ORGANIC LETTERS

2008
Vol. 10, No. 2
173−175

# A Facile Synthesis of 2-Methylquinolines via Pd-Catalyzed Aza-Wacker Oxidative Cyclization

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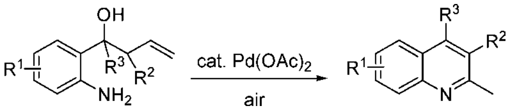
**Received September 19, 2007**

## ABSTRACT



**A novel Pd-catalyzed Wacker-type oxidative cyclization under air is described. By using this cyclization, a series of 2-methylquinolines are readily prepared with good yields under mild conditions.**

Quinoline derivatives exist in many natural products,[1] and most of them exhibit various biological activities.[2,3] Many methods have been developed for the construction of quinolines due to their great importance.[2] Among various synthetic routines, transition metal-catalyzed processes are highly attractive.[4] Metal-free paths to quinolines have also been reported recently.[5] Despite this progress, the development of novel approaches to quinoline derivatives is still desired because of their extreme significance.

Palladium-catalyzed processes play a vital role in the synthesis of heterocycles.[6] Recently, we reported a palladium-catalyzed intramolecular oxypalladation of phenol derivatives to synthesize 2-methylchromanones.[7] In light of the success of this Wacker-type oxidative cyclization, we turned our attention to a more challenging aza-Wacker oxidative cyclization.[8−9] Compared to the previous report,[7] the unusual 1,5-hydride alkyl to palladium migration is not observed in this aza-Wacker reaction, but a dehydration process is

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[1] For representative reviews, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223−246. (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627−646. (c) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650−668.

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[3] For recent reports, see: (a) Höglund, I. P. J.; Silver, S.; Engström, M. T.; Salo, H.; Tauber, A.; Kyyrönen, H.-K.; Saarenketo, P.; Hoffrén, A.-M.; Kokko, K.; Pohjanoksa, K.; Sallinen, J.; Savola, J.-M.; Wurster, S.; Kallatsa, O. A. *J. Med. Chem.* **2006**, *49*, 6351−6363. (b) Kaila, N.; Janz, K.; DeBernardo, S.; Bedard, P. W.; Camphausen, R. T.; Tam, S.; Tsao, D. H. H.; Keith, J. C., Jr.; Nickerson-Nutter, C.; Shilling, A.; Young-Sciame, R.; Wang. Q. *J. Med. Chem.* **2007**, *50*, 21−39. (c) Klingenstein, R.; Melnyk, P.; Leliveld, S. R.; Ryckebusch, A.; Korth. C. *J. Med. Chem.* **2006**, *49*, 5300−5308.

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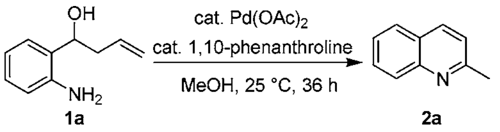
[6] See, for recent reviews: (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644−4680. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285−2310. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127−2198. (d) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362−367. (e) Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625−655.

10.1021/ol702153x CCC: $40.75

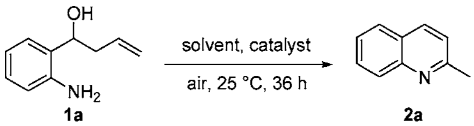
involved and generates a quinoline derivative. In this study, we disclose a novel route to the synthesis of quinoline derivatives **2** by the aza-Wacker cyclization of aniline derivatives **1** catalyzed by palladium(II) under air (Scheme 1).[10] This discovery not only represents a new method for the building of a quinoline skelecton but also extends the scope of the aza-Wacker reaction.

**Scheme 1.** Aza-Wacker Oxidative Amination of **1a**



At the beginning of the research, **1a** was used to optimize the reaction in various solvents and with different catalysts (Table 1). When different solvents were tested in the presence of air at room temperature with $Pd(OAc)_2$ as catalyst (entries 1−12), MeOH gave the best result with 68% yield (entry 3) and EtOH afforded a similar result with 65% yield (entry 4), while other solvents furnished the desired product with less than 50% yields. Also, other palladium sources, including $PdCl_2$, $PdCl_2(CH_3CN)_2$, and $PdCl_2(PhCN)_2$, were examined (entries 13−15). The results indicated that $Pd(OAc)_2$ was the best among these tested catalysts.

