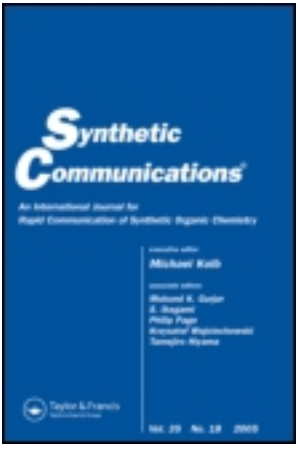

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Biomimetic Synthesis of Symmetric Acyclic Diketones

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ABSTRACT

A convenient synthetic method for the preparation of symmetric acyclic diketones from dicarboxylic acids is provided. Three *bis*-benzimidazolium salts were used as tetrahydrofolate coenzyme model, thus the biomimetic synthesis of three symmetric acyclic diketones was successfully accomplished by using the addition-hydrolysis reaction of corresponding *bis*-benzimidazolium salts with methyl magnesium iodide.

Key Words: Biomimetic synthesis; Symmetric acyclic diketone; *bis*-Benzimidazolium salt; Grignard reagent.

Acyclic diketones are an important class of compounds in view of their distinct structural feature and wide utility in the medical industry, dyeing

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industry, and organic synthesis.[1] A number of methods have been reported so far for the synthesis of diketones.[2] However, some of these methods suffer from disadvantages with respect to convenience, selectivity, or efficiency and have limited applicability in preparing diketones containing fewer than six methylenes.

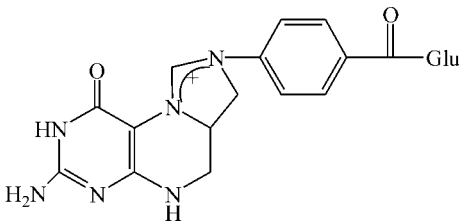
Recently, the function of tetrahydrofolate coenzymes for organisms and the use in biomimetic synthesis have been an important subject of biochemistry.[3] The tetrahydrofolate coenzymes are involved in the biochemical transfer of a one-carbon fragment at different oxidation levels. The structure is as shown in Sch. 1, which is at the formic acid oxidation level.

The five-membered ring structure is the active site.[4] *bis*-Benzimidazolium salt contains two of this kind of five-membered ring and can be used as the tetrahydrofolate coenzyme model at formic acid oxidation level.

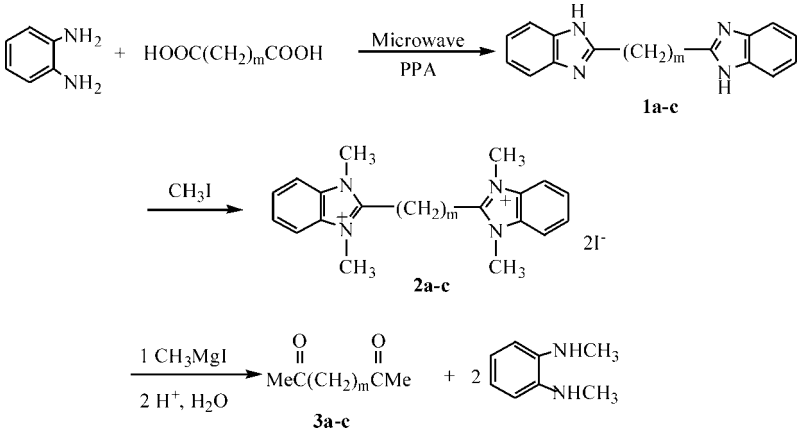
We reported the reaction of benzimidazolium salts with Grignard reagents in which a novel synthetic method for ketone was provided.[5] In extention of our method, the reaction of *bis*-benzimidazolium salts with methyl magnesium iodide was studied, and a convenient synthetic method for the preparation of several symmetric acyclic diketones containing more than six methylenes was provided (Sch. 2).

