## Rapid and Efficient Synthesis of 1*H*-Indol-2-yl-1*H*-quinolin-2-ones

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## ABSTRACT



A concise and efficient synthesis of the novel indol-2-yl-1*H*-quinolin-2-one ring system found in the potent and selective KDR kinase inhibitors 1–3 is presented.

Tyrosine kinases are a class of enzymes that are believed to play a critical role in the signal transduction of a number of cellular functions and have contributed to a wide range of diseases.<sup>1</sup> The kinase insert domain receptor (KDR) is a tyrosine kinase that has a high affinity for vascular endothelial growth factor (VEGF) and is thought to be a primary mediator of tumor-induced angiogenesis.<sup>2</sup> Inhibition of the KDR receptor may be useful for the prevention and treatment of tumor-induced angiogenesis. Recently, a number of potent and selective KDR inhibitors such as 1-3 have been identified for the potential use in a range of cancer indications.<sup>3-5</sup> In this letter, we describe a rapid and efficient synthesis of the 1*H*-indolyl-2-yl-1*H*-quinolin-2-one ring system, the key pharmacophore present in compounds 1-3.

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Conventional approaches to 2-aryl indoles typically rely upon cross coupling of 2-indolyl halides, boronic acids, or stannanes and silanes.<sup>6</sup> Although effective methods are available for the preparation of 2-indolyl boronic acids and silanes,<sup>7</sup> the major limitation with most of these approaches are the additional steps needed for the preparation of the coupling partners to enter the palladium-catalyzed reaction. While a number of other classical methods (e.g., Fisher, Madelung, Bischler, Reissert, Nenitzescu, and Leimgruber– Batcho)<sup>8</sup> have been successfully employed for the synthesis

 <sup>(1) (</sup>a) Carmeliet, P.; Jain, R. K. Nature 2000, 407, 249. (b) Folkman, J. Nature Med. 1995, 1, 27. (c) Zetter, B. R. Annu. Rev. Med. 1998, 49, 407.
 (d) Folkman, J. N. Engl. J. Med. 1995, 333, 1757. (e) Traxler, P. Expert Opin. Ther. Targets 2003, 7, 215 and references therein.

 <sup>(2) (</sup>a) Veikkola, T.; Karkkainen, M.; Claesson-Welsh, L.; Alitalo, K.
 *Cancer Res.* 2000, 60, 203. (b) Thomas, K. A. J. Biol. Chem. 1996, 271, 603.

<sup>(3)</sup> Fraley, M. E.; Antanavage, J.; Arrington, K. L.; Ciecko, P. A.; Coll, K. E.; Gribbs, J. B.; Hambaugh, S. R.; Hartman, G. D.; Heimbrook, D. C.; Hoffman, W. F.; Hungate, R. W.; Kohl, N. E.; Mao, X.; McFall, R. C.; Rands, E.; Rickert, K.; Sepp-Lorenzino, L.; Shipman, J. M.; Tebben, A. J.; Thomas, K. A. Presented at the 224th National Meeting of the American Chemical Society, Boston, MA, Sept 2002; Abstract MEDI-221.

<sup>(4) (</sup>a) DeFeo-Jones, D.; Helmbrook, D. C.; Jones, R. E. US Patent US2002/0041880 A1, 2000. (b) Fraley, M. E.; Arrington, K. L.; Bilodeau, M. T.; Hartman, G. A.; Hoffman, W. F.; Kim, Y.; Hungate, R. W. US Patent 6,306,874 B1, 2001.

<sup>(5)</sup> Fraley, M. E.; Hoffman, W. F.; Arrington, K. L.; Hungate, R. W.; Hartman, G. D.; McFall, R. C.; Coll, K. E.; Richert, K.; Thomas, K. A.; McGaughey, G. B. *Curr. Med. Chem.* **2003**, in press.

of 2-subsitituted indoles, each has their limitations due to either construction of the starting materials or harsh reaction conditions, which may interfere with other sensitive functionalities often located within the target molecule. Therefore, mild synthetic methods that provide rapid assembly of the indole ring and tolerate a wide range of functional groups continue to offer significant advantages. Reactions leading to increasing molecular complexity are important synthetic tools, and it was envisioned that the reductive cyclization<sup>9</sup> of a suitably substituted *ortho*-nitrostyrene would be an attractive method for the construction of the indol-2-yl-1*H*quinolin-2-ones.

