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Biradicals/Zwitterions from Enallene-Isonitriles. Formal [4 + 1] Cycloadditions Leading to 11*H*-Indeno[1,2-*b*]quinoline and Related Compounds

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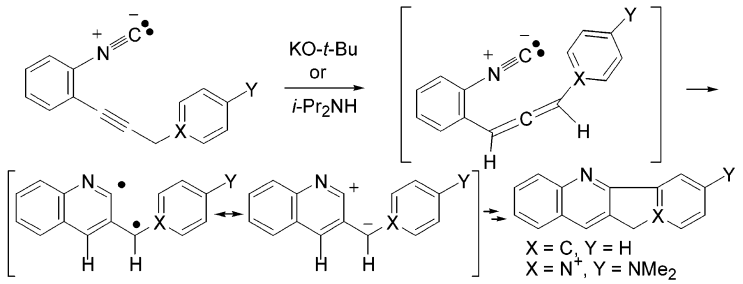
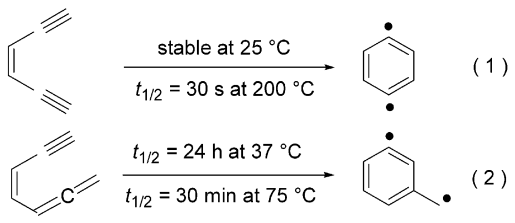
ABSTRACT



1,3-Prototropic rearrangement of the benzannulated enyne-isonitriles to the corresponding enallene-isonitriles followed by cycloaromatization generated the putative quinoline biradicals/zwitterions. A subsequent intramolecular radical−radical coupling or electrophilic aromatic substitution then gave the formal [4 + 1] cycloaddition adducts leading to 11*H*-indeno[1,2-*b*]quinoline and related compounds.

Thermolysis of (*Z*)-3-hexene-1,5-diynes (enediynes) at elevated temperatures provides direct access to 1,4-didehydrobenzene biradicals. Specifically, the parent (*Z*)-3-hexene-1,5-diyne, which is stable at 25 °C, undergoes the Bergman cyclization reaction at 200 °C with a half-life of ca. 30 s (eq 1).[1]



Replacing one of the alkynyl groups of enediynes with an allenic group causes the resulting (*Z*)-1,2,4-heptatrien-6-ynes (enyne-allenes) to be thermally much more labile. The parent (*Z*)-1,2,4-heptatrien-6-yne undergoes the Myers−Saito cyclization reaction to form the α,3-didehydrotoluene biradical at 37 °C with a half-life of 24 h (eq 2).[2] A different mode of cyclization of enyne-allenes leading to fulvene biradicals (Schmittel cyclization) under mild thermal conditions has also been reported.[3] Several heterocumulenes such as ketene,

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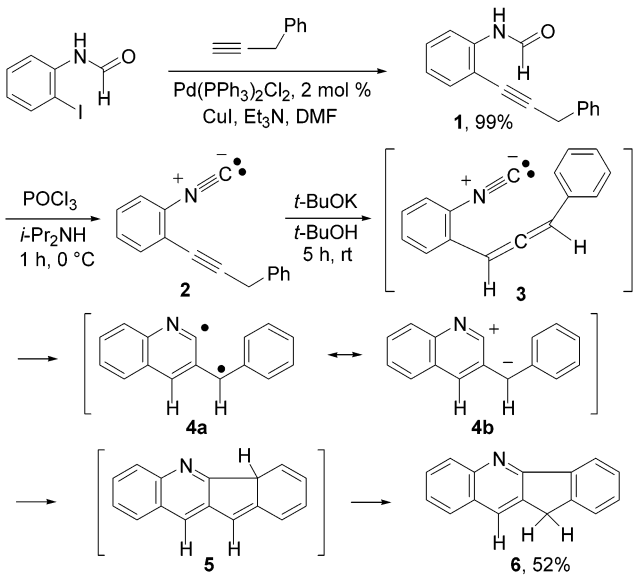
ketenimine, and carbodiimide have also been successfully employed to form enyne-ketenes (Moore cyclization),[4] enyne-ketenimines,[5] and enyne-carbodiimides[6] for biradical-forming reactions.

