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An unusual de-nitro reduction of 2-substituted-4-nitroquinolines

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Abstract—The treatment of a variety of 2-substituted-4-nitroquinolines with Sn in the presence of concentrated hydrochloric acid in ethanol at 70 °C for 2–4 h afforded unusual de-nitro products 2-substituted-quinolines in good yields.

Nitroaromatics compounds are important chemicals and commonly used precursors of other valuable organic products.[1] The reduction of nitro compounds leads to various classes of products such as amines, hydroxylamines, hydrazines, nitroso-, azo-, or azoxy compounds.[1] The commonly employed reducing reagents include hydrogen with palladium-on-carbon as catalyst, metal hydride, metal-acid reducing system, and so on. Although Sn and concentrated hydrochloric acid as a reducing system have become less important since the development of catalytic hydrogenation and of metal hydride reducing agents, this method is still used, most notably for the reduction of aromatic nitro compounds to the corresponding amines.[2] In our previous research,[3] 2-(3-chlorophenyl)-4-aminoquinoline (**3a**), as a key intermediate in the synthesis of novel chemical inhibitors of human cyclophilin A, was not obtained by reduction of 2-(3-chlorophenyl)-4-nitroquinoline (**1a**) with Sn and concentrated HCl (Scheme 1). Unexpectedly, a de-nitro product 2-(3-chlorophenyl)-quinoline (**2a**) was isolated in 60% yield, whose ^{1}H NMR and MS spectral data are identical to the reported data of 2-(3-chlorophenyl)-quinoline.[4] This result drew our great attention to the reaction mechanism and application of the reduction of 2-substituted-4-nitroquinolines with Sn/HCl.

Using 2-(3-chlorophenyl)-4-nitroquinoline (**1a**) as a model compound, we tested the reduction conditions by using four different reductants, H_2/Pd/C, $SnCl_2$, Fe/NH_4Cl, and Sn/HCl. The results are summarized in Table 1. It is interesting to notice that the amino product 2-(chlorophenyl)-4-aminoquinoline (**3a**) was obtained by the reaction of **1a** with Tin(II) chloride and concentrated hydrochloric acid in ethanol with an excellent yield (85%). Likewise, 88% yield of the amino product **3a** was achieved using Fe and ammonium chloride in ethanol. In the case of Pd/C, compound **3a** was also afforded in 42% yield. However, de-nitro product 2-(3-chlorophenyl)-quinoline (**2a**) was isolated exclusively in the presence of Sn and concentrated hydrochloric acid in ethanol at 70 °C in 60% yield.

When we applied this condition to more substrates, especially various 2-aryl-4-nitroquinolines, good yields of the desired de-nitro products were isolated and the results are summarized in Table 2. 2-Aryl-4-nitroquinolines (**1a**–**i**) and 2-cyclohexyl-4-nitroquinoline (**1j**) were synthesized similar to the methods reported by Atkinson et al.[5] and Brown et al.[6] by using α-bromoaryl ketone as the starting materials. In general, the condensation of α-bromoaryl ketone with potassium phthalimide in DMF afforded α-phthalimide-aryl ketones, which further reacted with isatins in KOH aqueous solution to give 2-aryl-3-phthalimide-quinoline-4-carboxylic acid. After sequential hydrazinolysis and rearrangement reaction, the target compounds, 2-aryl-4-nitroquinolines (**1a**–**i**) and 2-cyclohexyl-4-nitroquinoline (**1j**), were prepared.

Keywords: 2-Substituted-4-nitroquinonlines; Nitro group reduction; Sn/HCl.
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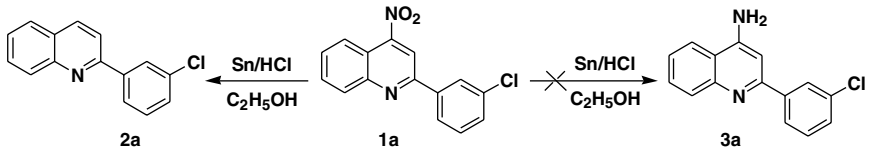
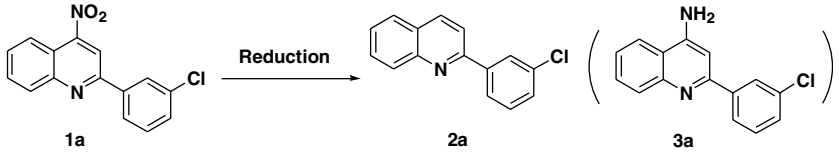


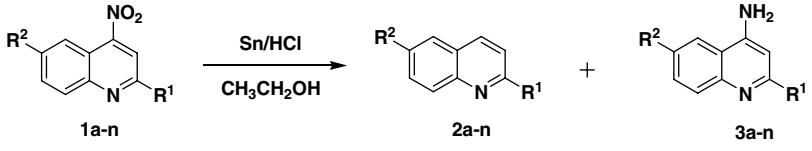
Scheme 1.

