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New Synthetic Approach to 4-(3-Aminopropyl)-5-amino-1-methylpyrazole Starting from 3-Cyanopyridine

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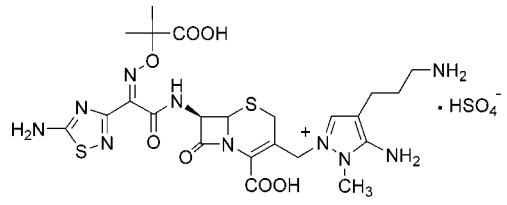
Abstract:

A short and practical method for the synthesis of 4-(*N*-Boc-3-aminopropyl)-5-(*N*-tritylamino)-1-methylpyrazole (3), side chain of an anti-*Pseudomonas aeruginosa* cephalosporine FR259647, 1, was established by utilizing a regioselective enamine exchange with *N*-methylhydrazine and 1,4,5,6-tetrahydro-pyridine-3-carbonitrile (8), followed by a subsequently occurring intramolecular cyclization and aromatization, starting from a cheap 3-cyanopyridine (7).

Introduction

In the field of antibacterial active pharmaceutical ingredients (API), imipenem,[1] meropenem,[2] ceftazidime,[3] and ciprofloxacin[4] are most commonly used against *Pseudomonas aeruginosa* for the treatment of infectious disease. Regarding carbapenems and cephalosporines, the increased bacterial resistance has become a major issue to be overcome. Recently, a medicinal group of our company investigated and successfully discovered that FR259647, **1**, had not only a superiority to current carbapenems in the antibacterial activity against *P. aeruginosa* but also a strong resistance to β-lactamase. Consequently, there was an urgent need of active ingredient supply for preclinical studies with the design of a robust and cost-effective manufacturing process in mind. With the aim of cost reduction and process simplification, we started to look for an alternative route to pyrazole **3** which was the most expensive moiety of FR259647, **1**. Here we wish to describe our new synthetic approach to pyrazole **3**.



FR259647 **1**

Results and Discussion

The synthetic route[5] to pyrazole **3** used by the medicinal chemists had some drawbacks, namely (1) starting materials 5-amino-1-methylpyrazole (**2**) and Horner−Wadsworth−Emmons reagent were expensive, (2) phosphorus oxychloride was poisonous and hazardous, and (3) sodium hydride was dangerous and not suitable for scale-up production (Scheme 1). First, we surveyed the reported synthetic methods of 5-amino-1-alkylpyrazole to assemble the most effective route for large-scale production. In these reports,[6−13] the reaction of cyanoenamines with alkylhydrazines seemed to be promising because the enamine as leaving group might be useful for the formation of the amino propyl substituent in pyrazole **3**. As described in Scheme 2, Dusza and Albright[12] started from *N*-alkyl cyanoacetamide derivatives **4** (R^1 = alkyl-NH, R^2 = Me) and established the new synthetic route to 4-substituted-5-amino-1-methylpyrazole **6** via cyanoenamine **5** using enamine exchange. Another group[13] also reported a similar method using methyl cyanoacetate (R^1 = OMe, R^2 = CH_2CH_2OH) instead of *N*-alkyl cyanoacetamide **4**. Although there were no reports which made it clear whether the esters or amides could be replaced by alkyl groups to obtain the target compound **3**, we postulated that the alkyl substituent deactivated neither the enamine as leaving group nor the cyano group as electrophile. Then we first decided to make the cyclic cyanoenamine **8** which might be transferable into the desired precursor **9a** at a stretch; if an enamine exchange of compound **8** with *N*-methylhydrazine proceeds while losing the resulting aminopropyl moiety, then a spontaneous intramolecular cyclization with the cyano group proceeds.

