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Oxidative Debenzylation and Acetylation of Hexabenzylhexaazaisowutzitane

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Abstract: The oxidative reactivity of hexabenzylhexaazaisowutzitane (HBIW) under different conditions was studied. It was found that the N-benzyl groups were found to form benzoyl group after oxidation. They might also be first debenzylated and then acetylated by potassium permanganate in acetic anhydride/DMF.

Key words: N-benzyl; oxidation; debenzylation; acetylation

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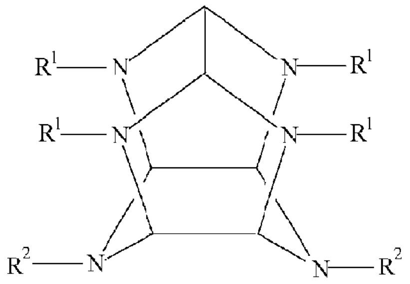
1 Introduction

2, 4, 6, 8, 10, 12-hexabenzyl-2, 4, 6, 8, 10, 12-hexaazatetracyclo [5, 5, 0, $0^{5,9}$, $0^{3,11}$] dodecane (hexabenzylhexaazaisowutzitane, HBIW, 1), an interesting cage compound, was first successfully synthesized by the condensation of benzyl amine and glyoxal by Nielsen[1]. It is the starting material of hexanitrohexaazaisowutzitane, (HNIW, 2)[2~4], which is a high energy density material attracting considerable interest because of its multifarious uses. There are two slightly different methods for producing 2. According to one method, 1 is subject to a two-step catalytic hydrogenolysis so as to produce tetraacetyldiformylhexaazaisowutzitane, (TADF, 3)[5], which is then nitrolyzed by following the standard method to afford 2. According to another method, 1 is subject to hydrogenolysis in acetic anhydride so as to replace four of the six benzyl groups to give tetraacetyldibenzylhexaazaisowutzitane, (TADB, 4)[2]. Nitrosation of TADB would then result in the formation of tetraacetyldinitrosohexaazaisowutzitane 5[2], which is then nitrolyzed to obtain 2. In either case, the removal of the benzyl groups requires a catalytic hydrogenolysis with Pd as the catalyst, which has its drawbacks[6] when used on an industrial scale. So, in order to develop non-hydrogenolytic methods for removing the benzyl groups of 1, we have explored a series of oxidative reactions of 1.



1. $R^1 = R^2$ = benzyl 2. $R^1 = R^2 = NO_2$

3. R^1 = acetyl, R^2 = formyl 4. R^1 = acetyl, R^2 = benzyl

5. R^1 = acetyl, R^2 = NO 6. $R^1 = R^2$ = benzoyl

7. R^1 = benzoyl, R^2 = benzyl

2 Results and discussion

For removing the benzyl group from 1, some single-electron oxidants were examined under various conditions. Ceric ammonium nitrate (CAN) is an efficient reagent for chemoselective oxidative debenzylation of tertiary N-benzyl amines[7]. But treated with CAN, 1 failed to undergo debenzylation, and an oxidative cleavage of C(1)-C(7) bond occurred instead. The peroxydisulfate ion, $S_2O_8^{2-}$, one of the strongest oxidizing agents[8], turned out to be able to successfully remove the benzyl group of N-benzyldenosines[9]. Treating 1 with ammonium peroxydisulfate in Ac_2O only resulted in a retrieval of the reactant. Metal salt catalysis is particularly important in many oxidations because it often governs the overall selectivity[8], our research aimed at finding out a metal-ion

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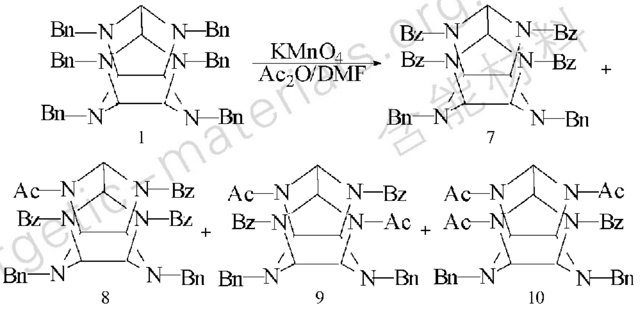
catalyst that can carry out the Oxidation of $(NH_4)_2S_2O_8$ under milder debenzylation conditions has proved unsuccessful. When the reaction was carried out in the presence of Fe^{3+} or Cu^{2+}, the cage broke quickly. Although potassium *t*-Butoxide-Dimethyl Sulphoxide, an autoxidation system, can remove N-benzyl rapidly by bubbling the air through reaction mixture[10], yet under the same conditions, 1 failed to react. When Ac_2O was added to the system the cage of 1 broke.

