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A short route to 3-alkynyl-4-bromo(chloro)cinnolines by Richter-type cyclization of *ortho*-(dodeca-1,3-diynyl)aryltriaz-1-enes

Olga V. Vinogradova, Viktor N. Sorokoumov, Irina A. Balova *

Saint-Petersburg State University, 26 Universitetskij pr., Petrhoff, St. Petersburg, 198504, Russia

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Synthesis: pyrrolo[3,2-*c*]cinnolines, thieno[3,2-*c*]cinnoline, 3,4-diethynylcinnoline

ABSTRACT

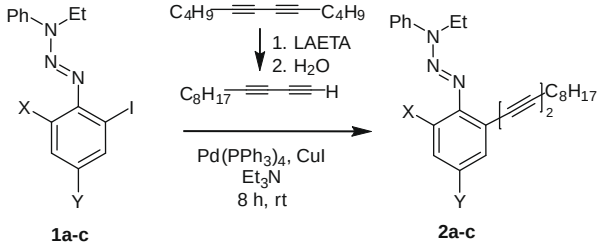
Cleavage of *ortho*-(dodeca-1,3-diynyl)triazenes in HCl or HBr medium and subsequent cyclization of the resulting diazonium salts is investigated. In the absence of a strong electron-withdrawing substituent, the reaction affords 3-alkynyl-4-bromo(chloro)cinnolines as the only product. A methoxycarbonyl group promotes hydrolysis of 4-halocinnolines which results in the formation of by-products: furo[3,2-*c*]cinnoline and cinnolinone. Substitution of bromine in 3-(alk-1-ynyl)-4-bromocinnolines is achieved with methylamine, Na_2S and ethynylbenzene affording pyrrolo[3,2-*c*]cinnoline, thieno[3,2-*c*]cinnoline and 3,4-diethynylcinnoline, respectively.

Many recent studies have shown the cyclization of functionally substituted aryl- and hetarylacetylenes to be an efficient method for preparing a wide variety of fused nitrogen heterocyclic systems such as indoles,[1] indolo[1,2-*c*]quinazolines,[2] quinolines[3] and isoquinolines,[4] furopyridine,[5] and pyrazolopyridines.[6]

In particular, *ortho*-ethynylsubstituted aryltriazenes have been used to produce an isoindazole and/or a cinnoline, depending on the conditions.[7] Cleavage of a triazene moiety with aqueous hydrogen chloride or hydrogen bromide favors Richter cyclization[8] to yield cinnoline derivatives via generation of an *o*-ethynenearyldiazonium salt.[9] While the cyclization of *o*-substituted ethynylarenes is well-known, there are only a few examples of cyclization of buta-1,3-diynyl derivatives, due to their poor stability and availability.

We recently reported the Richter-type cyclization of *o*-(alka-1,3-diynyl)arenediazonium salts, which were generated by diazotization of the corresponding arylamines.[10,11] The reaction leads to 3-alkynyl-4-chloro(bromo)cinnolines, but the yields of the target products were moderate due to the formation of by-products during the reaction.[11] The use of aryltriazenes for the Richter cyclization would be more promising in the case of diacetylene derivatives, since this approach would allow separate diazotization and cyclization steps. Herein, we present our studies on the cyclization of *ortho*-(dodeca-1,3-diynyl)arenediazonium salts obtained from the corresponding diacetylene derivatives of aryltriazenes by cleavage with hydrobromic or hydrochloric acid.

Starting compounds **2** were prepared in excellent yields via cross-coupling of iodotriazenes **1**[12] with dodeca-1,3-diyne under Sonogashira conditions. The latter was obtained from the internal isomer using the 'diacetylene zipper' reaction (Scheme 1). Undoubtedly, this approach can be extended to other homologs, as the methodology of sequential 'diacetylene zipper' and Sonogashira reactions was tested on a related series of internal diynes for the synthesis of functionalized (alka-1,3-diynyl)arenes.[13]



LAETA : lithium 2-aminoethylamide
2a: X=H, Y=Br (79%); **2b**: X=Br, Y=CH_3 (78%);
2c: X=H, Y=COOMe (95%)

Scheme 1. Synthesis of *ortho*-(dodeca-1,3-diynyl)aryltriazenes via Pd/Cu-catalyzed cross-coupling of iodotriazenes with dodeca-1,3-diyne.

* Corresponding author.
E-mail address: irinabalova@yandex.ru (I.A. Balova).