Our first goal was the development of an efficient synthesis of the ortho-nitrostyrene, and our approach was inspired by the unique versatility of nitrobenzenes due to their ability to serve as both nucleophilic and electrophilic partners.<sup>10</sup> Addition of trimethylsilylmethylmagnesium chloride to a solution of  $9^{11}$  in THF at -15 °C followed by oxidation of the resulting nitronate intermediate with DDQ<sup>12</sup> gave addition compound 10 in 81% yield (Scheme 1). Alternatively, the oxidation could be carried out with *p*-chloranil and gave 10 in 79% yield. Oxidation with aqueous iodine<sup>13</sup> greatly simplified the workup and gave 10 in 83% yield. Treatment of a mixture of 10 and aldehyde 6a with catalytic TBAF furnished the desired alcohol 11 in 87% isolated yield.<sup>14</sup> However, it was more convenient to use 11 without purification and convert it to styrene 12 by reaction with TFAA in isopropyl acetate. Upon elimination with DBU, the transnitro styrene 12 was obtained in 81% isolated yield by direct crystallization from the reaction mixture.

With the key nitrostyrene in hand, the reductive cyclization of **12** was verified by the classic Cadogan/Sundberg conditions using refluxing P(OEt)<sub>3</sub> to give indole **13** in 76% yield.<sup>15</sup> Alternatively, palladium-catalyzed reductive cyclization of **12** using carbon monoxide as the terminal reductant, i.e., the Söderberg conditions [6 mol % Pd(OAc)<sub>2</sub>, 24 mol % PPh<sub>3</sub>,CO (6 atm), 70 °C] gave **13** in 94% isolated yield.<sup>16</sup> The quinolinone functionality was unmasked by

- (7) Vazquez, E.; Davies, I. W.; Payack, J. F. J. Org. Chem. 2002, 67, 7551.
- (8) Gribble, G. W. J. Chem. Soc., Perkin Trans. 1 2000, 1045.
- (9) Söderberg, B. C. G. Curr. Org. Chem. 2000, 4, 727.
- (10) Ricci, A.; Fochi, M. Angew. Chem., Int. Ed. 2003, 42, 1444 and references therein.
- (11) Horstmann, H.; Andrews, P.; Goennert, R. Eur. J. Med. Chem. Chim. Ther. **1980**, 15, 399.
- (12) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Todesco, P. E. J. Org. Chem. 1986, 51, 3694.
- (13) Oxidation of nitronates with iodine has previously been reported to occur in low yield (~20%). RajanBabu, T. V.; Reddy, G. S.; Fukunaga, T. *J. Am. Chem. Soc.* **1985**, *107*, 5473.

<sup>(14)</sup> Bartoli, G.; Bosco, M.; Caretti, D.; Dalpozzo, R.; Todesco, R. E. J. Org. Chem. **1987**, *52*, 4381.





hydrolysis of chloroquinoline **13** in a 1:1 mixture of refluxing AcOH/ $H_2O^5$  and gave **1**, which crystallized from the reaction mixture in analytically pure form in 91% yield.

While optimizing the reaction of 10 with aldehyde 6a, we discovered an interesting side reaction (Scheme 2). The expected alcohol 11 was the primary reaction product (85%); however, compound 14 was identified as the major byproduct (10%) together with a small quantity of protiodesilylation byproduct 15<sup>14</sup> (3%). Presumably, 14 arises by addition of the carbanion to the 4-position of **6a** in Michael-type fashion giving intermediate 16. Protonation of 16 then leads to 14. Interestingly, upon aging of 14 for >3 h in either CDCl<sub>3</sub> or CD<sub>2</sub>Cl<sub>2</sub>, compound 14 decomposes to give a mixture of aldehyde 6a, peroxide 17, aldehyde 18, and alcohol 19. We speculate that retroaddition of 14 would give the nitrostabilized anion  $(pK_a = 25)$ .<sup>17</sup> Subsequent reaction with molecular oxygen occurs to give 17. Compounds 18 and 19 most likely are derived from the known decomposition pathways of 17.18

The synthesis of tertiary amine analogues 2 and 3 began with ethers  $20a^{19}$  and 20b (Scheme 3). Addition of trimeth-

(16) Söderberg, B. C.; Shiver, J. A. J. Org. Chem. 1997, 62, 5838.

<sup>(6) (</sup>a) Johnson, C. N.; Stemp, G.; Anand, N.; Stephen, S. C.; Gallagher, T. Synlett 1998, 1025. (b) Danieli, B.; Lesma, G.; Martinelli, M.; Passarell, D.; Perettlo, I.; Silvani, A. Tetrahedron 1998, 54, 14081. (c) Krizan, T. D.; Martin, J. C. J. Am. Chem. Soc. 1983, 105, 6155. (d) Caron, S.; Hawkins, J. M. J. Org. Chem. 1998, 63, 2054. (e) Hiyama, T. In Metal-Catalyzed Cross-Coupling Reactions; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1988; Chapter 10. (f) Tamao, K.; Kobayashi, K.; Ito, Y. Tetrahedron Lett. 1989, 30, 6051. (g) Mowery, M.; DeShong, P. J. Org. Chem. 1999, 64, 3266. (l) Lee, H. M.; Nolan, S. P. Org. Lett. 2000, 2, 2053. (j) Denmark, S. E.; Wehrli, D. Org. Lett. 2000, 2, 565. (k) Denmark, S. E.; Neuville, L. Org. Lett. 2000, 2, 3221. (l) Denmark, S. E.; Pan, W. Org. Lett. 2001, 3, 61.

