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An efficient oxidation of 2-aryl-1,2,3,4-tetrahydro-4-quinolones employing ferric chloride hexahydrate–methanol: synthesis of naturally occurring 4-alkoxy-2-arylquinolines

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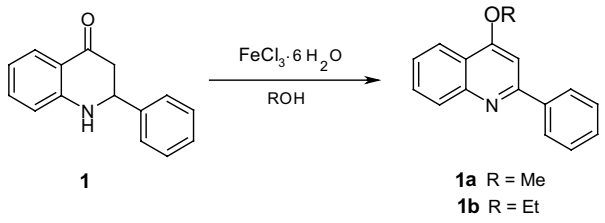
Abstract—A simple, inexpensive and efficient oxidation of 2-aryl-1,2,3,4-tetrahydro-4-quinolones has been carried out by employing $FeCl_3{\cdot}6H_2O$–methanol under mild conditions. This method has been investigated for the synthesis of an endothelin receptor antagonist, benzofuro[3,2-*b*]pyridine core structure.

Quinolines are widely distributed in the plant family *Rutaceae*. The alkaloid **1a** has been isolated as a natural product from *Lunarira amara*.[1,2] The synthesis of 4-alkoxy-2-aryl-quinoline derivatives continues to attract attention due to their biological activities.[1,3] Only a few methods for the synthesis of 4-alkoxy-2-aryl-quinolines are available in literature and most involve multiple steps[2,4] or corrosive and toxic reagents.[5–7]

In continuation of our studies on the synthesis of heterocyclic compounds with medicinal potential from 2-aminochalcones[8] in this letter we wish to describe an efficient oxidative aromatization of 2-aryl-1,2,3,4-tetrahydroquinolones to 4-alkoxy-2-arylquinolines (Scheme 1) employing $FeCl_3{\cdot}6H_2O$–methanol under mild conditions. This method has been investigated for the synthesis of endothelin receptor antagonists, benzofuro[3,2-*b*]-pyridines[9] (Scheme 2).

Recently $FeCl_3{\cdot}6H_2O$ has been increasingly utilized in a wide variety of organic reactions such as the oxidation of benzoin[10] and Hantzsch 1,4-dihydropyridine[11] synthesis and as a catalyst for Biginelli[12] condensations and Michael[13] and esterification[14] reactions. The treatment of 2-phenyl-1,2,3,4-tetrahydroquinolone with 2.5 equiv of $FeCl_3{\cdot}6H_2O$ in methanol afforded exclusively 2-phenyl-4-methoxyquinoline.[15] In an analogous reaction, treatment with $FeCl_3{\cdot}6H_2O$ in ethanol resulted in the formation of 2-phenyl-4-ethoxyquinoline.



1

1a R = Me
1b R = Et

Scheme 1.

A screening study carried out to assess the efficacy of different oxidizing agents revealed that manganese(III) acetate and CAN in methanol at room temperature led to the formation of 2-phenyl-4-hydroxyquinolines in low yields. Copper(II) acetate–manganese(III) acetate, copper(II) acetate–$K_2S_2O_8$ and NBS in methanol did lead to the formation of 2-phenyl-4-methoxyquinoline in moderate yields, whereas $Co(NO_3)_2$–$K_2S_2O_8$ and $NH_2CONH_2{\cdot}HNO_3$ failed to oxidize the substrates to 2-phenyl-4-methoxyquinoline. The results are summarized in Table 1.

Among the oxidizing agents screened in this work $FeCl_3{\cdot}6H_2O$ in methanol was found to be a mild, inexpensive and efficient oxidizing agent. The generality of

Keywords: Oxidation; $FeCl_3{\cdot}6H_2O$–methanol; 2-Aryl-1,1,2,3,4-tetrahydroquinolones and benzofurodihydropyridinones.
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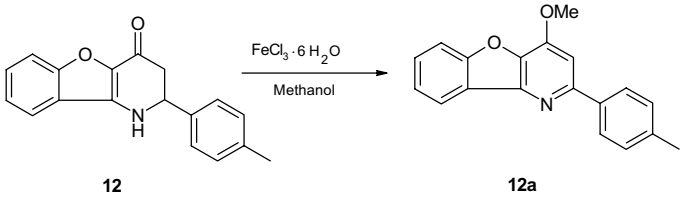


12 12a

Scheme 2.

