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

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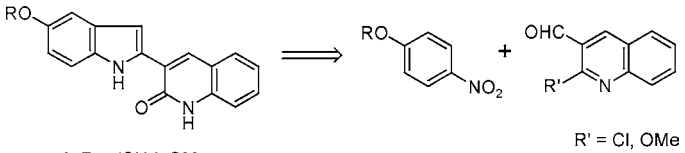
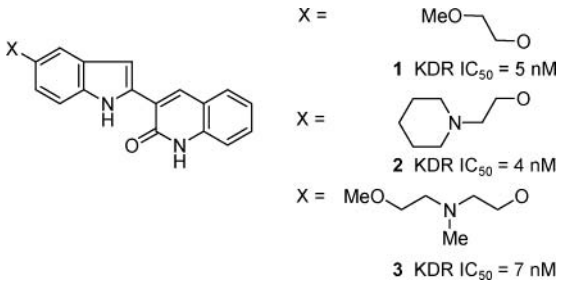
## ABSTRACT




**1** R = $(CH_2)_2OMe$
**2** R = $(CH_2)_2NC_5H_{10}$
**3** R = $(CH_2)_2NMe(CH_2)_2OMe$

**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.[1] 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.[2] 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.[3−5] 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**.




Conventional approaches to 2-aryl indoles typically rely upon cross coupling of 2-indolyl halides, boronic acids, or stannanes and silanes.[6] Although effective methods are available for the preparation of 2-indolyl boronic acids and silanes,[7] 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)[8] have been successfully employed for the synthesis

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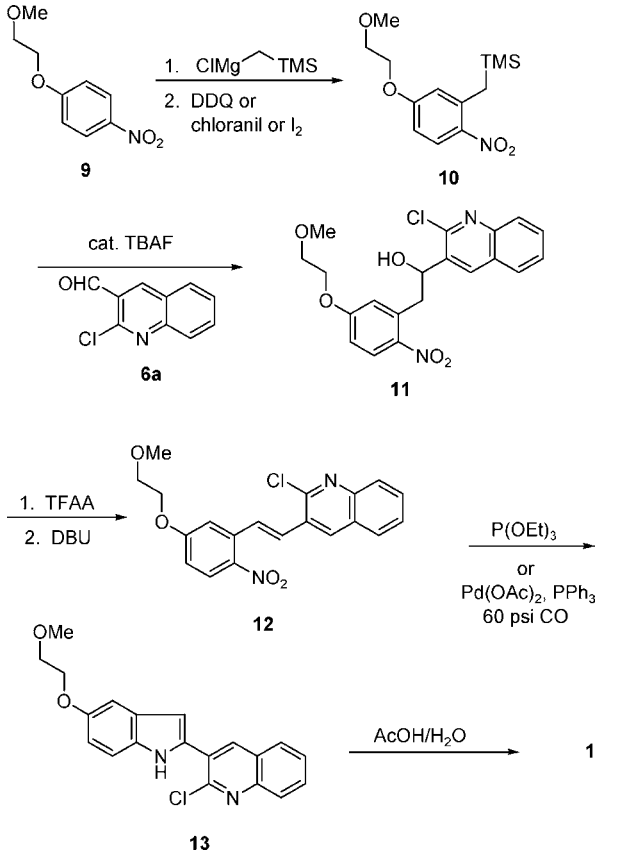
of 2-subsitituted indoles, each has their limitations due to either construction of the starting materials or harsh reaction conditions, which may interfere with other sensitive functionalities often located within the target molecule. Therefore, mild synthetic methods that provide rapid assembly of 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[9] 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.[10] 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[12] 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[13] 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.[14] 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 *trans*-nitro 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 $P(OEt)_3$ to give indole **13** in 76% yield.[15] Alternatively, palladium-catalyzed reductive cyclization of **12** using carbon monoxide as the terminal reductant, i.e., the Söderberg conditions [6 mol % $Pd(OAc)_2$, 24 mol % $PPh_3$,CO (6 atm), 70 °C] gave **13** in 94% isolated yield.[16] The quinolinone functionality was unmasked by

**Scheme 1.** Synthesis of KDR Kinase Inhibitor **1**




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**[14] (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 $CDCl_3$ or $CD_2Cl_2$, 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 nitro-stabilized anion ($pK_a = 25$).[17] 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-