The use of the isoelectronic nitrile group as a substitute for the alkynyl group was less successful. (*Z*)-*β*-Alkynyl-acrylonitriles apparently did not exhibit any propensity to undergo aza-Bergman cyclization in 1,4-cyclohexadiene at 150 °C for 2 h.[7] (*Z*)-2,4,5-Hexatrienenitriles and related compounds also showed remarkable thermal stability at 150−260 °C.[8] Only in a benzannulated example where the allenic terminus was substituted with a sulfone group was the cycloaromatization reaction observed.[9]

The chemical reactivities of isonitrile in the benzannulated enyne-isonitrile system were exploited for tin- and sulfur-mediated intramolecular free-radical cyclization as well as nucleophile-induced intramolecular cyclization, producing substituted indoles and quinolines.[10] However, the feasibility of generating biradicals by thermolysis of enyne-isonitriles did not appear to have been explored. Theoretical studies suggest a relatively low barrier of activation enthalpy and favorable exothermicity for the aza-Bergman cyclization reaction of (*Z*)-but-1-en-3-yn-1-yl isonitrile to form 2,4-didehydropyridine compared to other types of Bergman cyclization reaction.[11] We envisioned that by placing the reactive isonitrile and allenic moieties on the adjacent carbon atoms of benzene, the resulting benzannulated enallene-isonitrile system could provide excellent opportunities for generating biradicals under mild thermal conditions.

Scheme 1



1,3-Prototropic rearrangement of enyne-isonitriles provided a simple synthetic route to enallene-isonitriles as outlined in Scheme 1. The 2-alkynylformanilide **1** was prepared by the palladium-catalyzed cross-coupling between 2-iodoformanilide and 3-phenyl-1-propyne. Dehydration of **1** with $POCl_3$/*i*-Pr_2NH[12] then afforded in situ the enyne-isonitrile **2**, which exhibited IR signals at 2121 and 2202 cm^{-1} attributable to the isonitrile and the alkynyl functionalities, respectively. The enyne-isonitrile **2** did not appear to undergo cycloaromatization even after it was kept at 0 °C for 6 h and then at room temperature for an additional 2 h. However, treatment of **2** with potassium *t*-butoxide at room temperature then afforded 11*H*-indeno[1,2-*b*]quinoline (**6**) in 52% yield from **1**.

Presumably, the reaction proceeded through an initial 1,3-prototropic rearrangement, induced by potassium *t*-butoxide, to form the desired enallene-isonitrile **3**. Potassium *t*-butoxide was selected because it was known to be inert to aryl isonitriles.[13] It was also reported that the 1,3-prototropic rearrangement of 3-phenylpropyne and 1,3-diarylpropynes could be promoted by potassium hydroxide and basic alumina, respectively, at ambient temperature.[14] The enallene-isonitrile **3**, generated in situ, then underwent cycloaromatization to give the biradical **4a**. It is worth noting that the biradical **4a** could also be regarded as the zwitterion **4b** with the aryl cationic center being stabilized by the lone pair electrons on the adjacent nitrogen atom. A subsequent intramolecular radical−radical coupling of **4a** or an intramo-

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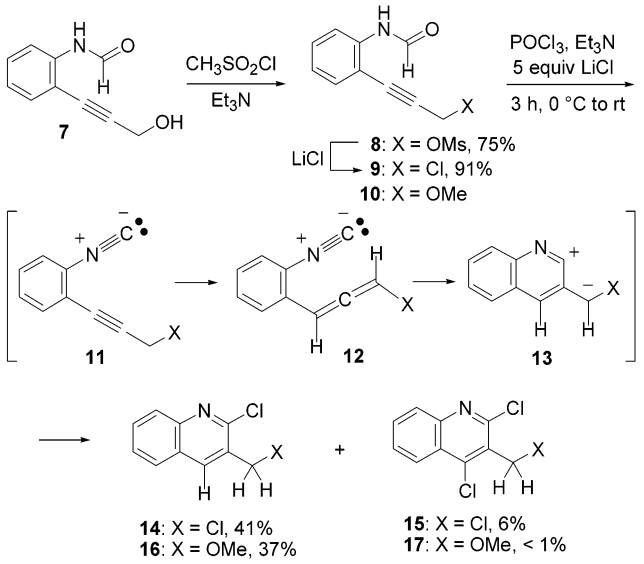
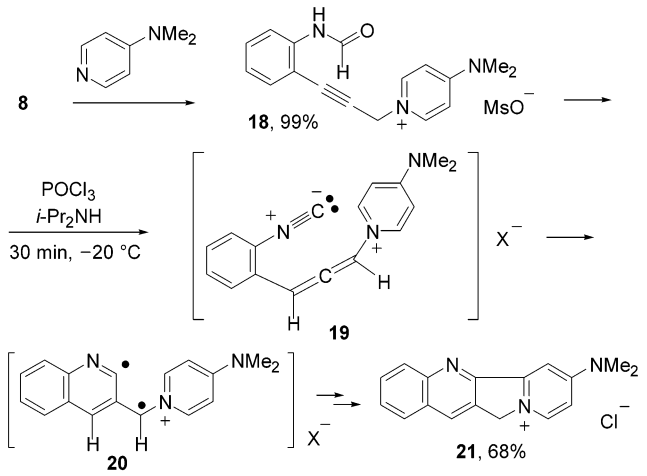
Scheme 2



