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Steric effects of polymethylcarboranes. Unusual reactivity of *N*-(deca-*B*-methyl-1,12-dicarba-*closo*-dodecaborane-1-carbonyl)pyridinium

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Abstract

Reaction of deca-*B*-methyl-1,12-dicarba-*closo*-dodecaborane-1-carbonyl chloride with aniline in pyridine gives predominantly deca-*B*-methyl-1,12-dicarba-*closo*-dodecaborane-1-carboxamide, accompanied by a small amount of the expected anilide. The results may be interpreted in terms of nucleophilic attack of aniline at the 2′-position of the *N*-(deca-*B*-methyl-1,12-dicarba-*closo*-dodecaborane-1-carbonyl)pyridinium intermediate, followed by ring-opening of the pyridine nucleus and recyclization.

Keywords: carboranes; pyridinium salts; steric effect; strain effect; Reissert compounds.

The electronic structures of icosahedral *closo* carboranes have been described as three-dimensional aromatic systems, and the implications for electronic interactions with substituents have been of particular interest since the first studies of these compounds.[1] This feature of the icosahedral structure gives rise to unusual properties. In addition, the carborane cage is highly stable, and its hydrophobic character is comparable to that of hydrocarbons. Recently, we have been interested in new medicinal applications of the boron clusters as hydrophobic pharmacophores, and we have reported examples of the design, synthesis and biological evaluation of potent nuclear receptor ligands, such as retinoids[2] and estrogens[3] containing a carborane cage.

The synthesis of deca-*B*-methyl-1,12-dicarba-*closo*-dodecaborane (**1**) has been achieved by electrophilic methylation of 1,12-dicarba-*closo*-dodecaborane with methyl trifluoromethane-sulfonate.[4,5] The polymethyl carborane **1** provides a unique hydrocarbon surface due to its methyl substituents, and is termed a 'camouflaged' carborane. It may have a potential as a new bulky and hydrophobic unit for biologically active molecules. However, an understanding of the fundamental reactivity of **1** is required before polymethylcarborane can be used as a component of designed molecules. Recently, we have reported the preparation and reactivity of deca-*B*-methyl-1,12-dicarba-*closo*-dodecaborane-1-carboxylic acid (**2**) and its derivatives.[6] The reactivity of the carboxyl group of **2** was greatly reduced by the

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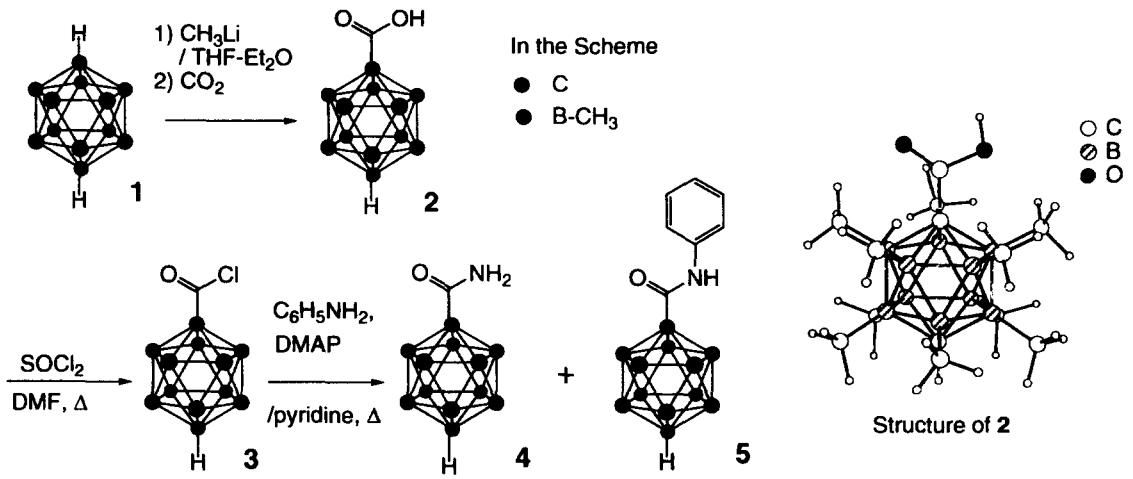