In the first step, as shown in Scheme 3, Yamada and Kikugawa[14] reported that 3-cyanopyridine **7** could be converted to cyclic cyanoenamine **8** with moderate yields by a simple $NaBH_4$−ethanol reduction system. On the basis of the literature, we improved their operating conditions and determined the optimum volume ratio of ethyl alcohol solvent

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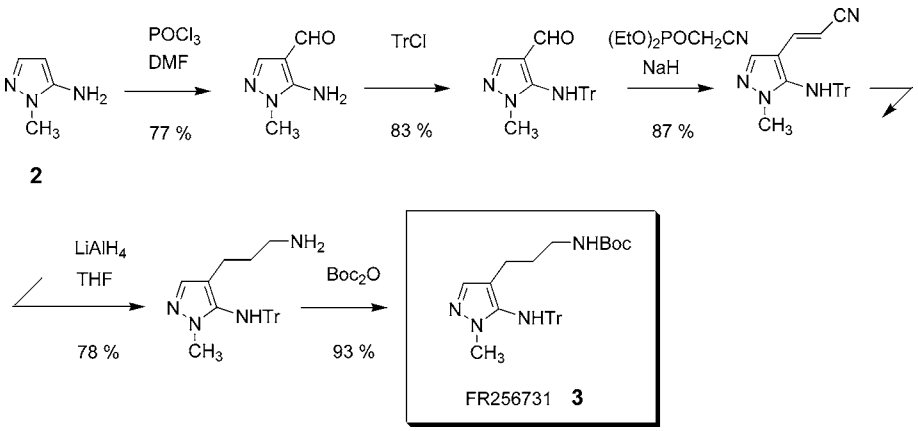
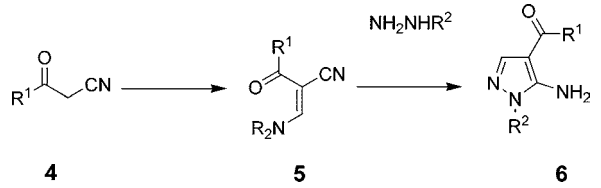
Scheme 1. **Medicinal synthetic route**



Scheme 2. **Reported synthetic methods of 4-substituted-5-amino-1-methylpyrazole 6**



to be 25 volumes (as depicted in Figure 2) and the optimum $NaBH_4$ stoichiometry to be 2 mol equiv relative to that of cyanoenamine **8** (as depicted in Figure 1). In terms of solvents, $NaBH_4$ reduction systems in methyl alcohol, ethyl alcohol, and 2-propanol gave **8** in 6, 74, and 42% HPLC conversion, respectively. In methyl alcohol, 36% of 3-cyanopyridine **7** still remained after 2 h refluxing. As a result, we succeeded in the isolation of **8** in 70% yields.

In the pyrazole step formation, the regioselective chemistry of cyclic cyanoenamine **8** with *N*-methylhydrazine was not only essential to build up an alternative synthetic route but was also found to be extremely interesting. Although we were uncertain of the reaction selectivity at first, it became clear, following useful experimental results, that the primary amino moiety of *N*-methylhydrazine attacked the most electrophilic carbon of cyclic cyanoenamine **8**, and then the secondary nitrogen moiety spontaneously attacked the nitrile group followed by aromatization to preferably provide the thermodynamically stable pyrazole **9a** (Scheme 3). The reaction did not proceed without catalysts (entry 1, Table 1) but proceeded smoothly with Brønsted acid. The use of H_2SO_4 and $KHSO_4$ gave disappointing results (entries 2, 3, and 4). The reaction was accelerated by either MsOH or concentrated HCl with satisfactory regioselectivity (entries 5 and 6). The cyclic cyanoenamine **8** was not so unstable even in the aqueous acidic condition. As a result, one equivalent of HCl was chosen from the point of regioselectivity and conversion to obtain **9a** (entries 7 and 8). Increasing the equivalents of HCl prompted the increased formation of regioisomer **9b** with the similarity to results with H_2SO_4. It was supposed that excess acid gathered around the primary amine of hydrazine to lower the nucleophilicity and reaction selectivity. As shown in Figure 3, the conversion ratio (**9a**/**9b)** was observed almost constantly from the beginning of the reaction (entry 7). Fortunately, we could obtain the sole regioisomer **9b** as bis-hydrochloride in 40% isolated yield by simply cooling the reaction mixture, due to the differences of the solubilities of **9a** and **9b** in ethanol (entry 9).

