

# Reductive Cyclization of *o*-Nitrophenyl Propargyl Alcohols: Facile Synthesis of Substituted Quinolines<sup>†</sup>

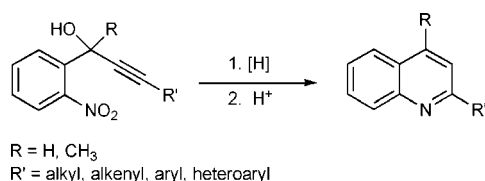
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## ABSTRACT



Reduction of secondary and tertiary *o*-nitrophenyl propargyl alcohols followed by acid-catalyzed Meyer–Schuster rearrangement gave 2-substituted and 2,4-disubstituted quinolines, respectively. Tertiary propargyl alcohols gave excellent yields of the quinoline derivative, while the yields of quinolines were slightly reduced when secondary propargyl alcohol derivatives were utilized.

The synthesis of the quinoline ring system has been extensively studied since its discovery by Gerhardt in 1842.<sup>1</sup> The quinoline ring system is found in a variety of compounds including dyes, organic materials, and pharmaceuticals. Among the pharmaceuticals, quinoline derivatives have been employed for treatment of parasitic infections such as malaria<sup>2</sup> and leishmaniasis,<sup>3</sup> as well as being present in antitumor agents such as streptonigrin,<sup>4</sup> luotonin A,<sup>5</sup> dyne-micin A,<sup>6</sup> and camptothecin.<sup>7</sup> In addition, natural product isolations and biological activity assays continue to identify

new, potentially useful quinoline alkaloids from both plant and marine animal sources.<sup>8</sup>

In our studies on the synthesis of streptonigrin (**1**, Figure 1), McElroy developed an efficient route to the functionalized CD pyridyl triflate intermediate **2**.<sup>9</sup> The initial strategy for the synthesis of streptonigrin was to couple triflate **2** to an AB quinoline ring system precursor affording the intact carbon skeleton of the natural product. Since direct aryl–aryl cross coupling to form 2-(2'-pyridyl)quinolines met with limited success,<sup>10</sup> an alternative method for the synthesis of quinoline was investigated.

Previous streptonigrin syntheses have utilized classical Friedländer<sup>11</sup> or Borsche<sup>12</sup> methodology to prepare the

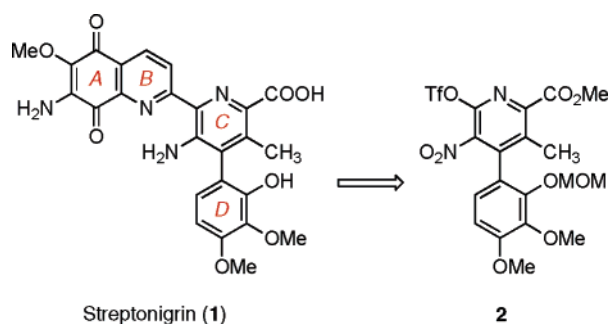
<sup>†</sup> The views expressed in this article are those of the author and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the U.S. Government.

(1) Manske, R. H. F. *Chem. Rev.* **1942**, *30*, 113–144.  
(2) Foley, M.; Tilley, L. *Pharmacol. Ther.* **1998**, *79*, 55–87.  
(3) Croft, S. L.; Coombs, G. H. *Trends Parasitol.* **2003**, *19*, 502–508.  
(4) (a) Bringmann, G.; Reichert, Y.; Kane, V. V. *Tetrahedron* **2004**, *60*, 3539–3574. (b) Hibino, S.; Weinreb, S. M. *J. Org. Chem.* **1977**, *42*, 232–236.  
(5) Wang, H.; Ganesan, A. *Tetrahedron Lett.* **1998**, *39*, 9097–9098.  
(6) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072–6094.  
(7) (a) Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120–5121. (b) Shen, W.; Coburn, C. A.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 611–617.

(8) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 476–493.

(9) McElroy, W. T.; DeShong, P. *Tetrahedron* **2006**, *62*, 6945–6954.

(10) (a) Deshayes, K.; Broene, R. D.; Chao, I.; Knobler, C. B.; Diederich, F. *J. Org. Chem.* **1991**, *56*, 6787–6795. (b) Godard, A.; Rovera, J. C.; Marsais, F.; Ple, N.; Queguiner, G. *Tetrahedron* **1992**, *48*, 4123–4134. (c) Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron Lett.* **1993**, *34*, 2937–2940. (d) Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron* **1993**, *49*, 3325–3342. (e) Godard, A.; Fourquez, J. M.; Tamion, R.; Marsais, F.; Queguiner, G. *Synlett* **1994**, 235–236. (f) Kimber, M.; Anderberg, P. I.; Harding, M. M. *Tetrahedron* **2000**, *56*, 3575–3581. (g) Nguyen, T.; Wicki, M. A.; Snieckus, V. *J. Org. Chem.* **2004**, *69*, 7816–7821.



