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# THE FIRST SYNTHESIS OF PROTECTED 5-HYDROXYMETHYL-2-CYANOMETHYLBENZIMIDAZOLE

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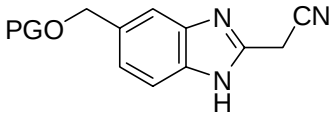
**Abstract** – Protected 5-hydroxymethyl-2-cyanomethylbenzimidazole **4** has successfully been synthesized starting from 3,4-diaminobenzoic acid **1**. The benzimidazole **4** is expected to be a useful intermediate for the synthesis of new functional molecules such as drugs, agrochemicals, dyes, perfumes, and cosmetics.

## INTRODUCTION

Fused heterocycles such as benzimidazoles, benzoxazoles, and benzothiazoles, are quite important compounds for the development of functional organic molecules such as pharmaceuticals,[1] DNA-binding molecules,[2] functional dyes,[3] and heteroaromatic polymers.[4] Benzimidazoles, in particular, 2-cyanomethylbenzimidazoles are often used as intermediates for the synthesis of numerous benzimidazole-containing compounds, for example, imidazopyridines as antifungal agents,[5] benzimidazolyl-coumarins as fluorecent dyes,[6] benzimidazolyl-ethanones as HIV-integrase inhibitors,[7] benzimidazolyl-acrylonitriles with cytotoxic activities,[8] pyrrolo[1,2-*a*]benzimidazoles with many applications,[9] and Ln(**III**) and Y(**III**) complexes of benzimidazol-2-acetic acid as plant growth promoters.[10] Some 5-substituted 2-cyanomethylbenzimidazoles are known compounds; the 5-alkyl,

alkoxy, and carboxy-substituted derivatives are reported to be prepared.[11] Protected 5-hydroxymethyl-2-cyanomethylbenzimidazole was an essential synthetic intermediate for an our project aimed at the development of a new coloring agent. No papers, however, have been reported for the 5-hydroxymethyl-substituted derivative as far as we know. The hydroxymethyl group is well known to be a good hydrogen donor/accepter, and more importantly it can be converted into numerous functional groups. The hydroxymethyl-substituted benzimidazole, therefore, is expected to be a useful intermediate for the synthesis of benzimidazole-containing functional molecules such as drugs, agrochemicals, dyes, perfumes, and cosmetics. This paper describes the first synthesis of protected 5-hydroxymethyl-2-cyanomethylbenzimidazole **4** (Figure 1).