Scheme 3



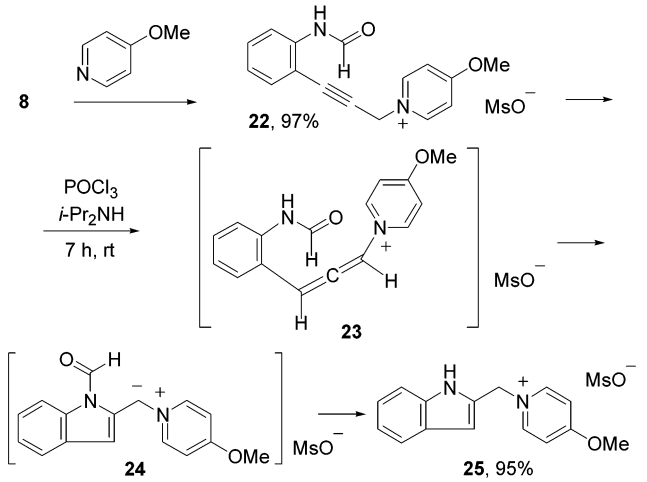
lecular electrophilic aromatic substitution of **4b** afforded the formal [4 + 1] cycloaddition adduct **5**, which then produced, after a 1,3-prototropic rearrangement, the aromatized adduct **6**.

The palladium-catalyzed coupling reaction between 2-iodoformanilide and propargyl alcohol produced the alcohol **7** (96% yield), which was then converted to the mesylate **8** and the chloride **9** (Scheme 2). Interestingly, when the chloride **9** was subjected to a similar dehydration condition, the cycloaromatized dichloride **14**[15] (41%) was produced directly along with a small amount of the trichloride **15** (6%). The use of diisopropylamine instead of triethylamine for dehydration under otherwise identical condition also furnished **14** (38%) and **15** (12%) in a single operation. Presumably, under the reaction conditions, the benzannulated enallene-isonitrile **12** was formed directly. Subsequent cycloaromatization led to the zwitterion **13**, which was then protonated and chlorinated to produce **14**. The reaction pathway that led to the formation of **15** is not clear at the present time. Similarly, by starting from **10**, the reaction sequence also led to **16**. A trace amount of a dichloride, attributable to **17**, was also detected by GC/MS.

Treatment of **8** with 4-(dimethylamino)pyridine produced the pyridinium mesylate **18**, which upon exposure to $POCl_3$ for dehydration afforded **21**[15] (Scheme 3). It is worth noting that **21** has the core heteroaromatic ring system of the important camptothecin family of antitumor agents.[16] Presumably, dehydration followed by the 1,3-prototropic rearrangement of the propargylic pyridinium salt as observed previously[17] produced in situ **19**, which then underwent a sequence of reactions, including cycloaromatization, intramolecular radical−radical coupling or electrophilic aromatic substitution, and 1,3-prototropic rearrangement as described for **6**.

Surprisingly, when **22** having a 4-methoxypyridinium substituent was treated with $POCl_3$, the 2-substituted indole **25** was produced in essentially quantitative yield (Scheme 4). One of the pathways that could be used to account for

Scheme 4



the formation of **25** involves a rapid 1,3-prototropic rearrangement to produce the putative intermediate **23** before dehydration to form the isonitrile could occur. A subsequent intramolecular attack of the central carbon of the allenic moiety[17] by the nitrogen of the formanilide or of the corresponding formimino phosphate could give **24** or a related phosphate derivative leading to **25**.

The change of the reaction pathway may be attributed to the lower ability of the 4-methoxyl group in **22** to donate electrons to the pyridinium ring than that of the 4-dimethylamino group in **18**, making the positive charge more

(15) Structure was established by X-ray structure analysis.