**Figure 1.** Retrosynthesis of streptonigrin (1).

quinoline AB ring system. In Weinreb's synthesis, a Wadsworth–Emmons–Horner condensation produced a nitrochalcone intermediate that gave the quinoline AB ring following reduction. Kende's synthesis employed condensation of an iminoaniline with a 2-methyl ketone functionalized CD ring intermediate to form the AB quinoline system. While both strategies were effective, they required considerable modifications to their CD ring systems before the AB rings could be introduced. Our goal was to develop a Friedländer-like method that would minimize modification of the McElroy CD intermediate (**2**), allow facile attachment to a functionalized A-ring substrate, and undergo quinoline formation using mild conditions.

The development of a new quinoline synthesis (Scheme 1) depended on the well-precedented transformation of

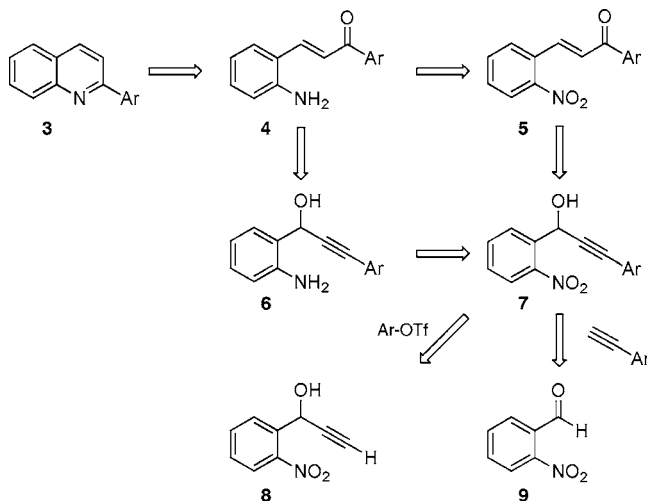
derivatives. Propargylic alcohols are at the same oxidation state as enones and rearrange to enones under acidic conditions (Meyer–Schuster rearrangement),<sup>14</sup> and we proposed to study the viability of this approach. We were heartened by the observation by Choudhury and co-workers<sup>15</sup> of the propensity of tertiary propargyl alcohols to form quinolines during deprotection of an *o*-aniline derivative. Although a quinoline was an undesired byproduct in Choudhury's work, the mild conversion of *o*-anilino-propargyl alcohols to quinolines seemed to be a potential solution to the introduction of the quinoline required in the streptonigrin synthesis. Analogously, propargyl alcohols have been utilized in the synthesis of quinolines by Jiang, via Zn(II)-mediated alkynylation of *o*-trifluoroacetyl-anilines;<sup>16</sup> by Cho, via Sonogashira coupling to *o*-iodoanilines;<sup>17</sup> and by Flynn, via 6-*endo*-digonal iodocyclization.<sup>18</sup>

Our approach to the synthesis of quinolines is outlined in Scheme 1, starting from readily available *o*-nitrobenzaldehyde **9**. Addition of lithium or magnesium acetylides to aldehyde **9** provided *o*-nitrophenyl propargyl alcohols **7** or **8**, respectively. The required reduction and rearrangement necessary to convert *o*-nitrophenyl propargyl alcohol **7** to *o*-aminochalcone **4** could be accomplished in either **7** → **5** → **4** or **7** → **6** → **4** order. However, repeated attempts to promote acid-catalyzed Meyer–Schuster (M–S) rearrangement of nitrochalcones (**7** → **5**, Ar = phenyl) were typically unsuccessful and gave very low yields of the desired enone. Analogous studies of M–S rearrangements have been reported by Engel and Dudley<sup>19</sup> via gold(III) catalysis, however, only in moderate yield with secondary propargyl alcohols.

We anticipated that reduction of the nitro group prior to M–S rearrangement would increase the electron density of the phenyl ring, hopefully facilitating the M–S rearrangement **6** → **4**. Once **4** is produced, quinolines are expected to be formed following spontaneous ring closure and aromatization. This strategy had several appealing features, the major one being that introduction of the CD-fragment (Ar in Scheme 1) could be accomplished either prior to formation of the propargylic alcohol (**9** → **7**) with an aryl acetylide or after the nucleophilic addition of the acetylide functionality via Sonogashira coupling of terminal propargyl alcohol **8**.

In practice, lithium acetylides of 1-hexyne and phenylacetylene added to *o*-nitroacetophenone providing the propargyl alcohols **10a** and **10b**, respectively, in excellent yield. Reduction of the nitroarenes, followed by in situ Meyer–Schuster rearrangement provided the desired quinolines. A

**Scheme 1.** Retrosynthesis of 2-Arylquinolines



nitrochalcones (**5**) to quinoline by reduction (the Friedländer method).<sup>13</sup> Our synthetic plan diverged from classical approaches, however, in the preparation of nitrochalcone

(11) Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Wu, T.-T. *J. Am. Chem. Soc.* **1981**, *104*, 536–544.

