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Synthesis of Novel KDR Kinase Inhibitors through Catalytic Reductive Cyclization of *o*-Nitrobenzylcarbonyl Compounds

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Abstract: An efficient synthesis of *o*-nitrobenzylcarbonyl compounds is demonstrated through the Swern-type oxidation of readily accessible phenethanol analogues. Reductive cyclization of *o*-nitrobenzylcarbonyl **3** using catalytic Raney nickel gives 1*H*-indol-2-yl-1*H*-quinoline **2** in 95% yield. Hydrolysis of **2** affords the KDR kinase inhibitor **1** in quantitative yield. The examination of the reductive cyclization reaction and optimization of conditions is described.

Vascular endothelial growth factor (VEGF) is a family of proteins implicated in angiogenic activity, which is key to normal tissue repair. However, at elevated levels, VEGF can also add to the progression of several diseases including solid tumors, which require new blood vessels for growth.[1] The mitogenic cell surface receptor for VEGF is the tyrosine kinase KDR (kinase insert domain-containing receptor), which upon activation through ligand binding initiates the formation and in-growth of new blood vessels.[2] Tumor growth inhibition has been demonstrated through blockade of endothelial cell growth signaling by antibodies against the ligand VEGF and the receptor KDR, as well as small molecule inhibitors of KDR kinase activity.[3,4a] Recently, the potent and selective KDR inhibitor **1** was identified as a clinical candidate for use in the treatment of cancer.[4] The novel 1*H*-indol-2-yl-1*H*-quinolin-2-one ring system of **1**,[5] which is the key pharmacophore, was envisioned as arising from reductive cyclization of the highly functionalized nitroketone **3** (Scheme 1). In this paper, we present the synthesis of **3** and related nitroketones and optimized conditions for their conversion to 2-substituted indoles of type **2**.

One of the oldest effective methods for the construction of indoles and indolinones is reductive cyclization of *o*-nitrobenzylcarbonyl compounds.[6] The transformation has been carried out with a variety of reagents including H_2/Pd,[7] H_2/RaNi,[8] $SnCl_2$,[9] Fe/AcOH,[10] Zn/AcOH,[11] $TiCl_3$/NH_4OAc,[12] and $Na_2S_2O_4$.[13] However, the availability of starting materials has severely limited the utility of this approach. While recent advances by Buchwald,[12a] Rawal,[12b] RajanBabu,[14] and others[15] have given ready access to *o*-nitrobenzylcarbonyl compounds, there is still a need for methods which provide highly functionalized *o*-nitrobenzylcarbonyl compounds and their subsequent conversion to indoles. It was envisioned that nitroketone **3** could be derived by oxidation of nitrocompound **9** which may be prepared by employing chemistry previously reported from these laboratories.[16]

The synthesis of **9** began with 4-nitrobenzyl bromide **4** (Scheme 2). Reaction of **4** with 1-methanesulfonylpiperazine **5**[17] in the presence of Na_2CO_3 in DMF afforded nitropiperazine derivative **6** in 99% yield after direct crystallization of the product from the crude reaction mixture. Addition of trimethylsilylmethylmagnesium chloride to **6** in THF at −15 °C followed by oxidation of the intermediate nitronate with aqueous iodine gave silyl-nitro compound **7** in 85% yield.[16] Condensation of **7** with formylquinoline **8**[18] in the presence of a catalytic amount of TBAF (25 mol %) provided alcohol **9** as a colorless foam in 89% isolated yield.[19]

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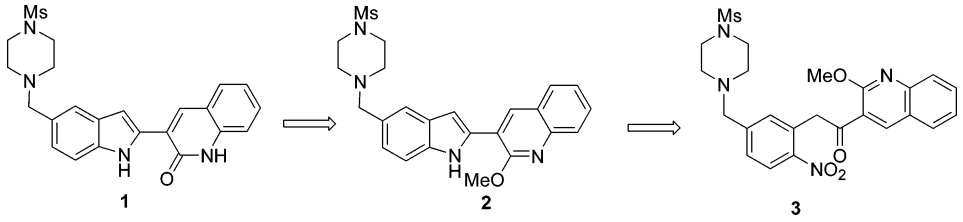
SCHEME 1. Retrosynthetic Approach to 1