Table 1. Reduction of 2-(3-chlorophenyl)-4-nitroquinoline (**1a**) with several different reductants



Substrate	Reagents	Temperature (°C)	Time (h)	Product (yield, %)	
				2a	**3a**
1a	Sn/HCl (C_2H_5OH)	70	2	60	—
1a	Pd/C (C_2H_5OH)	rt	15	—	42
1a	$SnCl_2$/HCl (C_2H_5OH)	70	2	—	85
1a	Fe/NH_4Cl (C_2H_5OH)	70	2	—	88

Table 2. Reduction of 2-(3-chlorophenyl)-4-nitroquinoline analogues (**1a–n**) with Sn/HCl



1	R^1	R^2	Time (h)	Product[a] (yield, %)	
				2	**3**
a	3-Cl–C_6H_4	H	2	60	—
b	4-F–C_6H_4	H	2	59	—
c	2,4-Cl_2–C_6H_3	H	3	45	—
d	Phenyl	H	2	75	—
e	4-Me–C_6H_4	H	2	78	—
f	3-MeO–C_6H_4	H	2	80	—
g	2,5-$(MeO)_2$–C_6H_3	H	2	82	—
h	2,3-Dihydro-1,4-benzodioxin-6-yl	H	2	76	—
i	Naphthyl	H	4	53	—
j	Cyclohexyl	H	2	26	70
k	CH_3	H	2	67	15
l	H	H	2	34	—
m	H	OCH_3	2	—	35
n	H	CH_3	2	—	41

[a] Typical procedure for target product preparation refers to Ref. 7.

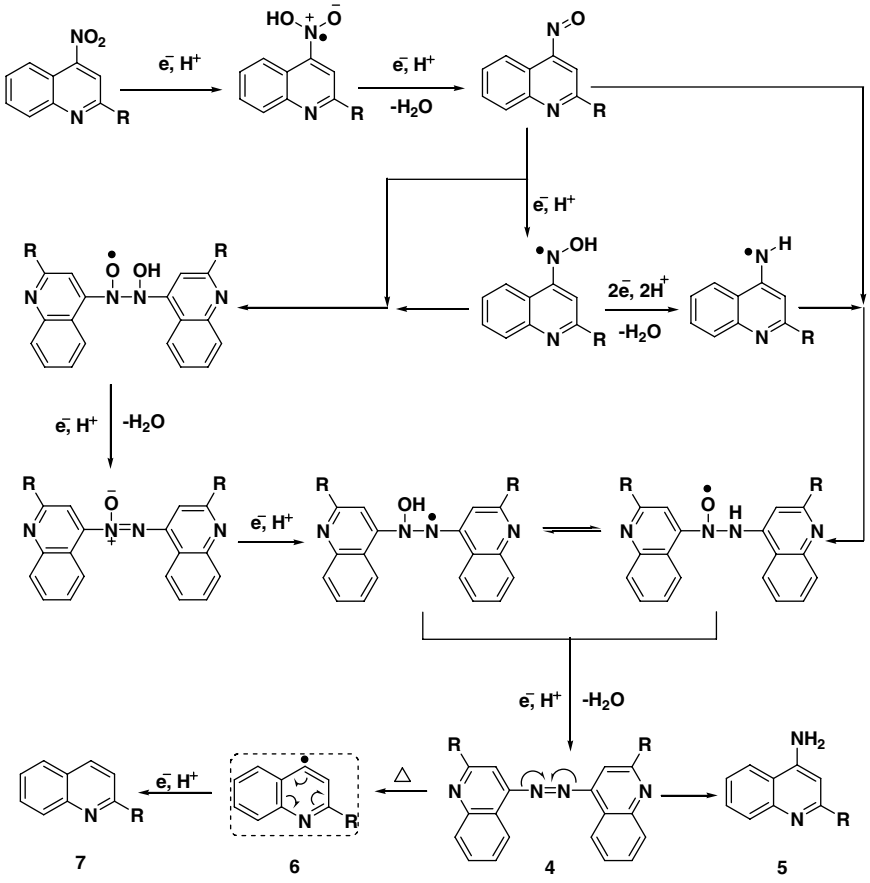
As shown in Table 2, compounds **1e–h,** bearing strong electron-donating substitutions at the phenyl ring of 2-position of quinoline, are easy to be converted to the corresponding de-nitro products (**2e–h**) in 76–82% yields. On the other hand, compounds **1a–c** with halogen-substituted groups at the phenyl ring of 2-position of quinoline afforded 60%, 59%, and 45% of de-nitro products **2a–c** for 2–3 h at 70 °C, respectively. Compound **1d**, with no substituted group at the phenyl ring of 2-position of quinoline, afforded the de-nitro product (**2d**) in average yield (75%) (Table 2). However, only 53% yield of the de-nitro product 2-naphthyl-quinoline (**2i**) was isolated despite of prolonging the reaction time to 4 h.