(12) Kende, A. S.; Lorah, D. P.; Boatman, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 1271–1273.

(13) (a) Han, R.; Chen, S.; Lee, S. J.; Qi, F.; Wu, X.; Kim, B. H. *Heterocycles* **2006**, *68*, 1675–1684. (b) Shi, D.; Rong, L.; Wang, J.; Zhuang, Q.; Wang, X.; Tu, S.; Hu, H. *J. Chem. Res. (S)* **2003**, 342–343. (c) Barros, A. I. R. N. A.; Silva, A. M. S. *Tetrahedron Lett.* **2003**, *44*, 5893–5896. (d) Wang, X.; Zhang, Y. *Synth. Commun.* **2002**, *32*, 3617–3620. (e) Fischer, F.; Arlt, W. *Z. Chem.* **1964**, *4*, 100–101.

(14) Meyer, K. H.; Schuster, K. *Chem. Ber.* **1922**, *55*, 819.

(15) Choudhury, A.; Pierce, M. E.; Confalone, P. N. *Synth. Commun.* **2001**, *31*, 3707–3714.

(16) Jiang, B.; Si, Y.-G. *J. Org. Chem.* **2002**, *67*, 9449–9451.

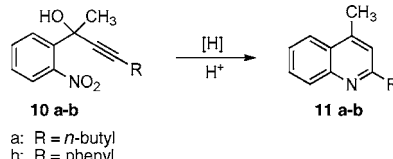
(17) Cho, C. S. *J. Organomet. Chem.* **2005**, *690*, 4094–4097.

(18) Hessien, K. O.; Flynn, B. L. *Org. Lett.* **2006**, *8*, 243–246.

(19) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027–4029.

number of reduction methods were investigated, including Fe/HCl,<sup>20</sup> Zn/NH<sub>4</sub>Cl,<sup>21</sup> TiCl<sub>3</sub>/HCl,<sup>22</sup> and SnCl<sub>2</sub>/HCl.<sup>23</sup> In each case, *o*-anilinopropargyl alcohols were not observed as intermediates; the quinolines **11a** and **11b** were formed directly. It was observed that Zn-, Fe-, and Sn-reductions generally gave excellent yields, while TiCl<sub>3</sub> reduction gave a poor yield of the desired product (Table 1).

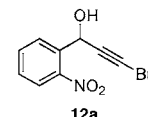
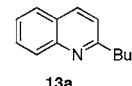
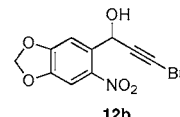
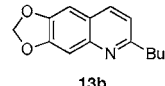
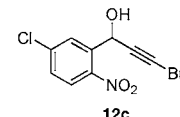
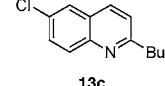
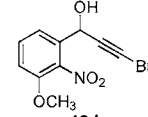
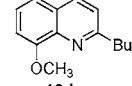
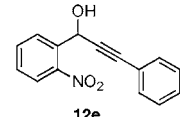
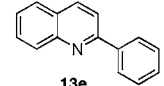
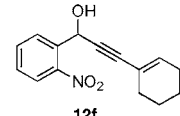
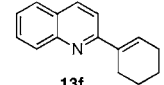
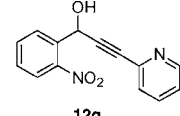
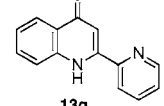
**Table 1.** Reduction/Rearrangement/Heteroannulation

 <p><b>10 a-b</b> a: R = <i>n</i>-butyl b: R = phenyl</p> <p><b>11 a-b</b></p>				
entry	R	[H]	H <sup>+</sup>	yield, <sup>a</sup> %
1	<i>n</i> -butyl	Fe	HCl	95
2	<i>n</i> -butyl	Zn	AcOH	95
3	<i>n</i> -butyl	SnCl <sub>2</sub>	HCl	91
4	<i>n</i> -butyl	TiCl <sub>3</sub>	HCl	<40 <sup>b</sup>
5	phenyl	Fe	HCl	82

<sup>a</sup> Isolated. <sup>b</sup> By GC.