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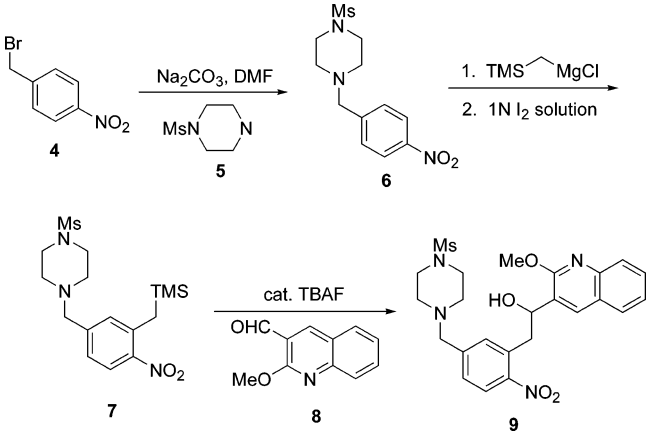

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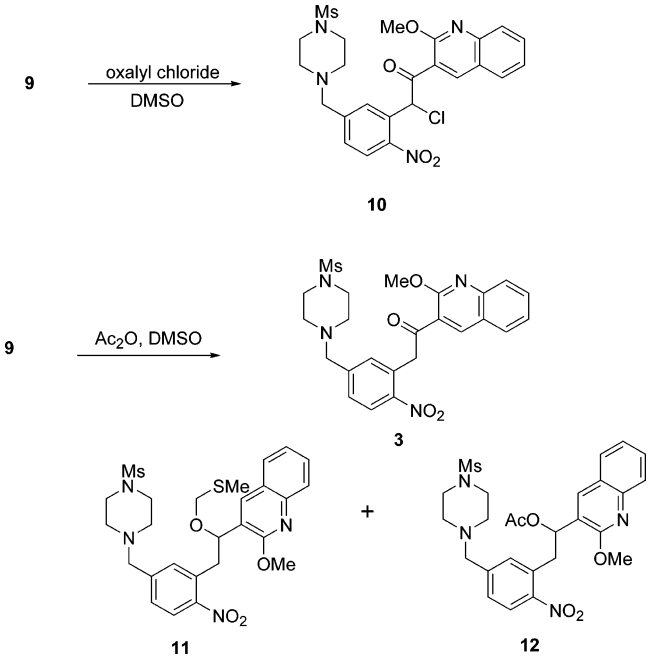
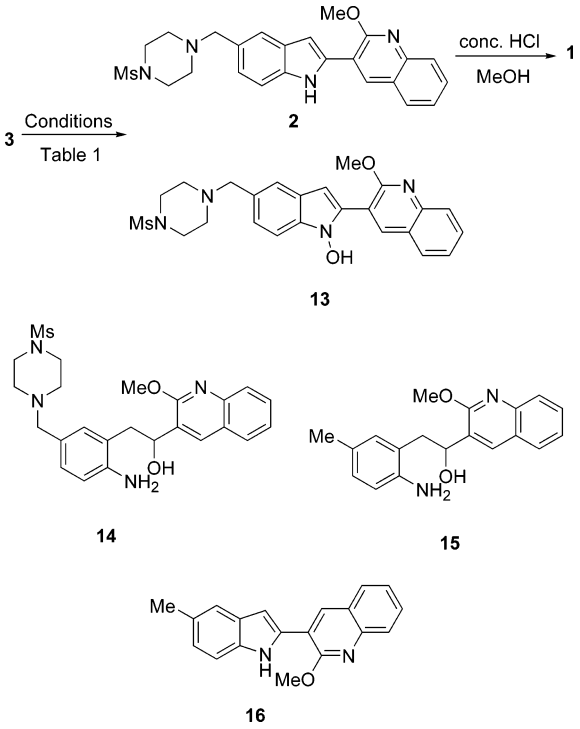


With the desired alcohol **9** in hand, efforts turned to the oxidation of **9** to ketone **3.** Reaction of **9** under standard Swern oxidation conditions (oxalyl chloride/DMSO)[20] afforded α-chloroketone **10** as the sole identifiable product in 47% isolated yield (Scheme 3). The formation of **10** was unanticipated but not unprecedented[21] and most likely arises from deprotonation of the initially formed ketone **3** with NEt_3 followed by reaction with excess activated DMSO. By switching the competing electrophile generated from DMSO/oxalyl chloride to DMSO/acetic anhydride,[22] the expected nitroketone **3** was obtained in 78% yield, through direct chromatography of the reaction mixture. In addition to **3**, sulfide **11** (10%) and acetate **12** (3%)[23] were also observed in the crude reaction mixture. The optimal conditions for the oxidation of **9** to **3** involved heating an isopropyl acetate solution of **9** to 80 °C containing DMSO (12 equiv) followed by the addition of Ac_2O (6 equiv).

