Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 22 (2011) 253–255
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Synthesis of mono-substituted derivatives of 6-aminoquinoline

Tian Lan [a,b], Xian Xia Yuan [a,*], Jiang Hong Yu [a,c], Chao Jia [a], Yu Shi Wang [a], Hui Juan Zhang [a], Zi Feng Ma [a], Wei Dong Ye [c]

[a] School of Chemistry and Chemical Engineering, Shanghai Jiaotong University, Shanghai 200240, China
[b] School of Pharmacy, Shanghai Jiaotong University, Shanghai 200240, China
[c] Xinchang Pharmaceutical Factory, Zhejiang Pharmaceutics Co. Ltd., Xinchang 312500, China

Received 17 June 2010
Available online 22 December 2010

Abstract

Several 6-aminoquinoline derivatives, which could be used in drug design, have been synthesized. The reaction conditions were comparatively studied, and the *p*-chloroaniline was used as optimum oxidant in Skraup–Doebner–Von Miller reaction. The nitro group was reduced effectively by $SnCl_2$ with no halo-removed occurred.

Keywords: 6-Aminoquinoline; 6-Nitroquinoline; Skraup reaction; Oxidant

Aminoquinoline derivatives are useful moieties in drug discovery, such as choloroquine [1] and primaquine [2] against malaria. Although many aminoquinoline compounds have been synthesized in recent years, the systematical description of the 6-aminoquinolines is still not so comprehensive.

In general, aminoquinoline could be prepared from the corresponding nitroquinoline by reduction reaction, because of the easier availability of the nitroquinoline [3]. And the 6-nitroquinoline derivatives could be synthesized from two routes (Scheme 1): modification directly on 6-nitroquinoline for pyridine-substituted quinolines (route 1) and Skraup ring-closing reaction for benzene-substituted structures (route 2).

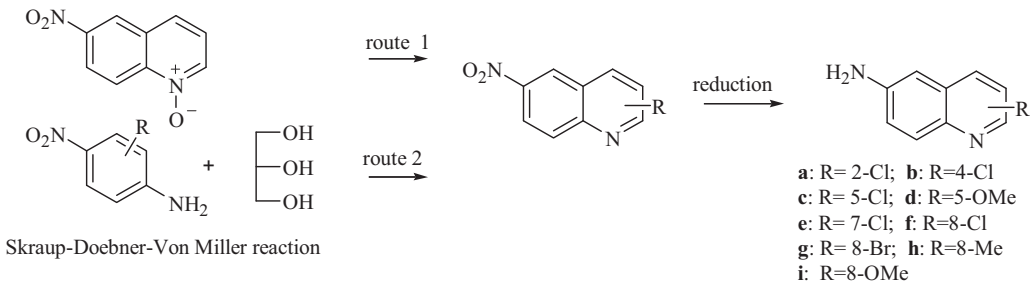
In the present paper, several 6-aminoquinoline derivatives, as listed in Table 1, had been obtained. The conditions of Skraup reaction and the reduction reaction have been examined in detail. And the target compounds could be obtained effectively from the modified method.

6-Nitroquinoline was stable with halogenation reagents because the benzene was passivated by the strong electrowithdrawing group NO_2. The pyridine ring could be activated by *N*-oxide group, and then could be chlorinated by $POCl_3$ (route 1). The 2- and 4-substituted quinolines (entries a and b, Table 1) were obtained respectively, which was after the process of column chromatography. But the 3-substituted compound could not be obtained because of the much lower yield than expected [4]. The *N*-oxide could be removed when the NO_2 was reduced to NH_2.

Skraup reaction (route 2) was useful for the synthesis of quinoline, especially for the benzene-substituted compounds. And the oxidants played key role in the reaction. In general, nitrobenzene was used in the reaction as

* Corresponding author.
E-mail address: yuanxx@sjtu.edu.cn (X.X. Yuan).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2010.10.005



Scheme 1. The synthesis of 6-animoquinolines.

Table 1
The synthesis of 6-nitroquinolines and 6-aminoquinolines.

