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Thermal Cyclization of (2-Ethynylphenyl)triazenes: Facile Synthesis of Substituted Cinnolines and Isoindazoles

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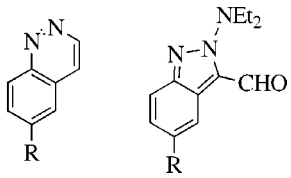
ABSTRACT



High-temperature intramolecular cyclization of *N*,*N*-dialkyl-*N*′-(4-substituted-2-ethynylphenyl)triazenes provides under neutral conditions both 6-substituted cinnolines and 5-substituted isoindazoles in moderate to excellent yields.

When installing functional groups on a benzene ring, dialkyltriazenes are often used to mask a particular position.[1] Triazenes are stable under a variety of conditions and can easily be removed using iodomethane,[1] generating an aryl iodide in place of the triazene. In combination with metal-mediated cross-coupling reactions, the ability to mask a phenyl halide allows the generation of many specific substitution patterns that might be difficult or impossible using other methods. Triazenes provide a facile route to the synthesis of complex phenylacetylene oligomers and dendrimers[2] through iterative cross-coupling methods. Additionally, our group has used triazenes extensively in preparing expanded macrocycles based on the dehydrobenzoannulene (DBA) substructure[3] as well as a wide variety of DBAs with differing topologies and functionalization.[4]

Recently we came upon an interesting tendency of dialkyltriazenes *ortho* to a terminal phenylacetylene (e.g., **1**) to undergo ring closure, forming substituted cinnolines (**2**) and isoindazoles (**3**) in fair to very good yields (Table 1). For example, heating *N*,*N*-diethyl-*N*′-(4-cyano-2-ethynylphenyl)triazene in *o*-dichlorobenzene at 170 °C produces the corresponding cinnoline and isoindazole products in about a 1:1 ratio in 95% combined yield (Table 1, entry i). To our knowledge, this is the first example of a triazene cyclizing with an unactivated alkyne to form a cinnoline or an isoindazole under neutral conditions.

The synthesis of cinnolines is dominated by the Richter cyclization,[5] in which 4-hydroxy- or 4-halocinnolines are generated from the reaction of a phenyldiazonium ion with an activated *ortho* alkyne.[6] It is a mechanistically simple reaction, involving simultaneous attack of a nucleophile on the alkyne carbon proximal to the phenyl ring and cyclization of the distal alkyne carbon with the diazonium group in a

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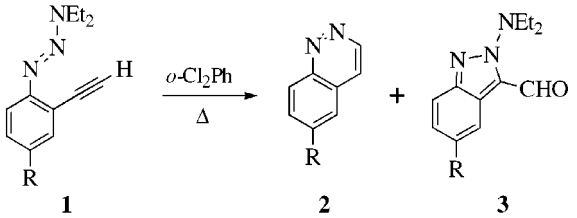
Table 1. Effect of R Group on the Yield of Cinnoline (**2**) and Isoindazole (**3**)



1 **2** **3**

entry	R	cinnoline (**2**)[a,b]	isoindazole (**3**)[a]
a	H	35% (99%)	55%
b	Me	51% (97%)	20%
c	*t*-Bu	61% (98%)	22%
d	C≡CH	39% (83%)	36%
e	Br	70% (98%)	15%
f	Cl	58% (97%)	14%
g	F	35% (90%)	25%
h	CO_2Me	28% (96%)	63%
i	CN	45% (98%)	50%
j[c]	NO_2	25% (93%)	60%

[a] Yield at 170 °C. [b] Yield at 200 °C in parentheses. [c] Yields using the *N*,*N*-pentamethylene triazene derivative.

pseudo-Michael type fashion. Although other routes to cinnolines have been reported,[7] the Richter cyclization is by far the most prevalent. Recently, this type of cyclization has been modified to include triazenes in a solid-phase synthesis of cinnolines;[8] however, acidic media were necessary to regenerate a diazonium which could cyclize in typical Richter fashion. A significant limitation to the Richter method is that synthesis of the cinnoline backbone necessitates substitution at the 4- and often 3-position.[6] For cinnolines having R groups exclusively on the benzene portion, extensive transformations and often harsh conditions are required to remove substituents on the pyridazine ring. This restricts both the R groups that can be used as well as the overall yield.