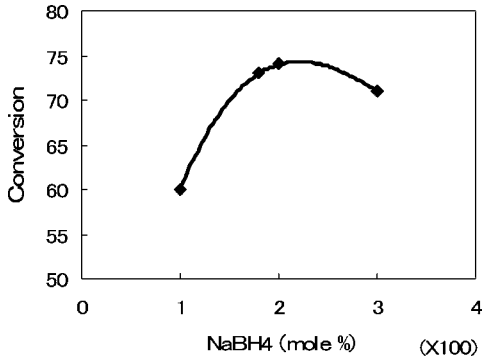


Figure 1. **Optimization of $NaBH_4$ (mol %).**

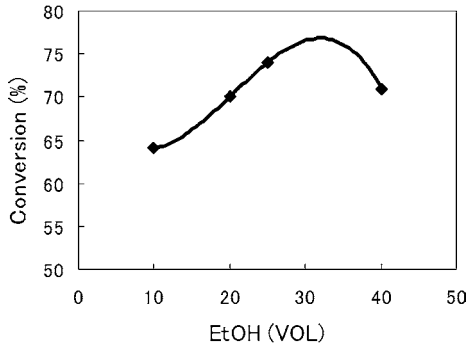


Figure 2. **Optimization of EtOH (volume).**

On the other hand, we could obtain pure **9a** easily by deprotecting the pyrazole **3** already prepared by the medicinal route. The distinction between **9a** and **9b** on HPLC analysis[15] could be done comparatively easily by using these standard samples. The chemical shift (7.65 ppm) of **9a** at the 3 position was higher than that (7.55 ppm) of **9b** at the 5 position in ^1H NMR analysis (D_2O). The reported correlation[16] in chemical shift between 5-amino-1,4-dimethylpyrazole and 3-amino-1,4-dimethylpyrazole stands for the analytical result.

(15) HPLC isocratic method: column: YMC-gel ODS-AM (150 mm), wavelength: 254 nm, mobile phase: KH_2PO_4 (2 g) in distilled water (970 mL) and acetonitrile (30 mL), flow rate: 1 mL/min., retention time: 2.2 min (**9a**) and 2.6 min (**9b**).

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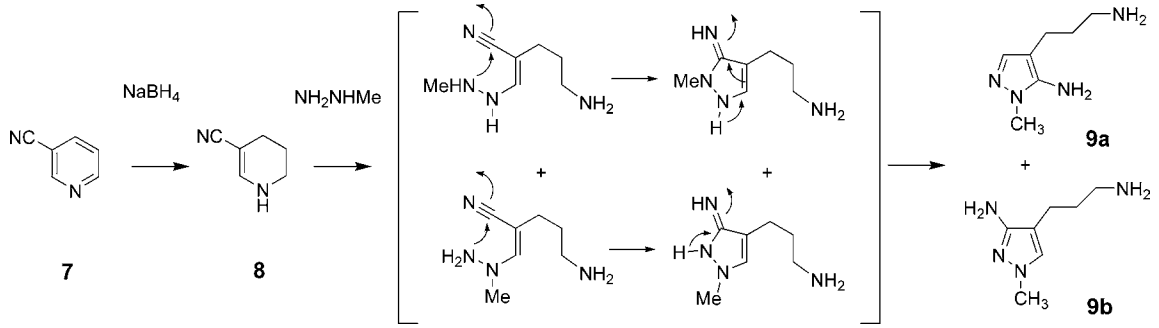
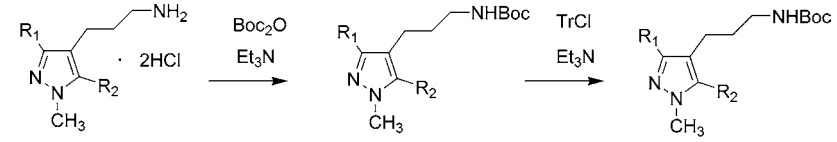
Scheme 3. **Cyclization mechanism of cyclic cyanoenamine 8 with *N*-methylhydrazine**



Scheme 4. **Stepwise protections of amino groups in pyrazole 9**



9a : R_1 = H, R_2 = NH_2 **10a** : R_1 = H, R_2 = NH_2 **3** : R_1 = H, R_2 = NHTr
9b : R_1 = NH_2, R_2 = H **10b** : R_1 = NH_2, R_2 = H **11** : R_1 = NHTr, R_2 = H

