RING CLEAVAGE OF DICYANO-SUBSTITUTED BENZIMIDAZOLES BY DIBAL

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Abstract : Ring cleavage of 1-butyl-2-(4-cyanophenyl)-1*H*-benzimidazole-5-carbonitrile (**5**) and 1-benzyl-2-(4-cyanophenyl)-1*H*-benzimidazole-5-carbonitrile (**6**) using diisobutylaluminum hydride is reported.

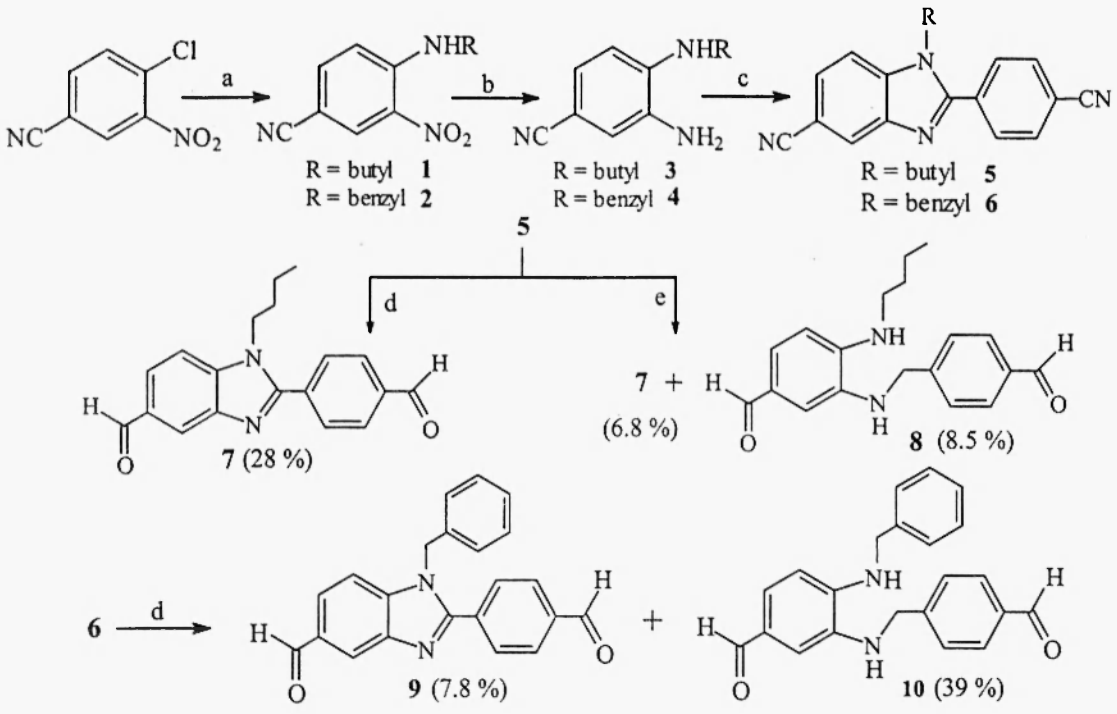
Introduction

The chemistry of benzimidazoles has received extensive attention over the years as a consequence of their utility in a variety of commercial areas including veterinary medicine, plant disease control and the photographic industry.[1] Our laboratories have reported significant antifungal activity for a number of benzimidazole based molecules.[2, 3] As part of a continuing program focused on development of antifungals we had need of diformylbenzimidazoles. Aryl aldehydes are often made by reduction of carboxylic acids or esters to the corresponding carbinol followed by reoxidation to the aldehyde. This approach has been used with heterocyclic systems.[4] On the other hand, we have had success in making diformyl-substituted heterocycles using DIBAL reduction of bis-nitriles.[5] The yields in these reductions rarely exceed 50-60 %; however, the desired dialdehydes are obtained in one step. This report describes the DIBAL reduction of dicyanobenzimidazoles.