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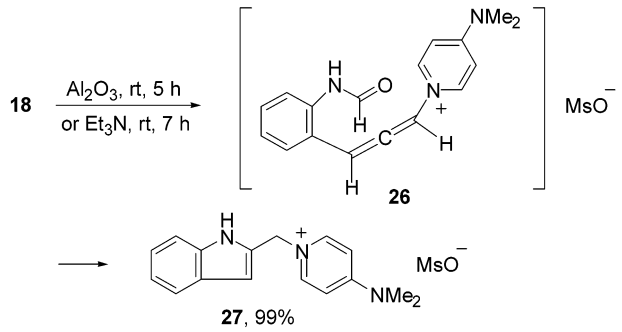
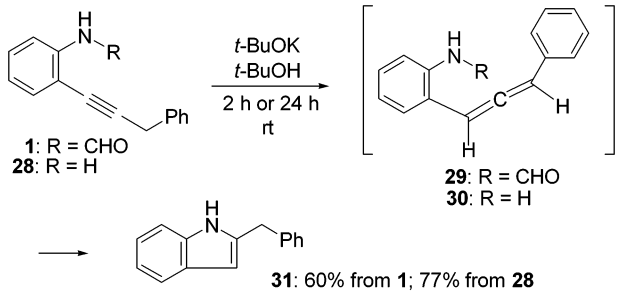
Scheme 5



localized on the pyridinium nitrogen in **22**.[18] As a result, the propargylic hydrogens in **22** are more acidic and thus more prone to 1,3-prototropic rearrangement.

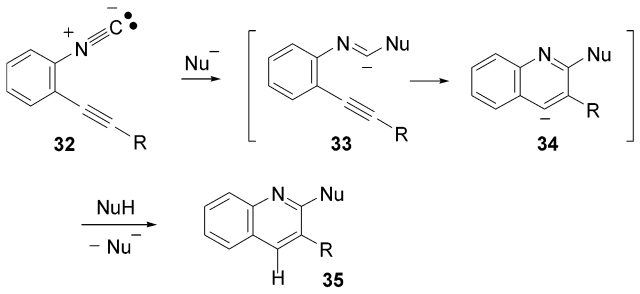
It was also observed that when **18** was treated only with neutral alumina or triethylamine, the 2-substituted indole **27** was produced in quantitative yield (Scheme 5). Presumably, the allene **26** was generated in situ as a reactive intermediate, which then underwent cyclization to give **27**. Similarly, treatment of **1** with potassium *t*-butoxide at room temperature for 2 h afforded 2-(phenylmethyl)indole (**31**) (Scheme 6).

Scheme 6



While the allenic derivatives **26** and **29** are proposed as the intermediates for cyclization, it should be noted that the base-induced formation of 2-substituted indoles from systems similar to **1** but without the possibility of a prior 1,3-prototropic rearrangement was also observed.[19] The rate of cyclization of **28** was considerably slower than that of **1**, allowing the formation of **30** to be detected by ^{13}C NMR during the course of reaction. A signal at δ 206.9 attributable to the central carbon of the allenic moiety was observed.

Scheme 7



It also needs to be mentioned that a nucleophile-triggered 6-endo cyclization of the benzannulated enyne-isonitriles **32** was proposed to account for the formation of the 2,3-disubstituted quinolines **35** (Scheme 7).[10c] While such a mechanism may also explain the formation of **14** and **16**, although the chloride is a very poor nucleophile and is unlikely to attack the isonitrile, it is not applicable to account for the formation of **6** and **21**.

In conclusion, a new synthetic pathway involving transformation of the benzannulated enyne-isonitriles to 11*H*-indeno[1,2-*b*]quinoline and related compounds was established. The reaction presumably proceeded through an initial 1,3-protrotropic rearrangement to form the corresponding benzannulated enallene-isonitriles followed by a facile cycloaromatization reaction to generate the putative quinoline biradicals/zwitterions. A subsequent intramolecular radical−radical coupling or electrophilic aromatic substitution then furnished the formal [4 + 1] cycloaddition adducts leading to 11*H*-indeno[1,2-*b*]quinoline and related compounds. While the putative quinoline biradicals/zwitterions were proposed as key reaction intermediates by drawing on the analogy with the Myers−Saito cyclization reaction of enyne-allenes, additional investigations would be needed to provide concrete evidence of their existence and to further explore the nature of their chemical reactivities.

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Supporting Information Available: Experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra for **1**, **6**, **8**−**10**, **14**−**16**, **18**, **21**, **22**, **25**, **27**, **28**, and **31**; ORTEP drawings for **14** and **21**; and tables of crystallographic data for the X-ray diffraction analysis of **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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