The effect of alkyl substitutions at 2-position and 6-position of the quinoline ring (**1j–n**) was also investigated (Table 2). The amino compound, 2-cyclohexyl-4-aminoquinoline (**3j**), was the major product under the same reaction condition from compound **1j**, along with 26% of de-nitro compound, 2-cyclohexyl-quinoline (**2j**). In contrast, treatment of compound **1k**[8] under the same condition afforded 67% of de-nitro product, 2-methyl-quinoline (**2k**) and 15% of the amino product, 2-methyl-4-aminoquinoline. Nevertheless, only 34% yield of de-nitro product quinoline (**2l**) was isolated from compound **1l**,[8] while no trace amino compound was detected (Table 2). Compounds **1m–n**[8] were reduced with Sn/HCl in ethanol to give only 4-amino-quinolines

(**3m**–**n**) in very low yields, of 35% and 41%, respectively. The above results show that the quinolines bearing 2-aryl substitutions (**1a**–**i**) are particularly prone to form the de-nitro products. For example, the electron-donating substituents (**1e**–**h**) and halogen substituents (**1a**–**c**) at the phenyl ring of 2-position of quinoline increase the reaction yields. 2-Alkyl (**1j**–**k**) or 6-alkyl (**1m**–**n**) substituents lead to the generation of amino products (**3j**–**k**, **3m**–**n**). However, compounds **1j**–**k** gave simultaneously de-nitro products (**2j**–**k**) in the process of the reduction with Sn/HCl. With respect to the effect of reaction time, compounds **1j**–**l** as model compounds were reduced for three different reaction times (2 h, 4 h, and 8 h). The results show that the yields of target products were not significantly affected by prolonging the reaction time.

Based on the above experimental results, a plausible mechanism for the reduction of 2-substituted-4-nitroquinolines by Sn and concentrated hydrochloric acid in ethanol was proposed (Scheme 2). A literature survey reveals that reduction of aromatic nitro compounds proceeds by single electron transfer (SET) mechanism to form amines through intermediate stages involving azo-compounds (**4**), which are often reduced further to the corresponding amines (**5**).[1] Moreover, it was reported that free aryl radicals (**6**) could be generated by the thermal decomposition of azo-compounds.[9] On the other hand, the Sn, bearing a long atomic radius, is probably easy to lose the valence electron to further facilitate the formation of free quinolyl radicals. Furthermore, the free quinolyl radical is probably stabilized by the paired electrons of *N*-atom of quinoline ring, and subsequently captures an electron and a proton to form quinolines in the presence of Sn and HCl. It is clear that the 2-aryl substituents of 4-nitroquilines (**1a**–**i**) through the p-π conjugated effect can stabilize the corresponding free radicals more efficiently than 2-alkyl (**1j**–**k**) or 6-alkyl (**1m**–**n**) substituents. 2-Alkyl substituents can partially stabilize the free quinolyl radicals simply through donor electron action, so compounds (**1j**–**k**) afforded a mixture of de-nitro and amino products. However, when 6-alkyl substituents exert donor electron action, the conjugated system of quinoline ring would be destroyed, which is disadvantageous to molecular energy balance, so compounds **1m**–**n** are prone to give exclusively amino products. The detailed mechanism is still unclear, and will be investigated by further experiments.