Table 1. **Regioselective cyclization of 8 with *N*-methylhydrazine**

entry	EtOH (vol)	acid (mol %)	reaction conditions	conversion (%)[a] 8	9a	9b
1	50	none	reflux, 5 h	100	0	0
2	10	H_2SO_4 (50)	reflux, 2 h	77	22	1
3	10	H_2SO_4 (100)	reflux, 1 h	48	36	16
4	10	$KHSO_4$ (100)	reflux, 2 h	76	22	2
5	10	MsOH (100)	reflux, 7 h	46	50	4
6	10	cc. HCl (100)	reflux, 4 h	49	47	4
7	10	cc. HCl (100)	reflux, 69 h	2	80	18
8[b]	10	cc. HCl (100)	reflux, 69 h	0.5	90	9.5
9	10	cc. HCl (200)	reflux, 3 h	0	51	49[c]
10[d]	10	cc. HCl (300)	reflux, 3 h	0	45	37

[a] A ratio of each HPLC peak areas among **8**, **9a**, and **9b**. [b] 5-g-scale experiment. Other experiments were 200-mg scale. [c] Crystals of **9b** preferably appeared. [d] Many byproducts were observed.

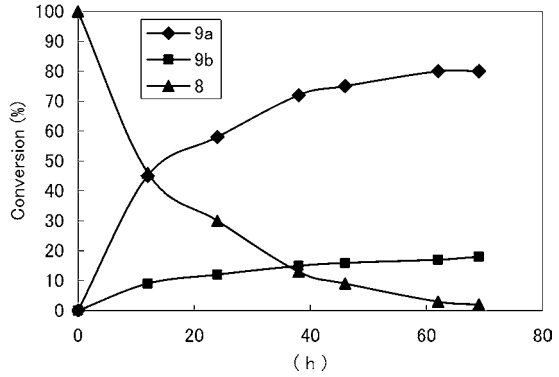


Figure 3. **Reaction conversion (%) of 9a, 9b in (entry 7, Table 1).**

As mentioned above, the best result was obtained using the conditions of entry 8. Compound **9a** was isolated in 107% yield by an addition of 1.5 equiv of HCl and 2-propanol into the reaction mixture after reaction completion, to form bis-hydrochloride salt. The crude compound **9a** contaminated with corresponding **9b** at a 9% AUC level was run without any purification into the next step. The next *N*-Boc protection, successive *N*-trityl protection and silica gel chromatographic purification successfully afforded the target compound **3** in 56% yield from crude **9a**. In the similar way, sole product **9b** isolated in step two using 2 equiv of HCl was also converted into **11** successfully in 57% isolated yield (Scheme 4).

Conclusion

We established a short, practical, and regioselective synthesis of pyrazole **3** derived from 3-cyanopyridine **7**. This method can avoid some expensive materials, some hazardous chemicals, and long production steps. We believe that additional optimizations in every step and efficient separation method for the regioisomer **11** without recourse to chromatography would make the present process more industrialized hereafter.

Experimental Section

All reagents and solvents were commercially available. ^{1}H NMR spectra were recorded with a Bruker AC200P (200 MHz) spectrometer using tetramethylsilane as an internal standard. HPLC analysis was performed with a Shimadzu 10A. Mass and IR were carried out by Analytical Science Laboratories, Inc. Melting points were determined in open capillary tubes and uncorrected.

1,4,5,6-Tetrahydro-pyridine-3-carbonitrile (8). To a mixture of 3-cyanopyridine **7** (20 g, 0.192 mol) and ethanol (500 mL) was added carefully sodium borohydride (14.5 g, 0.384 mol) in portion at room temperature. The reaction mixture was refluxed for 2 h and cooled to ambient temperature, then treated by addition of acetone (40 mL) and water (100 mL). The solution was concentrated to ca. 100 mL and then treated with water (500 mL) and ethyl acetate (400 mL) for extraction. The aqueous layer was back-extracted with ethyl acetate (100 mL), and the combined organic layers were washed with 20% (w/v) aqueous sodium chloride. The final organic layer was concentrated under

reduced pressure to dryness to afford 1,4,5,6-tetrahydropyridine-3-carbonitrile (**8**) as a dark oil (14.6 g, 70% yield). ^{1}H NMR ($CDCl_3$): δ 1.77−1.88 (2H, m), 2.21 (2H, t, J = 7.7 Hz), 3.17−3.24 (2H, m), 4.70 (1H, broad s), 6.92 (1H, d, J = 6.0 Hz). Mass (*e*/*z*): 131 (M + Na).

