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Richter cyclization and co-cyclization reactions of triazene-masked diazonium ions

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ABSTRACT

The conventional Richter cyclization involves diazotization of 2-alkynylanilines with HX (aq) (X = Br or Cl) and $NaNO_2$, followed by spontaneous ring closure to give a mixture of 4-halocinnoline and 4-cinnolinone products. The different products result from competing attack of X^- and H_2O, respectively, upon an intermediate 2-alkynylphenyl diazonium ion during the cyclization step. In order to improve the chemoselectivity of this reaction, we have utilized triazenes as masked diazonium ions. These can be unmasked using $MeSO_3H$ in anhydrous solvents and the resultant 2-alkynylphenyl diazonium ion cyclized chemoselectively by the incorporation of a specifically added nucleophile. This process has been extended to tethered nucleophiles, leading to a Richter induced co-cyclization process to give ring-fused cinnolines.

Cinnolines are a valuable heterocyclic class from which a number of biologically active compounds have been identified, including anti-cancer, fungicidal, antibacterial, and anxiolytic compounds, among others.[1] The first cinnolines were prepared by von Richter over 125 years ago by diazotization of 2-alkynylanilines **1** and heating to form cinnolinones **4** as the major product (Scheme 1).[2] Although it was the first reported method for the synthesis of cinnolines, it was subsequently superseded by the related Borsche–Herbert and Widman–Stoermer reactions as the preferred methods of preparing these heterocycles, due to the greater ease with which the starting materials could be accessed and the increased generality of the reactions.[1,3] However, with the emergence of efficient palladium-mediated coupling methods for accessing 2-alkynylanilines **1** (e.g., Sonogashira coupling) the synthetic potential of the Richter reaction has been enhanced significantly.[4,5] Recent studies into the mechanism of the Richter reaction have revealed that the initially formed diazonium ion **2** cyclizes to **3** and **4** at room temperature upon competitive nucleophilic attack of the halide and water (Nu = X^- or H_2O), respectively (**2** solid arrows).[1a,6,7] Heating this mixture, as initially performed by Richter, hydrolyzes **3** into **4**. Depending on the nature of substituents $R^{1/2}$, cyclization can be redirected through the α-carbon of the alkyne to give indazoles **6** and **7** (**2** dashed arrows), instead of cinnolines.[6,7] When R^1 in **2** is a C5 electron-withdrawing group (i.e., EWG *para* to the alkyne) or R^2 is an electron-donating group, the alkyne becomes polarized so as to favor cyclization through the α-carbon and attack of the nucleophile at the β-carbon to give products **6/7**.

While diazoniums **2,** used in most studies to date, have generally been formed from the treatment of 2-alkynylanilines **1** with HBr (aq) or HCl (aq) and $NaNO_2$, they can also be formed by the reaction of (2-alkynylphenyl)triazenes **5** with HBr (aq) or HCl (aq) (Scheme 1).[5] While only a few examples of the use of triazenes **5** in the Richter reaction exist, similar chemoselectivity issues have been reported, where selective formation of either **3** or **4** is complicated by the competitive formation of the other (see also below).[5a] While hydrolysis of **3** can be used to gain selective access to cinnolinones **4**, albeit under forcing conditions, chemoselective access to **3** is more difficult. In this respect, Fedenock and coworkers have utilized high concentrations of chloride ions during the Richter reaction of 2-alkynylanilines **1** to favor formation of **3** (X = Cl).[7] However, we have found this to be problematic, particularly for the selective formation of bromides **3** (X = Br). In many cases the cinnolinone **4** still prevails and/or brominated by-products are formed, which is known to be an issue for diazotizations involving HBr.[4c] We anticipated that triazenes **5** might prove more useful substrates for highly selective formation of variously substituted cinnolines by using an acid that has a non-nucleophilic conjugate base (e.g., $MeSO_3H$) to form a stable diazonium **2**-$MeSO_3^-$ that can then be treated with a nucleophile to afford variously substituted cinnolinones **3**/**4**/**8** (Scheme 2). In order to form 4-halocinnolines **3** selectively, **2**-$MeSO_3^-$ could be formed in an anhydrous solvent and a tetraalkylammonium halide added to induce cyclization to **3**, avoiding competitive formation of **4**. Alternatively, selective formation of cinnolinone **4** could be achieved by using $MeSO_3H$ in an aqueous solvent, favoring direct attack of