In summary, we have encountered an unusual reduction of 2-substituted-4-nitroquinolines with Sn and concentrated hydrochloric acid in ethanol, which gives de-nitro products 2-substituted-quinolines in good yields. A plausible reaction mechanism involving SET mechanism of the formation of azo-compound from nitro group and the formation of free quinolyl radicals was provided. Further studies will be developed to elucidate



Scheme 2. Plausible mechanism for the reduction of 2-substituted-4-nitroquinolines by Sn and concentrated hydrochloric acid. Definitive influence on the product by the different R group, when R = aryl or H, giving product **7**; and R = alkyl, giving products **5** and **7**.

the scope and limitation of this reaction, and will be reported in due course.

Acknowledgements

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References and notes

1. Ung, S.; Falguieres, A.; Guy, A.; Ferroud, C. *Tetrahedron Lett.* **2005**, *46*, 5913–5917.
2. Burke, S. D.; Danheiser, R. L. *Handbook of Reagents for Organic Synthesis Oxidizing and Reducing Agents*; Willy: London, 1999; pp 458–461.
3. Li, J.; Zhang, J.; Chen, J.; Luo, X. M.; Zhu, W. L.; Shen, J. H.; Liu, H.; Shen, X.; Jiang, H. L. *J. Comb. Chem.* **2006**, *8*, 326–337.
4. Shi, D. Q.; Rong, L. C.; Wang, J. X.; Zhuang, Q. Y.; Wang, X. S.; Tu, S. J.; Hu, H. W. *J. Chem. Res. Synop.* **2003**, *6*, 342–343.
5. Atkinson, C. M.; Mattocks, A. R. *J. Chem. Soc.* **1957**, *4*, 3718–3721.
6. Brown, R. F. C.; Coulston, K. J.; Eastwood, F. W.; Jurss, C. J. *Aust. J. Chem.* **1994**, *47*, 567–569.
7. A mixture of 1.0 mmol of **1a**–**n** and 2.0 mmol of Sn in 25 mL of C_2H_5OH including 4 mL of concentrated hydrochloric acid was stirred at 70 °C for 2–4 h. The reaction was monitored by TLC. After cooling, the mixture was filtered, and the filtrate was neutralized with NaOH. Water (20 mL) was added and the solution was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with water (2×10 mL) and dried with anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 1/50, v/v) to give the target compound. These products **2a**–**b**, **2d**–**g**, **2i**–**l** and **3m**–**n** are known compounds, which was estimated by ^{1}H NMR and EI-MS spectrum in comparison with the reported spectral data. And the spectral data of **2c**, **2h** and **3j** are as follows: Compound (**2c**), ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19–8.27 (2H, m), 7.89 (1H, d, $J = 7.8$ Hz), 7.73–7.80 (2H, m), 7.68 (1H, d, $J = 8.4$ Hz), 7.61 (1H, t), 7.54 (1H, d), 7.41 (1H, dd, $J = 8.1$, 1.8 Hz); EI-MS m/z 273 (M^+). Compound (**2h**), ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (2H, d, $J = 8.7$ Hz), 7.81 (2H, d, $J = 8.7$ Hz), 7.67–7.76 (3H, m), 7.51 (1H, t), 7.01 (1H, d, $J = 8.4$ Hz), 4.33 (4H, s); EI-MS m/z 263 (M^+). Compound (**3j**), ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.80 (1H, d, $J = 8.1$ Hz), 7.32 (1H, t), 7.19 (1H, d, $J = 8.1$ Hz), 7.01 (1H, t), 5.97 (1H, s), 2.24–2.33 (1H, m), 1.14–1.90 (10H, m); EI-MS m/z 226 (M^+).
8. Typical procedure for **1k**–**n** preparation: the target compounds were prepared by using various quinolines as the starting materials. In general, treatment of quinolines with 29% of H_2O_2 in glacial acetic acid gave the quinolines 1-oxide, which were further nitrated by nitric acid in the presence of sulfuric acid to afford 4-nitroquinolines 1-oxide. Subsequently, 4-nitroquinolines 1-oxide in CH_2Cl_2 in the presence of trimethyl-phosphite was irradiated by a daylight lamp under nitrogen to give the target compounds.
9. (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Structure and Mechanisms*; Springer: New York, 2000; pp 672–675; (b) Bridger, R. F.; Russell, G. A. *J. Am. Soc.* **1963**, *85*, 3754–3765.