<sup>(15) (</sup>a) Cadogan, J. I. G.; Cameron-Wood, M. Proc. Chem. Soc. 1962,
361. (b) Cadogan, J. I. G.; Mackie, R. K.; Todd, M. J. J. Chem. Soc.,
Chem. Commun. 1966, 491. (c) Sundberg, R. J. J. Org. Chem. 1965, 30,
3604.

<sup>(17)</sup> Lelievre, J.; Farrell, P. G.; Terrier, F. J. Chem. Soc., Perkin Trans. 2 1986, 333.

<sup>(18)</sup> Santamaria, J.; Jroundi, R. Tetrahedron Lett. 1991, 32, 4291.



ylsilylmethylmagnesium chloride to a THF solution of either **20a** or **20b** at -15 °C followed by oxidation with aqueous iodine solution gave silyl compounds **21a** and **21b** in 84 and 81% yields, respectively. To eliminate any unwanted side reactions between the anion of **21a** or **21b** and the 4-position



of the quinoline moiety, the electron-rich 2-methoxy-3quinoline carboxaldehyde 6b<sup>20</sup> was used. Treatment of a 1:1 mixture of crude 21a and 6b with catalytic TBAF furnished alcohol 22a in 84% yield. In similar fashion, alcohol 22b was formed in 96% yield. There was no evidence of the formation of 1,4-dihydroquinoline products of type 14. Conversion of crude 22a and 22b to styrenes 23a and 23b, respectively, was effected by reaction with TFAA followed by elimination of the trifluoroacetate with DBU at 60 °C, which afforded nitrostyrenes 23a (65%) and 23b (74%). There was no detectable amount of the corresponding cisstyrene in the crude reaction mixture. Reductive cyclization of 23a in refluxing P(OEt)<sub>3</sub> gave indole 24a in 63% yield. On the other hand, catalytic reductive cyclization with 6 mol % Pd(OAc)<sub>2</sub> and 24 mol % PPh<sub>3</sub> in an atmosphere of CO (60 psi) at 70 °C gave 24a in 88% yield. Reductive cyclization of 23b gave indole 24b in 57% yield for the Sundberg conditions and 92% yield for the Söderberg catalytic conditions. Deprotection of 24a,b was accomplished with HCl and afforded 2 and 3, respectively, in near quantitative yield.

The pyridone analogues 27 and 28 were accessed in a similar manner by starting with silyl compound  $21c^{14}$  and aldehydes 25 and 26 <sup>21</sup> (Figure 1). Catalytic reductive



cyclization using Pd(OAc)<sub>2</sub>/PPh<sub>3</sub>/CO of these isomeric styrenes gave the corresponding indoles, which were hydrolyzed in a one-pot procedure by the direct addition of aqueous HCl to provide pyridones **27** (83%) and **28** (82%).

In conclusion, we have demonstrated an efficient and rapid means of constructing highly functionalized *o*-nitrostyrenes from 4-nitrophenol in four synthetic steps with only one isolation. Catalytic reductive cyclization with  $Pd(OAc)_2/PPh_3/CO$  provides the desired 1*H*-indolyl-2-yl-quinolines in excellent yield. The desired quinone functionality of the potent KDR kinase inhibitor 1-3 was unmasked from either the chloroquinoline or methoxyquinoline by simple hydrolysis. The overall sequence as described does not require the use

<sup>(19)</sup> Chabrien, P.; Najor, H.; Giudicelli, R. Bull. Soc. Chim. Fr. 1955, 1353.

<sup>(20)</sup> Wai, J. S.; Williams, T. M.; Bamberger, D. L.; Fisher, T. E.; Hoffman, J. M.; Hudcosky, R. J.; MacTough, S. C.; Rooney, C. S.; Saari, W. S.; Thomas, C. M.; Schleif, W. A.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 249.

<sup>(21)</sup> Comins, D. L.; Killpack, M. O. J. Org. Chem. 1990, 55, 69.

of chromatography. We are currently exploring alternative routes to the novel 1*H*-indolyl-2-yl-1*H*-quinolin-2-one ring system.

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**Supporting Information Available:** Experimental details and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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