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One-pot synthesis of 5-amino 4-cyano pyrrole derivatives

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ABSTRACT

One-pot synthesis of 5-amino 4-cyano pyrrole derivatives is herein disclosed. The described method consists of four steps and gives new pyrrole derivatives in moderate to good yields. This synthesis can be used for a large scale preparation.

1. Introduction

Dipeptidyl peptidase IV (DPP-4) inhibitors have recently been the focus for a new treatment for type 2 diabetes.[1] DPP-4 is an ubiquitous serine protease that modulates the biological activity of various peptides. One of the peptides cleaved by DPP-4 is glucagon-like peptide 1, which plays an important role in maintaining normal blood glucose level.[2,3] DPP-4 inhibitors avert cleavage of GLP-1 and prolong its lifetime in the blood. Based on this mechanism of action, a number of DPP-4 inhibitors have already been approved for the treatment of type 2 diabetes, while other promising candidates are undergoing clinical or preclinical development.[4–7] We have previously reported novel DPP-4 inhibitors, such as the pyrolo[3,2-*d*]pyrimidines **1** and deazahypoxanthines **2** (X = H).[8] Subsequently, Novartis researchers have shown that structures similar to **1** and **2** (X = ester, amide or nitrile) with an electron withdrawing group (EWG) at position 7 also have strong inhibitory activity against DPP-4.[9]

Synthetic methods for preparing a series of pyrrole structures substituted by amines at position 5 have rarely been reported.[10–12] In our synthesis of the previously reported DPP-4 inhibitors, we constructed a novel synthetic method for preparation of 5-amino 4-*tert*-butyl ester pyrrole derivatives (**3**) as main intermediates.[8] The pyrrole structure of **3** is suitable for preparation of the unsubstituted, 7-ester and amide substituted structures **1** and **2** (X = H, ester and amide). However, for preparation of 7-cyano structures, **1** and **2** (X = CN), compound **3** is inappropriate as intermediate because transformation of the *tert*-butyl ester into a nitrile requires additional steps with harsh reaction conditions, including the use of strong acids, which limit the selection of protecting groups and other substituents. In addition, a long process with additional steps is not suitable for preparing a wide variety of compounds or a large scale synthesis. As for the synthetic route described by Novartis researchers, the desired compounds are obtained by a microwave reaction, which can be difficult to apply to a large scale synthesis and requires special equipment.

Based on these findings, we were interested in expanding our previous work by constructing 5-amino 4-cyano pyrrole derivatives (**4**) that can conveniently afford various 7-cyano compounds. An extensive effort led to a new synthetic method that can give unique pyrrole derivatives having amino substituents at α-position, which are difficult to synthesize by traditional ways. In addition, it can be carried out as a one-pot reaction suitable for collecting a wide range of SAR information and a large scale synthesis. Here, we disclose the scope and limitations of this new method (Fig. 1).

2. Results and discussion

First, we examined the conditions of our previous work (Scheme 1). In the first step (A) for R^1R^2N, the *tert*-butyl [(*R*)-3-piperidine-3-yl]carbamate was selected due to its strong inhibitory activity against DPP-4.[8,9] On the other hand, in the second step (B) for R^3, 2-chloro benzylamine was used because this substituent showed good DPP-4 inhibitory activity among all our compounds. In our experiments, we found that cyclization proceeded to a certain extent under the third conditions (C), K_2CO_3 in DMF at 50 °C. Based on this finding, we assumed that it was possible to carry out one-pot reaction, and accordingly investigated its conditions.

As the first step (A) proceeded smoothly in various solvents, such as toluene, CH_3CN, and THF, without any base, the conditions of the second step (B) were investigated. Preliminary research