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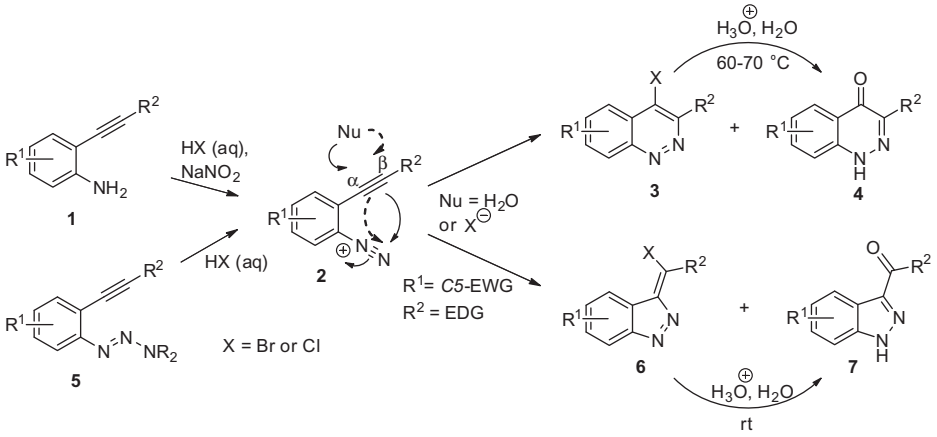
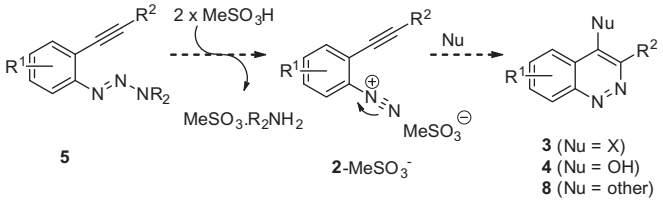


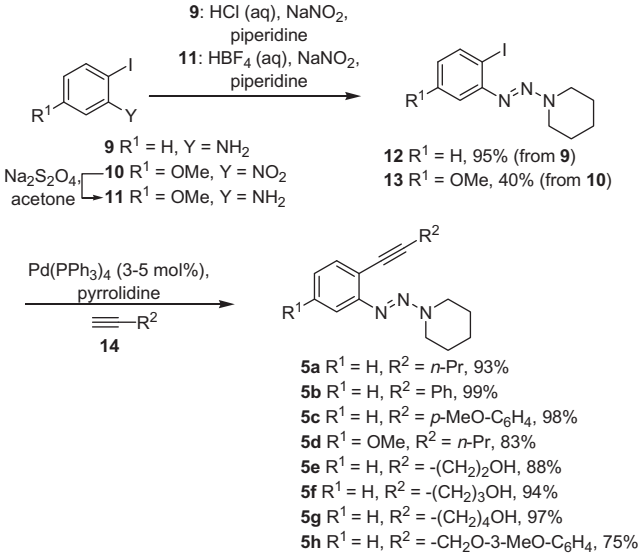
Scheme 1. Cinnolines and indazoline via Richter-type reaction pathways.

2-$MeSO_3^-$ by water to give **4** directly, avoiding interception of **2** by X^- to give **3** (as above).[8] Potentially, this concept could be extended to other suitable nucleophiles, including tethered nucleophiles to give other substituted cinnolines **8**. Herein, we report our preliminary studies toward this approach, with a particular focus on its application to the selective formation of **3** and **4** and a preliminary investigation of other nucleophiles **8**.