Table 1. Effect of different oxidizing agents on the oxidation of 2-phenyl-1,2,3,4-tetrahydroquinolone **1**

Entry	Oxidizing agent	Equiv	Reaction time	Yield (%)
1	$Mn(OAc)_3$[a]	2.5	30 min	10
2	CAN[a]	2.5	10 min	20
3	$Mn(OAc)_3$–$Cu(OAc)_2$	2:1	6.0 h	65
4	$Cu(OAc)_2$–$K_2S_2O_8$	1:1	8.0 h	70
5	$FeCl_3·6H_2O$	2.5	2.5 h	78
6	NBS	1.0	8.0 h	65
7	$NH_2CONH_2·HNO_3$	3.0	10 h	—
8	$Co(NO_3)_2$–$K_2S_2O_8$	1:1	10 h	—

[a] 4-Hydroxy-2-phenylquinoline was obtained at room temperature.

the new transformation was checked by treating a wide range of substituted and structurally diverse tetrahydroquinolones and benzofurodihydropyridinones (Table 2, entries 11 and 12) with $FeCl_3·6H_2O$ in methanol under similar conditions. The products were obtained in high yields. 4-Alkoxy-2-phenylquinolines and benzofuro[3,2-*b*]pyridines[16] (Scheme 2) were synthesized and the results are summarized in Table 2.

In conclusion, this procedure promoted by $FeCl_3·6H_2O$–methanol provides a simple, inexpensive, safe and efficient synthesis of an important class of naturally

Table 2. $FeCl_3·6H_2O$–methanol mediated oxidation of 2-aryl-1,2,3,4-tetrahydro-4-quinolones and benzofurodihydropyridinones

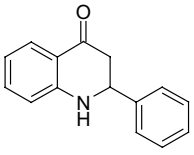
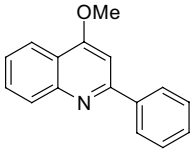
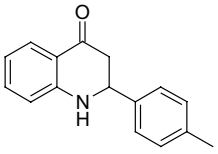
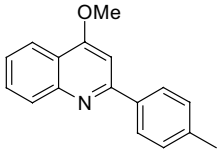
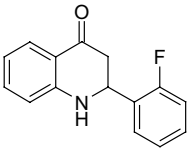
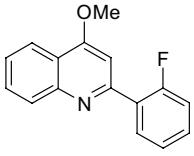
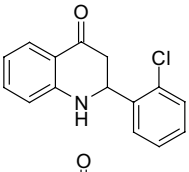
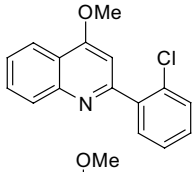
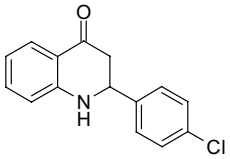
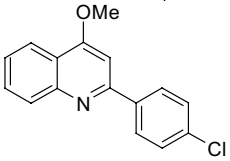
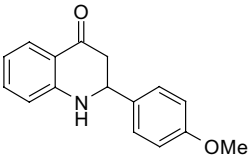
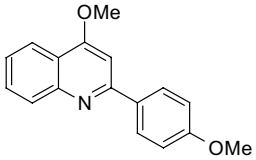
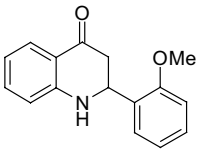
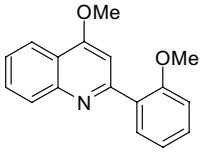
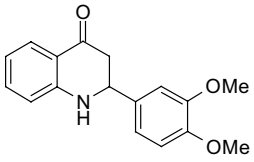
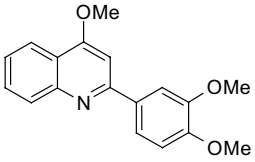
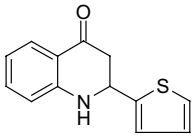
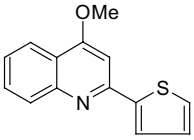
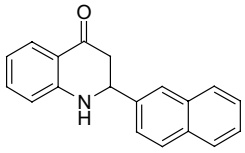
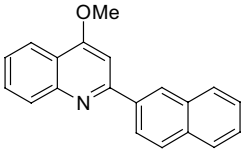
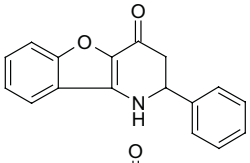
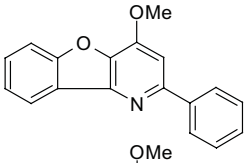
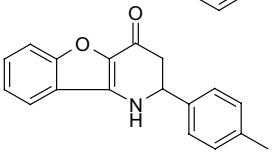
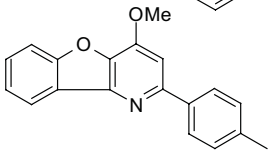
Entry	Substrate	Product[a]	Time (h)	Yield (%)[b]
1			2.5	78
2			2.5	85
3			3	84
4			3	82
5			3	75
6			3	85