It has been reported that compounds with a quaternary C═N doubly group react with Grignard reagents.[6] But the method for preparing symmetric acyclic diketones containing more than six methylenes from dicarboxylic acids and methyl magnesium iodide as Grignard reagent via *bis*-benzimidazolium salts has not been reported in literature. Since *bis*-benzimidazole can be prepared from dicarboxylic acid, the method provides an important route for preparing symmetric acyclic diketones from dicarboxylic acid and Grignard reagent.

In our experiments, the addition of Grignard reagent to *bis*-benzimidazolium salt was carried out. *bis*-Benzimidazolidine obtained from the addition reaction could be hydrolyzed directly to give diketone in acidic solution after the addition reaction was finished, so a convenient and simple synthetic method for symmetric diketone was realized.



Scheme 1.



PPA = Polyphosphoric acid; a: m = 6; b: m = 7; c: m = 8

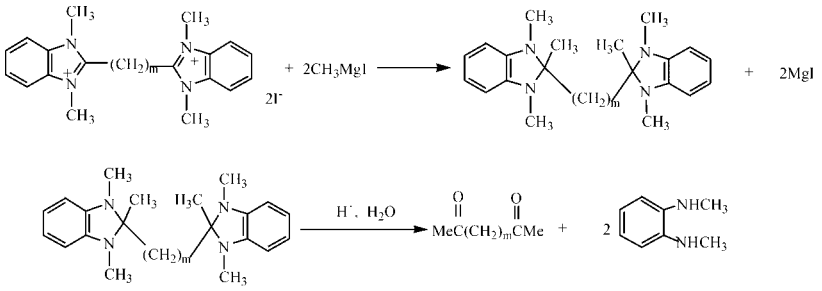
Scheme 2.

Compared with the synthetic methods described in the literature, our method employed *o*-phenylenediamine, dicarboxylic acids, and iodomethane as starting materials, which are readily available. Three symmetric acyclic diketones (**3a**, **3b**, and **3c**) were synthesized in two steps from *bis*-benzimidazolium salts and Grignard reagent. *bis*-Benzimidazolium salts (**2a**, **2b**, and **2c**) can be synthesized from dicarboxylic acids, phenylenediamine, and iodomethane.[7,8] Grignard reagent was prepared according to the literature.[9] The method is simple and the yield is high. This is a new entry to the synthesis of symmetric acyclic diketones containing more than six methylenes.

The mechanism for the reaction of benzimidazolium salt with nucleophile has been proposed in our earlier paper.[5] The preparative reaction described in this paper can be reasonably explained by the addition reaction of nucleophilic Grignard reagent with polarized C=N bond of *bis*-benzimidazolium salt and the formation of *bis*-benzimidazolidine, which can be hydrolyzed in acidic solution to give the corresponding diketone (Sch. 3).

EXPERIMENTAL

Melting points were taken on a XT-4 micro-melting apparatus (Beijing) and uncorrected. TLC analysis was carried out on glass plates coated with silica gel-G, and spots were visualized using an ultraviolet (UV) lamp. Elemental analyses were performed with a Vario EL-III instrument (Germany) infrared (IR) spectra in cm^{-1} were recorded on a Brucker



Scheme 3.

EQUIOX-55 spectrometer (Germany). ^{1}Proton magnetic resonance spectra (H NMR) spectra were recorded at 400 MHz on a Varian INOVA-400 spectrometer (USA), and chemical shifts were reported relative to internal Me_4Si.

General Procedure for the Preparation of *bis*-Benzimidazolium Salts (2a, 2b, and 2c)

