New synthetic method for cycloalkanedione*

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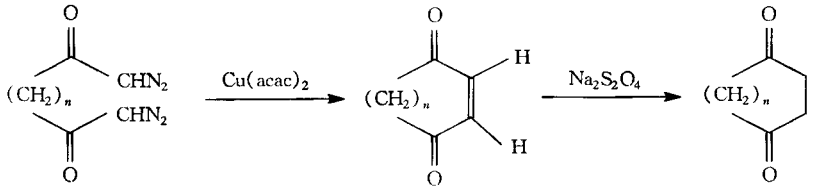
Received September 19, 1997

Abstract Four kinds of cycloalkanedione were prepared from bis-benzimidazole methiodide salt and bis-Grignard reagent, the addition-hydrolysis reaction of bis-benzimidazole methiodide salt with bis-Grignard reagent is reported and a novel method for the preparation of various kinds of cycloalkanedione is provided.

Keywords: bis-benzimidazole methiodide salt, bis-Grignard reagent, cycloalkanedione, synthesis.

The synthetic methods in literature for preparing cycloalkanedione compounds used as valuable perfume usually are special, the syntheses of some cycloalkanedione compounds are extremely difficult. 1,6-Cyclododecanedione was prepared previously by Fonken et al.[1] via microbiological hydroxylation of monocyclic alcohols and by Niles and Snyder[2] via ozonolysis of bicyclic olefin obtained by treatment of cyclododecatriene with strong sulfuric acid. Blomquist and Spencer[3] reported that acid chlorides were dehydrohalogenated by tertiary aliphatic amines to form the bifunctional ketene derivatives. Under conditions of high dilution, cyclic ketene derivatives were obtained. Hydrolysis and decarboxylation of the derivatives gave the large-ring ketones and diketones, but the yield of the diketones was quite low. 1,4-Cycloalkanediones were prepared by Kulkowit et al.[4] via the reduction of 1,4-cycloalkanediones obtained by intramolecular coupling of bis-diazoketones in the presence of bisacetylacetonatocopper. It provided a useful procedure for the preparation of 1,4-cycloalkanediones (scheme 1).



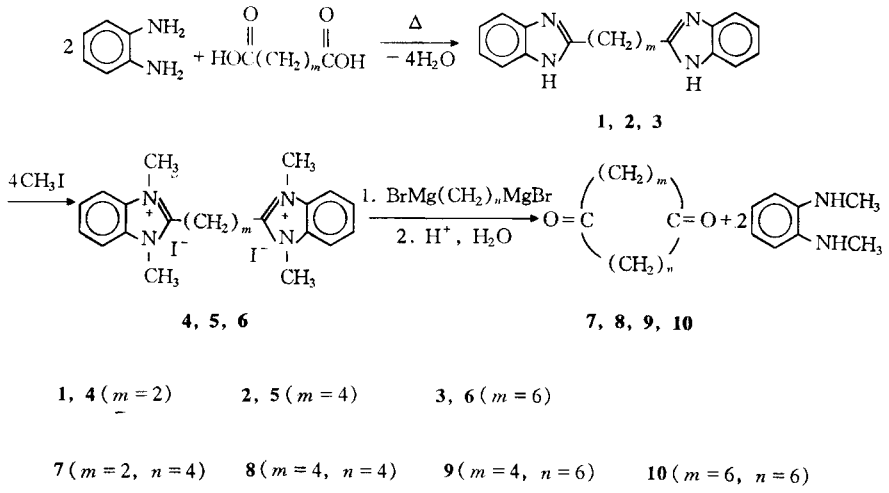
$n = 4, 7, 8, 9, 10, 12, 15$

Scheme 1

We reported the addition reaction of benzimidazole methiodide salts with Grignard reagent, providing a new method for the preparation of aldehydes and ketones via the addition reaction[5]. In this paper, the addition-hydrolysis reaction of bis-benzimidazole methiodide salt with bis-Grignard reagent is reported. Bis-benzimidazoles (**1**—**3**) and bis-benzimidazole methiodide salts (**4**—**6**) were prepared from *o*-phenylenediamine and dicarboxylic acids. 1,4-Cyclooctanedione

* Project supported by the Natural Science Foundation of Shaanxi Province.

(7), 1,6-cyclodecanedione (8), 1,6-cyclododecanedione (9), 1,8-cyclotetradecanedione (10) were prepared successfully from the addition-hydrolysis reaction of bis-benzimidazole methiodide salts with bis-Grignard reagents (scheme 2).



Scheme 2

The syntheses of bis-benzimidazole (1—3) and bis-benzimidazole methiodide salt (4—6) have been reported[6], but the reaction of bis-benzimidazole methiodide salt with bis-Grignard reagent has not been reported. The synthetic method for the preparation of cycloalkanedione compounds has not been reported, either.

According to the synthetic route of four cycloalkanediones, if dicarboxylic acids and bis-Grignard reagents with different structures are used for the preparation of cycloalkanediones, the corresponding cycloalkanediones with different structures can be obtained. In general, the synthetic methods in literature are only used for some special cycloalkanediones; for example, the method for the preparation of cycloalkanedione in the presence of bis-acetylacetonatocopper catalyst described by Kulkowit et al. can only be used for 1,4-cycloalkanedione. The method described in this paper may be used for the preparation of a variety of cycloalkanediones with different membered ring and carbonyl groups at different positions, it thus provides an important synthetic method for the preparation of a variety of cycloalkanediones, especially for a variety of large-ring cycloalkanediones.

