A FACILE METHOD FOR DIRECT CONVERSION OF DIHYDROFUROQUINOLONES TO DIHYDROPYRROLOQUINOLONES

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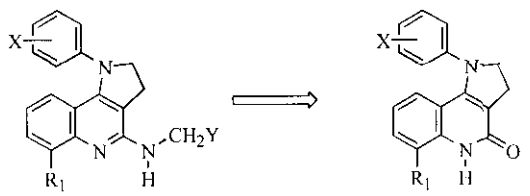
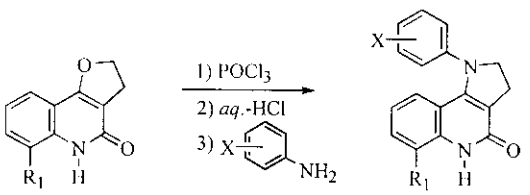
Abstract - A novel and efficient method is described for one-step conversion of dihydrofuroquinolones to dihydropyrroloquinolones in high yields under mild conditions.

1-Aryl-4-alkylaminopyrrolo[3,2-*c*]quinolines (1) were known to be K^+-competitive inhibitors of the gastric (H^+/K^+)-ATPase.[1,2] These compounds have therapeutic potential in the treatment of disorders such as peptic ulcer and gastroesophageal reflux disease, particularly if they could be shown to avoid the sustained hypergastrinemia observed after chronic exposure to omeprazole.[3] A convergent synthesis of pyrroloquinoline (1) from the dihydropyrroloquinolones (2) was reported (eq. 1).[2]



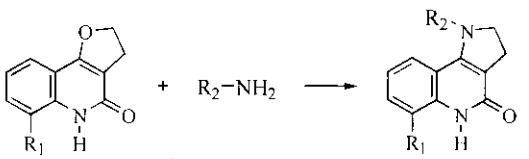
1 2 (eq. 1)

The key intermediates (2) were prepared *via* a sequence involving chlorination of 4-oxo-2,3-dihydrofuro[3,2-*c*]quinolones (3), acid hydrolysis, and cyclization with anilines in about 20 % overall yield (eq. 2). Thus, this method had limitations, such as three step sequence in low yields and limited variation of the anilines.



3 2 (eq. 2)

In connection with our research program toward the development of new drug for peptic ulcers,[4] we have had occasion to study pyrroloquinoline (1). It was desired a more efficient synthesis of intermediate (2) that would supply pyrroloquinoline (1) in a fewer steps. We report here a convenient and versatile synthesis of dihydropyrroloquinolones (2) by direct conversion from dihydrofuroquinolones (3) (eq. 3).

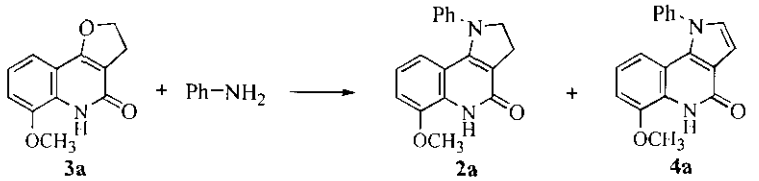


3 { a R_1= OCH_3 b R_1= CH_3 } 2 (eq. 3)

It was postulated that the conversion could be accomplished in one-pot process. Initial reaction of dihydrofuroquinolone (3a) (R_1= OCH_3), which was readily prepared by the reported method,[5] with 2.5 equiv. of aniline in phenol at 190 °C for 48 h gave 2a (R_1= OCH_3, R_2= Ph) in 40 % yield along with air oxidation product (4a) in 32 % yield (Table 1). Encouraged with this result, we investigated the present reaction in detail. We examined a number of solvents and temperature to optimize the reaction

conditions and the results were summarized in Table 1.

Table 1. Effects of Solvent on the Reaction.



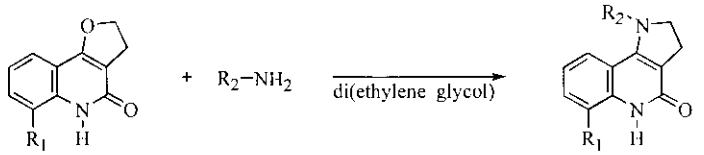
3a **2a** **4a**

solvent	reaction condition[a] (°C / h)	isolated yield (%) **2a**	**4a**	**3a**
phenol	190 / 48	40	32	16
1,4-dioxane	110 / 24	-	-	87
DMF	160 / 15	-	-	85
ethylene glycol	205 / 15	37	5	45
di(ethylene glycol)	250 / 15	83	5	-
poly(ethylene glycol)	220 / 15	63	10	7

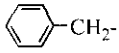
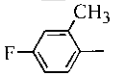
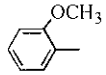
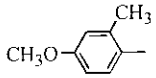
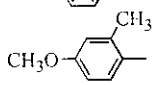
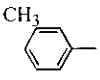
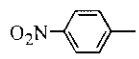
[a] All reactions were carried out using 2.5 equiv. of aniline.