Entry	R	6-Nitroquinolines			6-Aminoquinolines		
		Entry	Route	Yield[a] (%)	Entry	Reductant	Yield[a] (%)
a	2-Cl	**1a**	1	24	**2a** [10]	$SnCl_2$/HCl	89
b	4-Cl	**1b**	1	52	**2b**	$SnCl_2$/HCl	92
c	5-Cl	**1d** [9]	2	48	**2d**	$SnCl_2$/HCl	85
d	7-Cl	**1e** [9]	2	22	**2e**	$SnCl_2$/HCl	87
e	8-Cl	**1f**	2	44	**2f**	$SnCl_2$/HCl	90
f	8-Br	**1g**	2	51	**2g**	$SnCl_2$/HCl	91
g	8-Me	**1h**	2	61	**2h**	H_2/Pd-C	78
h	8-OMe	**1i**	2	66	**2i**	H_2/Pd-C	94
i	5-OMe	**1c**	–[b]	32	**2c**	H_2/Pd-C	81

[a] Isolate yields.
[b] Directly substituted reaction between MeOK and 6-nitroquinoline.

oxidant [5–7], but the yield was low (Table 2) and it was difficult to be removed out. So, several oxidants were examined when using 8-chloro-6-nitroquinoline as model reaction. Because quinolines were not stable for strong oxidants, the weak oxidants should be chosen carefully. It was proved that the inorganic oxidants exhibited higher activity than nitrobenzene, although the yields were still low. The highest yields were obtained using the 1,4-benzoquinone and *p*-chloroaniline as oxidants, probably because that they could dissolve well in the organic solvent. And the *p*-chloroaniline was chosen as the best oxidant in this reaction.

It was unusual for the 5-methoxy-6-nitroquinoline (entry i, Table 1) that could not be prepared by the 2 routes discussed above. It could be synthesized from 6-nitroquinoline directly by electrophilic substitution, because the NO_2 could activate the adjacent 5-position [8].

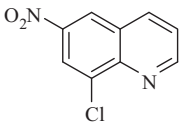
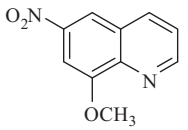
Pd/C and H_2 were wildly used for the reductive conversion of NO_2 to NH_2, and the 6-aminoquinolines (entries g–i, Table 1) were prepared with high yields. But the halo-substituted compounds were not obtained because the halogens were removed under this condition. And several reductive conditions were screened carefully (Table 3). It indicated that the catalyst always induced the remove of halogen. Both Fe and Zn could form the corresponding compounds, but it was difficult to remove the residues. So, the $SnCl_2{\cdot}2H_2O$/HCl was the best reagent for the reductive reaction, and halo-substituted 6-aminoquinolines (entry a–f, Table 1) were effectively obtained.

Table 2
Effects of oxidants on the 8-chloro-6-nitroquinoline yield.

Oxidant	8-Chloro-6-nitroquinoline yield (%)[a]	Oxidant	8-Chloro-6-nitroquinoline yield (%)[a]
Nitrobenzene	24	$CuCl_2$	33
$FeCl_3$	38	1,4-Benzoquinone	46
p-Chloroaniline	55		

[a] Isolated yield.

Table 3
Reduction of **1f** and **1i** *via* different methods.

Reductant				
	Product	Yield (%)	Product	Yield (%)
$NH_2NH_2{\cdot}H_2O$/C	**2f** + **6**-AQ[a]	–	**2i**	96
$NH_2NH_2{\cdot}H_2O$/Pd–C	**6**-AQ	96	**2i**	95
H_2/Pd–C	**6**-AQ	92	**2i**	94
Fe/HCl	**2f**	42	**2i**	53
Zn/HAc	**2f**	56	**2i**	58
$SnCl_2{\cdot}2H_2O$/HCl	**2f**	90	**2i**	92

[a] 6-AQ: 6-aminoquinoline.

In conclusion, several 6-aminoquinolines had been synthesized effectively. The oxidants in Skraup reaction were examined carefully, and the soluble *p*-chloroaniline was used as the optimal reagent. The problem of halogen removal by Pd catalyst could be overcame by using $SnCl_2{\cdot}2H_2O$/HCl as reductant.

Acknowledgments

The authors are grateful for the financial support of this work by the National Science Foundation of China (No. 20776085), the 973 Program of China (No. 2007CB209700), the STCSM of China (Nos. 10JC1406900 and 09XD1402400), the Foundation of Zhejiang Pharmaceutics Co. Ltd. and the Opening Foundation of Zhejiang Provincial Top Key Discipline.