Results and Discussion

Scheme 1 outlines the synthesis of **5** and **6**, 1-butyl- and 1-benzyl-2-(4-cyanophenyl)-5-cyano-1*H*-benzimidazole, and their reaction with DIBAL. The synthesis starts with the widely used[6] nucleophilic displacement of the chlorine atom of 4-chloro-3-nitrobenzonitrile by reaction with the corresponding amine to form the 4-(substituted amino)-3-nitrobenzonitriles **1** and **2** in good yields. Catalytic hydrogenation of **1** and **2** over Pd-C gave the expected phenylenediamines **3** and **4** in high yields. Using the method of Ridley,[7] coupling of the bisulfite adduct of 4-cyanobenzaldehyde with the phenylenediamines gave the bis-nitriles **5** and **6** in approximately 50 % yields. Reduction of **5** with DIBAL using 3 mmol of DIBAL per mmol of the dinitrile gave only 28 % of the expected diformyl compound **7**. When the reaction was carried out with a 5 to 1 ratio of DIBAL to dinitrile, only a 7 % yield of **7** was obtained and a new product **8** was isolated in 9 %

Scheme 1



Reagents **a** : butyl or benzylamine **b** : H_2 . Pd-C **c** : $NaHSO_3$ adduct of 4-cyanobenzaldehyde
d : DIBAL (3 mmol) **e** : DIBAL (5 mmol)

yield. Compound **8** apparently arises from the unexpected reductive cleavage of the benzimidazole ring. The DIBAL reduction of the benzyl derivative **6**, using a 3 to 1 ratio of DIBAL to dinitrile gave more of the ring cleavage product **10** (39 %) than the simple dinitrile reduction product **9** (8 %). The ^{1}H-NMR chemical shifts for the N-CH_2 moieties in the diformylbenzimidazoles **7** and **9** and their ring cleaved analogs **8** and **10** are consistent with the structural assignments. As expected, in both sets of compounds the N-CH_2 signals for the benzimidazoles are downfield from their ring cleaved counterparts. In the spectra of **7** and **9**, the N^1-CH_2 signals are observed at δ 4.40 (t) and 5.72 (s), and the corresponding signals in **8** and **10** appear at higher field at δ 3.17 (*m* in DMSO-d_6 , *t* in D_2O+ DMSO-d_6) and 4.46 (*d* in DMSO-d_6, *s* in D_2O+DMSO-d_6], respectively.

A similar ring cleavage has been reported[8] for the reduction of 4-nitrobenzoxazole with sodium borohydride in ethanol which led to 3-nitro-2-methylaminophenol in a 30 % yield. The unexpected reductive cleavage of the benzimidazole ring by DIBAL is apparently associated with the presence of the two strong electron withdrawing cyano groups, since no such cleavage is observed for mono-cyano benzimidazoles.[9] The higher yield of cleavage of **6** versus **5** is consistent with the smaller electron donating effect of a benzyl group compared to a butyl group. Further study of the requirements of DIBAL mediated cleavage of the benzimidazole ring is ongoing.

Experimental

Uncorrected melting points were measured on a Mel Temp 3.0 capillary melting point apparatus. ^{1}H-NMR and ^{13}C-NMR spectra were recorded employing Varian GX400 spectrometer; chemical shifts (δ) are in ppm relative to TMS and coupling constants (J) are reported in hertz. Mass spectra were recorded at Georgia Institute of Technology, Atlanta, GA. Microanalyses were performed by Atlantic Microlab Inc, (Norcross, GA). All chemicals and solvents were purchased from Aldrich Chemical Co. or Fischer Scientific.

4-Butylamino-3-nitrobenzonitrile (1)

Butylamine (2.2 g, 30 mmol) was added to a solution of 4-chloro-3-nitrobenzonitrile (2 g, 11 mmol) in DMF (3 ml), cooled by an ice bath. After being warmed to room temperature, the mixture was heated on a water bath until the starting material was consumed (followed by TLC, 2 h). The mixture was allowed to cool and water was added. The resultant precipitate was filtered and washed with water. Crystallization from EtOH gave **1** (2.2 g, 93 %) , mp 71-72 °C, lit [10] mp 69 °C.

4-Benzylamino-3-nitrobenzonitrile (2)

Benzylamine (2.14 g, 20 mmol,) and 4-chloro-3-nitrobenzonitrile (2 g, 11 mmol) were allowed to react as described above. The resultant yellow precipitate was filtered, washed with water and crystallized from EtOH to yield 1.46 g (53 %), mp 130 °C, lit [11] mp 128 °C.

3-Amino-4-butylaminobenzonitrile (3)

Compound **1** (1.75g, 8 mmol) in EtOH (75 ml) was reduced by hydrogenation using 40 psi of H_2 and 10 % Pd-C (200 mg) until cessation of H_2 uptake. The catalyst was filtered through a bed of Celite, washed with EtOH, and solvent was removed *in vacuo*. The crude diamine was used directly without purification; brown solid, yield 1.37 g (91 %), mp 102-3 °C.