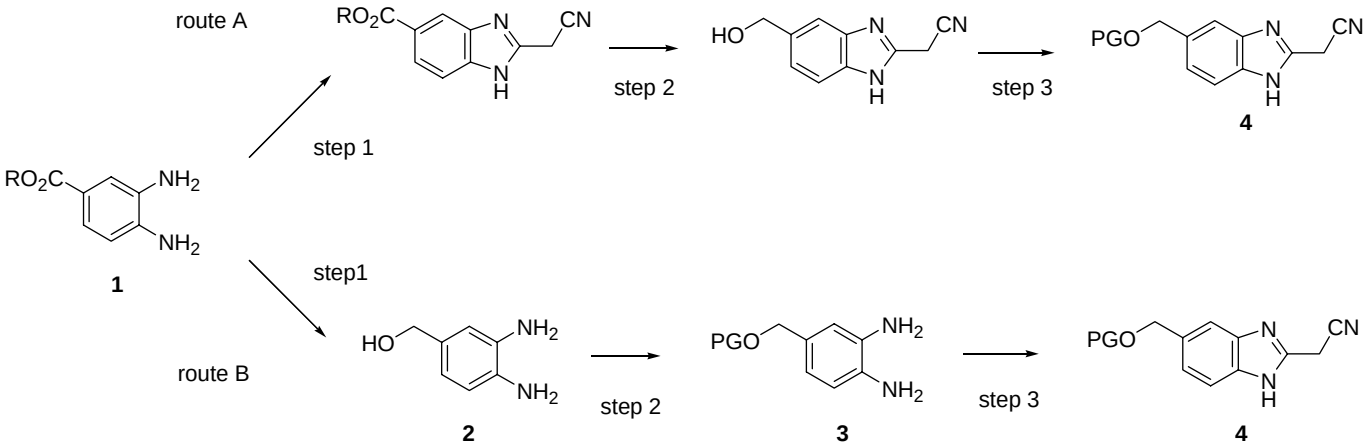



**4** (PG=TBDPS)

**Figure 1**

## RESULTS AND DISCUSSION

Two possible routes to **4** (route A and route B) were at first considered starting from 3,4-diaminobenzoic acid derivatives **1** as shown in Scheme1.

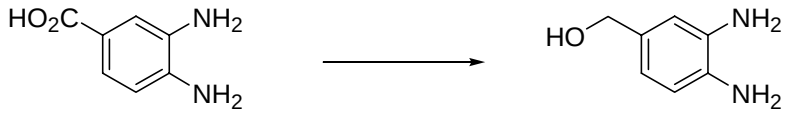



**Scheme 1**

Although the route A appears to be a reasonable process with a view to obtaining **4**, there are a few problems that should be resolved: (i) step 1 is reported to give the product in a low yield (34%) according to a literature,[11a] (ii) step 2 requires selective reduction of carboxy groups in the presence of cyano group, (iii) step 2 and/or step 3 may cause side reaction such as self condensation because cyanomethyl group

would be activated to react with electron-deficient moieties under acidic and/or basic conditions, which are usually necessary for reduction of carboxy group and introduction of protective groups. Although the route B may be an unusual process for this study, it seems to be widely applicable; the precursor **3** should be used not only for the synthesis of the desired **4** but also for that of many 1,3-benzoazoles including other benzimidazoles. At this time, therefore, we have decided to choose the route B.

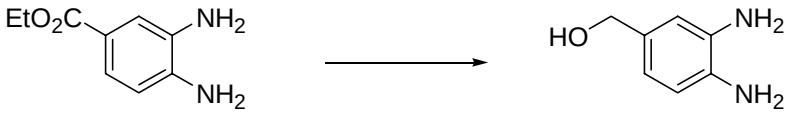
A few papers have been reported for the preparation of the intermediate 3,4-diaminobenzyl alcohol **2**[12]; they require severe reaction conditions, expensive starting materials, and/or long step procedures. Surprisingly, there are no reports for the synthesis of the alcohol **2** starting from the acid derivatives **1** in spite of a short step protocol. A direct synthesis of **2** was at first attempted by the reduction of commercially available 3,4-diaminobenzoic acid **1** as a starting material (Scheme 2).




**1** **2**

**Scheme 2**

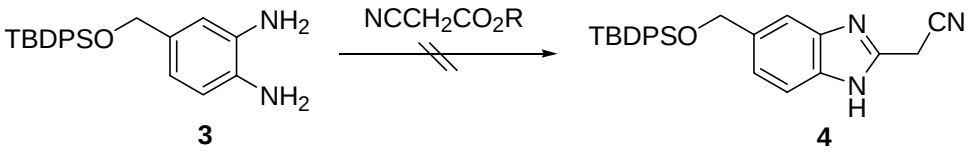
The reduction of the acid **1** with $LiAlH_4$ or $BH_3$-THF gave only a trace amount (3-6%) of **2** along with several by-products including 3,4-diaminotoluene, while that of **1** with Red-Al hardly proceeded. These results suggest that the conversion of the acid **1** into the alcohol **2** is quite difficult. As an alternative manner, the synthesis of **2** was tried by the reduction of ethyl 3,4-diaminobenzoate **1'**, which was readily prepared by the esterification of **1** (Scheme 3).