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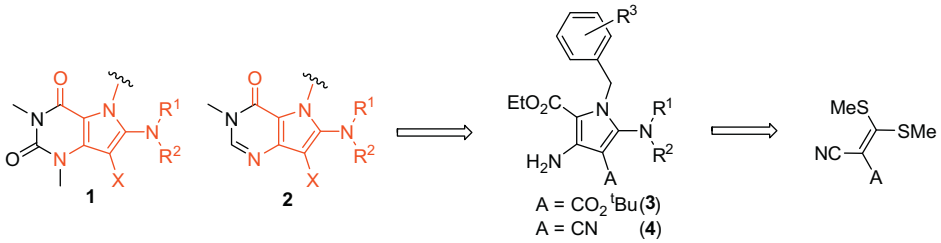
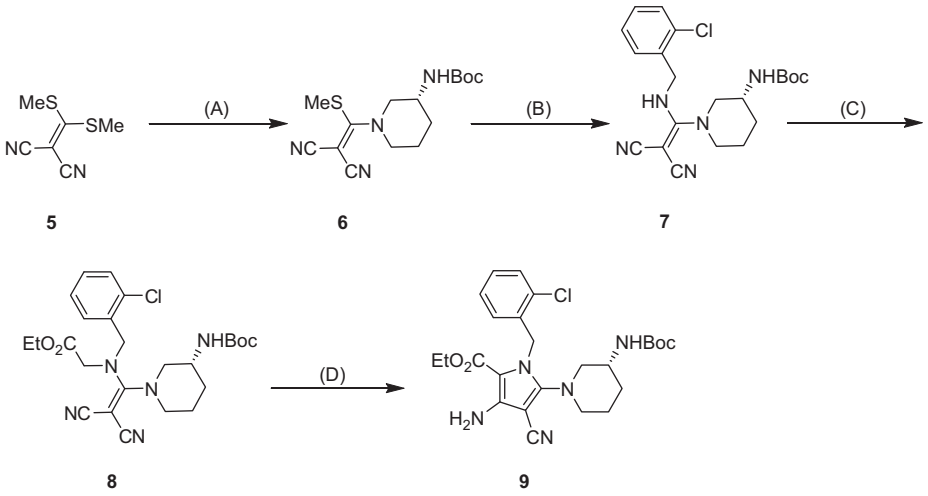


Figure 1. 5-Amino pyrrole based DPP-4 inhibitors.



Scheme 1. Synthesis of compound **9**. Reagents and conditions: (A) *tert*-butyl [(*R*)-3-piperidine-3-yl]carbamate (1.0 equiv), toluene, 60 °C, 4 h; (B) benzylamine (1.2 equiv), 1,8-diazabicyclo[5,4,0]undeca-7-ene (DBU) (2.0 equiv), CH_3CN, 80 °C, 5 h; (C) ethyl bromoacetate (1.1 equiv), K_2CO_3 (1.2 equiv), DMF, 50 °C, 1 h; (D) $LiNH_2$ (2.0 equiv), *t*-BuOH (20 equiv), CH_3CN, heptane, rt, 1 h.

indicated that a base is required in the second step (B). Accordingly, we focused on K_2CO_3, which is used in the third reaction conditions (C) (Table 1). The reaction did not finish in toluene at 80 °C (entry 1). The reason for this seems to be toluene's inability to dissolve inorganic bases. In addition, the more polar solvent DMF was not appropriate for this step because the reaction gave a complex mixture (entry 2). It was assumed that DMF was unstable under basic conditions and heat. Therefore, other solvents were investigated, and *n*-BuCN was proved to be a good choice (entry 3). The use of K_2CO_3 in *n*-BuCN gave better results than the use of 1,8-diazabicyclo[5,4,0]undeca-7-ene (DBU) in CH_3CN. However, 1.2 equiv of K_2CO_3 did not finish the reaction, and 1.5 equiv was necessary for reaction completion (entries 3 and 4). As for the temperature, the reaction at 130 °C afforded slightly less yields, and 2.0 equiv of K_2CO_3 at 130 °C did not show any improvement (entries 5 and 6).

Table 1
Reaction conditions for the second step (B)

Entry	Base	Solvent	Temp (°C)	Yield[a] (%)
1	K_2CO_3 (1.5 equiv)	Toluene	80	42[b]
2	K_2CO_3 (1.5 equiv)	DMF	80	––
3	K_2CO_3 (1.5 equiv)	*n*-BuCN	80	75 (59)[c]
4	K_2CO_3 (1.2 equiv)	*n*-BuCN	80	20[b]
5	K_2CO_3 (1.5 equiv)	*n*-BuCN	130	68
6	K_2CO_3 (2.0 equiv)	*n*-BuCN	130	69

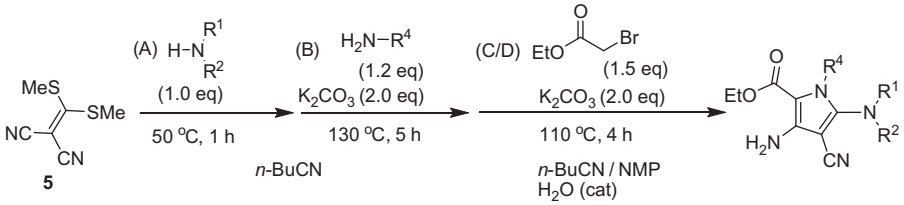
[a] Isolated yield.
[b] Uncompleted reaction.
[c] Yield of the previous conditions (2.0 equiv of DBU, CH_3CN, 80 °C, 10 h).