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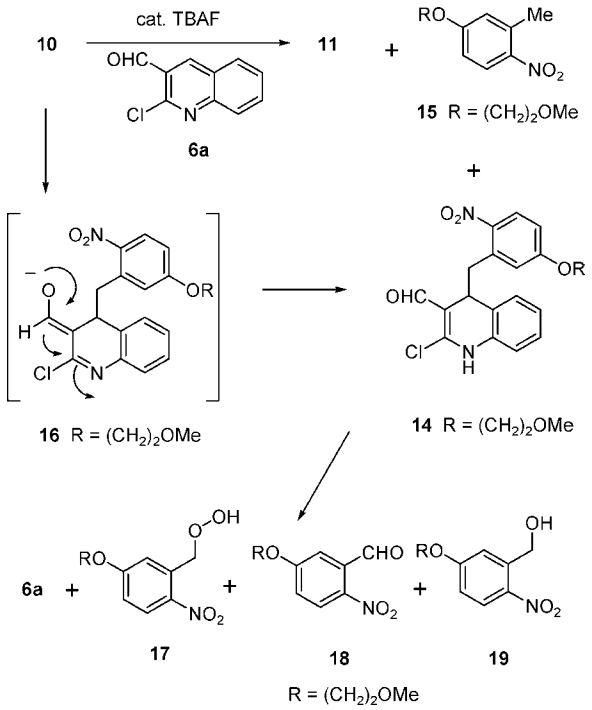
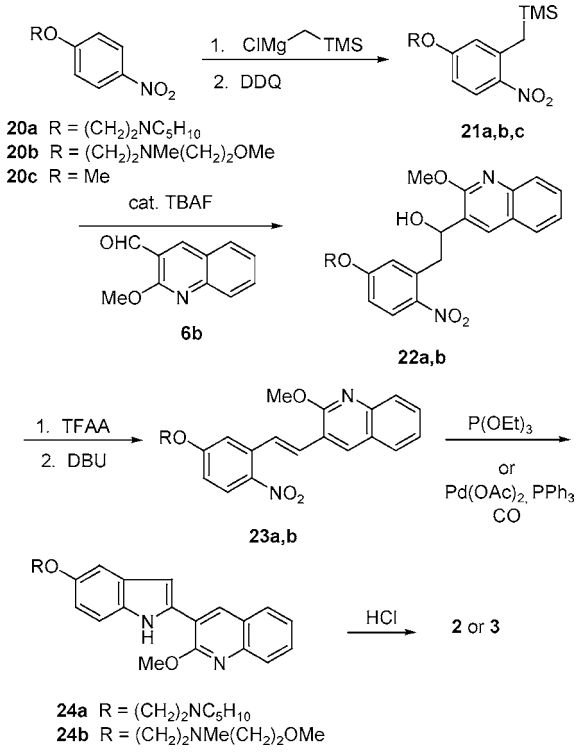
**Scheme 2.** Oxidative Decomposition Pathway for **14**




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-3-quinoline carboxaldehyde **6b**[20] 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 *cis*-styrene in the crude reaction mixture. Reductive cyclization of **23a** in refluxing $P(OEt)_3$ gave indole **24a** in 63% yield. On the other hand, catalytic reductive cyclization with 6 mol % $Pd(OAc)_2$ and 24 mol % $PPh_3$ 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** [21] (Figure 1). Catalytic reductive cyclization using $Pd(OAc)_2/PPh_3/CO$ 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%).

**Scheme 3.** Synthesis of KDR Kinase Inhibitors **2** and **3**



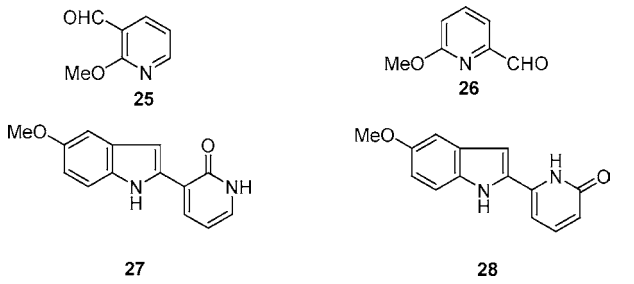




**Figure 1.** Preparation of pyridone derivatives **27** and **28**.

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

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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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