Figure 1. Transformation of deca-*B*-methyl-1,12-dicarba-*closo*-dodecaborane (Scheme) and structure of **2**

steric effect of the surrounding five *B*-methyl groups. For example, esterification of **2** did not proceed by acid-catalyzed condensation with alcohol, but was achieved via the stable crystalline acid chloride (**3**). Furthermore, the methyl ester of **2** was not hydrolyzed under basic conditions.[6] The exceptional steric character of polymethylcarboranes may allow their application to obtain an unusual reactivity in various reaction systems. In this paper, we describe the unusual reaction of deca-*B*-methyl-1,12-dicarba-*closo*-dodecaborane-1-carbonyl chloride (**3**) in pyridine, and a preparation of a novel pyridine Reissert compound stabilized by steric character.

The chloride **3** reacted with cyclohexylamine in pyridine in the presence of 4-*N*,*N*-dimethylamino-pyridine (DMAP) to give the amide in high yield. However, reaction of **3** with aniline in pyridine in the presence of DMAP at 120°C afforded deca-*B*-methyl-1,12-dicarba-*closo*-dodecaborane-1-carboxamide (**4**)[7] in a yield of 83%, accompanied with the expected anilide (**5**)[8] (12%) (Fig. 1). When the reaction was performed without pyridine, the anilide **5** was obtained in quantitative yield. Therefore, the formation of **4** can be explained in terms of nucleophilic attack of aniline at the 2′-position of the *N*-(deca-*B*-methyl-1,12-dicarba-*closo*-dodecaborane-1-carbonyl)pyridinium intermediate (**6**), followed by ring-opening and reconstruction of the pyridine ring (Fig. 2). The expected product, *N*-phenylpyridinium (**7**) chloride, was isolated by aqueous extraction of the reaction mixture in a yield of 62%.

The characteristic stability of the pyridine ring is lost when quaternization by certain nucleophilic agents takes place. For example, *N*-2,4-dinitrophenylpyridinium chloride was heated with aniline to give 2,4-dinitroaniline and *N*-phenylpyridinium chloride.[9] The reaction is used for the preparation of *N*-phenylpyridinium chloride, as well as in the synthesis of glutaconaldehydes and 5-amino-2,4-pentadienals.[10] Pyridine ring opening is favored by the presence of a substituent at the pyridine nitrogen such as 2,4-dinitrophenyl, cyano, sulfonate, etc. An *N*-carbonyl substituent is usually unfavorable for pyridine ring opening because of its electrophilic character. Steric hindrance of the carbonyl group of **6** by the surrounding five *B*-methyl groups changes the position of nucleophilic attack of aniline from the carbonyl group to 2′-position of the pyridine ring. Analogously, reaction of 2,4,6-trimethylbenzoyl chloride (**8**), which was obtained from the acid, with aniline under the same conditions gave 2,4,6-trimethylbenzamide (**9**, 64%) and the anilide (**10**, 8%). On the other hand, the parent 1,12-dicarba-*closo*-dedecaborane-1-carbonyl chloride with aniline under the same condition afforded the corresponding anilide in a quantitative yield. These results suggest that the reaction depends on the steric effect.[11]

The suppression of attack of the nucleophile on the carbonyl carbon and reaction with the 2′-position