**1'** **2**

**Scheme 3**

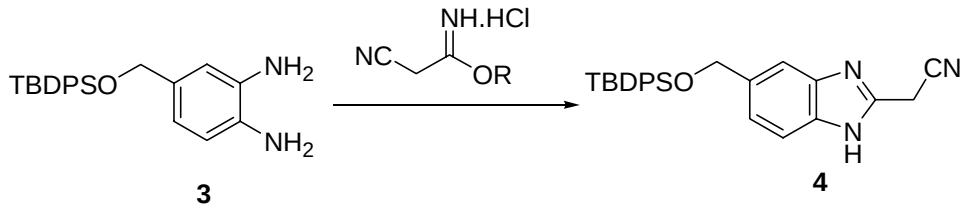
When the ester **1'** was treated with $LiAlH_4$ or Red-Al, no formation of **2** was observed because of polymerization and/or decomposition. On the other hand, the reduction of **1'** with $LiBH_4$ finally gave the desired **2** in a moderate yield (40-45%) along with the starting material **1'** (29%). Although this method is not quite versatile, this is the first example for a direct synthesis of **2** by the reduction of **1'** without protecting amino groups. When the hydroxy group in **2** was then protected with the TBDPS group by the reaction with TBDPSCl, diaminobenzyl TBDPS ether **3** was obtained in a high yield (87%). The synthesis of **4** was subsequently attempted by the reaction of **3** with cyano acetic ester according to a general method for the preparation of cyanomethylbenzimidazole (Scheme 4).[11b, 13]




**3** **4**

**Scheme 4**

When the ether **3** was treated with butyl cyanoacetate in phenetole or DMF at 150 °C, substantial unidentified materials were formed. The reaction at lower temperature was then performed in reflux toluene or MeCN. Under these conditions, however, no reaction occurred. These results indicate that the reported method is not suitable for the synthesis of substituted cyanomethylbenzimidazole such as **4**. As an alternative procedure, the reaction of **3** with cyanoacetimidate instead of cyanoacetic ester was then investigated for the synthesis of **4** (Scheme 5).




**3** **4**

**Scheme 5**

When **3** was treated with methyl cyanoacetimidate hydrochloride[14] in reflux EtOH, decomposition occurred. On the other hand, the reaction in EtOH at room temperature finally provided the desired **4** in a moderate yield (58%). The use of MeOH instead of EtOH led to a further improvement in the yield of **4** (85%). The reaction conditions have been optimized in MeOH at room temperature.

In conclusion, the first synthesis of TBDPS-protected 5-hydroxymethyl-2-cyanomethylbenzimidazole **4** has been successful in four steps starting from 3,4-diaminobenzoic acid **1**. Because the benzimidazole **4** possesses active methylene, cyano, and protected hydroxymethyl groups, this new compound can be transformed into many kinds of benzimidazole-containing derivatives. The application of **4** to a possible benzimidazole-containing functional molecule will be reported as a separate paper.

## EXPERIMENTAL

$^{1}H$ and $^{13}C$ NMR spectra were recorded with a Varian VXR-300 spectrometer using tetramethylsilane (TMS) as an internal standard. IR spectrum was measured with a JASCO FT-IR 4200 spectrometer.

All the commercially available reagents were used without further purification. Methyl cyanoacetimidate hydrochloride was prepared according to a literature method.[14a]

**Synthesis of Ethyl 3,4-diaminobenzoate 1':** 3,4-Diaminobenzoic acid **1** (8.0 g, 52.6 mmol) was suspended in EtOH (150 mL). Sulfuric acid (15.5 g) was added and the mixture was then refluxed while being stirred for 6 h. After the EtOH was removed, the residue was dissolved in water and basified with $Na_2CO_3$. The formed precipitate was filtrated, and washed with water and acetone/hexane (1/3) to give **1'** (8.05 g, yield: 85%). $^1$H NMR ($CDCl_3$): $\delta$ 1.36 (t, 3H, $J$ = 7.1 Hz), 3.46 (brs, 4H), 4.31 (q, 2H, $J$ = 7.1 Hz), 6.68 (d, 1H, $J$ = 7.8 Hz), 7.42 (d, 1H, $J$ = 2.1 Hz), 7.48 (dd, 1H, $J$ = 7.8 and 2.1 Hz).

