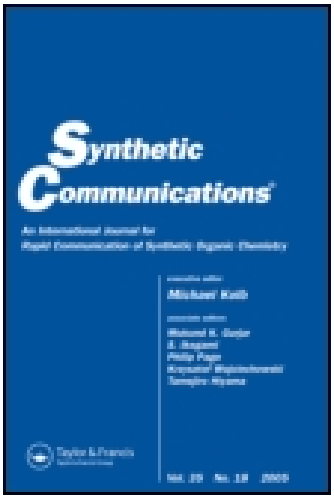

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Convenient Method for the Preparation of 2-Aryl-1H-benzimidazole-4-carboxy Acids

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Abstract: The oxidative cyclization of 2,3-diaminobenzoic acid and aromatic aldehydes to give 2-aryl-1H-benzimidazole-4-carboxylic acids is reported. Moreover, three methods were compared in different perspectives from experimental manipulation to yield.

Keywords: Benzimidazole, pharmaceutical synthesis, potassium ferricyanide

INTRODUCTION

Inhibition of PARP (poly [ADP-ribose] polymerase) may strengthen radiotherapy and some kinds of cancer chemotherapy.[1–3] 2-Aryl-1H-benzimidazole-4-carboxamides (**1**) are proved to be a class of potent PARP inhibitors.[4,5]

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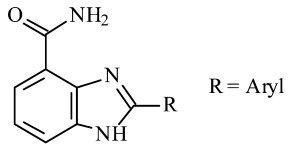

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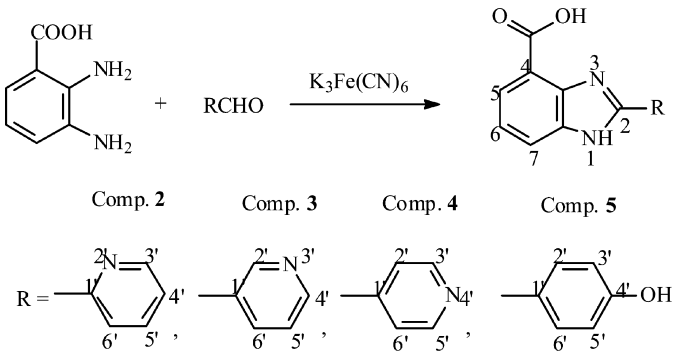
In the synthetic route of 2-aryl-1H-benzimidazole-4-carboxamides (**1**), the benzimidazole ring formation is the key step. In Phillips synthesis,[6,7] 2-substituted-1H-benzimidazoles were obtained by heating o-phenylenediamine and carboxylic acids in the presence of hydrochloric or polyphosphoric acid. Although Phillips synthesis is very suitable for benzimidazole cyclization of o-phenylenediamine and carboxylic acids, the condensation of 2,3-diaminobenzoic acid and benzoic acids is not that efficient.[8] White et al.[5] designed a multistep synthetic route that was complicated and also lacked good yields. Another method is the cyclization of 2,3-diaminobenzoic acid and appropriate aromatic aldehydes in the presence of copper acetate.[9]

DISCUSSION AND RESULTS

In this article, the oxidative cyclization of 2,3-diaminobenzoic acid and aromatic aldehydes is reported, and potassium ferricyanide acted as an oxidant. Using the same oxidant, different procedures were employed. To compare two methods, Denny synthesis[9] was also practiced. Detailed procedures are shown in the Experimental section. Method I adopted Denny synthesis. Method II and method III both employed potassium ferricyanide but different solvents, methanol–water and DMF respectively.

We made the compound according to Denny Methods but found that it needed too much methanol to dissolve 2,3-diaminobenzoic acid. An acidic medium was necessary for the existence of copper acetate. In addition, the posttreatment was very burdensome. Therefore, potassium ferricyanide was chosen as an oxidant to act in an alkaline medium. In this case, the solvent quantity decreased deeply and the yields were similar to Denny synthesis. An absolute water environment was tried and proved to be inefficient because of the occurrence of by-products, indicating that the existence of methanol was necessary. The employment of DMF as a solvent on account of its good solubility was further considered. As shown in method III, the reaction procedure was simplified greatly and gave good yield. The reaction temperature should be controlled at about 60°C. When the temperature rose to about 80°C, by-products appeared (Scheme 1).

The cyclizations of 2,3-diaminobenzoic acid, 2-, 3-, and 4-pyridylaldehyde, and 4-hydroxylphenylaldehyde were investigated in all three methods. The yields are respectively shown in Table 1. Method I and method II gave similar yields, but the posttreatment of method II was far easier than that



Scheme 1. Synthesis of 2-aryl-1H-benzimidazole-4-carboxylic acid.

of method I, and solvent quantity in method II was much less than that in method I. Compared with method II, method III not only simplified the experimental process but also gave better yields.