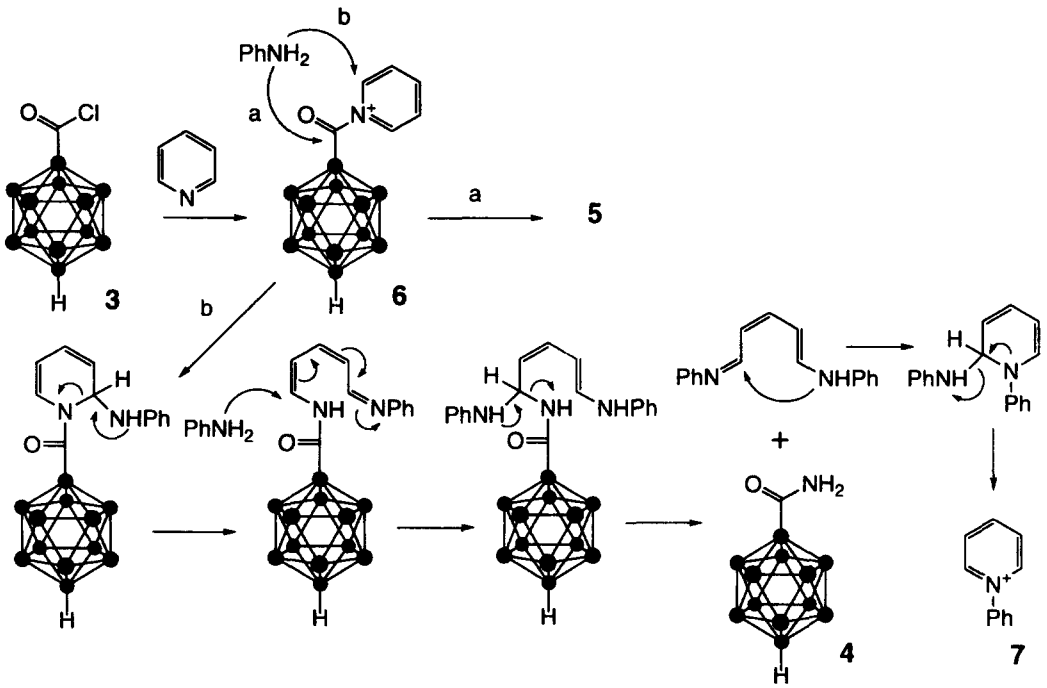

Figure 2. Mechanism for the reaction of deca-*B*-methyl-1,12-dicarba-*closo*-dodecaborane-1-carbonyl chloride with aniline

of the pyridine ring of **6** owing to the steric factor would be applicable to prepare pyridine Reissert compounds. Although Reissert compounds have been prepared from quinoline, isoquinoline, and a large number of aromatic nitrogen heterocyclic systems, the first pyridine Reissert compounds were reported only in 1987. 1-Benzoyl-2-cyano-1,2-dihydropyridine has been prepared from pyridine, benzoyl chloride and trimethylsilyl cyanide in the presence of aluminum chloride in a yield of 3.5%. Some 3-substituted pyridines have also been converted to Reissert compounds in yields of 13–45%.[12] Other Reissert analogs have been obtained with the pyridine-*N*-carbamates.[13]

Our attempts to prepare pyridine Reissert compounds using the polymethylcarboranyl chloride **3**, pyridine and trimethylsilyl cyanide in the presence of aluminum chloride were unsuccessful. However, the reaction of 2,4,6-trimethylbenzoyl chloride (**8**) with equimolar amounts of pyridine and trimethylsilyl cyanide afforded 1-(2,4,6-trimethylbenzoyl)-2-cyano-1,2-dihydropyridine (**11**)[14] in 96% yield (Fig. 3).