The synthesis of indazoles and isoindazoles is typically carried out in acidic media using either an aryl azide or a diazonium as the N−N source as well as an activated alkyl or vinyl group *ortho* to the nitrogen group.[9] Some thermal rearrangements have been reported,[10] but they require either the presence of an activated methyl carbon *ortho* to the nitrogen functionality or a good leaving group to generate the N−aryl bond. Still other groups have used alkyne precursors[11] for indazole synthesis, although the more reactive azide is necessary for cyclization.

To determine the generality of the cyclization of triazenes under neutral conditions, we synthesized a series of (4-substituted-2-ethynylphenyl)triazenes which were heated in *o*-dichlorobenzene to generate the cinnoline and isoindazole products. Reactions were performed in a sealed glass pressure tube previously open to air.[12] A temperature of 170 °C was necessary for each reaction to go to completion in 24 h. The results are summarized in Table 1. In most cases the cinnoline product dominated or was produced in amounts almost equal to the isoindazole. It is noteworthy that the highest yields of isoindazole occurred in the case of electron-withdrawing substituents *para* to the triazene. A unique feature of this synthetic route is the preparation of cinnolines and isoindazoles that might not withstand typical acid-catalyzed cyclization conditions (entries h, i).

We have found little correlation between the amount of water present or solvent effects and the product yield/distribution. Neither heterocycle arises from the other. Heating pure samples of each results in recovery of unchanged material. The addition of water has no effect, whereas a strict oxygen environment inhibits the reaction. Heating the triazene precursors in nitrobenzene produces similar yields, while other common organic solvents (benzene, toluene, acetonitrile, etc.) do not produce appreciable amounts of products. We have had some success in changing the ratio of cinnoline to isoindazole produced. Specifically, the cyclization reaction is temperature sensitive and will generate the cinnoline compounds in high yield (90%) at elevated temperatures (ca. 200 °C). Since the triazene precursors are easily synthesized in four steps from readily available starting materials, the excellent efficiency of this high-temperature cinnoline synthesis corresponds to an overall yield of ca. 65% for each substituent.

At lower temperatures, cinnoline formation occurs preferentially to the isoindazole, but considerable starting material is present even after 4 d at 145 °C. Although addition of a radical trap (1,4-cyclohexadiene) has no effect on the yield nor are trapped products observed, it is interesting to note that for the fluoro compound (entry g) a third heterocycle, 6-diethylaminocinnoline, is produced in modest yield (ca. 35%). As activated aryl fluorides are excellent candidates for nucleophilic aromatic substitution, this result suggests that diethylamine is generated during cinnoline formation.

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(12) **General cyclization conditions:** A solution of *N*,*N*-diethyl-*N*′-(4-substituted-2-ethynylphenyl)triazene in *o*-dichlorobenzene (4 mL, 0.035 M) was heated in a sealed glass pressure tube to 170 °C. After 24 h of stirring, the tube was cooled and the solvent was evaporated. Preparative TLC (1:1:4 CH_2Cl_2:EtOAc:hexanes) provided the isoindazole (R_f = 0.50−0.65) and cinnoline (R_f = 0.10−0.20) products, respectively.

Conjugation with the electron-withdrawing pyridazine ring would allow resonance stabilization of the intermediate arising from attack of the diethylamine nucleophile. Cyclization of **1i** in *o*-dichlorobenzene-d_4 at 200 °C revealed the formation of cinnoline **2i** and free diethylamine, supporting the above hypothesis.

In conclusion, we have developed an efficient cyclization route at 200 °C for the synthesis of 6-substituted cinnolines from (4-substituted-2-ethynylphenyl)triazenes. At slightly lower temperatures (170 °C), competitive formation of 5-substituted isoindazoles also occurs. Efforts to determine the scope and the mechanism of these unusual transformations are in progress.

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Supporting Information Available: Experimental details and spectroscopic data for all new cinnolines and isoindazoles. This material is available free of charge via the Internet at http://pubs.acs.org.

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