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An Efficient Conversion of 5-Nitroisatin Into 5-Nitroindole Derivative

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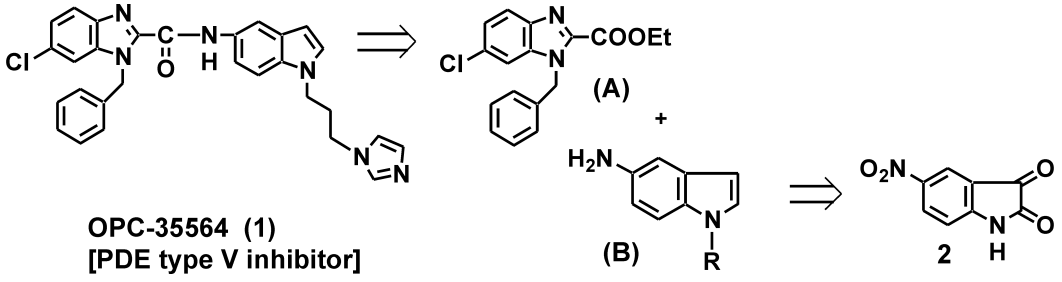
Abstract—Our process research on OPC-35564 revealed that a mixed borohydride reducing agent ($ZrCl_4/NaBH_4$) in DME (Itsuno system) afforded a rapid and direct conversion of *N*-alkyl-nitroisatin into nitroindole nucleus. Comparison with other reducing agents indicated the superiority of the present system and the key function of $ZrCl_4$. For the manipulation of base-labile isatin, a useful procedure for its *N*-alkylation using Cu_2CO_3 is also presented. © 2001 Elsevier Science Ltd. All rights reserved.

In our on-going research for cyclic nucleotide phosphodiesterase (PDE) type V inhibitors, a novel compound OPC-35564 (**1**) emerged as a promising candidate for further evaluation.[1] Both a benzimidazole and an aminoindole segment are incorporated as an important structural core as shown below. We have already developed an efficient method for the preparation of the benzimidazole segment (**A**) via I_2 induced cyclization.[2] In relation to our synthetic study on the aminoindole segment (**B**), a new method has been sought for the direct access to nitroindoles (or aminoindoles) from readily available indole congeners such as isatins, oxyindoles and indolines. We thus began to investigate some reductive transformation of readily available isatin derivatives to indoles as a general and convenient route for the ring-substituted indoles. We estimated that 5-substituted isatins are a more useful starting material than other congeners because of their availability.

Few reports have described useful and general protocols for such transformation (isatins into indoles), except for the reports which utilized BH_3/THF generated from $BF_3OEt_2/NaBH_4$. This combination was applicable to *N*-protected derivatives such as *N*-acylisatins and *N*-acylpyrroles.[3] Some over-reduction to indoline was mentioned as the drawback of this method. In other cases, $LiAlH_4$ can be utilized for this conversion, but only in moderate yields.[4] Under these circumstances, we are interested in the utilization of modified $M(BH_4)_n$ species (Lewis acid plus $NaBH_4$) for the rapid conversion of nitroisatin into nitroindoles. Although no successful (chemoselective) transformation has been reported in the lactams bearing nitro group, our previous search in a different lactam reduction[5c] prompted us to use the $ZrCl_4/NaBH_4$ reduction protocol (Itsuno system)[6] on the labile nitroisatins. Described herein is our preliminary survey on the rapid conversion of