4-(3-Aminopropyl)-5-amino-1-methylpyrazole bihydrochloride (9a). To a mixture of compound **8** (5.0 g, 46.2 mmol) and ethyl alcohol (50 mL) were added *N*-methylhydrazine (2.34 g, 50.8 mmol) and 35% (w/w) hydrochloric acid (4.8 g, 46.2 mmol) at between 0 and 10 °C. The reaction mixture was refluxed for 69 h, then cooled below 10 °C, followed by addition of 35% (w/w) hydrochloric acid (7.22 g, 69.3 mmol) and evaporation at room temperature to dryness. The residue was treated with IPA (30 mL) and subsequently concentrated to dryness under reduced pressure. The residue was suspended with IPE (100 mL). The crystals were filtrated, washed with IPE (10 mL), and subsequently dried under reduced pressure to give compound **9a** (11.22 g, 106.8%). ^{1}H NMR (D_2O): δ 1.88−2.00 (2H, m), 2.49 (2H, t, J = 7.4 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.73 (3H, s), 7.65 (1H, s). Side product derivative **9b** was estimated at 9 mol % by integration of proton at 7.55 ppm (1H, s). Mass (*e*/*z*): 155 (M + H^+). IR (cm^{-1}): 2880 (NH_2). Chloride ion: calcd 32.0%, found 29.35% (bis-hydrochloride).

4-(3-Aminopropyl)-3-amino-1-methylpyrazole bihydrochloride (9b). To a mixture of compound **8** (5.0 g, 46.2 mmol) and ethyl alcohol (50 mL) were added *N*-methylhydrazine (2.34 g, 50.8 mmol) and 35% (w/w) hydrochloric acid (9.6 g, 92.4 mmol) at between 0 and 10 °C. The reaction mixture was refluxed for 3 h, and solids appeared after 1 h. The precipitate was filtered at between 0 and 10 °C, washed with IPA (10 mL), and then dried under reduced pressure overnight to give compound **9b** (4.20 g, 40% yield). ^{1}H NMR (D_2O): δ 1.83−1.99 (2H, m), 2.51 (2H, t, J = 7.5 Hz), 3.02 (2H, t, J = 7.6 Hz), 3.77 (3H, s), 7.52 (1H, s). Mass (*e*/*z*): 155 (M + H^+). IR (cm^{-1}): 2800 (NH_2). Chloride ion: calcd 32.0%, found 31.19% (bis-hydrochloride).

4-(*N*-Boc-3-aminopropyl)-5-(*N*-tritylamino)-1-methylpyrazole (3). To a mixture of compound **9a** (2.0 g, 8.8 mmol), acetone (10 mL), and water (5 mL) was added triethylamine (1.78 g, 17.6 mmol) followed by a solution of Boc_2O (2.11 g, 9.7 mmol) in acetone (4 mL) at between 0 and 10 °C. The reaction mixture was stirred for 2 h at room temperature and then was concentrated under reduced pressure, followed by the addition of water (20 mL). The aqueous solution was adjusted to around pH 9.5 using aqueous sodium hydroxide. The aqueous solution was extracted twice with ethyl acetate (20 mL). The combined organic layer was washed with saturated aqueous sodium chloride (10 mL) followed by evaporation to dryness to give mono Boc compound **10a** (2.2 g, 98.2% yield). To a mixture of **10a**, dichloromethane (11 mL) and *N*, *N*-diisopropylethylamine (1.12 g, 8.7 mmol) was added trityl chloride (2.41 g, 8.7 mmol) at room temperature. After stirring for 2 h, the resulting crystals were filtered and washed with water (30 mL) and subsequently dried under reduced pressure to afford a crude compound **3**. Purification by silica gel column chromatography (SiO_2: 125 g, elution: *n*-heptane/ethyl acetate, 4:1) gave compound **3** as a white solid (2.45 g, 57.0% yield). ^{1}H NMR ($CDCl_3$): δ 1.24−1.31 (2H, m), 1.45 (9H, s), 1.80 (2H, t, J = 7.8 Hz), 2.83 (3H, s), 2.90 (2H, broad s), 4.18 (1H, broad s), 4.32 (1H, broad s), 7.12 (1H, s), 7.15−7.18 (6H, m), 7.23−7.31 (9H, m). Mass (*e*/*z*): 519 (M + Na). IR (cm^{-1}): 1700 (CO). Mp: 119 °C.