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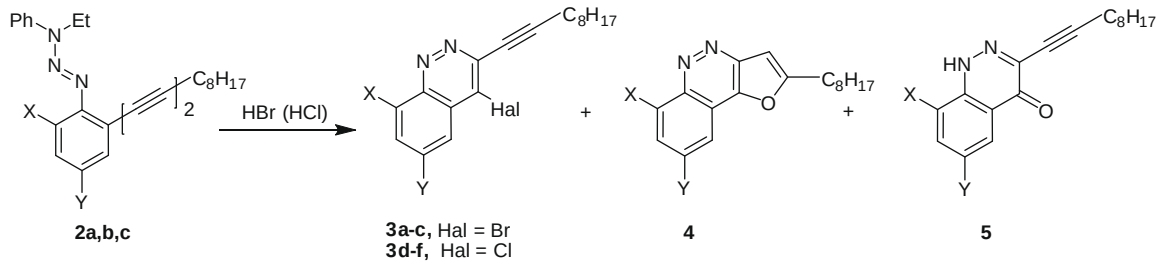


Scheme 2. Richter cyclization of *ortho*-(dodeca-1,3-diynyl)aryltriazenes.

Table 1
Studies on the Richter reaction of *ortho*-(dodeca-1,3-diynyl)aryltriazenes and the yields of products[14,15]

Entry	Triazene	X	Y	Solvent (reaction time, h)	HHal (concentration)	Products, yield (%)		
						3	4	5
1	**2a**	H	Br	Acetone (5)	HBr (1M)[a]	**3a**, 13	—	—
2	**2a**	H	Br	Acetone (2)	HBr_{concd}	**3a**, 55	—	—
3	**2b**	Br	CH_3	Acetone (2)	HBr_{concd}	**3b**, 75	—	—
4	**2a**	H	Br	Acetone (5)	HCl (6M)	**3d**, 38	—	—
5	**2b**	Br	CH_3	Acetone (5)	HCl_{concd}	**3e**, 34	—	—
6	**2a**	H	Br	Acetone (24)	HCl (6M)	**3d**, 26	—	—
7	**2a**	H	Br	Et_2O (2)	HBr_{concd}	**3a**, 75	—	—
8	**2c**	H	COOMe	Acetone (2)	HBr_{concd}	**3c**, 17	**4**, 5	**5**, 25
9	**2c**	H	COOMe	Acetone (2)	HCl_{concd}	**3f**, 15	**4**, 17	
10	**2c**	H	COOMe	Acetone (0.5)	HBr_{concd}	**3c**, 41	**4**, 3	**5**, 10

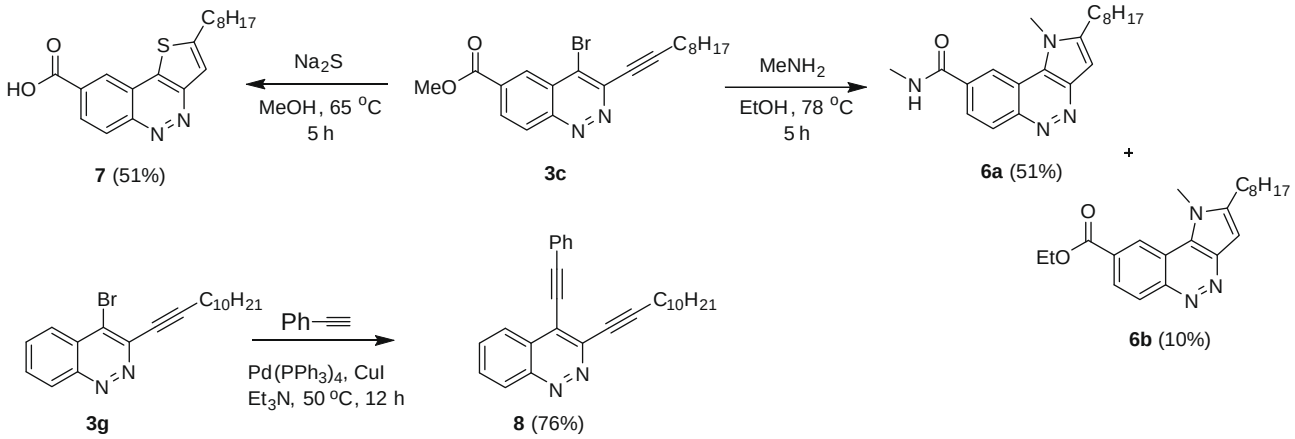
[a] Same conditions used for the cyclization of *ortho*-ethynyltriazenes.[9]