**Synthesis of 3,4-Diaminobenzyl alcohol 2**: To a solution of ethyl 3,4-diaminobenzoate **1'** (3.60 g, 20.0 mmol) in anhydrous THF (40 mL) was added $LiBH_4$ (0.56 g, 25.5 mmol) while being stirred at rt under nitrogen atmosphere. The mixture was further stirred at 57-60 °C for 6 h. After being cooled to rt, ice water was gradually added to destroy excess hydride. After filtration of the insoluble material, the aqueous filtrate was extracted with AcOEt for a few times and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel using AcOEt/MeOH (5/1) as an eluent to give **2** (1.23 g, yield: 45%) along with starting material **1'** (1.04 g, recovery: 29%). $^1$H NMR ($CDCl_3$): $\delta$ 2.95 (brs, 4H), 4.52 (s, 2H), 6.65-6.75 (m, 3H).

**Synthesis of 4-(*tert*-Butyldiphenylsilyl)oxymethyl-1,2-benzenediamine 3:** To a suspension of the alcohol **2** (1.18 g, 8.6 mmol) in anhydrous $CH_2Cl_2$ (30 mL) were added sequentially $Et_3N$ (1.73 g, 17.1 mmol), 4-*N*, *N*-dimethylaminopyridine (100 mg, 0.7 mmol), and *tert*-butyldiphenylchlorosilane (3.53 g, 12.8 mmol) at rt while being stirred under nitrogen atmosphere. The mixture was further stirred for 3 h at this temperature. The reaction was quenched with sat. aqueous $NaHCO_3$. The organic layer was separated and washed with brine, and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel using $CH_2Cl_2$/AcOEt (1/1) as an eluent to give **3** as an oily semisolid (2.82 g, yield: 87%). $^1$H NMR ($CDCl_3$): $\delta$ 1.08 (s, 9H), 3.30 (brs, 4H), 4.63 (s, 2H), 6.66 (s, 2H), 6.68 (s, 1H), 7.34-7.42 (m, 6H), 7.70 (dd, 4H, $J$ = 7.8 and 1.8 Hz); MS m/z (%) 376 ($M^+$, 21), 301 (100), 241 (58), 199 (95), 121 (89).

**Synthesis of 2-Cyanomethyl-5-(*tert*-butyldiphenylsilyl)oxymethylbenzimidazole 4**: To a solution of the diamine **3** (3.33 g, 8.86 mmol) in MeOH (22 mL) was added methyl 2-cyanoacetimidate hydrochloride (2.40 g, 17.82 mmol) at rt. The mixture was then stirred for 2 h at this temperature. The

reaction was quenched with sat. aqueous $NaHCO_3$ and extracted with AcOEt. After filtration of the insoluble material, the organic layer was separated and washed with water and brine, and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel using $CH_2Cl_2$/AcOEt (1/1) as an eluent to give **4** as an oily semisolid (3.21 g, yield: 85%). IR (KBr) $\nu$ 2200 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.09 (s, 9H), 4.12 (s, 2H), 4.88 (s, 2H), 7.22 (d, 1H, $J$ = 8.2 Hz), 7.33-7.44 (m, 6H), 7.54 (d, 1H, $J$ = 8.2 Hz), 7.63 (s, 1H), 7.69 (d, 4H, $J$ = 7.8 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 19.2, 19.3, 26.8, 65.6, 115.1, 121.9, 127.7, 129.7, 133.5, 135.5, 142.5. HRFABMS: *m/z* calcd for $C_{26}H_{28}N_3OSi$ $(M + H)^+$ 426.2002, found 426.1963.

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