# Synthesis of 3-Alkyl-1*H*-quinolin-2-ones via Palladium-Catalyzed Intramolecular Cyclization of Benzyl Halides and α,β-Unsaturated Amides

Zhangqin Liu,[a,b] Changqing Shi,[a,b] Yuanwei Chen*[a]

[a] Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, P. R. of China
Fax +86(28)85232228; E-mail: chenyw@cioc.ac.cn

[b] Graduate School, Chinese Academy of Sciences, Beijing 100039, P. R. of China

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**Abstract:** An efficient synthesis of 3-alkyl-1*H*-quinolin-2-ones was achieved in high yield (up to 91%) via $Pd_2(dba)_3$-catalyzed intramolecular cyclization of benzyl halides and electron-deficient olefins, followed by treatment with DBU.

**Key words:** palladium, cyclization, benzyl halides, electron-deficient olefins, quinolinone

Since modern palladium chemistry started in 1960, palladium catalysts have received considerable attention because of their wide applications in carbon–carbon bond formations such as Heck reaction,[1] Sonogashira coupling,[2] and Suzuki coupling.[3] However, palladium-catalyzed coupling of benzyl halides and olefins have not been studied extensively. Negishi's group first reported the intramolecular cyclization of benzyl halides and unfunctionalized olefins to form five- to seven-membered rings.[4] Several other groups also reported the cyclization of benzyl halides and simple olefins or electron-rich olefins.[5] However, as far as we are aware of, there are no further studies on the cyclization of benzyl halides and electron-deficient olefins. Here, we report the first synthesis of 3-alkyl-1*H*-quinolin-2-ones via palladium-catalyzed intramolecular cyclization of benzyl halides and electron-deficient olefins. The 3-alkyl-1*H*-quinolin-2-one moiety is present in a number of biologically active compounds such as R207910 (Figure 1), which has been described to have significant activity against drug-sensitive and drug-resistant *Mycobacterium tuberculosis*[6] and elicit antitubercular activity.[7]

In search of the optimized reaction conditions, we began our initial study by examining the intramolecular cyclization of *N*-acetyl-*N*-[2-(bromomethyl)phenyl]acrylamide (**1a**,[8] Scheme 1). The reaction was initially performed in refluxing MeCN for 12 hours with $Pd(PPh_3)_4$ (5% mol) and 3 equivalents of $Et_3N$. Besides the expected 3-alkyl-1*H*-quinolin-2-one was obtained, another three cyclization products **3a–c** were also isolated. Compounds **3a** and **3c** are the acetylated products of **3b** and **2a**, respectively. By treatment of the reaction mixture with DBU, **3a–c** were successfully converted to 3-methyl-1*H*-quinolin-2-one (**2a**) as a single product in moderate yield (67%).[9]

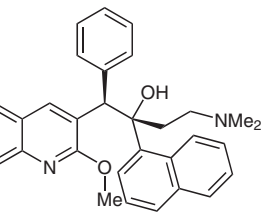
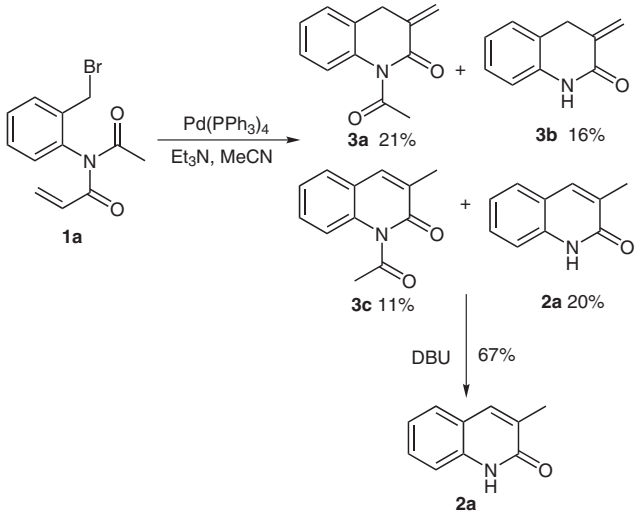



**Figure 1** Structure of R207910




**Scheme 1** Palladium-catalyzed cyclization of *N*-acetyl-*N*-[2-(bromo-methyl)phenyl]acrylamide (**1a**) to yield 3-methyl-1*H*-quinolin-2-one (**2a**)

Encouraged by the successful intramolecular cyclization of acrylamide **1a**, we further investigated a variety of ligands to promote the reaction (Table 1, entries 1–9). To our surprise, the combination of $Pd_2(dba)_3$ and dppf or $L_2$ dramatically increased the yield of **2a** to 91% and 90%, respectively (entries 3 and 9). Other ligands such as $L_1$, $L_3$,[10] dppm, dppe, dppb, and Xantphos (entries 2, 4–8) gave moderate yields after longer reaction time. Inorganic bases, such as $K_2CO_3$, $Na_2CO_3$, $Cs_2CO_3$, and organic bases such as DABCO and DBU were found to provide no products for this reaction (entries 10–14). In nonpolar solvents such as toluene (entry 15), no cyclization products could be isolated and the starting material **1a** was quantitatively recovered. In apolar solvents other than MeCN, poor or moderate yields were obtained (entries 16–19).