Among the solvents employed, di(ethylene glycol) was found to be the most effective and the reaction was completed within 15 h at 250 °C. Tri(ethylene glycol) and poly(ethylene glycol) were also effective, while the reaction did not proceed in DMF and 1,4-dioxane. We also examined various amines under the standard reaction conditions. Table 2 shows experimental results and illustrates the efficiency, the applicability, and the scope of the present method. In general, the reaction was carried out with a 2.5 equiv. of amines in di(ethylene glycol) at 250 °C for 15 h.[6] Air oxidation was possibly blocked by using pressure bottle under nitrogen atmosphere. The reaction of 3 with aromatic amines proceeded smoothly to afford the corresponding 2 in high yields. For example, the reaction with *o*-toluidine gave 2b in 82 % yield with no detectable side products. Employment of electron-donating groups at *para*-position of aromatic amine accelerated the reaction,

Table 2. Direct Conversion of Dihydrofuroquinolones (3) to Dihydropyrroloquinolones (2).



3 2

No.	R_1	R_2	yield (%)[a]	No.	R_1	R_2	yield (%)[a]
2a	OCH_3		87	**2g**	OCH_3		43 (20)
2b	OCH_3		82	**2h**	CH_3		89
2c	OCH_3		57 (20)	**2i**	CH_3		81
2d	OCH_3		86	**2j**	CH_3		77
2e	OCH_3		81	**2k**	CH_3		86
2f	OCH_3		5 (80)	**2l**	CH_3	$(CH_3)_2CHCH_2$	40 (15)

[a] The numbers in parentheses indicate the recovered starting material (3a) or (3b).

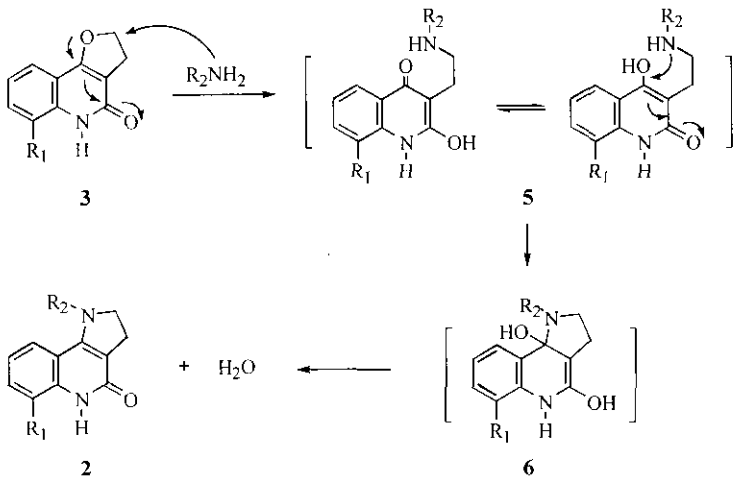
while electron-withdrawing groups at *para*-position slowed the reaction. The reaction with 4-amino-*m*-cresol gave the corresponding dihydropyrroloquinolone (2k) in 86 % yield after 10 h. In case of 4-fluorotoluidine, 2c was obtained in 57 % yield along with the 20% recovery of 3a. With *p*-nitroaniline, the starting material (3a) was recovered in 80 % yield even after 24 h. The reaction of aliphatic amines such as benzylamine or isobutylamine with 3 gave no good results after 24 h, yielding in below 40 %.

Although clear conclusions regarding the reaction mechanism await further study, the reaction may proceed *via* the intermediacy of 5 and 6 as shown in Scheme. Further study on this mechanism is in progress in our laboratory.

In conclusion, a novel one-step synthesis of dihydropyrroloquinolones (2) from dihydrofuroquinolones (3) has been developed.[7] We believe that this could be a powerful method for the synthesis of diverse

pyrrolo[3,2-*c*]quinoline derivatives which are useful as (H^+/K^+)-ATPase inhibitors.

Scheme. Proposed Mechanism for Conversion of 3 to 2.



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6. Typical Experimental Procedure: To a solution of 4-oxo-6-methoxy-2,3-dihydrofuro[3,2-*c*]quinoline (3a) (217 mg, 1.0 mmol) in di(ethylene glycol) (5 mL) under N_2-atmosphere in pressure bottle was added *o*-toluidine (267 mL, 2.5 mmol). The reaction mixture was stirred at 250 °C for 15 h, diluted with methylene chloride (30 mL), and washed with water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography with ethyl acetate as an eluant to give 1-(2-methylphenyl)-4-oxo-6-methoxy-2,3,4,5-tetrahydropyrrolo-[3,2-*c*]quinoline (2b) (251 mg, 82 %) as colorless solid: mp 166-168 °C (methylene chloride); MS m/z 306(M^+, 100 %); ^{1}H-NMR (200 MHz , $CDCl_3$) δ 2.34(s, 3H), 3.11-3.41(m, 2H), 3.72-3.91(m, 1H), 3.97(s, 3H), 4.06-4.28(m, 1H), 6.28(d, *J*=7.9 Hz, 1H), 6.73(t, *J*=8.2 Hz, 1H), 6.82(d, *J*=7.9 Hz, 1H), 7.05-7.42(m, 4H), 8.91(br s, 1H).

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