3-Amino-4-benzylaminobenzonitrile (4)

In similar way as for **3**, using **2** (2.53 g, 10 mmol) compound **4** was prepared; yield 1.91g (86 %), mp 128 °C.

1-Butyl-2-(4-cyanophenyl)-5-cyano-1*H*-benzimidazole (5)

4-Cyanobenzaldehyde (1.96 g, 15 mmol) was dissolved in EtOH (50 mL). Sodium bisulfite (1.6 g) in water (10 ml) was added in portions. The mixture was kept in a refrigerator for several hours. The precipitate was filtered and dried to yield 3.06 g (87 %). The mixture of this adduct (1.86 g, 7.9 mmol) and compound **3** (1.5 g, 7.9 mmol) in DMF (5 ml) was heated at 130 °C for 4 h. The reaction mixture was cooled, poured into water and the resultant solid was filtered. Crystallization of crude product from aqueous EtOH (80 %) gave

5; yield 1.45g (61 %), mp 181-2 °C. ^{1}H-NMR (DMSO-d_6) δ 0.73 (t, 3H, J = 7.6), 1.14 (m, 2H), 1.61 (m, 2H), 4.37(t, 2H, J = 7.5), 7.71(d, 1H, J = 8.4), 7.92 (d, 1H, J = 8.4), 8.01 (d, 2H, J = 7.4), 8.07 (d, 2H, J = 7.4), 8.27 (s, 1H). ES-MS *e/z* 300 (M+1, 100).

1-Benzyl-2-(4-cyanophenyl)-5-cyano-1*H*-benzimidazole (6)

Using **4** (0.5 g, 2.2 mmol) and $NaHSO_3$ adduct of 4-cyanobenzaldehyde (0.52 g, 2.2 mmol), the reaction was performed as with **5** above. Crude product (0.56 g, mp 175 °C) was purified by column chromatography (EtOAc/*n*-hexane, 1:1) to yield 0.36 g (48 %), mp 179-181 °C. ^{1}H-NMR (DMSO-d_6) δ 5.68 (s , 2H), 6.95 (m ,2H), 7.25 (m, 3H), 7.70 (d, 1H), 7.76 (d, 1H), 7.93 (d, 2H), 8.02 (d, 2H), 8.33 (s, 1H). MS *e/z* 334 (M^+, 2), 243 (3), 91(100).

1-Butyl-2-(4-formylphenyl)-5-formyl-1*H*-benzimidazole (7)

To a solution of **5** (0.285 g, 0.95 mmol) in dry CH_2Cl_2 (30 ml), 3 ml of DIBAL (1.0 M solution in CH_2Cl_2, 3 mmol) was added and the mixture was heated at reflux for 2 h under a nitrogen atmosphere. Cold dilute H_2SO_4 (15 ml) was added and the mixture was stirred overnight. Then CH_2Cl_2 was removed and the residue was chromatographed (EtOAc/*n*-hexane, 1:1) to yield 0.081g (28 %), mp 143-5 °C. ^{1}H-NMR (DMSO-d_6) δ : 0.73 (t, 3H, J = 7.5), 1.13 (m, 2H), 1.66 (m, 2H), 4.40 (t, 2H, J = 7.5), 7.89 (m, 2H), 8.01 (d, 2H, J = 8.2), 8.12 (d, 2H, J = 8.2), 8.31 (s, 1H), 10.08 (s, 1H), 10.13 (s, 1H). ^{13}C-NMR (DMSO-d_6) δ 13.2, 19.1, 31.1, 44.2, 111.9, 123.0, 123.1, 129.7, 129.9, 131.6, 135.2, 136.8, 140.1, 142.3, 154.2, 192.5, 192.8. MS *e/z* 306 (M^+, 100), 277(19), 263 (13), 235(40), 77(12). Anal. Calcd. for $C_{19}H_{18}N_2O_2 \cdot$ 1/4 H_2O: C, 73.41 ; H, 5.96 ; N, 9.01. Found : C, 73.89 ; H, 5.98 ; N, 9.08

4-Butylamino-3-(4-formylbenzylamino)-benzaldehyde (8)