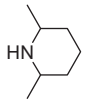
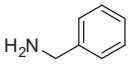
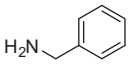
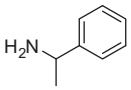
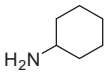
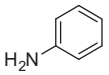
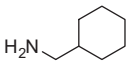
As all reaction conditions in the table above could be applied to the next alkylation step (C), the reaction conditions of entry 3 were selected. However, the first/second (A/B) step did not proceed to completion under these conditions. Therefore, the conditions of entries 5 and 6 were examined, and found to be both suitable for the smooth progression of the first/second step.

The preliminary research described above suggested that alkylation and cyclization (C/D) under K_2CO_3 in DMF can proceed at once, however, under K_2CO_3 in *n*-BuCN even the alkylation (C) did not finish. This is probably due to the low polarity of *n*-BuCN as compared to DMF. DMF on the other hand was inappropriate for the second step (B). Based on these findings, a combination of solvents was used in the third/fourth step (C/D). As *N*-methyl pyrrolidinone (NMP) was more stable than DMF under basic conditions and heat, the combination, NMP and *n*-BuCN, was selected as solvent. The most important factor for these two steps was found to be the temperature as alkylation/cyclization (C/D) proceeded smoothly at 110 °C with additional 2.0 equiv of potassium carbonate and a catalytic amount of water, which seemed to help dissolve K_2CO_3. Next, we explored the limitations of this one-pot reaction[13] (Table 2).

To examine the limitations of this reaction under harsh conditions, the conditions of entry 6 in Table 2 were selected for the second step (B). When 2,6-dimethyl piperidine was used in the first step (A), the reaction did not proceed (entry 1). Steric hindrance around NH seems to have a big impact on the progression of the first step. The use of 2-methyl piperidine in the first step and 1-phenyl ethylamine or cyclohexylamine in the second step did not allow the second reaction to proceed to completion (entries 2–4). In addition, when aniline was used instead of benzylamine, the reaction did not proceed (entry 5). As the use of cyclohexanemethylamine

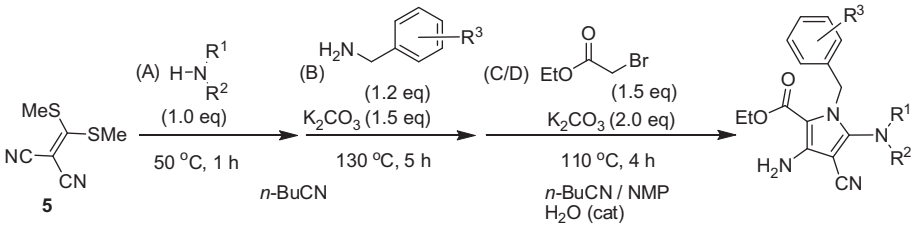
Table 2
Limitations of this reaction

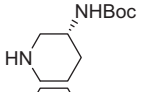
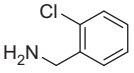
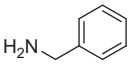
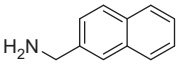
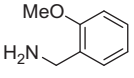
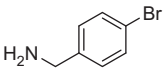
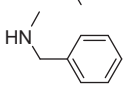
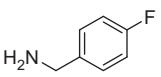


Entry	R^1R^2NH	R^4-NH_2	(A)	(B)	(C/D)	Yield[a] (%)
1			Not proceed	--	--	--
2			→	Not finish	--	--
3			→	Not finish	--	--
4			→	Not finish	--	--
5			→	Not proceed	--	--
6			→	→	→	60

[a] Isolated yield.

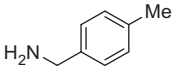
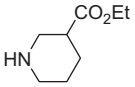
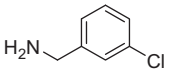
Table 3
Applications of the one-pot synthesis



Entry	R^1R^2NH	R^3-$BnNH_2$	Yield[a] (%)
1 (**9**[14])			66 (54)[b]
2 (**10a**[15])			58
3 (**10b**)			41 (54) [c]
4 (**10c**)			59 [c]
5 (**10d**)			55 [c]
6 (**10e**)			28 [c]

(*continued on next page*)

Table 3 (*continued*)

Entry	R^1R^2NH	R^3-$BnNH_2$	Yield[a] (%)
7 (**10f**)			77
8 (**10g**)			41 (60)[c]

[a] Isolated yield.
[b] Reaction performed at 25 mmol scale.
[c] 2.0 equiv of K_2CO_3 was used in the second step (B).

was accepted in this synthetic method (entry 6), it is assumed that the basicity of NH_2 and steric hindrance caused by R^1R^2 or R^4 are important in the second step. Based on these findings, it is believed that a series of dialkylamines is suitable for R^1R^2NH, and benzylamines and some kinds of alkylamines are appropriate for R^4-NH_2. As our aim was to prepare proper pyrrole derivatives for DPP-4 inhibitors synthesis, we investigated the applications of this one-pot reaction, while focusing on a combination of dialkylaminnes and benzylamies (Table 3).