For application in the streptonigrin project, a 2-substituted quinoline is desired and this required preparation from a secondary propargylic alcohol derivative. To demonstrate the generality of this technique, a series of secondary propargyl alcohol derivatives were converted to quinolines and the results are summarized in Table 2. Entries 1 and 5 are analogous to the *n*-butyl and phenyl tertiary propargyl alcohol analogues in Table 1. Both quinolines **13a** and **13e** were obtained in good yield, although the yield was slightly lower than their tertiary counterparts. Entries 2, 3, and 4 examine the electronic effects of substituents on the A ring in the cyclization and will be similar to the effects anticipated in the synthesis of streptonigrin. The presence of electron-donating substituents on the A-ring had minimal effect on the yield of quinoline (entry 2), unless the substituent was in the ortho position. For example, the yield of quinoline was dramatically reduced for the methoxy-substituted alcohol **13d** (entry 4). Propargyl alcohol **12f** (entry 6) also gave a low yield of 2-alkenylquinoline **13f** under the reduction conditions; however, the diminished yield in this case appears to result from difficulty isolating the sensitive product rather than inherent limitations with the reaction in question. It is important to note that the purification of these quinolines (**13a–f**) was done by a combination of acid–base extractions and/or bulb-to-bulb distillation since these low molecular weight quinolines were generally unstable to either silica or florisil chromatography. In most cases the NMR spectra of

**Table 2.** 2-Alkyl and 2-Aryl Quinolines

entry	propargyl alcohol	[H]/H <sup>+</sup>	quinoline	isolated yield
1		Zn AcOH		79%
2		Fe HCl		82%
3		Fe HCl		68%
4		Fe HCl		44%
5		Fe HCl		64%
6		Zn AcOH		34%
7		Fe HCl		53%

prior crude product indicated the presence of the desired quinoline in high purity; however, significant mass loss occurred during purification (see the Supporting Information for experimental details).

Despite repeated attempts, the transformation of pyridyl-substituted alcohol **12g** into the quinoline derivative (entry 7) corresponding to the ABC-ring system of streptonigrin did not occur as expected. Treatment of pyridine **12g** under reducing conditions gave quinolone **13g**, not the expected quinoline derivative, as the only product isolated from the reductive cyclization reaction. This was the only reaction that produced quinolone, rather than the quinoline derivative. In addition, formation of a quinolone is not mechanistically consistent with the quinolines produced in this study. Further studies will be conducted to examine the mechanism of this novel transformation. The proposed mechanism of quinoline formation is depicted in Scheme 2. Acid-catalyzed Meyer–Schuster rearrangement of tertiary propargyl alcohols is well preceded;<sup>24</sup> however, the analogous rearrangement of secondary substrates is known

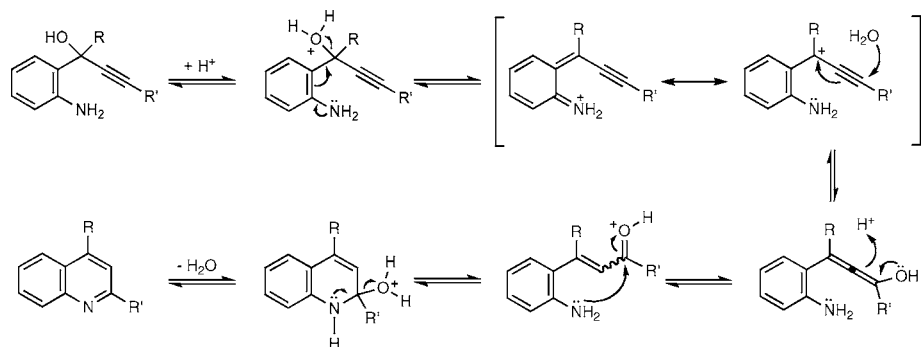
(20) Liu, Y.; Lu, Y.; Prashad, M.; Repic, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 217–219.

(21) Tsukinoki, T.; Tsuzuki, H. *Green Chem.* **2001**, *3*, 37–38.

(22) Somei, M.; Kato, K.; Inoue, S. *Chem. Pharm. Bull.* **1980**, *28*, 2515–2518.

(23) Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839–842.

**Scheme 2.** Proposed Mechanism: Resonance-Stabilized Meyer–Schuster Rearrangement/Heteroannulation



to result in lower yields of enone. This result is consistent with the observations that are reported above in Tables 1 and 2. Even so, the conversion of secondary propargylic alcohols provided acceptable yields of the desired quinoline derivatives in most instances.

In conclusion, the facile reductive cyclization of *o*-nitrophenyl propargyl alcohol derivatives provided 2-aryl- and 2-alkylquinolines in good to excellent yield. The methodology is tolerant of both electron-donating and electron-withdrawing functionality on the A-ring and to substitution on the alkyne. Attempts to prepare model systems for the ABC-pyridyl-quinoline ring system of streptonigrin led to formation of quinolone derivatives resulting from an aberrant cyclization pathway. Application of this methodology to the total synthesis of strepto-

nigrin, lavendamycin, and related natural products is underway and the results of these studies will be reported in due course.

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**Supporting Information Available:** Detailed experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(24) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, 71, 429–438.