A series of (2-alkynylphenyl)triazenes **5a–h** were prepared from commercially available aryl iodides **9** and **10** (Scheme 3). Treatment of **9** with HCl (aq), $NaNO_2$, and piperidine afforded 2-iodoaryl triazene **12** in excellent yield (95%). Nitro reduction of



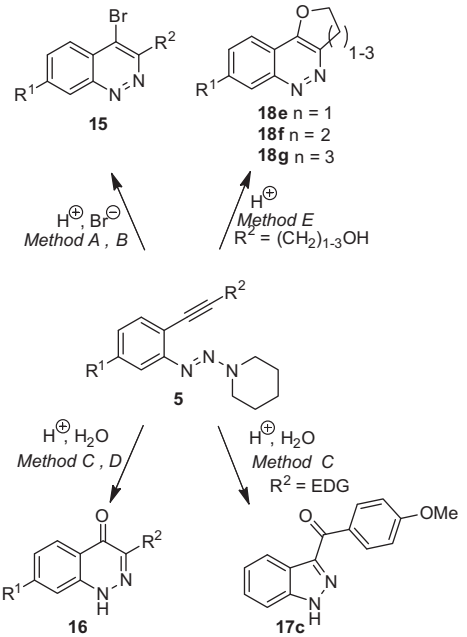
Scheme 2. Proposed chemoselective Richter cyclization.



Scheme 3. Synthesis of 2-(alkynyl)phenyltriazenes **5**.

10 using sodium dithionite in acetone gave **11**, which was reacted with HBF_4 (aq), $NaNO_2$ and piperidine giving **13** in moderate yield (40%, over two-steps). Initial attempts to couple **12** and **13** to terminal alkynes **14** using standard Sonogashira conditions[5] met with mixed results, and in many cases, competitive homo-coupling of the alkyne limited our access to triazenes **5**. This was overcome by using a copper-free variant of the Sonogashira reaction [$Pd(PPh_3)_4$ in pyrrolidine],[9] which proved to be a particularly effective method for accessing (2-alkynylphenyl)triazenes **5a–h** (75–99%).[10] While triazenes **12**, **13,** and **5a–h** were stable under storage conditions, they were not stable to mass spectral analysis and were only partially characterized. Nonetheless, the ^1H NMR spectra of these were highly diagnostic and the cyclization products of each were fully characterized, supporting the structural assignment of the triazenes.[11]

Given the proven utility of 4-bromocinnolines **15** as substrates in palladium-mediated coupling reactions,[5] our attention was first given to accessing these in an efficient and general manner (Scheme 4, entries 1–11, Table 1). Cyclization of **5a–h**, using previously described conditions, HBr (aq) 48% w/v in acetone (Method A, see below),[12] worked well for many substrates giving the desired 4-bromocinnoline **15** in good yield (entries 1–8, Table 1). However, there were some notable exceptions. In the case of **5c**, where R^2 is an electron-donating, 4-methoxyphenyl group, the 4-bromocinnoline **15c** (10%) was only isolated as the minor product (entry 3, Table 1). Unsurprisingly, the reaction proceeded predominantly through an *exo*-cyclization pathway to give the indazole **17c** (55%) as the major product. Interestingly, in the case of cyclization of **5f** to form **15f** (entry 6, Table 1), the major product was the co-cyclized pyrano-fused product **18f**. Substrate **5h** also gave a low yield of 4-bromocinnoline **15h** (21%), with a significant amount of the cinnolinone **16h** (63%) being formed (entry 8, Table 1). Accordingly, the combination of commercially available *N*-alkylpyridinium bromide salt, 1-(2-ethoxy-2-oxoethyl)pyridinium bromide, and $MeSO_3H$ in dichloromethane (Method B)[12] was explored as an alternative method for cyclizing (2-alkynylphenyl)triazenes **5** to 4-bromocinnolines **15**.[13] Only a selected set of substrates were reacted in this manner (entries 9–11, Table 1). In the case of **5e**, cyclization to **15e** (95%) using Method B proceeded in a comparable yield to that using Method A (compare entries 5 and 9, Table 1). In order to achieve selective formation of **15f**, compound **5f** was first acetylated to give acetate **20** (100%), which was then cyclized using Method B to give **21** (84%) and deacetylated to produce **15f** (87%) (Scheme 5 and entry 10 Table 1). Method B proved particularly effective in the cyclization of **5h**, where the anhydrous reaction conditions completely avoided the formation of any cinnolinone **16h**, giving only **15h** (99%) (entry 11, Table 1).