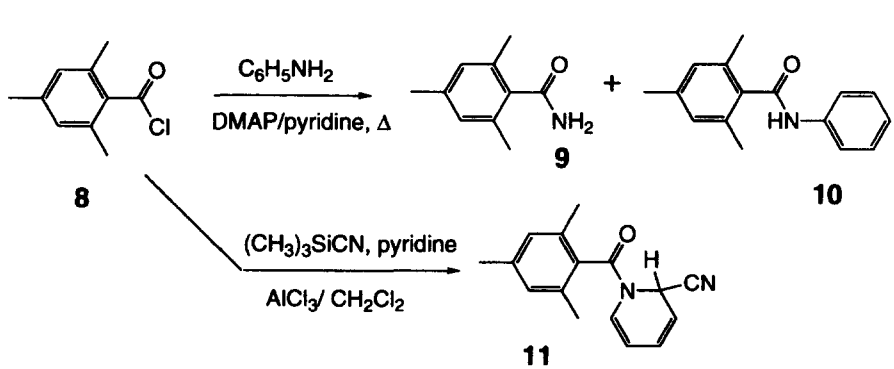

Figure 3. Reaction of 2,4,6-trimethylbenzoyl chloride

The pyridine Reissert compound **11** was obtained in a 71% yield by heating a mixture of **8**, trimethylsilyl cyanide and excess pyridine without a Lewis acid catalyst.

In summary, we have found that nucleophilic attack on the carbonyl group of *N*-acylpyridinium was suppressed by the steric effect of the polymethylcarboranyl group to afford a product derived from attack at the 2-position of the pyridinium ring. A similar steric effect was observed in the case of the 2,4,6-trimethylphenyl group, and was employed to prepare a pyridine Reissert compound.

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7. Colorless prisms (CH_3CN); mp 210–211°C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.08, 0.19 (each s, 15H, BCH_3), 2.21 (s, 1H, CH), 5.19 (br s, 2H, NH_2). HRMS calcd: 327.3565 for $C_{13}{}^{10}B_2{}^{11}B_8H_{33}ON$. Found: 327.3563; anal. calcd for $C_{13}B_{10}H_{33}ON$: C, 47.67; H, 10.16; N, 4.28. Found: C, 47.59; H, 9.96; N, 4.23.
8. Colorless prisms (CH_3OH); mp 173–174°C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.11, 0.27 (each 15H, s, BCH_3), 2.25 (1H, s, CH), 6.94 (1H, br s, NH), 7.10 (1H, t, *J*=7.3 Hz), 7.28 (2H, t, *J*=7.3 Hz), 7.33 (2H, d, *J*=8.5 Hz). Anal. calcd for $C_{19}B_{10}H_{37}ON$: C, 56.54; H, 9.24; N, 3.47. Found: C, 56.83; H, 9.03; N, 3.54.
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14. Pale yellow prisms (CH_3Cl_2-*n*-hexane); mp 121–122°C; ^1H NMR ($CDCl_3$, 400 MHz). Two conformational states (95:5), resulting from *cis–trans* isomerization of the amide C–N bond, were observed in $CDCl_3$. Major conformer: δ 2.09 (s, 3H, Ar-CH_3), 2.25 (s, 3H, Ar-CH_3), 2.30 (s, 3H, Ar-CH_3), 5.36 (m, 1H, 5′-H), 5.71 (m, 1H, 3′-H), 6.13 (dd, 1H, *J*=8.4, 0.6 Hz, 6′-H), 6.22 (m, 1H, 4′-H), 6.32 (dd, 1H, *J*=6.1, 0.6 Hz, 2′-H), 6.86 (s, 1H, Ar-H), 6.92 (s, 1H, Ar-H). Minor conformer: δ 2.17 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-CH_3), 2.35 (s, 3H, Ar-CH_3), 5.15 (d, 1H, *J*=6.4 Hz, 2′-H), 5.55 (m, 1H, 3′-H), 5.85 (m, 1H, 5′-H), 6.32 (m, 1H, 4′-H), 6.98 (s, 2H, Ar-H), 7.36 (d, 1H, *J*=7.0 Hz, 6′-H). Anal. calcd for $C_{16}H_{16}ON_2$: C,76.17; H, 6.39; N, 11.10. Found: C, 76.10; H, 6.54; N, 10.98.