Compared with the synthetic methods described in literature, the method described in this paper employs more available starting materials, *o*-phenylenediamine, dicarboxylic acids and dihaloalkanes, requires a moderate reaction condition and gives a good yield. This method provides a valuable synthetic procedure for the preparation of cycloalkanediones, especially for valuable large-ring cycloalkanediones. It will take an important role in the syntheses of cycloalkanediones and in the perfume industry.

1 Experimental

1.1 Apparatus

IR spectra were recorded on a Perkin Elmer IR-440 spectrophotometer on a KBr matrix. Melting points were taken on a Model X4 melting point apparatus and uncorrected. Reactions

were monitored by thin layer chromatography using Alugram silica gel/UV_{254}.

1.2 Synthesis of bis-benzimidazole (**1**—**3**) and bis-benzimidazole methiodide salt (**4**—**6**)

Bis-benzimidazole (**1**—**3**) and bis-benzimidazole methiodide salt (**4**—**6**) were prepared by literature procedures[6]. *o*-Phenylenediamine and dicarbonic acid were heated, and then water was removed to give bis-benzimidazole. The preparation of bis-benzimidazole methiodide salt was achieved in high yield by the reaction of bis-benzimidazole with methyliodide and sodium methoxide in refluxing benzene for 18 h. The crude products were recrystallized from acetone or ethanol.

1.3 Synthesis of bis-Grignard reagent

Bis-Grignard reagents were prepared by literature procedures[7].

1.4 Synthesis of cycloalkanedione (**7**—**10**)

Bis-Grignard reagent (0.015 mol) in tetrahydrofuran (200 mL) was injected into a three-necked round-bottomed flask. Bis-benzimidazole methiodide salt (0.01 mol) was than added in small portion to the bis-Grignard reagent solution over 30 min. The mixture was stirred for 28—30 h, a saturated aqueous solution of oxalic acid (20 mL) was then added, and the mixture was heated in hot water bath for 1.0—1.5 h with stirring. Tetrahydrofuran was removed and the residue was extracted with benzene or chloroform (5 × 30 mL). The extracts were washed with 5% sodium bicarbonate and dried over anhydrite $MgSO_4$. After removal of benzene or chloroform by distillation, the crude product was crystallized from acetone (10%)-petroleum ether.

Compound **7**: slightly yellow crystals, yield 52.0%, m.p. 44—46℃ [lit.[8] m.p. 46.8℃], IR: 1 690 (C=O) cm^{-1}. Compound **8**: slightly yellow crystals, yield 54.0%, m.p. 92—94℃ [lit.[9] m.p. 92—95℃], IR: 1 670 (C=O) cm^{-1}. Compound **9**: colorless crystals, yield 48.0%, m.p. 93—94℃ [lit.[2] m.p. 94—95℃], IR: 1 659 (C=O) cm^{-1}. Compound **10**: colorless crystals, yield 31.5%, m.p. 146—148℃ [lit.[3] m.p. 147.5—148℃], IR: 1 640 (C=O) cm^{-1}.

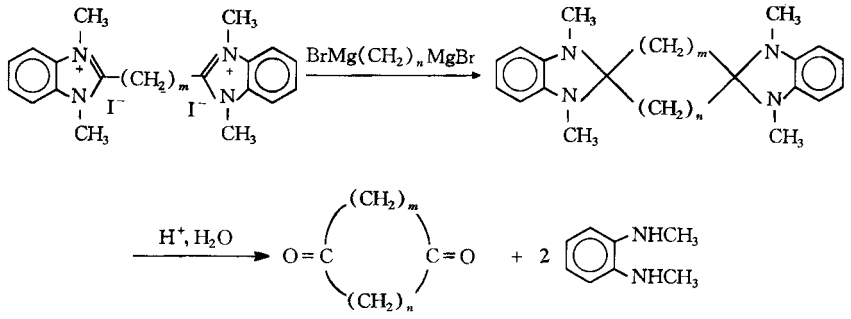
2 Results and discussion

2.1 Mechanism

The reaction of bis-benzimidazole methiodide salt with bis-Grignard reagent has not been reported in literature. It was found that free bis-benzimidazole could not successfully undergo the reaction with bis-Grignard reagent. So the reaction of bis-benzimidazole methiodide salt with bis-Grignard reagent is probably the nucleiphilic addition reaction of bis-Grignard reagent with polarized C=N double bond. The intermediate of the reaction is bis-benzimidazolidine, which is then hydrolysed to cycloalkanedione in the acidic condition. The probable mechanism of the reaction is as shown by scheme 3.

2.2 Effect of reaction condition on the yield of cycloalkanedione

It was found that the reaction of bis-benzimidazole methiodide salt with bis-Grignard reagent was finished in high yield when tetrahydrofuran was used as solvent. Since the reaction is a cycle-closed reaction between the molecules, more tetrahydrofuran should be used in order to raise the yield. It is not necessary to separate the product of addition of bis-benzimidazole methiodide salt with bis-Grignard reagent, the addition product is hydrolysed directly to cycloalkanedione after the addition reaction is finished.



Scheme 3

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