The above-mentioned one-pot reaction gave the target pyrrole **9** in good yield, but large-scale experiment resulted in a slight decrease in the yield (entry 1). As a magnetic stirrer was used in the large-scale experiment, the discrepancy in yield is thought to be related to stirring and/or heat efficiency. As shown in Table 1, although other primary amines were inappropriate for this reaction, other ways to remove benzyl protection have already been reported.[8] Therefore, other structures will be synthesized from these pyrrole derivatives (entry 2). While a series of carbamate was accepted as R^1R^2 (entries 1 and 7), some R^1R^2NH having an amine substituent, such as NMe_2, could not be used (data not shown). The use of amine substituted reagents in the first step finally gave complex mixtures, and the reason is thought that a series of amine substituents are capable of reacting with ethyl bromoacetate. Ester, which can easily be changed to other substituents, such as alcohol or amide (entry 8), was also accepted in the first step. As for R^3, a wide variety of substituents were allowed (entries 4–8). Bromo or chloro substituted benzylamines gave moderate to good yields and were useful in introducing various other substituents (entries 1, 5, and 8). In some cases, the use of 2.0 equiv of potassium carbonate in the second step (B) was considered as suitable (entries 4–6 and 8).

In conclusion, we herein report a one-pot synthesis of 5-amino 4-cyano pyrrole derivatives and show its limitations and possible scale up. This new synthetic method could easily give unique compounds that are difficult to synthesize by conventional methods.

Acknowledgment

We are thankful to Ms. M. Honma for recording high MS spectra.

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13. *General procedure*: to a solution of **3** (1.0 mmol) in *n*-BuCN (1.0 ml), R^1R^2NH (1.0 equiv) was added, and then the resulting solution was stirred at 50 °C for 1 h. K_2CO_3 (2.0 equiv) and R^3-$BnNH_2$ (1.2 equiv) were added to the solution, and the mixture was stirred for 5 h at 130 °C. After cooling to room temperature, K_2CO_3 (2.0 equiv), NMP (1.0 ml), ethyl bromoacetate (1.5 equiv), and H_2O (10 μl) were added. The resulting mixture was stirred for 4 h at 110 °C. The slurry was filtered through Celite, then filtrate was concentrated, and the residue was purified by SiO_2 in a column chromatgraphy (hexane/EtOAc = 8:1–3:1).
14. *Analytical data of ethyl ethyl 3-amino-5-{(3R)-3-[(tert-butoxycarbonyl) amino]piperidin-1-yl}-1-(2-chlorobenzyl)-4-cyano-1H-pyrrole-2-carboxylate* (**9**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.07 (3H, t, J = 6.9 Hz), 1.36–1.43 (1H, m), 1.50–1.70 (2H, m), 1.75–1.83 (1H, m), 2.80–3.00 (3H, m), 3.36(1H, dd, J = 11.2, 3.3 Hz), 3.71 (1H, s), 4.12 (2H, q, J = 7.1 Hz), 4.56 (1H, s), 5.33–5.43 (2H, m), 6.53 (1H, d, J = 6.8 Hz), 7.18–7.20 (2H, m), 7.32–7.40 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 23.0, 28.2, 29.4, 46.2, 52.3, 56.5, 59.6, 75.3, 79.3, 101, 114, 126, 127, 128, 129, 131, 136, 146, 150, 155, 161, 171. HR-MS (ESI+): m/z 502.2213 (calcd m/z 502.2216 for $C_{25}H_{32}ClN_5O_4$+H).
15. *Analytical data of ethyl 3-amino-1-benzyl-4-cyano-5-(piperidin-1-yl)-1H-pyrrole-2-carboxylate* (**10a**): ^{1}H NMR (400 MHz, DMSO) δ: 1.10 (3H, t, J = 7.1 Hz), 1.45–1.57 (6H, m), 3.00–3.10 (4H, m), 4.07 (2H, q, J = 7.1 Hz), 5.21 (2H, s), 5.83 (2H, s), 6.97 (2H, d, J = 7.7 Hz), 7.18–7.24 (1H, m), 7.25–7.32 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 23.6, 28.9, 48.4, 52.7, 59.4, 74.3, 101, 115, 126, 127, 128, 138, 146, 152, 161. HR-MS (ESI+): m/z 353.1973 (calcd m/z 353.1972 for $C_{20}H_{24}N_4O_2$+H).