Ruthenium-Catalyzed Consecutive Reduction and Cyclization of Nitroarenes with Tetraalkylammonium Bromides Leading to Quinolines

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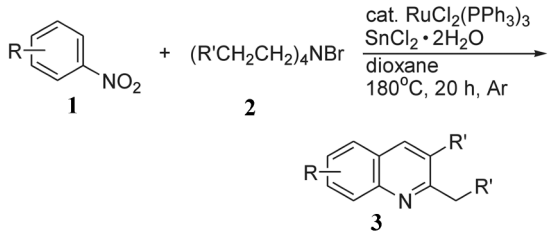
It is known that several quinoline containing compounds exhibit pharmacological activity for malaria. The quinoline skeleton is generally constructed by conventional named routes such as Skraup, Döbner-von Miller, Conrad-Limpach, Friedlaender and Pfitzinger syntheses.[1] However, homogeneous transition metal-catalyzed versions have been introduced recently for the synthesis of quinolines because of facility and efficiency of reaction and wide availability of substrate.[2] In our studies of ruthenium-catalyzed organic syntheses,[3-13] we have also developed on the ruthenium-catalyzed synthesis of quinolines by an alkyl group transfer from alkylamines to the nitrogen atom of anilines (amine exchange reaction or amine scrambling reaction[14])[5-8] and an oxidative cyclization of 2-aminobenzyl alcohol with ketones (modified Friedlaender synthesis).[9] Prompted by the amine exchange reaction, we have directed our attention to the use of nitroarenes instead of anilines for the synthesis of *N*-heterocycles under our precedented ruthenium catalyst systems since nitroarenes are precursors of anilines from the viewpoint of industrial organic chemistry.[15,16] Herein we report a ruthenium-catalyzed reductive *N*-heteroannulation of nitroarenes with tetraalkylammonium bromides leading to quinolines *via* an amine exchange reaction.

Treatment of nitrobenzene (**1a**) with tetrabutylammonium bromide (**2a**) in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ (3 mol% based on **2a**) along with $SnCl_2 \cdot 2H_2O$ in dioxane at 180 ºC for 20 h afforded the reductive cyclization product, 3-ethyl-2-propylquinoline (**3a**) in 67% GLC yield (based on **2a**) with concomitant formation of aniline and *N*-butylaniline (12% based on **2a**). The addition of $SnCl_2 \cdot 2H_2O$ was necessary for the effective formation of **3a** and complete conversion of **1a** (Eq. 1 and Table 1). Performing the reaction in the absence of $SnCl_2 \cdot 2H_2O$ resulted in incomplete conversion of **1a** (51%) and lower yield of **3a** (24%). It is well-known that nitroarenes can be easily converted into anilines in the presence of $SnCl_2 \cdot 2H_2O$ under nonacidic and nonaqueous media.[17] However, as has been observed in our recent report on the ruthenium-catalyzed synthesis of indoles and quinolines from anilines and alkylamines, another feature of $SnCl_2 \cdot 2H_2O$ seems to play a decisive role in either alkyl group transfer or heteroannulation step.[3-8] Interestingly, although **3a** was produced in only 24% yield, much more *N*-butylaniline (54% based on **2a**) was formed under the employment of an aqueous solvent system (dioxane/H_2O = 9 mL/1 mL) in place of dioxane.



1 **2** **3** (1)

The several attempted reductive *N*-heteroannulations of nitroarenes **1** with tetraalkylammonium bromides **2** leading to quinolines **3** are listed in Table 1. The quinoline yield was considerably affected by the position of the substituent on nitroarene. With *meta*- and *para*-substituted nitroarenes (**1b** and **1c**), the quinoline yield was higher than that with *ortho*-substituted nitroarene **1d**. In the case of 3-nitrotoluene (**1c**), the corresponding quinolines **3c** were obtained as a regioisomeric mixture, favoring 7-methyl isomer which was formed *via* less sterically hindered position on **1c**. Nitroarenes **1** also reacted with an array of tetraalkylammonium bromides (**2b**-**2d**) and the corresponding quinolines were obtained in the range of 40-61% yields irrespective of the alkyl chain length on **2b**-**2d**.

As the reaction pathway based on our recent reports[3-8,15] and others,[18] this seems to proceed *via* a sequence involving initial reduction of nitroarenes to anilines and formation of tertiary amines by cleavage of C-N bond of **2**,[19] alkyl group transfer from alkylamines to anilines to form an imine, dimerization of imine, and *N*-heteroannulation.

In summary, we have demonstrated that nitroarenes can be reductively cyclized with tetraalkylammonium bromides in the presence of a ruthenium catalyst and $SnCl_2 \cdot 2H_2O$ to afford quinolines in moderate to good yields. The present reaction is a novel synthetic approach for the formation of quinolines *via* consecutive reduction and cyclization of nitroarenes with tetraalkylammonium bromides.