**Table 1.** Screen for Different Solvents and Catalysts[a]

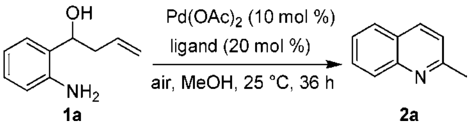


| entry | solvent | catalyst (10 mol %) | yield[b] (%) |
|---|---|---|---|
| 1 | Tol | $Pd(OAc)_2$ | 30 |
| 2 | THF | $Pd(OAc)_2$ | 34 |
| 3 | MeOH | $Pd(OAc)_2$ | 68 |
| 4 | EtOH | $Pd(OAc)_2$ | 65 |
| 5 | *i*-PrOH | $Pd(OAc)_2$ | 34 |
| 6 | DMF | $Pd(OAc)_2$ | 32 |
| 7 | $CH_2Cl_2$ | $Pd(OAc)_2$ | 42 |
| 8 | $CHCl_3$ | $Pd(OAc)_2$ | 46 |
| 9 | $CCl_4$ | $Pd(OAc)_2$ | 28 |
| 10 | $CH_3CN$ | $Pd(OAc)_2$ | 40 |
| 11 | 1,4-dioxane | $Pd(OAc)_2$ | trace |
| 12 | acetone | $Pd(OAc)_2$ | 37 |
| 13 | MeOH | $PdCl_2$ | trace |
| 14 | MeOH | $PdCl_2(CH_3CN)_2$ | 52 |
| 15 | MeOH | $PdCl_2(PhCN)_2$ | 50 |

[a] Reaction conditions: 0.2 M of **1a** in solvent. [b] Isolated yield.

Subsequently, the effect of ligands was further investigated under the above-optimized solvent and catalyst since some reports indicated that ligands played an important role in the palladium-catalyzed Wacker reaction.[11] All the results are listed in Table 2. We were delighted to find that 1,10-phenanthroline was the most effective ligand for the aza-Wacker reaction. In the presence of 1,10-phenanthroline the cyclization of **1a** afforded **2a** with 87% yield under the same conditions (entry 1). In comparison with the aza-Wacker reaction without this ligand, the reaction yield was enhanced by 19%. Both pyridine and 2,2′-bipyridine had little influence on the cyclization (entries 2 and 4) while other ligands retarded the reaction to different degrees.

**Table 2.** The Effect of Various Ligands on the Aza-Wacker Reaction[a]



| entry | ligand | yield[b] (%) |
|---|---|---|
| 1 | 1,10-phenanthroline | 87 |
| 2 | pyridine | 67 |
| 3 | *N*,*N*-dimethylpyridin-4-amine | 42 |
| 4 | 2,2′-bipyridine | 65 |
| 5 | ethane-1,2-diamine | trace |
| 6 | benzene-1,2-diamine | trace |
| 7 | *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine | 50 |
| 8 | 1*H*-imidazole | trace |
| 9 | triphenylphosphine | trace |

[a] Reaction conditions: 0.2 M of **1a** in methanol. [b] Isolated yield.

Finally, the reaction conditions were optimized. The solvent methanol, the catalyst palladium acetate, and the ligand 1,10-phenanthroline were chosen to promote this reaction. Under these optimized conditions, the reaction was examined with different substrates, and it was found that the corresponding quinolines were obtained with moderate to good yields (Table 3). An electron-withdrawing group on the aryl ring favored this reaction while an electron-donating group disfavored this reaction a little (entries 1−3). Generally, the substituents on the aryl ring had a little influence on this cyclization. Even **1d**, which contains a hydroxy and is sensitive to palladium catalysts, gave 8-hydroxyquinoline **2d**

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(7) Zhang, Z. H.; Pan, C. F.; Wang, Z. Y. *Chem. Commun.* **2007**, 4686−4688.

(8) For intramolecular aza-Wacker reaction, see: (a) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142−1152. (b) Liu, G. S.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328−6335. (c) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910−1923. (d) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584−3585. (e) Hegedus, L. S.; Allen, G. F.; Waterman, E. L. *J. Am. Chem. Soc.* **1976**, *98*, 2674−2676.

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(10) For recent reviews on the catalytic Pd(II) oxidations under air or $O_2$, see: (a) Stahl, S. S. *Science* **2005**, *309*, 1824−1826. (b) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420. (c) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221−229.