SCHEME 4



With nitroketone **3** in hand, our attention turned to the key reductive cyclization of **3** and the formation of indole **2** (Scheme 4). A variety of conditions were examined for the conversion of **3** to **2** (Table 1). While the reduction of **3** with Fe/AcOH (29%), $TiCl_3$ (70%), or sodium hydrosulfite (38%) provided the desired product **2**, these reactions were plagued with significant levels of unidentified byproducts which were difficult to remove. Interestingly, reduction with either Pd/H_2 (1 mol %, 5% Pd/C, 65 °C) or Pt/C (10 mol %, 5% Pt/C, rt) gave hydroxy

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(23) The formation of acetate **12** was confirmed through independent synthesis by reaction of alcohol **6** with Ac_2O, which yielded **12** in 65% yield. See the Supporting Information.

TABLE 1. Summary of Reductive Cyclization on 3

entry	catalyst	solvent	time[a] (h)	H_2 (psi)	**2**[f] (%)	**13** (%)	**14** (%)
1	Fe/AcOH	MeOH/H_2O	6	0	29	3	0
2	$TiCl_3$[b]	MeOH	0.5	0	70	0	0
3	$Na_2S_2O_4$	MeOH/THF	4	0	38	0	0
4	10 mol % 5% Pt/C[b]	THF	20	40	1	40	0
5	1 mol % 5% Pd/C[c]	THF	12	40	6.6	76	0
6	30% Raney Ni 2800 (H_2O)	THF	15	40	93	0	4.7
7	30% Raney Ni 2800 (H_2O)	THF	6	60	88	2.8	5.8
8	30% Raney Ni 2800 (H_2O)	THF	6	80	81	5.2	5.2
9	40% Raney Ni 2800 (H_2O)	THF	7.5	40	95	0	1.3
10	60% Raney Ni 2800 (H_2O)	THF	6	20	89	2	4.3
11	60% Raney Ni 2800 (H_2O)	THF	6	30	91	0	3.8
12	60% Raney Ni 2800 (H_2O)	THF	6	40	95	0	1
13	50% Raney 2400 (H_2O)[d]	THF	6	40	94	0.5	2
14	60% Raney 3100 (H_2O)[e]	THF	9	40	95	0	1.2

[a] Reactions were performed at 65 °C unless otherwise noted. [b] Reaction at room temperature. [c] Johnson Matthey, type A503023-5. [d] Chromium-promoted nickel. [e] Molybdenum-promoted nickel. [f] Yield determined by HPLC.

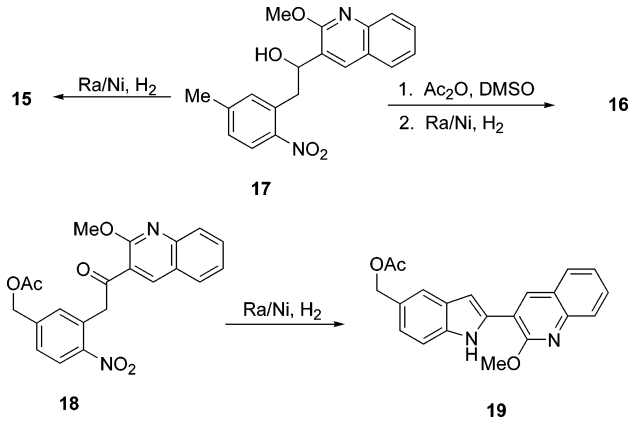
indole **13** as the major product[24] with small amounts of **2** (<7%) formed. Ketone **3** was subjected to lead-promoted reductive cyclization conditions[25] for forming hydroxy indoles to give **13** as the sole product in 92% yield. Increased catalyst loading (10 mol % 5% Pd/C) or increased temperature (65 °C for 10 mol % Pt/C) afforded only a modest increase in the level of **2** (up to 45%); however, significant levels of unidentified impurities were formed, with <2% of ketone **3** and only 6% of hydroxy indole **13** observed. When Raney catalysts 2700 (cobalt) and 2724 (chromium promoted cobalt) were employed, hydroxy indole **13** was observed to be the major product (82% and 70% yield, respectively). When catalytic Raney Nickel 2800 (66 wt % of a 55 wt % slurry in water, rt, 20 h) was employed, the desired indole **2** was obtained in 59% yield, with no detectable amount of *N*-hydroxy indole **13** present in the NMR and HPLC of the crude reaction mixture. Encouraged by the success of this reaction, optimal conditions were sought with regard to Raney nickel catalyst, catalyst loading, and reaction solvent. Reduction with Raney nickel catalysts 3100 and 2400 resulted in clean conversion to indole **2**; however, high catalyst loadings (60 wt %) were required for the reaction to approach completion. The optimal catalyst loading was observed to be 40 wt % of Ra/Ni 2800 (H_2O) catalyst. Less than 40 wt % catalyst led to incomplete reactions and higher levels of impurities such as amino alcohol **14**. The formation of **14** arises from competitive reduction of the carbonyl group prior to reduction of the nitro group. It was hypothesized that the formation of **14** may be due to the enolization of ketone **3** under the basic reaction conditions induced by the pH >9 slurry of Ra/Ni (H_2O). However, adjusting the pH between 5 and 7, using Ra/Ni in EtOH, or washing the catalyst in THF or water to reduce the basicity did not correspondingly decrease the observed amount of aniline alcohol **14**. Efforts to eliminate the formation of **14** by the addition of competitively reducible ketones (acetone or cyclohexanone) did not significantly improve the reaction profile. Solvent choice was also critical to the success of the reaction. For example, the use of alcoholic solvents such as IPA or MeOH gave **2** (65%) and varying amounts of **13** and **14**, and solvents such as toluene and isopropyl acetate led to increased levels of other unidentified impurities and lower yields of **2**. The optimal reaction conditions were 40 wt % Ra/Ni 2800 (55 wt % in H_2O), 40 psi H_2, 65 °C, in THF for 7.5 h and gave **2** in 95% yield. Detectable impurities present in the crude reaction mixture were identified as **14** (1.3%), **15** (0.7%), and methyl derivative **16** (0.6%). The isolation of **2** was simply a matter of filtering the catalyst, concentrating the solution, and adding MeOH which precipitated the product in analytically pure form in an unoptimized 90% isolated yield.

