversal-polar catalysis[11,12]. This is the reason why thiols efficiently promote carbonyl radical cyclization onto CC double bonds, whereas this reaction is very sluggish in the absence of thiols because nucleophilic alkyl radical intermediates are incapable of abstracting hydrogen from the aldehyde, whereas sulfanyl radicals, electrophilic in character, can do it. Even though the Roberts' statement has been strongly contested[13], it could successfully take into accounts our findings, because aminyl radicals can behave (like carbonyl radicals) as nucleophilic ones[14-16].

Owing to the easy work-up and the ready availability of starting materials we believe that our reaction could open a facile route to aminyl radical cyclizations and it will deserve of further consideration from both a synthetic and a mechanistic standpoint.

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References

[1] Montevecchi PC, Navacchia ML. J. Org. Chem. 1997; 62:5600-5607.
[2] Montevecchi PC, Navacchia ML. J. Org. Chem. 1998; 63:537-542.
[3] Montevecchi PC, Navacchia ML, Spagnolo P. Eur. J. Org. Chem. 1998:1219-1226.
[4] Montevecchi PC, Navacchia ML. Work in progress.
[5] Bowman WR, Clark DN, Marmon RJ. Tetrahedron 1994; 50:1275-1294.
[6] Newcomb M, Deed TM, Marquardt DJ. Tetrahedron 1990; 46:2317-2328.
[7] Kim S, Joe GH, Do JY. J. Am. Chem. Soc. 1993; 115:3328-3329.
[8] Maxwell BJ, Tsanaktsidis J. J. Am. Chem. Soc. 1996; 118:4276-4283.
[9] Dang H-S, Roberts BP. J. Chem. Soc., Perkin Trans 1 1998:67-75.
[10] Dang H-S, Roberts BP. Chem. Commun. 1996:2201-2202.
[11] Roberts BP, Steel AJ. J. Chem. Soc., Perkin Trans 2 1994: 2155-2162.
[12] Roberts BP. J. Chem. Soc., Perkin Trans 2 1996:2719-2725.
[13] Zavitsas AA, Chatgilialoglu C. J. Am. Chem. Soc. 1995; 117:10645-10654.
[14] Michejda CJ, Campbell DH. Tetrahedron Lett. 1977; 18:577-580.
[15] Bowman WR, Clark DN, Marmon RJ. Tetrahedron Lett. 1992; 33:4993-4994.
[16] Kim S, Yoon KS, Kim SS, Seo HS. Tetrahedron 1995; 51:8437-8446.