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An Unusual Reductive Ring-opening Reaction of Phthalimide with Sodium Hydride in DMF

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Abstract: An unusual reductive ring-opening reaction of phthalimide with sodium hydride in anhydrous DMF was observed for the first time. The presumed mechanism was described in detail.

Keywords: Phthalimide, benzylation, reduction, ring-opening.

The phthaloyl group was an amino protecting group used widely in carbohydrate and peptide chemistry. It was quite stable under various conditions and usually removed with hydrazine hydrate in refluxing alcohol [1, 2].

We choose phthaloyl to protect a primary amino group in the synthesis of an oligosaccharide intermediate. After reduction of the azide group of compound **1** by hydrogenation, the resulting amine was treated with phthalic anhydride to give the phthalimide **2**. Then the 3′, 4′-dihydroxyl was regioselectively protected with isopropylidene. When the intermediate **3** was treated with sodium hydride (1.1 equiv per OH) and benzyl bromide (1.5 equiv per OH) in anhydrous N, N-dimethyl formamide (DMF), unexpected reaction of the phthalimide occurred. Compound **5** was isolated from the complex reaction mixture as the main product in 29% yield. The more polar products (more than 5 spots on TLC) were speculated as incomplete benzylated products. After the protecting group manipulation, NMR and MS identified the product **6**, as illustrated in the following **Scheme**. Compound **5** was the main product even when the reaction was quenched with methanol in 2 hours and an equal amount of sodium hydride was used. The reduction was proved to be more competitive than the benzylation.

The hydride ion can attack the carbonyl carbon to give the delocalized amide anion (transition state **C**), which was further benzylated to give the aldehyde (**D**). The reduction and benzylation (**E**) of the aldehyde were running repeatedly to give the product **5**.

To the best of our knowledge, this is the first report of a phthalimido group was reduced under the classical condition of benzylation.

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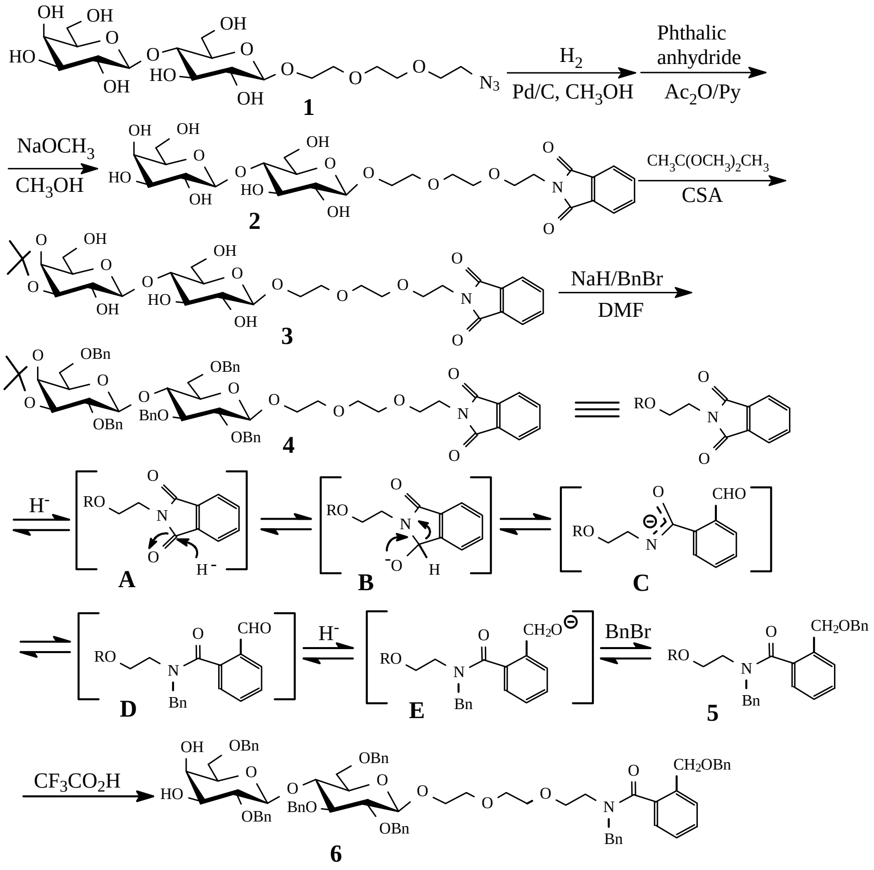

Acknowledgments

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References and Notes

1. Lemieux R U, Takeda T, Chung, B Y, *Am. Chem. Soc. Symposium Series*, **1976**, *39*, 90.
2. Stangier P, Hindsgaul O, *Synlett.*, **1996**, 179.
3. Data for compound **6**:

   $[\alpha]^{25}_{D}$ +30.6 (*c* 0.85, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00 (m, 1 H), 7.48-7.12 (m, 38 H), 4.98~4.55 (m, 7 H), 4.46~4.36 (m, 6 H), 4.05~3.92 (m, 3 H), 3.87 (s, 2 H, $PhCH_2$), 3.83-3.19 (m, 24 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.2 (C=O), 139.2, 138.7, 138.4, 138.2, 138.1, 137.5, 136.7, 132.6, 132.4, 130.5, 128.9, 128.5, 128.4, 128.3, 128.2, 128.2, 128.0, 127.7, 127.5, 127.5, 127.1, 127.0 (aromatic carbon), 103.9, 102.5 (C-1, C-1′), 82.7, 81.7, 80.1, 76.5, 75.1, 74.8, 74.7, 73.6, 73.5, 73.2, 73.0, 70.6, 70.5, 70.3, 69.0, 68.8, 68.7, 68.4, 53.5, 52.2, 48.3, 47.5. MALDI-TOF MS *(m/z)*: $C_{78}H_{87}O_{15}N$, 1238.3 $[M+H]^+$.

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