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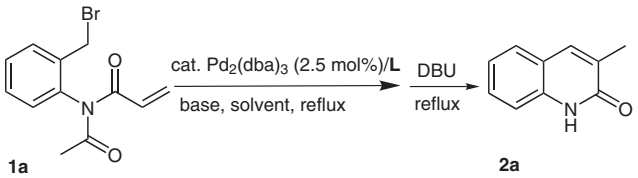
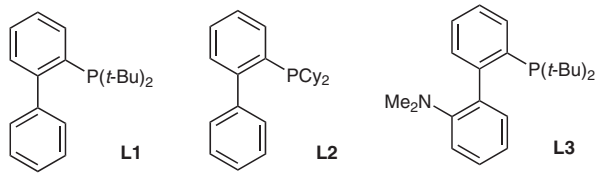
**Table 1** Optimization of the Pd-Catalyzed Cyclization Reaction[a]



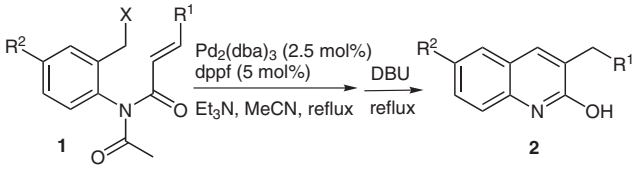

| Entry | Ligand | Base | Solvent | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1[c] | $(PPh_3)_4$ | $Et_3N$ | MeCN | 15 | 67 |
| 2 | $L_1$ | $Et_3N$ | MeCN | 30 | 66 |
| 3 | $L_2$ | $Et_3N$ | MeCN | 12 | 90 |
| 4 | $L_3$ | $Et_3N$ | MeCN | 30 | 43 |
| 5 | dppm | $Et_3N$ | MeCN | 30 | 52 |
| 6 | dppe | $Et_3N$ | MeCN | 18 | 71 |
| 7 | Xantphos | $Et_3N$ | MeCN | 30 | 36 |
| 8 | dppb | $Et_3N$ | MeCN | 18 | 73 |
| 9 | dppf | $Et_3N$ | MeCN | 8 | 91 |
| 10[d] | dppf | $K_2CO_3$ | MeCN | 3 | NR |
| 11[d] | dppf | $Na_2CO_3$ | MeCN | 3 | NR |
| 12[d] | dppf | $Cs_2CO_3$ | MeCN | 3 | NR |
| 13[e] | dppf | DABCO | MeCN | 3 | NR |
| 14[e] | dppf | DBU | MeCN | 3 | NR |
| 15 | dppf | $Et_3N$ | Toluene | 30 | Trace |
| 16 | dppf | $Et_3N$ | 1,4-Dioxane | 32 | Trace |
| 17 | dppf | $Et_3N$ | THF | 30 | 36 |
| 18 | dppf | $Et_3N$ | DMF | 12 | 51 |
| 19 | dppf | $Et_3N$ | DMSO | 15 | 49 |

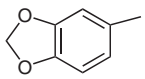
[a] Conditions: **1a** (1.0 equiv), $Et_3N$ (3 equiv), $Pd_2(dba)_3$ (2.5 mol%), diphosphine ligand (5 mol%) or monophosphine ligand (10 mol%), solvent (5 mL).
[b] Yield of isolated product.
[c] $Pd(PPh_3)_4$ instead of $Pd_2(dba)_3$ and ligand was used.
[d] Starting material was completely destroyed by the inorganic base.
[e] Starting material disappeared without cyclization products.

This novel palladium-catalyzed intramolecular cyclization can be applied to a wide range of acrylamide (Table 2). In addition to the benzyl bromides,[12] benzyl chloride could be employed to give the cyclization product **2a** in 67% yield (entry 3). But the cyclization reaction failed with benzyl acetate even when more catalysts were used (entry 2). A number of 3-aryl acrylamides were also examined.

The phenyl ring can be substituted at the 3- or 4-position, and the group can be electron-donating or electron-withdrawing (entries 4–8).[13] When heterocyclic acrylamide substrate was employed, the corresponding cyclization product was also obtained in 71% yield (entry 10). However, the cyclization did not happen with the 2-nitrophenyl acrylamide substrate (entry 9), probably due to steric hindrance. 3-Alkyl substitution on acrylamide (entry 11) could also give the desired cyclization product **2h**, though in a lower yield. Methyl substitution on benzene ring also cyclized smoothly to give the corresponding products in moderate yield (entries 12 and 13).