4-(*N*-Boc-3-aminopropyl)-3-amino-1-methylpyrazole (10b). To a mixture of compound **9b** (1.0 g, 4.4 mmol), acetone (7 mL) and water (3 mL) was added triethylamine (1.32 g, 13.1 mmol) followed by solid Boc_2O (1.41 g, 6.5 mmol) at between 0 and 10 °C. The reaction mixture was stirred for 2 h at room temperature, and then acetone was removed by evaporation, followed by the addition of ethyl acetate (15 mL) and 20% (w/v) aqueous sodium bicarbonate (5 mL). The separated aqueous layer was extracted twice with ethyl acetate (10 mL). The combined organic layer was washed with saturated aqueous sodium chloride (10 mL) and concentrated to dryness to afford crude compound **10b** (1.43 g). Purification by silica gel column chromatography (SiO_2: 10 g, elution: *n*-heptane/ethyl acetate, 1:2 then CH_2Cl_2/MeOH, 10:1) afforded side product di-Boc derivative (0.61 g, 39% yield) and desired compound **10b** (0.64 g, 57.6% yield). Di-Boc compound: ^{1}H NMR ($CDCl_3$): δ 1.43 (9H, s), 1.49 (9H, s), 1.70−1.74 (2H, m), 2.43 (2H, t, J = 7.3 Hz), 3.09−3.13 (2H, m), 3.78 (3H, s), 5.05 (1H, broad s), 6.55 (1H, broad s), 7.10 (1H, s). Mass (*e*/*z*): 377 (M + Na). IR (cm^{-1}): 1673 (CO), 1692 (CO). **10b**: ^{1}H NMR ($CDCl_3$): δ 1.45 (9H, s), 1.66−1.74 (2H, m), 2.33 (2H, t, J = 7.3 Hz), 3.10−3.20 (2H, m), 3.67 (3H, s), 4.65 (1H, broad s), 6.95 (1H, s). Mass (*e*/*z*): 277 (M + Na). IR (cm^{-1}): 3327 (NH_2), 1683 (CO).

4-(*N*-Boc-3-aminopropyl)-3-(*N*-tritylamino)-1-methylpyrazole (11). To a solution of compound **10b** (0.50 g, 2 mmol) in dichloromethane (3 mL) was added triethylamine (0.24 g, 2.4 mmol) followed by solid trityl chloride (0.61 g, 2.2 mmol) at room temperature. After stirring for 3 h, the reaction mixture was washed with 5% (w/v) aqueous sodium bicarbonate (5 mL) then 20% (w/v) aqueous sodium chloride (5 mL). The organic layer was concentrated to dryness under reduced pressure to afford a crude residue. Purification by silica gel column chromatography (SiO_2: 10 g, elution: *n*-heptane/ethyl acetate, 6:1) afforded desired compound **11** as a white sticky solid (0.99 g, 101.2% yield). ^{1}H NMR ($CDCl_3$) δ 1.43 (9H, s), 1.53−1.60 (2H, m), 2.07 (2H, t, J = 7.3 Hz), 3.0−3.1 (2H, m), 3.39 (3H, s), 4.29 (1H, broad s), 4.48 (1H, broad s), 6.72 (1H,s), 7.14−7.29 (9H, m), 7.40−7.43 (6H, m). Mass (*e*/*z*): 519 (M + Na). IR (cm^{-1}): 1692 (CO).

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