Permanganate has been widely used as a strong, readily available and versatile oxidant[11]. In the presence of a phase transfer catalyst, permanganate can oxidize benzylamines to produce amides efficiently[12]. By treating 1 with potassium permanganate in CH_2Cl_2 in the presence of tetraethytammoniumbromide, some oxidized products, not debenzylated products, but N-benzoylated products, hexabenzoylhexaazaisowurtzitane (HBzIW 6) and tetrabenoyldibenzyl-hexaazaisowurtzitane 7 could be obtained[13]. In order to remove the benzyl groups, some other solvents were examined, when acetic anhydride/DMF was used as a solvent, debenzylation and acetylation of N-benzyl occurred; Compounds 7, 8, 9 and 10 were obtained in 15%, 14%, 10% and 10% yield, respectively. The structure of compund 8, 9 or 10 was identified as monoacetyltribenzoyldibenzylhexaazaisowutzitane, diacetyldibenzoyldibenzylhexaazaisowutzitane and triacetylmonobenzoyldibenzyl-hexaazaisowutzitane by IR, ^{1}HNMR and MS. Products from decomposition of the cage system or the partial acylation were also observed; and such a yield raised as the reaction temperature raised. Anhydrous sodium carbonate was added to improve the pH, the yield of compound 8, 9 and 10 raised in small quantity. The above results indicate that the reaction of N-benzyl might have two mechanisms: changing into benzoyl group or debenzylating and then acetylating. The lack of selectivity of permanganate is due, at least in part, to its ability to react readily by either one-electron or two-electron pathways and to convert into even stronger oxidants such as MnO_3^{+}[12]. But the mechanisms are not clear yet. The permanganate/acetic anhydride system could be developed to a new convenient debenzylation and acetylation reagents, and be developed to a non-hydrogenolytic method for removing the benzyl groups of HBIW(1). Further research is now underway.



Bn = benzyl　　Bz = benzoyl　　Ac = acetyl

3 Experimental

^{1}HNMR spectra were recorded by using tetramethylsilane as an internal standard on an ARX-400 spectrameter for DMSO-d_6 solution and acetone solution. IR spectra were taken with a Shimadzu IR-408. MS(FAB) spectra were recorded with a VG zabspec VG-ZAB-HS.

The mixture of acetic anhydride (15 ml) and DMF (10 ml) was cooled to 0 ℃, hexabenzylhexaazaisowurtzitane (1 708 mg, 1 mmol), anhydrous sodium carbonate (300 mg, 2.8 mmol) and tetraethytammoniumbromide (400 mg, 1.9 mmol) were added. Potassium permanganate (1 g, 6.3 mmol) was then added with vigorous stirring over a 2 h period. After the reaction mixture was stirred for a total of 8 h at 0 ~ 5 ℃. Sodium hyposulfite ($Na_2S_2O_3 \cdot 5H_2O$) and water were added for deoxidizing the excessive permanganate. Then the mixture was extracted with chloroform (20 ml × 4), washed with water (20 ml × 4), and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure to give slight yellow solid (450 mg), which was purified on a flash column of silica gel (ethanol/hexane, *v/v* 1 : 2) to give 7 (106 mg, 15%), 8 (100 mg, 14%), 9 (70 mg, 10%) and 10 (70 mg, 10%).

The IR, ^{1}HNMR and MS spectra of compound 7 were identical to those reported[13] respectively.

Compound 8: white crystal, m.p. 172 ~ 173 ℃. IR (KBr, cm^{-1}): 1 652 (C=O), 1 382 (C—N), 1 143 (C—N), 699 (Ar—H).

^{1}HNMR (acetone, 400 MHz): δ 7.11 ~ 7.67 (m, 25 H, Ph), 5.56 ~ 6.75 (m, 6 H, CH), 3.79 ~ 4.27 (m, 4 H, CH_2), 1.98 ~ 2.37 (s, 3 H, Ac).

MS(EI), m/z(%): 702 (M, 8), 487 (4), 425 (5), 359(5), 317(8), 277(15), 171(15), 105(100), 43(8).

Anal. Calcd for $C_{43}H_{38}N_6O_4$: C 73.50, H 5.41, O 11.97, N 9.12; found C 73.45, H 5.43, O 11.89, N 9.05.

Compound 9: white crystal, m.p. 218 ~ 220 ℃. IR (KBr, cm^{-1}): 1 652(C═O), 1 382(C—N), 1 138(C—N), 699(Ar—H).

^{1}HNMR (acetone, 400 MHz): δ 7.03 ~ 7.66(m, 20 H, Ph), 5.27 ~ 6.74(m, 6 H, CH), 3.14 ~ 4.27(m, 4 H, CH_2), 1.97 ~ 2.45(s, 6 H, Ac).

MS(FAB), m/z(%): 641(M+1, 20), 380(2), 318(3), 262(4), 215(7), 171(17), 105(100), 91(100).

Anal. Calcd for $C_{38}H_{36}N_6O_4$: C 71.25, H 5.63, O 10.00, N 13.13; found C 70.93, H 5.68, O 10.05, N 13.06.

Compound 10: white crystal, m.p. 233 ~ 234 ℃, IR(KBr, cm^{-1}): 1 652(C═O), 1 382(C—N), 1 140(C—N), 699(Ar—H).

^{1}HNMR(DMSO, 400 MHz): δ 7.28 ~ 7.57(m, 15 H, Ph), 5.39 ~ 6.70(m, 6 H, CH), 3.94 ~ 4.22(m, 4 H, CH_2), 1.73 ~ 2.21(m, 9 H, Ac).

MS(FAB), m/z(%): 579(M+1, 24), 346(2), 257(4), 217(28), 181(18), 105(39), 91(100).

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