5 ml of DIBAL (1.0 M solution in CH_2Cl_2, 5 mmol) and the same amount of **5** as used above was treated in the same way as for **7** . From the column, first compound **8** (yellow, 0.025 g, 9 %) and later compound **7** (0.02 g, 7 %) were isolated. Compound **8**: mp 102-3 °C, ^{1}H-NMR (DMSO-d_6) δ 0.94 (t, 3H, J = 7.5), 1.46 (m, 2H), 1.65 (m, 2H), 3.18 (m, 2H), 4.46 (d, 2H, J = 5.1), 5.73 (m, 2H), 6.56 (d, 1H, J = 8.1), 6.71 (s, 1H), 7.14 (d, 1H, J= 8.1), 7.57 (d, 2H, J = 7.8), 7.87 (d, 2H, J = 7.8), 9.47 (s, 1H), 9.96 (s, 1H). (DMSO-d_6+D_2O) δ 0.92 (t, 3H, J = 7.1), 1.41 (m, 2H), 1.61 (m, 2H), 3.17 (t, 2H, J = 7), 4.44 (s, 2H), 6.55 (d, 1H, J = 8.1), 6.69 (s, 1H), 7.15 (d, 1H, J= 8.1), 7.57 (d, 2H, J = 7.8), 7.87 (d, 2H, J = 7.8), 9.47 (s, 1H), 9.96 (s, 1H). ^{13}C-NMR (DMSO-d_6) δ 14.0, 20.1, 30.6, 42.8, 46.7, 107.0, 107.5, 125.7, 126.0, 127.9, 129.9, 134.6, 135.3, 142.9, 147.4, 190.4, 193.0 ES-MS *e/z* 311(M+1, 100). Anal. Calcd. for $C_{19}H_{22}N_2O_2$. : C, 73.52 ; H, 7.14 ; N, 9.03. Found : C, 73.4; H, 7.16 ; N, 8.95

4-Benzylamino-3-(4-formylbenzylamino)benzaldehyde (10)

To a solution of **6** (0.25 g, 0.75 mmol) in dry CH_2Cl_2 (30 ml), 3 ml of DIBAL (1.0 M solution in CH_2Cl_2, 3 mmol) was added and the mixture was heated at 45 °C, for 3 h under a nitrogen atmosphere. Cold dilute H_2SO_4 (15 ml) was added and the mixture was stirred and heated for 1h at 50 °C. CH_2Cl_2 was removed and the residue was chromatographed using EtOAc/*n*-hexane (30: 70) as eluent to yield 0.1 g (39 %) of a yellow compound, mp 154-156 °C. ^{1}H-NMR (DMSO-d_6) δ 4.48 (2d, overlapped, 4H), 5.72 (t, 1H), 6.45 (t, 1H), 6.50 (d, 1H, J = 8.4), 6.79 (s, 1H), 7.06 (d, 1H, J = 8.4), 7.21-7.36 (m, 5H), 7.58 (d, 2H, J = 8.1), 7.87 (d, 2H, J = 8.1), 9.43 (s, 1H), 9.96 (s, 1H). ^{1}H-NMR (DMSO-d_6 + D_2O) δ 4.46 and 4.49 (s, s, 4H), 6.50 (d, 1H, J = 8.4), 6.79 (s,1H), 7.06 (d, 1H, J = 8.4), 7.21-7.36 (m, 5H), 7.58 (d, 2H, J = 8.1), 7.84 (d, 2H, J = 8.1), 9.43 (s, 1H), 9.93 (s, 1H). MS *e/z* 344 (M^+, 53), 253(63), 225(65), 91(100). Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72 ; H, 5.85 ; N, 8.13. Found : C, 76.77 ; H, 6.05 ; N, 8.16

1-Benzyl-2-(4-formylphenyl)-5-formyl-1*H*-benzimidazole (9)

A second product (which is eluted after **10**) from chromatography above was a white colored powder, yield 0.02 g (8 %), mp 137-8 °C. ^{1}H-NMR (DMSO-d_6) δ 5.72 (s, 2H), 6.99 (m, 2H), 7.27 (m, 3H), 7.76 (d, 1H, J = 8.5), 7.86 (d, 1H, J = 8.5), 8.01 (d, 2H, J = 8.1), 8.07 (d, 2H, J = 8.1), 8.36 (s, 1H), 10.09 (s, 1H), 10.1 (s, 1H). ^{13}C-NMR (DMSO-d_6) δ 46.6, 47.0, 107.7, 108.6, 126.0, 126.3, 127.5, 127.6, 128.2, 128.9, 130.2, 135.13, 135.5, 139.4, 142.9, 147.5, 191.1, 193.4. ES-MS *e/z* 341 (M+1). Anal. Calcd. for $C_{22}H_{16}N_2O_2 \bullet$ ¼ H_2O: C, 76.60 ; H, 4.82 ; N, 8.12. Found : C, 76.42 ; H, 4.88 ; N, 8.15

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