The presence of impurities **14**, **15**, and **16** was unambiguously established by independent synthesis, which also serves to address the scope of the reaction conditions (Scheme 5). For example, reduction of nitro alcohols **9** and **17** with Ra/Ni afforded **14** and **15** in 86% and 58% yields, respectively. Alternatively, oxidation of **17** followed by reductive cyclization under the optimized reaction conditions afforded **16** in 52% overall yield. An additional example which highlights the methodology is the reductive cyclization of nitroketone **18** to give **19** in 83% yield.

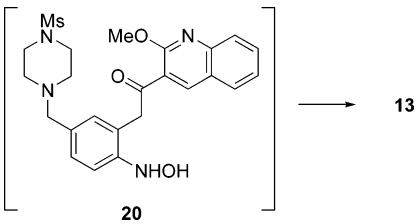
Deprotection of the masked quinolinone **2** was achieved by hydrolysis of **2** with concentrated HCl in methanol and afforded the KDR kinase inhibitor **1** in quantitative yield.

In summary, a practical and efficient three-step synthesis of highly functionalized 2-nitrobenzyl alcohol compounds from 4-nitrobenzene derivatives has been demonstrated. The alcohols are easily oxidized to the

SCHEME 5



(24) We speculate that hydroxyl indole **13** arises by cyclization on a hydroxylamine intermediate **20** onto the adjacent ketone.



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corresponding ketones with DMSO/Ac_2O, at which point intramolecular Ra/Ni-catalyzed reductive cyclization smoothly furnishes the desired 1*H*-indol-2-yl-1*H*-quinoline ring system in 95% yield (90% isolated yield). The quinolinone functionality of the potent KDR kinase inhibitor is then easily revealed through hydrolysis. Alternate approaches to the 1*H*-indol-2-yl-1*H*-quinoline are currently being explored in this laboratory.