Scheme 4. Cyclization of 2-alkynylaryl triazenes **5** under different conditions (see Table 1).

Table 1
Cyclization of triazenes **5** (Scheme 4)

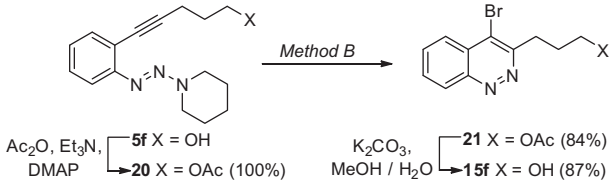
Entry	5	R^1	R^2	Method[a]	Product (yield %)
1	**5a**	H	*n*-Pr	A	**15a** (95)
2	**5b**	H	Ph	A	**15b** (94)
3	**5c**	H	4-$MeOC_6H_4$	A	**15c** (10), **17c** (55)
4	**5d**	OMe	*n*-Pr	A	**15d** (98)
5	**5e**	H	$(CH_2)_2OH$	A	**15e** (92)
6	**5f**	H	$(CH_2)_3OH$	A	**15f** (10), **18f** (54)
7	**5g**	H	$(CH_2)_4OH$	A	**15g** (86)
8	**5h**	H	CH_2O–(3-$MeOC_6H_4$)	A	**15h** (21), **16h** (63)
9	**5e**	H	$(CH_2)_2OH$	B	**15e** (95)
10	**5f**	H	$(CH_2)_3OH$	B[b]	**15f** (66)
11	**5h**	H	CH_2O–(3-$MeOC_6H_4$)	B	**15h** (99)
12	**5a**	H	*n*-Pr	C	**16a** (86)
13	**5b**	H	Ph	C	**16b** (73)
14	**5c**	H	4-$MeOC_6H_4$	C	**17c** (72)
15	**5d**	OMe	*n*-Pr	C	**16d** (83)
16	**5e**	H	$(CH_2)_2OH$	C	**16e** (61)
17	**5f**	H	$(CH_2)_3OH$	C	**16f** (68)
18	**5g**	H	$(CH_2)_4OH$	C	**16g** (83)
19	**5h**	H	CH_2O–(3-$MeOC_6H_4$)	D	**16h** (55)
20	**5e**	H	$(CH_2)_2OH$	E	**18e** (66)
21	**5f**	H	$(CH_2)_3OH$	E	**18f** (68)
22	**5g**	H	$(CH_2)_4OH$	E	**18g** (80)[c]

[a] Method A: 48% aq HBr, acetone. Method B: $MeSO_3H$, 1-(2-ethoxy-2-oxoethyl)pyridinium bromide, CH_2Cl_2. Method C: $MeSO_3H$, acetone containing 10–30% water. Method D: H_2SO_4, 1:1 acetone and water mixture heated to 50 °C for 20 h. Method E: $MeSO_3H$, CH_2Cl_2.

[b] Involves additional steps of protection and deprotection, see Scheme 5.

[c] Yield based on recovered mass balance and ^1H NMR of the crude product.

We next turned to the use of triazenes **5** as substrates in direct cyclization to cinnolinones **16** (Scheme 4), where H_2O replaces X^- as the nucleophile. Treatment of triazenes **5a–g** with $MeSO_3H$ in aqueous acetone (Method C)[12] produced cinnolinones **16a,b,d–g** and indazole **17c** at room temperature in good to excellent yields (61–86%) (entries 12–18, Table 1). Our initial attempt to convert



Scheme 5. Formation of **15f** (entry 10, Table 1).

5h into **16h** using Method C returned mostly starting material (not shown) and the reaction was repeated using H_2SO_4 and heating to 50 °C (Method D) to give **16h** in reasonable yield (55%).