Table 2 (*continued*)

Entry	Substrate	Product	Time (h)	Yield (%)
7			3	82
8			3	87
9			3	82
10			4	70
11			8	77
12			8	75

[a]All products were characterized by IR, ^{1}H NMR and mass spectra.
[b]Yield of isolated products.

occurring alkaloids, alkoxylated 2-phenylquinolines and biologically important benzofuro[3,2-*b*]pyridines.

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References and notes

1. Goodwin, S.; Smith, A. F.; Valsquez, A. A.; Horning, E. C. *J. Am. Chem. Soc.* **1959**, *81*, 6209.
2. Goodwin, S.; Smith, A. F.; Horning, E. C. *J. Am. Chem. Soc.* **1957**, *79*, 2239.
3. Fournet, A.; Vagneur, B.; Rilchomme, P.; Bruneton, J. *Can. J. Chem.* **1989**, *67*, 2116.
4. Elderfield, E. C.; White, J. B. *J. Am. Chem. Soc.* **1946**, *68*, 1276.
5. Singh, O. V.; Kapil, R. S. *Synlett* **1992**, 751.
6. Verma, R. S.; Kumar, D. *Tetrahedron Lett.* **1998**, *39*, 9113.
7. Mphahlele, M. J.; Mogamisi, F. K.; Tsanwani, M.; Hlatshwayo, M. S.; Mampa, M. R. *J. Chem. Res. (S)* **1999**, 706.
8. (a) Hemanth Kumar, K.; Muralidharan, D.; Perumal, P. T. *Synthesis* **2004**, 63; (b) Hemanth Kumar, K.; Selvi, S.; Perumal, P. T. *J. Chem. Res. (S)* **2004**, 218.
9. Mederski, W. W. K. R.; Oswald, M.; Dorsch, D.; Christadler, M.; Schmitges, C.-J.; Wilm, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 619.
10. Shanxi, Y. *Huaxue Shiji* **1992**, *14*, 369; *Chem. Abstr.* **1993**, *118*, 254484.
11. Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Li, W. *Synth. Commun.* **2001**, *31*, 2625.
12. Lu, J.; Ma, H. *Synlett* **2000**, 63.
13. Christoffers, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3141.
14. Jiang, Y. F.; Yu, S. X.; Zhang, L. X. *Hecheng Huaxue* **1998**, *6*, 100; *Chem. Abstr.* **1998**, *129*, 27801.
15. General procedure: Synthesis of 4-methoxy-2-phenylquinoline **1a**. The preparation of **1a** is representative of the general procedure employed. To a solution of **1**, 0.223 g (1 mmol) in 15 mL methanol $FeCl_3{\cdot}6H_2O$, 0.67 g (2.5 mmol) was added and the mixture refluxed on a water bath for 2.5 h until the completion of the reaction as followed by TLC examination The mixture was allowed to cool. Water (50 mL) was added to the reaction mixture

and the product was extracted into ethyl acetate (4×20 mL) and the extract was dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave the crude product, which was further purified by column chromatography on silica gel ethyl acetate–hexane (1:9) as eluent to afford pure product 0.183 g (78%), mp 66–67 °C (lit. 67–68 °C).[6]

16. Spectral data for compound **12a** (Table 2, entry 12) mp 135–137 °C. ^{1}H NMR ($CDCl_3$): 2.42 (3H, s, CH_3), 4.15 (3H, s, OCH_3), 7.27 (1H, s, H_3), 7.29 (2H, d, $J = 8.0$ Hz H'_3, H'_5), 7.42 (1H, t, $J = 7.45$ Hz, H_7), 7.52 (1H, t, $J = 7.45$ Hz, H_8), 7.60 (1H, d, $J = 8.6$ Hz, H_9), 7.95 (2H, d, $J = 8.0$ Hz, H'_2, H'_6) 8.27 (1H, d, $J = 7.4$ Hz, H_6); ^{13}C NMR ($CDCl_3$): 21.37, 56.42, 102.7, 112.33, 121.52, 123.53, 123.99, 127.26, 128.85, 129.55, 137.30, 138.60, 138.75, 145.18, 151.50, 156.14, 157.40; MS *m/z* 289 (M^+, 100). Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found C, 78.64; H, 5.29; N, 4.81.