**Table 2** Synthesis of 2-Hydroxyquinolines




| Entry | X | $R^1$ | $R^2$ | Yield of **2** (%)[a] |
|---|---|---|---|---|
| 1 | Br | H | H | 91 (**2a**) |
| 2 | AcO | H | H | n.r. |
| 3 | Cl | H | H | 67 (**2a**) |
| 4 | Br | Ph | H | 73 (**2b**)[b] |
| 5 | Br | 3-$O_2NC_6H_4$ | H | 85 (**2c**) |
| 6 | Br | 4-$MeC_6H_4$ | H | 76 (**2d**)[b] |
| 7 | Br | 4-$MeOC_6H_4$ | H | 81 (**2e**) |
| 8 | Br | 4-$ClC_6H_4$ | H | 66 (**2f**)[b] |
| 9 | Br | 2-$O_2NC_6H_4$ | H | n.r. |
| 10 | Br |  | H | 71 (**2g**) |
| 11 | Br | Me | H | 36 (**2h**) |
| 12 | Br | H | Me | 61 (**2i**) |
| 13 | Br | Ph | Me | 65 (**2j**) |

[a] Yield of isolated product.
[b] See ref.[11] for structural confirmation.

In summary we have developed a novel practical approach to synthesize 3-alkyl-1*H*-quinolin-2-ones via the cyclization of benzyl halides with a,b-unsaturated amides promoted by $Pd_2(dba)_3$ and dppf as catalysts. Further studies to expand the scope of reaction are in progress.

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(8) **Typical Procedure for the Synthesis of *N*-Acetyl-*N*-[2-(bromomethyl)phenyl]acrylamide (1a)**
Acryloyl chloride (0.99 g, 11 mmol) was dropped slowly to the mixture of 2-[(trimethylsilyloxy)methyl]benzamine (1.95 g, 10 mmol) and 1 equiv $Et_3N$ in $CH_2Cl_2$ at 0 °C. After the reaction was complete, the solvent was removed, and the white solid was dissolved in MeOH, and then $K_2CO_3$ (2 equiv) was added. The reaction mixture was stirred for additional 2 h at r.t. and concentrated. The residue was dissolved in EtOAc and washed with $H_2O$. The organic extracts were dried ($Na_2SO_4$) and concentrated in vacuo. Flash chromatography (EtOAc–light PE = 20:80) of the residue gave *N*-[2-(hydroxymethyl)phenyl]acrylamide (1.45 g, 8.19 mmol) in 81.9% yield as a white solid. Then, $PBr_3$ (1 equiv) was dropped slowly to the solution of *N*-[2-(hydroxymethyl)phenyl]acrylamide in $CH_2Cl_2$ at 0 °C and stirred for 30 min. The reaction mixture was quenched with $H_2O$, and the aqueous layer was extracted with additional $CH_2Cl_2$, and the combined organic extracts were dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on $SiO_2$ by using 10% EtOAc–light PE as eluent to give *N*-[2-(bromomethyl)phenyl]acrylamide in 73% yield as a white solid. Then acetyl chloride (3 equiv) was added to *N*-[2-(bromomethyl)phenyl]acrylamide (5 mmol, 1.195 g) and $CaH_2$ (3 equiv), and stirred in dry THF for 24 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on $SiO_2$ by using 8% EtOAc–light PE as eluent to give acrylamide *N*-acetyl-*N*-[2-(bromomethyl)phenyl]acrylamide in 90% yield as a white solid.

(9) Acetyl protection of acrylamide **1a** is necessary to increase its activity.

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(12) **Typical Procedure for the Cyclization of *N*-Acetyl-*N*-[2-(bromomethyl)phenyl]acrylamide**
Under the nitrogen atmosphere, the mixture of acrylamide derivative *N*-acetyl-*N*-[2-(bromomethyl)phenyl]acrylamide (1 mmol, 0.281 mg), $Pd_2(dba)_3$ (2.5 mol%), dppf (5 mol%), and $Et_3N$ (3.0 equiv) was stirred in 5 mL refluxing MeCN for 5 h. Then, DBU (1 equiv) was added and the reaction mixture was refluxed for an additional 3 h. Solvent was removed and the residue was purified by flash chromatography on $SiO_2$ by using 20% EtOAc–light PE as eluent to give **2a** in 91% yield as a white solid.

(13) **Analytical Data of 3-(3-Nitrobenzyl)quinolin-2(1*H*)-one (2c)**
$R_f$ = 0.25 (25% EtOAc–light PE); mp 206–209 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ = 12.27 (s, 1 H, NH), 8.29 (s, 1 H, ArH), 8.10–8.07 (d, 1 H, ArH), 7.73–7.70 (d, 1 H, ArH), 7.63 (s, 1 H, ArH), 7.52–7.44 (m, 3 H, ArH), 7.32–7.19 (m, 2 H, ArH), 4.10 (s, 2 H, $CH_2$). $^{13}$C NMR (300 MHz, $CDCl_3$): δ = 163.8, 148.3, 141.5, 138.2, 137.8, 135.4, 131.6, 130.2, 129.3, 127.4, 124.2, 122.8, 121.6, 119.9, 115.7, 36.4. ESI-MS: *m/z* calcd for $C_{16}H_{12}N_2O_3$: 280.0848; found: 281.0921 [M + H].