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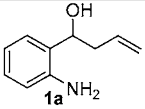
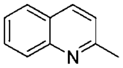
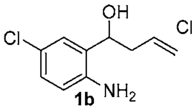
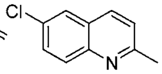
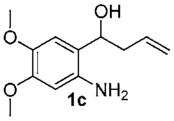
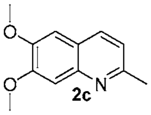
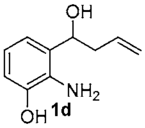
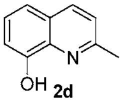
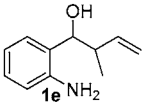
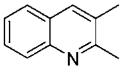
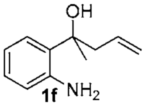
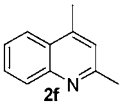
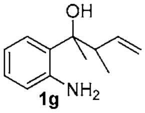
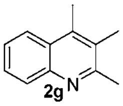
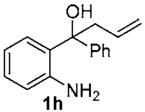
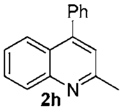
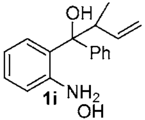
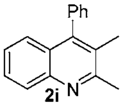
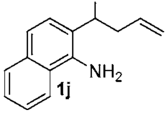
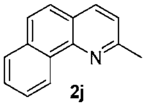
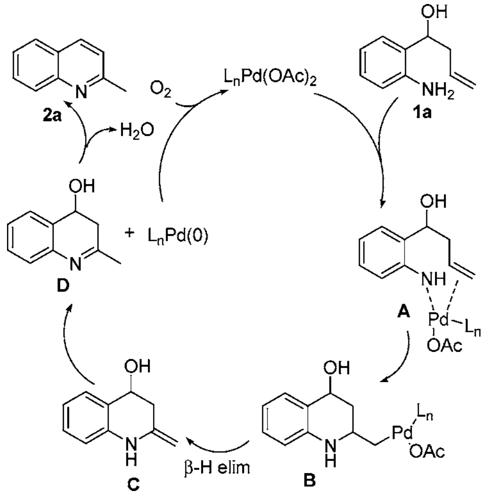
**Table 3.** Synthesis of 2-Methylquinolines by Aza-Wacker Oxidative Cyclization[a]

| entry | substrate | product | temp. (°C) | yield[b] (%) |
|---|---|---|---|---|
| 1 |  **1a** |  **2a** | 25 | 87 |
| 2 |  **1b** |  **2b** | 25 | 90 |
| 3 |  **1c** |  **2c** | 25 | 76 |
| 4 |  **1d** |  **2d** | 40 | 53 |
| 5 |  **1e** |  **2e** | 25 | 86 |
| 6 |  **1f** |  **2f** | 25 | 84 |
| 7 |  **1g** |  **2g** | 25 | 83 |
| 8 |  **1h** |  **2h** | 40 | 78 |
| 9 |  **1i** |  **2i** | 40 | 75 |
| 10 |  **1j** |  **2j** | 40 | 60 |

[a] Reaction conditions: **1** (1 mmol), Pd(OAc)$_2$ (0.1 mmol), and 1,10-phenanthroline (0.2 mmol %) under air in 5 mL of methanol at corresponding temperatures for 36 h. [b] Isoalted yield.

with moderate yield (entry 4), and the hydroxy group survived this reaction. Moreover, different substituted quinolines **2e**−**i** were obtained from the corresponding starting materials **1e**−**i** with good yields (entries 5−9). Besides, when the phenyl ring was replaced with a naphthyl ring, as shown in entry 10, the corresponding product **2j** could also be obtained in good yield.

**Scheme 2.** Proposed Mechanism for the Pd-Catalyzed Aza-Wacker Reaction To Form 2-Methylquinoline



A plausible mechanism for this novel transformation is proposed as outlined in Scheme 2. Initial coordination of palladium with the alkene and the nitrogen produce **A**. Aminopalladation then takes place to yield intermediate **B**.[12] Intermediate **B** then undergoes $\beta$-hydride elimination to generate **C**. Afterward, a $\beta$-hydride elimination/hydropalladation sequence of **C** leads to **D**, which gives the product **2a** after dehydration. The Pd(0) complex is reoxidized to a Pd(II) species by air, thus completing the catalytic cycle.

In conclusion, we have developed a novel aza-Wacker reaction catalyzed by palladium under mild conditions. By virtue of this new method, a variety of 2-methylquinoline derivatives were prepared with good yields. The starting materials for these aza-Wacker reactions can be readily obtained via aqueous allylation reactions. Therefore we provided a concise method for the preparation of quinoline derivatives. Further work is in progress to extend the scope of the reaction in our group.

**Acknowledgment.** The authors are grateful to the Natural Science Foundation of China (20472078 and 30572234) and for support from the Chinese Academy of Sciences

**Supporting Information Available:** Typical procedure for the reaction, preparation of starting materials, and characterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] Recent studies of aminopalladium suggest that these steps often proceed with cis-stereochemistry. See ref 8b.