References

[1] B. Priohit, A. Mahapatra, Stud. Ethno-Med. 3 (2009) 33.
[2] A.M. Dondorp, S. Yeung, L. White, et al. Nat. Rev. Microbiol. 8 (2010) 272.
[3] F.A. Carey, R.J. Sundberg, Adv. Org. Chem., 4th ed., New York, 2000.
[4] G.B. Bachman, D.E. Cooper, J. Org. Chem. 9 (1944) 302.
[5] R.E. Lutz, P.S. Bailey, T.A. Martin, J. Am. Chem. Soc. 68 (1946) 1324.
[6] M.V. Ramana, S.S. Malik, J.A. Parihar, Tetrahedron Lett. 45 (2004) 8681.
[7] Z. Song, M. Mertzman, D.L. Hughes, J. Heterocycl. Chem. 30 (1993) 17.
[8] T. Kawakami, H. Suzuki, J. Chem. Soc., Perkin Trans. 1 8 (2000) 1259.
[9] 5- and 7-chloro-6-nitroquinolines: To stirred liquid of *m*-chloroaniline (20 mL) was added acetic anhydride dropwise at room temperature until all the starting material consumed. The resulted mixture was neutralized by aqueous ammonia, and the obtained solid was filtered, washed thoroughly with water. After vacuum drying, 28 g nearly pure *m*-chloroacetanilide was obtained. To a well-stirred mixture of *m*-chloroacetanilide (18 g) and concentrated sulfuric acid (180 mL) was slowly added guanidinium nitrate (16 g) while maintaining the temperature at 5–10 °C. After the addition completed, the reaction mixture was poured into ice water (800 mL), and the solid obtained was filtered, washed with water and dried in vacuum oven for 8 h, a yellow product weighted 22 g was obtained, which was then purified through recrystallization to get 3-chloro-4-nitroacetanilide. A mixture of 3-chloro-4-nitroacetanilide (1.0 g), water (3.0 mL), concentrated sulfuric acid (4.0 mL), glycerol (2.5 mL), and *p*-chloroaniline (1.5 g) was boiled gently under reflux for 3 h. The product was cooled, diluted to 50 mL and filtered, the residue was disposed and the filtrate was adjusted to alkaline with aqueous ammonia. The precipitate was filtered off, washed and dried. Purification of the product by column chromatography gave the corresponding products. 5-Chloro-6-nitroquinolines: ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.14 (dd, 1H, J = 4.4, 1.6 Hz), 8.75 (d, 1H, J = 8.8 Hz), 8.28 (d, 1H, J = 8.8 Hz), 8.19 (d, 1H, J = 8.8 Hz), 7.84 (dd, 1H, J = 8.8, 4.4 Hz), 35%. 7-Chloro-6-nitroquinolines: ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (dd, 1H, J = 4.4, 1.6 Hz), 8.87 (s, 1H), 8.58 (d, 1H, J = 8.8 Hz), 8.33 (s, 1H), 7.72 (dd, 1H, J = 8.8, 4.4 Hz), 27%.
[10] General procedure for 6-aminoquinolines: The 6-nitroquinoline derivative (0.1 g) was added slowly with stirring to 1.0 g stannous chloride in 5 mL of 6 mol/L hydrochloric acid with gently heating for 1 h. After neutralizing the reaction mixture by aqueous ammonia, the precipitate was extracted with CH_2Cl_2 (4 × 20 mL). The combined CH_2Cl_2 layer was dried with anhydrous $MgSO_4$. Evaporating and chromatographing the extraction gave corresponding pure 6-aminoquinoline. 2-chloro-6-aminoquinoline: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.99 (d, 1H, J = 8.4 Hz), 7.61 (d, 1H, J = 8.8 Hz), 7.27 (d, 1H, J = 8.4 Hz), 7.17 (dd, 1H, J = 8.8, 2.8 Hz), 7.03 (d, 1H, J = 2.8 Hz), 5.71 (s, 2H); Anal. Calcd. for $C_9H_7N_2Cl$: C, 60.33; H, 3.91; N, 15.64. Found: C, 60.56; H, 3.74; N, 15.31.