The influence of the substituent and reaction conditions were considered for the Richter-type cyclization of *o*-(dodeca-1,3-diynyl)aryltriazenes **2** (Scheme 2, Table 1). Compared to monoacetylene derivatives,[9] cyclization of diacetylene analogs is slower and required more acidic conditions. Thus, in the presence of 20 equiv of 1 M HBr, cyclization of **2a** was complete within 5 h and afforded a low yield of cinnoline **3a** as the only product (Table 1, entry 1). Cyclization under these conditions is complicated by significant resinification. The use of concentrated HBr proved to be more favorable leading to a reduced cyclization time and dramatically increased yields for 3-alkynyl-4-bromo-cinnolines **3a** and **b** (Table 1, entries 2 and 3). The lower yields of 4-chlorocinnolines compared to the bromo derivatives can be explained by the lower stability of the former (Table 1, entries 4 and 5).

Moreover, in the presence of aqueous HCl the reaction took longer, which led to additional resinification of the reaction mixture and lower product yields. Thus, a reduction in the yield was observed for compound **3d** when the reaction was run for 24 h (Table 1, entry 6). Diethyl ether was also tested as a solvent, and in this case, 3-alkynyl-4-bromocinnoline **3a** was obtained in good yield (Table 1, entry 7).

It was reported earlier, that either cyclization of *o*-ethynylaryltriazenes in dilute acids or extended reaction times led to the formation of cinnolinones, as a result of hydrolysis of 4-bromo(chloro)cinnolines.[9] In our case, irrespective of the cyclization conditions, no products of 4-halocinnoline hydrolysis were detected in reactions with compounds **2a** and **b**. Different results were obtained for the triazene **2c** possessing an electron-withdrawing group on the aromatic ring. In spite of the concentrated acid media, the methoxycarbonyl group promotes hydrolysis of 4-halocinnolines within the usual reaction time, and results in the additional formation of furo[3,2-*c*]cinnoline **4** and cinnolinone **5** (Table 1, entries 8 and 9). However, bromocinnoline **3c** was obtained as the major product when the reaction mixture was quenched after 30 min (Table 1, entry 10).

4-Chloro-3-ethynylcinnolines were shown to be interesting starting materials for the synthesis of fused heterocycles by nucleophilic substitution of chlorine and subsequent cyclization involving the triple bond.[16] It was reported earlier that their reactions



Scheme 3. Reactions of 4-bromo-3-(alk-1-ynyl)cinnolines **3c**,**g** with $MeNH_2$, NaS_2 and phenylacetylene.

with nucleophiles, such as primary amines or hydrazines followed by cyclization, occurred at high temperature in the presence of Cu(I) as catalyst.[16]

Next we studied the reactivity of 4-bromo-3-decynylcinnoline **3c** in reactions with methylamine and Na_2S (Scheme 3). In contrast to previous work,[16] nucleophilic substitution–cyclization proceeded as a tandem process under rather mild conditions to give pyrrolo[3,2-*c*]cinnolines **6** or thieno[3,2-*c*]cinnoline **7**. The methoxycarbonyl group underwent hydrolysis or substitution of the methoxy group by $MeNH_2$ or EtOH under the reaction conditions.

The bromine at C-4 of the cinnoline system can also be replaced easily with an ethynyl moiety via Sonogashira reaction, as shown for compound **3g**.[17] This reaction leads to a cinnoline, possessing an enediyne system (Scheme 3).

In conclusion, the generation of *o*-(alka-1,3-diynyl)aryldiazonium salts from aryltriazenes for use in the Richter cyclization is a useful approach in comparison with diazotization of diynylarylamines,[11] and avoids side reactions. This cyclization provides a short route to 3-alkynyl-4-bromo(chloro)cinnolines which are obtained in good yields when a strong electron-withdrawing substituent is not present on the benzene ring. Their application in the synthesis of fused heterocycles containing a cinnoline system as well as for preparation of cinnoline derivatives possessing an enediyne moiety has been demonstrated.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.103.

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14. All compounds were characterized by NMR, MS, and CHN analysis and yields refer to isolated products.
15. A typical reaction procedure is as follows: to a solution of aryltriazene **2** (2 mmol) in acetone (10 mL) or diethyl ether (10 mL), concentrated HBr or HCl (20 equiv) was added quickly at 10 °C. The reaction mixture was stirred at room temperature for the specified time (see Table 1). The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layer was washed with water and brine until neutral, pH, and then dried over $CaCl_2$. Chloro cinnolines were purified by column chromatography, and bromo analogs were crystallized from Et_2O–hexane.
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