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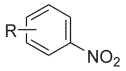
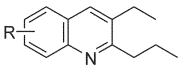
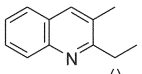
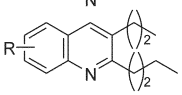
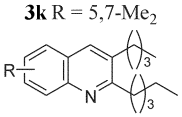
Table 1. Ruthenium-catalyzed synthesis of quinolines **3** from nitroarenes **1** and tetraalkylammonium bromides **2**[a]

1	2	3	Yield (%)[b]
			
1a R = H	**2a** Bu_4NBr	**3a** R = H	44
1b R = 4-Me	**2a** Bu_4NBr	**3b** R = 6-Me	46
1c R = 3-Me	**2a** Bu_4NBr	**3c** R = 7- and 5-Me	47[c]
1d R = 2-Me	**2a** Bu_4NBr	**3d** R = 8-Me	20
1e R = 4-OMe	**2a** Bu_4NBr	**3e** R = 6-OMe	32
1f R = 3,5-Me_2	**2a** Bu_4NBr	**3f** R = 5,7-Me_2	50
1g R = 4-acetyl	**2a** Bu_4NBr	**3g** R = 6-acetyl	33
1a	**2b** Pr_4NBr	 **3h**	40
			
1a	**2c** $[CH_3(CH_2)_4]_4NBr$	**3i** R = H	46
1b	**2c**	**3j** R = 6-Me	49
1f	**2c**	**3k** R = 5,7-Me_2	61
			
1b	**2d** $[CH_3(CH_2)_5]_4NBr$	**3l** R = 6-Me	46
1f	**2d**	**3m** R = 5,7-Me_2	61

[a]Reaction conditions: **1** (2 mmol), **2** (1 mmol), $RuCl_2(PPh_3)_3$ (0.03 mmol), $SnCl_2 \cdot 2H_2O$ (1 mmol), dioxane (10 mL), 180 °C, for 20 h, under argon. [b]Isolated yield based on **2**. In all cases, the corresponding anilines and *N*-alkylanilines were also produced on GLC analysis. [c]Regioisomeric distribution was calculated by ^1H NMR (500 MHz): 5-methyl/7-methyl = 1/6.

References

1. Jones, G. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 2, p 395.
2. For the formation of quinolines catalyzed by transition metals: Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett*. **2001**, *3*, 1109 and references cited therein.
3. Cho, C. S.; Lim, H. K.; Shim, S. C.; Kim, T. J.; Choi, H.-J. *Chem. Commun*. **1998**, 995.
4. (a) Cho, C. S.; Kim, J. H.; Shim, S. C. *Tetrahedron Lett.* **2000**, *41*, 1811. (b) Cho, C. S.; Kim, J. H.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2001**, *57*, 3321.
5. (a) Cho, C. S.; Oh, B. H.; Shim, S. C. *Tetrahedron Lett*. **1999**, *40*, 1499. (b) Cho, C. S.; Oh, B. H.; Shim, S. C.; Oh, D. H. *J. Heterocyclic Chem.* **2000**, *37*, 1315.
6. Cho, C. S.; Oh, B. H.; Shim, S. C. *J. Heterocyclic Chem*. **1999**, *36*, 1175.
7. Cho, C. S.; Kim, J. S.; Oh, B. H.; Kim, T.-J.; Shim, S. C.; Yoon, N. S. *Tetrahedron* **2000**, *56*, 7747.
8. Cho, C. S.; Oh, B. H.; Kim, J. S.; Kim, T.-J.; Shim, S. C. *Chem. Commun*. **2000**, 1885.
9. Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *Chem. Commun*. **2001**, 2576.
10. Cho, C. S.; Kim, B. T.; Lee, M. J.; Kim, T.-J.; Shim, S. C. *Angew. Chem. Int. Ed*. **2001**, *40*, 958.
11. Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Org. Chem*. **2001**, *66*, 9020.
12. Cho, C. S.; Kim, J. S.; Kim, H. S.; Kim, T.-J.; Shim, S. C. *Synth. Commun*. **2001**, *32*, 3791.
13. Cho, C. S.; Park, J. H.; Kim, T.-J.; Shim, S. C. *Bull. Korean Chem. Soc*. **2002**, *23*, 23.
14. For recent review on transition metal-catalyzed amine exchange reaction, see: Murahashi, S.-I. *Angew. Chem. Int. Ed.* **1995**, *34*, 2443.
15. As examples for the direct application of nitroarenes to amine exchange reaction leading to indoles and quinolines: (a) Cho, C. S.; Kim, T. K.; Yoon, S. W.; Kim, T.-J.; Shim, S. C. *Bull. Korean Chem. Soc*. **2001**, *22*, 545. (b) Cho, C. S.; Kim, T. K.; Kim, T.-J.; Shim, S. C.; Yoon, N. S. *J. Heterocyclic Chem*. in press. (c) Cho, C. S.; Kim, T. K.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Organomet. Chem*. in press.
16. For transition metal-catalyzed reductive N-heterocyclization of nitroarenes: (a) Akazome, M.; Kondo, T.; Watanabe, Y. *J. Chem. Soc., Chem. Commun*. **1991**, 1466. (b) Akazome, M.; Kondo, T.; Watanabe, Y. *Chem. Lett*. **1992**, 1275. (c) Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem*. **1993**, *58*, 310. (d) Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem*. **1994**, *59*, 3375.
17. Bellamy, F. D.; Ou, K. *Tetrahedron Lett*. **1984**, *25*, 839 and refernces cited therein.
18. Watanabe, Y.; Tsuji, Y.; Ohsugi, Y.; Shida, J. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2452.
19. White, E. L.; Woodcock, D. J. *The Chemistry of the Amino Group*; Patai, S. Ed.; Interscience: London, 1968; pp 407-497, Chapter 8.