Experimental Section

Preparation of 1-(2-Methoxyquinolin-3-yl)-2-[5-[[4-(methylsulfonyl)piperazin-1-yl]methyl]-2-nitrophenyl]ethanone (3). To a heated (80 °C) solution of 19.7 g (39.4 mmol) of alcohol **9** in 79 mL of isopropyl acetate and 36.9 g (473 mmol) of DMSO was added 24.1 g (236 mmol) of acetic anhydride. The reaction was heated at 80 °C for 2 h. After being cooled to rt, the reaction was neutralized with (175 mL) satd $NaHCO_3$ to a final pH of 8.0. The layers were separated, and the organic layer was washed with water (250 mL). The solvent was removed under reduced pressure. The residual oil was chromatographed over silica gel, eluting with 70% EtOAc/hexanes to yield 15.3 g (78%) of ketone **3** as an off-white solid. An analytical sample was obtained by recrystallization from THF/MeOH: mp 122−124 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.58 (m, 4H), 2.80 (s, 3H), 3.27 (m, 4H), 3.63 (s, 2H), 4.22 (s, 3H), 4.80 (s, 2H), 7.36 (s, 1H), 7.43 (ddd, 2H, J = 1.2, 8.0, 9.2 Hz), 7.73 (ddd, 1H, J = 1.6, 6.8, 8.4 Hz), 7.87 (d, 1H, J = 14.7 Hz), 7.85 (d, 1H, J = 15.6), 8.12 (d, 1H, J = 9.1 Hz), 8.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.3, 45.8, 48.8, 52.3, 53.9, 61.5, 122.9, 124.4, 124.9, 125.4, 127.0, 128.4, 129.2, 131.2, 131.9, 132.9, 133.9, 141.8, 144.2, 147.9, 159.1, 195.9. Anal. Calcd for $C_{24}H_{26}N_4O_6S$: C, 57.82; H, 5.26; N, 11.24. Found: C, 57.71; H, 5.20; N, 10.96.

2-Methoxy-3-[5-[[4-(methysulfonyl)-1-piperazinyl]methyl]-1*H*-indol-2-yl]quinoline (2). To a solution of 5.22 g (10.5 mmol) of ketone **3** in 60 mL of THF was added 2.10 g of Raney Nickel 2800 (H_2O). The reaction slurry was then heated to 65 °C for 7.5 h under 40 psi H_2. The cooled reaction mixture was filtered over Celite and the solution concentrated under reduced pressure. The indole was crystallized by addition of MeOH to the concentrated solution to yield 4.23 g (90%) of a light yellow solid: mp 197−198 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.61 (m, 4H), 2.78 (s, 3H), 3.27 (m, 4H), 3.66 (s, 2H), 4.31 (s, 3H), 7.07 (s, 1H), 7.18 (dd, 1H, J = 1.4, 8.3 Hz), 7.44 (m, 2H), 7.57 (s, 1H), 7.64 (t, 1H, J = 8.4 Hz), 7.81 (d, 1H, J = 8.1 Hz), 7.88 (d, 1H, J = 8.4 Hz), 8.48 (s, 1H), 9.68 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.0, 46.0, 52.3, 54.1, 63.3, 101.5, 111.3, 116.8, 121.1, 124.2, 124.8, 125.5, 127.0, 127.6, 128.3, 129.0, 129.6, 134.0, 135.2, 136.0, 145.3, 158.3. Anal. Calcd for $C_{24}H_{26}N_4O_3S$: C, 63.98; H, 5.82; N, 12.44. Found: C, 64.28; H, 5.68; N, 12.05.

Preparation of 3-[5-[[4-(Methanesulfonyl)-1-piperazinyl]-methyl]-1*H*-indol-2-yl]quinolin-2(1*H*)one Hydrochloride (1). To a slurry of 174 mg (0.386 mmol) of **2** in 3 mL of MeOH was added 0.48 mL of concentrated HCl. The slurry was heated at reflux for 8 h and stirred overnight at rt. The resulting solid was filtered to provide 180 mg (98%) of **1** as a mono-HCl salt: yellow solid; mp 250 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.98 (s, 3H), 3.12 (m, 2H), 3.33 (t, 2H, J = 12.6 Hz), 3.39 (m, 2H), 3.70 (d, 2H, J = 12.6 Hz), 4.42 (m, 2H), 7.25 (m, 1H), 7.39 (m, 2H), 7.41 (d, 1H, J = 8.2 Hz), 7.52 (ddd, 1H, J = 1.2, 7.2, 8.2 Hz), 7.60 (d, 1H, J = 8.4 Hz), 7.73 (d, 1H, J = 7.7 Hz), 7.82 (s, 1H), 8.63 (s, 1H), 11.45 (br s, 1H), 11.86 (s, 1H), 12.21 (s, 1H); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 35.2, 42.2, 49.7, 53.4, 102.2, 112.0, 115.0, 119.3, 119.9, 122.1, 122.3, 123.7, 124.9, 127.8, 130.3, 134.6, 134.8, 136.8, 137.7, 160.5. Anal. Calcd. For $C_{23}H_{24}N_4O_3S\cdot$HCl: C, 58.40; H, 5.33; N, 11.85. Found: C, 58.38; H, 5.26; N, 11.71.

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

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