EXPERIMENTAL

General Procedure of Method I

2,3-Diaminobenzoic acid (5 g) in methanol (200 ml) was made acidic with acetic acid, and a solution of corresponding aldehyde (1.05 eq) in methanol (100 ml) was added, followed by a solution of cupric acetate [$Cu(Ac)_2 \cdot H_2O$, 1.2 eq] in water (150 ml). The mixture was stirred vigorously and heated to boiling and then filtered hot. The precipitate was washed with water and dissolved in methanol (250 ml) containing concentrated hydrochloride acid (13 ml). A slight excessive water solution of sodium sulfide was added, and the mixture was filtered hot to get rid of the copper sulfide. The filtrate was adjusted to pH 5–6 with sodium hydroxide solution, diluted with water (100 ml), and concentrated to give crude product. The crude

Table 1. Yields using different methods

Compounds	Aromatic aldehydes	Yield of method I (%)	Yield of method II (%)	Yield of method III (%)
2	2-Pyridylaldehyde	62	56	78
3	3-Pyridylaldehyde	60	58	80
4	4-Pyridylaldehyde	56	63	81
5	4-Hydroxylphenylaldehyde	52	60	78

product was purified by column chromatography (acetone and slight ammonia) to give 2-aryl-1H-benzimidazole-4-carboxylic acid.

General Procedure of Method II

2,3-Diaminobenzoic acid (2 g) was added in methanol (30 ml), followed by sodium hydroxide (1 eq) dissolved in water (10 ml). The solution was stirred during the addition of appropriate aldehyde (1.05 eq), dissolved in methanol (10 ml), and followed by potassium ferricyanide (2 eq) and sodium hydroxide (2 eq) dissolved in water (50 ml). The resulting mixture was heated to boiling. After the reaction finished (monitored by TLC), sediment was filtrated out and filtrate was adjusted to pH 5–6. The precipitate was collected and purified to get pure product by column chromatography (acetone and slight ammonia).

General Procedure of Method III

2,3-Diaminobenzoic acid (2 g) was dissolved in DMF (30 ml), followed by a solution of appropriate aldehyde (1.05 eq) in DMF (10 ml) dropwise. Potassium ferricyanide (2 eq) was added directly into the solution. The suspension was stirred vigorously and heated to 60°C. The reaction lasted about 10 h. The sediment was filtrated out and DMF was removed by vacuum distillation to give crude product. The pure product was obtained by column chromatography (acetone and slight ammonia).

2-(2-Pyridyl)-1H-benzimidazole-4-carboxylic acid (**2**): 1H MNR (DMSO, 400 MHz) d: 7.34–7.38 (t, 1H, $J = 8.0$ Hz, H-6), 7.56–7.59 (m, 1H), 7.69–7.71 (d, 1H, $J = 8.0$ Hz, H-7), 7.87–7.89 (d, 1H, $J = 8.0$ Hz, H-5), 8.02–8.06 (m, 1H), 8.45–8.47 (d, 1H), 8.76–8.77 (m, 1H). MS: $M^+ = 239$. Anal. calcd. for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.77; N, 17.57. Found: C, 65.54; H, 3.68; N, 17.40.

2-(3-Pyridyl)-1H-benzimidazole-4-carboxylic acid (**3**): 1H MNR (DMSO, 400 MHz) d: 7.34–7.38 (t, 1H, $J = 8.0$ Hz, H-6), 7.60–7.63 (m, 1H), 7.74–7.76 (d, 1H, $J = 8.0$ Hz, H-7), 7.88–7.80 (d, 1H, $J = 8.0$ Hz, H-5), 8.56–8.59 (m, 1H), 8.71–8.73 (m, 1H), 9.45 (s, 1H, H-2′). MS: $M^+ = 239$. Anal. calcd. for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.77; N, 17.57. Found: C, 65.01; H, 3.80; N, 17.62.

2-(4-Pyridyl)-1H-benzimidazole-4-carboxylic acid (**4**): 1H MNR (DMSO, 400 MHz) d: 7.34–7.38 (t, 1H, $J = 8.0$ Hz, H-6), 7.86–7.87 (d, 1H, $J = 8.0$ Hz, H-7), 7.94–7.96 (d, 1H, $J = 8.0$ Hz, H-5), 8.26–8.27 (d, 2H, $J = 4.0$ Hz, H-3′, 5′), 8.75–8.76 (d, 2H, $J = 4.0$ Hz, H-2′, 6′). MS: $M^+ = 239$. Anal. calcd. for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.77; N, 17.57. Found: C, 65.15; H, 3.82; N, 17.72.

2-(4-Hydroxylphenyl)-1H-benzimidazole-4-carboxylic acid (**5**): 1H MNR (DMSO, 400 MHz) d: 6.92–6.94 (d, 2H, $J = 8.0$ Hz, H-3′, 5′),

7.28–7.32 (t, 1H, $J = 8.0$ Hz, H-6), 7.77–7.79 (d, 1H, $J = 8.0$ Hz, H-7), 7.84–7.86 (d, 1H, $J = 8.0$ Hz, H-5), 8.14–8.16 (d, 2H, $J = 8.0$ Hz, H-2′, 6′), 10.09 (s, 1H, OH-4′). MS: M + = 254. Anal. calcd. for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.94; N, 11.02. Found: C, 65.95; H, 4.08; N, 11.20.

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