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NOTE

A Convenient Way to Prepare the Key Intermediate 3-Aminomethyl-3-methyl-4-(methoxyimino)pyrrolidine Dihydrochloride of DW286: A New Naphthyridone Antibacterial

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We report herein a convenient way to prepare the key intermediate 3-aminomethyl-3-methyl-4-(methoxyimino)pyrrolidine dihydrochloride of DW286, a new fluoronaphthyridone antibacterial agent, *via* a 4-step sequence in an overall yield of 56 %. In this procedure, it was crucial that selective reduction of the cyano group of the cyano ketone (**5**) was done successfully using 5 % Pd/C as the catalytic hydrogenation.

Key Words: DW286, Key intermediate, Preparation, Selective reduction.

DW286, a methyl analog of fluoronaphthyridone antibacterial agent gemifloxacin, has completed Phase I clinical trial. Compared with gemifloxacin, DW286 shows better *in vitro* and *in vivo* activity against commonly pathogens in clinic, especially Gram-positive resistant bacteria[1-5].

However, the current synthetic process of DW286 is rather complex (16 steps in all), involving some reaction steps with high material cost, high production expenses and column chromatography separation techniques[6].

We have previously reported a new route and successfully synthesized DW286 by direct condensation of the naphthyridone nucleus 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid and the side-chain compound 3-(aminomethyl)-4-(methoxyimino)-3-methylpyrrolidine dihydrochloride **1** (**Scheme-I**). As the key intermediate (**1**) of DW286, it was prepared *via* a 9-step sequence. In other word, *N*-Boc-3-cyano-4-oxopyrrolidine (**2**) was first obtained by one-pot method from glycine ethyl ester hydrochloride and acrylonitrile as starting materials and then methylation, reduction of ketone moity by $NaBH_4$, hydrogenation of the cyano group, Jones oxidation, oximation and deprotection gave compound **1**[7]. However, the preparation of **1** was not suitable for industrial application due to the following reasons 1) heavy metal (Cr) pollution; 2) use of column chromato-graphy separation techniques.

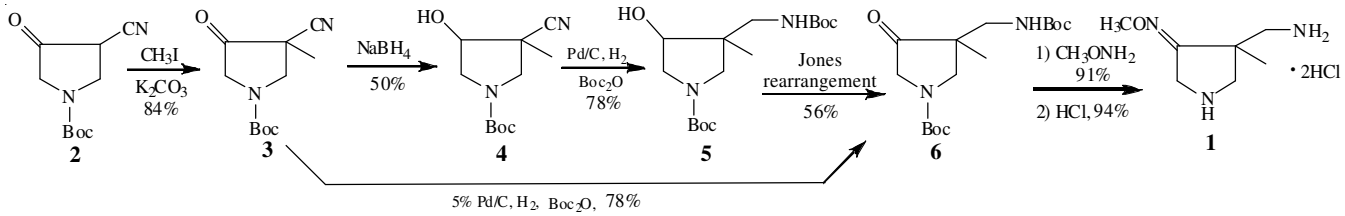
On the basis of the above considerations, we have recently focused on improving the synthetic route of the key intermediate **1**. From the cyano ketone (**2**), the title compound **1** was easily obtained *via* a 4-step sequence, or methylation, selective reduction and protection simultaneously, oximation and deprotection.

Melting points were determined in open capillaries and uncorrected. ^{1}H NMR spectra were determined on a Varian Mercury-400 spectrometer in DMSO-d_6 or $CDCl_3$ using tetramethylsilane as an internal standard. Electrospray ionization mass spectra and high resolution mass spectra were obtained on a MDSSCIEX Q-Tap mass spectrometer and AccuTOF CS JMS-T100CS (JEOL) mass spectrometer, respectively. Unless otherwise noted, the reagents were obtained from commercial supplier and used without further purification. TLC was performed on silica gel plates (Merck, ART5554 $60F_{254}$).

Synthesis

***N*-*tert*-butoxycarbonyl-3-cyano-3-methyl-4-oxopyrrolidine (3):** The compound **3** with a yield of 84 % was achieved by the procedure described in ref.[7] as a white solid, m.p.: 71-73 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.49 (9H, s, Boc-9H), 1.58 (3H, s, CH_3), 3.69-4.15 (4H, m, pyrrolidine). MS (ESI, *m/z*): 225 $(M + H)^+$.

***N*-*tert*-butoxycarbonyl-3-(*N*-*tert*-butoxycarbonyl) aminomethyl-3-methyl-4-oxopyrrolidine (6):** A mixture of the cyano pyrrolidone **3** (11.2 g, 50 mmol), $(Boc)_2O$ (10.9 g, 50 mmol) and 5 % Pd/C (2.0 g) in methanol (200 mL) was pressurized at 75 psi of hydrogen at room temperature for 8 h and the gas was slowly vented, then filtered. The filtrate was



Scheme-I: Improved synthetic route of the key intermediate **1**

concentrated under reduced pressure. The residue obtained was treated with petroleum ether (200 mL), filtered and then dried *in vacuo* to afford the title compound **6** (12.8 g, 78 %) as a white solid, m.p.: 106-108 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.15 (3H, s, CH_3), 1.43 (9H, s, Boc-9H), 1.50 (9H, s, Boc-9H), 3.26-3.64 (4H, m, pyrrolidine), 3.83 (2H, s, CH_2N), 4.77 (1H, brs, NH). MS (ESI, *m/z*): 329 $(M+H)^+$.

Aminomethyl-3-methyl-4-(methoxyimino)pyrrolidine dihydrochloride (1): The compound **1** was obtained by two steps with a yield of 85 % as described in ref.[7] as off-white solid. ^{1}H NMR ($CDCl_3$+D_2O, 400 MHz) δ (ppm): 1.10 (3H, s, CH_3), 3.06-3.69 (4H, m, pyrrolidine), 3.78 (3H, s, $NOCH_3$), 4.03 (2H, s, CH_2N).

Methylation of **2** was carried out with a yield of 84 %, but we were not able to obtain the desired products in direct reduction of both functional groups by $LiAlH_4$, or only reduction of ketone moiety of the cyano ketone (**3**) by $NaBH_4$ in acceptable yields (40-50 %), even when column chromatography separation technique was used. Also, protection of the carbonyl group of **3** by ketalization with diols such as glycol and neopentylglycol, *etc*. and subsequent reduction of the cyano group by typical reducing agents turned out to be unsuccessful. It was encouraging that 5 % Pd/C used as the catalytic hydrogenation was found to reduce selectively the cyano group to the primary amine with *in situ* Boc protection, in the presence of the ketone moiety of compound **3** and compound **6** was obtained in a good yield (78 %) by conventional treatments. The compound **1** was easily prepared by oxymation and Boc deprotection of **6**, respectively.

Conclusion

In summary, a convenient way to prepare 3-aminomethyl-3-methyl-4-(methoxyimino)pyrrolidine dihydrochloride (**1**), the key intermediate of DW286, was developed using inexpensive reagents and simple reaction conditions in an overall yield of 56 % (from **2**). In this strategy, it was crucial that selective reduction of the cyano group of the cyano ketone (**3**) was done successfully using 5 % Pd/C as the catalytic hydrogenation.

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