We next extended the principle of using independent sources of acid and nucleophile to co-cyclization reactions of substrates bearing tethered nucleophiles. Thus, treatment of **5e–g** with $MeSO_3H$ in dichloromethane (Method E) produced compounds **18e–g** in good yields (66–80%) (entries 20–22, Table 1). However, in the case of **18g**, the product rapidly hydrolyzed to give **16g** upon chromatography (silica gel or neutral alumina) and **18g** could only be obtained in a semi-pure, crude form.

In conclusion, 2-(alkynylphenyl)triazenes **5** represent convenient and effective substrates in modified Richter reactions giving chemoselective access to 4-bromocinnoline, cinnolinones, ring-fused cinnolines, and indazoles. Further investigation of the scope and limitations of this co-cyclization process is currently underway.

Acknowledgment

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Supplementary data

Supplementary data (experimental details and copies of ^1H NMR and ^{13}C NMR spectra for all other compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.122.

References and notes

1. For reviews on cinnolines, see: (a) Vinogradova, O. V.; Balova, I. A. *Chem. Heterocycl. Compd.* **2008**, *44*, 501–522; (b) Simpson, J. C. E. Condensed Pyridazine and Pyrazine Rings. The Chemistry of Heterocyclic Compounds In Weisberg, A., Ed.; Interscience: New York, London, 1953. p 3; (c) Singerman, G. M. In *The Chemistry of Heterocyclic Compounds*; Castle, R. N., Ed.; Interscience: New York, 1973; Vol. 27,. p 1 (d) Leonard, N. J. *Chem. Rev.* **1945**, *37*, 269; (e) Jacobs, T. L. In *Heterocyclic Compounds*; Elderfield, R. C., Ed.; Wiley: New York, 1957; Vol. 6,. p 136 (f) Haider, N.; Holzer, W. *Sci. Synth., Product Class 9: Cinnolines* **2004**, *16*, 251–313; (g) Brown, D. J. *Cinnolines and Phthalazines*; John Wiley & Sons, 2005. Suppl. II.
2. von Richter, V. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 677–683.
3. (a) Widman, O. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 722–727; (b) Stoermer, R.; Fincke, H. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3115–3132; (c) Borsche, W.; Herbert, A. *Liebigs Ann. Chem.* **1941**, *546*, 293–303.
4. (a) Villemin, D.; Goussu, D. *Heterocycles* **1989**, *29*, 1255–1261; (b) Le Fur, N.; Mojovic, L.; Turck, A.; Ple, N.; Queguiner, G.; Reboul, V.; Perrio, S.; Metzner, P. *Tetrahedron* **2004**, *60*, 7983–7994; (c) Vinogradova, O. V.; Sorokoumov, V. N.; Vasilevskii, S. F.; Balova, I. A. *Russ. Chem. Bull.* **2008**, *57*, 1725–1733.
5. (a) Vinogradova, O. V.; Sorokoumov, V. N.; Balova, I. A. *Tetrahedron Lett.* **2009**, *50*, 6358–6360; (b) Bräse, S.; Dahmen, S.; Heuts, J. *Tetrahedron Lett.* **1999**, *40*, 6201–6203; (c) Bui, C. T.; Flynn, B. L. *Mol. Divers.* Pub. Online March 2010, doi: 10.1007/s11030-010-9235-8.
6. (a) Vasilevsky, S. F.; Tretyakov, E. V. *Synth. Commun.* **1994**, *24*, 1733–1736; (b) Vasilevsky, S. F.; Tretyakov, E. V. *Liebigs Ann. Chem.* **1995**, 775–779; (c) Zolnikova, N. A.; Fedenok, L. G.; Polyakov, N. E. *Org. Prep. Proced. Int.* **2006**, *38*, 476–480.
7. (a) Fedenok, L. G.; Zolnikova, N. A. *Tetrahedron Lett.* **2003**, *44*, 5453–5455; (b) Fedenok, L. G.; Barabanov, I. I.; Bashurova, V. S.; Bogdanchikov, G. A. *Tetrahedron* **2004**, *60*, 2137–2145; (c) Zol'nikova, N. A.; Fedenok, L. G.; Peresypkina, E. V.; Virovets, A. V. *Russ. J. Org. Chem.* **2007**, *43*, 790–792; (d)