bis-Benzimidazolium salt (**2a**, **2b**, or **2c**) was prepared by literature procedures.[8] A solution of sodium (0.02 mol) in ethanol was treated with 0.01 mol of *bis*-benzimidazole (**1a**, **1b**, or **1c**), 0.06 mol of iodomethane, and 25 mL of benzene, then the mixture was refluxed for 18 hr. The solvent was removed and the residue was recrystallized from water-ethanol (1 : 1) to give *bis*-benzimidazolium salt (**2a**, **2b**, or **2c**). The *bis*-benzimidazole (**1a**, **1b**, or **1c**) was prepared from *o*-di-aminobenzene and dicarboxylic acids in polyphosphoric acid under microwave irradiation according to the literature.[7] Compound **2a** as a yellow solid, yield 90%, m.p. over 300°C. Anal. $C_{24}H_{32}I_2N_4$. Calcd: C 47.4, H 5.47, N 8.51. Found: C 47.1, H 5.25, N 8.17. Compound **2b** as a yellow solid, yield 88%, m.p. over 300°C. Anal. $C_{25}H_{34}I_2N_4$. Calcd: C 46.5, H 5.28, N 8.69. Found: C 46.3, H 4.96, N 8.32. Compound **2c** as a yellow solid, yield 91%, m.p. over 300°C. Anal. $C_{26}H_{36}I_2N_4$. Calcd: C 45.7, H5.08, N 8.89. Found: C 45.4, H 4.71, N 8.42.

General Procedure for the Synthesis of Symmetric Acyclic Diketones (3a, 3b, and 3c)

bis-Benzimidazolium salt (0.01 mol) (**2a**, **2b**, or **2c**) was added in small portions to a solution of Grignard reagent (0.05 mol) in tetrahydrofuran over 30 min. The mixture was stirred for 30 hr at room temperature. A 5% dilute HCl (30 mL) was added slowly and the mixture was heated in hot water

bath for 1.0–1.5 hr with stirring. Tetrahydrofuran was removed by distillation and the residue was extracted with chloroform (5 × 25 mL). The extract was successively washed with 5% sodium bicarbonate and water to make its pH 7. The chloroform solution was dried over anhydrous $MgSO_4$ and evaporated to give the crude product (**3a**, **3b**, or **3c**) as a white crystalline mass, which was purified by chromatography (SiO_2, chloroform).

Compound **3a** as a white solid, yield: 83%, m.p. 65°C–66°C (lit.[10] 64°C). υmax (KBr): 1710 (C═O), 2930, 2956, 729. 1H NMR (CDC_{13}/TMS), δ (ppm): 1.20–1.90 (m, 8H, 4 × CH_2), 2.10 (s, 6H, 2 × CH_3), 2.35 (t, J = 7 Hz, 4H, 2 × $COCH_2$). Anal. $C_{10}H_{18}O_2$. Calcd: C 70.59, H 10.59. Found: C 70.51, H 10.72.

Compound **3b** as a white solid, yield: 80%, m.p. 64°C–65°C (lit.[11] 63°C–65°C). υmax (KBr): 1708 (C═O), 2940, 2850, 726. 1H NMR (CDC_{13}/TMS), δ (ppm): 1.20–1.90 (m, 10H, 5 × CH_2), 2.13 (s, 6H, 2 × CH_3), 2.42 (t, J = 7 Hz, 4H, 2 × $COCH_2$). Anal. $C_{11}H_{20}O_2$. Calcd: C 71.74, H 10.87. Found: C 71.28, H 10.65.

Compound **3c** as a white solid, yield: 85%, m.p. 67°C–68°C (lit.[11] 64°C–66°C), υmax (KBr): 1706 (C═O), 2931, 2853, 718. 1H NMR (CDC_{13}/TMS), δ (ppm): 1.20–1.70 (m, 12H, 6 × CH_2), 2.13 (s, 6H, 2 × CH_3), 2.41 (t, J = 7 Hz, 4H, 2 × $COCH_2$). Anal. $C_{12}H_{22}O_2$. Calcd: C 72.73, H 11.11. Found: C 72.92, H 11.06.

CONCLUSIONS

A convenient and efficient procedure of synthesis for the preparation of symmetric acyclic diketone containing more than six methylenes was developed. The biomimetic synthesis of three symmetric acyclic diketones was successfully accomplished by using the addition-hydrolysis reaction of corresponding *bis*-benzimidazolium salts with methyl magnesium iodide.

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