Shvartsberg, M. S.; Ivanchikova, I. D.; Fedenok, L. G. *Tetrahedron Lett.* **1994**, *35*, 6749–6752; (e) Fedenok, L. G.; Barabanov, I. I.; Ivanchikova, I. D. *Tetrahedron Lett.* **1999**, *40*, 805–808; (f) Fedenok, L. G.; Barabanov, I. I.; Ivanchikova, I. D. *Tetrahedron* **2001**, *57*, 1331–1334; (g) Duan, J.-X.; Cai, X.; Meng, F.; Lan, L.; Hart, C.; Matteucci, M. *J. Med. Chem.* **2007**, *50*, 1001–1006.

8. For a previous report on the use of H_2SO_4 in the diazotization of 2-alkynylanilines **1** to give 4-cinnolinones, see Ref. 7f .
9. Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403–6406.
10. General coupling procedure for the formation of **5a–h**: The iodoaryl piperidinetriazene **12** or **13** (1 equiv) was dissolved in pyrrolidine (0.5 M) and N_2 (g) was bubbled through for 0.25 h. $Pd(PPh_3)_4$ was added and the reaction heated to 60 °C. A solution of the appropriate alkyne (2 equiv) in pyrrolidine (1 M) was added via syringe in small portions over 2 h. After complete addition of the alkyne, the mixture was left stirring at 60 °C overnight. After cooling to room temperature, H_2O was added and the mixture was extracted with Et_2O. The organic phase was washed with saturated NH_4Cl (aq), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel to give **5**.
11. See Supplementary data.
12. *Method A*: The triazene **5** (1 mmol) was dissolved in acetone (10 mL) and cooled in an ice bath. A solution of 48% HBr (aq) (8 mmol) was added dropwise and the mixture stirred at room temperature until all starting material was consumed (0.2–2 h). The acetone was evaporated and the residue was taken up in $CHCl_3$ (15 mL) and washed with H_2O (15 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure and the product purified by column chromatography on neutral alumina (deactivation II).
Method B: $MeSO_3H$ (2.5 mmol) was added dropwise to a solution of **5** (1 mmol) and 1-(2-ethoxy-2-oxoethyl)pyridinium bromide (1.2 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C and then stirred at room temperature for 1 h. The resulting mixture was then diluted with CH_2Cl_2 (15 mL) and washed with saturated $NaHCO_3$ (aq) (20 mL). The organic phase was washed with H_2O (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resultant solid residue was suspended in Et_2O (2 mL) filtered and washed with cold Et_2O (4 mL).
Method C: $MeSO_3H$ (5 mmol) was added dropwise to a stirred solution of **5** (1 mmol) in an acetone and H_2O mixture (1:1 to 9:1, depending on solubility, 10 mL) at 0 °C (ice bath). The mixture was stirred at room temperature for 20 h. Acetone was evaporated and generally the product precipitated and was filtered and rinsed with H_2O. Where no precipitate formed, the aqueous residue was neutralized with saturated $NaHCO_3$ (aq) and extracted with EtOAc (20 mL). Crude products were generally of good purity, however, further purification could be achieved by crystallization from hot EtOH (1–3 mL) or by washing the crude solid with Et_2O (2–3 mL). See Supplementary data for the variation of this procedure used to access **16h**, in Method D.
Method E: $MeSO_3H$ (2.5 mmol) was added dropwise to a solution of **5** (1 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C and then stirred at room temperature for 24 h. The resultant mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ (aq) (20 mL). The organic phase was washed with H_2O, dried over $MgSO_4$, concentrated under reduced pressure and the product purified by column chromatography on silica gel (CH_2Cl_2/MeOH 40:1, 20:1, 10:1) to give **18e** and **18f**. In the case of **18g**, the product decomposed during chromatography, giving mostly **16f** (hydrolysis). Accordingly, **18g** could only be isolated in crude form.
13. Tetrabutylammonium bromide can also be used but co-eluted with a number of products during column chromatography.