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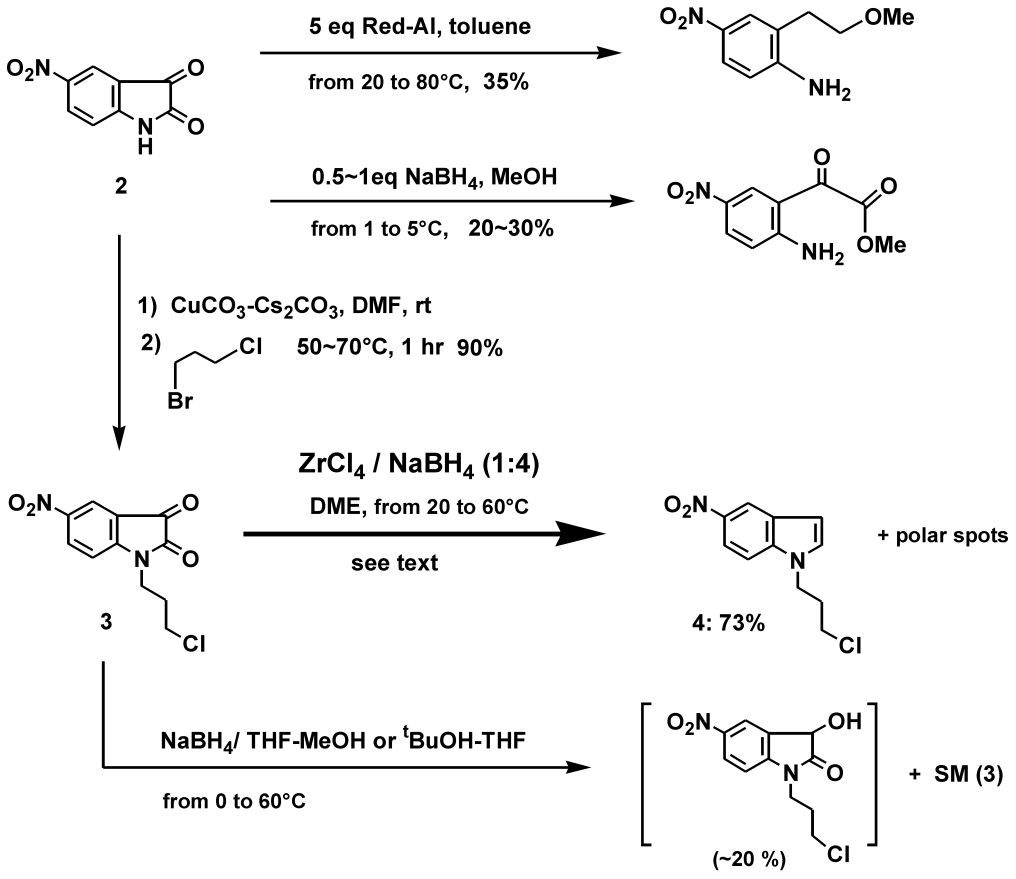
nitroisatin to nitroindole by the Itsuno system as well as a convenient *N*-alkylation of *N*H-isatin by the use of $CuCO_3/Cs_2CO_3$ system.

Initial survey. Initial attempts with 5-nitroisatin (**2**) are briefly summarized in Scheme 1. These trials indicated that the nitroisatin skeleton was quite susceptible to nucleophilic ring opening at the N1 CO bond in basic media. As shown in Scheme 1, attempted reduction of **2** either by Red-Al (5 equiv) or $NaBH_4$ (0.5∼1.0 equiv) gave undesired ring-opened products in modest yields along with large quantities of the unidentified polar materials. These results led us to the preparation of more stable *N*-alkyl isatins before crucial reduction, as summarized below.

***N*-Alkylation of isatin.** *N*-(3-Chloropropyl)-5-nitroisatin (**3**) was selected as an important intermediate, as this segment is incorporated in **1**. For the *N*-alkylation of **2**, we developed a mild base combination ($CuCO_3/Cs_2CO_3$ (1:2)) in anhydrous DMF, because strong basic conditions sometimes led to the ring opening of the isatin nucleus as mentioned above. As far as we surveyed, this reagent combination showed increased nucleophilicity at nitrogen by the complexation between Cu and amide nitrogen.[7,8]

Reduction of the protected isatin. The next survey on the reduction of the *N*-protected isatin (**3**) is summarized in comparison with the standard $NaBH_4$ reduction conditions. While basic reduction conditions resulted in sluggish reaction with a large amount of starting material remaining, a rapid conversion was realized with $ZrCl_4/NaBH_4$ system as shown in Scheme 1. Yields were satisfactory (70–73%) but some polar material was also present which contained the products from over-reduction. To control this problem we further surveyed other Lewis acid sources. In Scheme 2, results for the comparison with other reagent combinations are summarized showing the presumed active species.[9] All the attempts at modification in $ZrCl_n$ reagents (i.e., Cp_2ZrCl_2 or $ZrOCl_2$) could not produce any better results than the original $ZrCl_4$ system. Reaction with more active Cp_2TiCl_2 could not effect selective reduction and only gave polar materials. Reducing the molar ratio of $ZrCl_4$ (1 to 0.5 mol equiv) $NaBH_4$ (4 to 2.0 mol equiv) simply retarded reaction, requiring prolonged reaction time with heating. These attempts clearly demonstrated the usefulness of the $ZrCl_4/NaBH_4$ system for the desired transformation.

Further comparison with other reducing agents was investigated next. In the reaction with BH_3 derivatives (THF complex or DMS complex, etc.), B-containing complex formation was observed, from which the final reduction product was liberated after HCl work up in moderate yield (40–50% isolated yield). Furthermore, in our survey, NBu_4BH_4 gave no better result than $ZrCl_4/NaBH_4$ and BH_3/THF. Other reagent combination such as $SnCl_4/NaBH_4$ did not produce reproducible results.



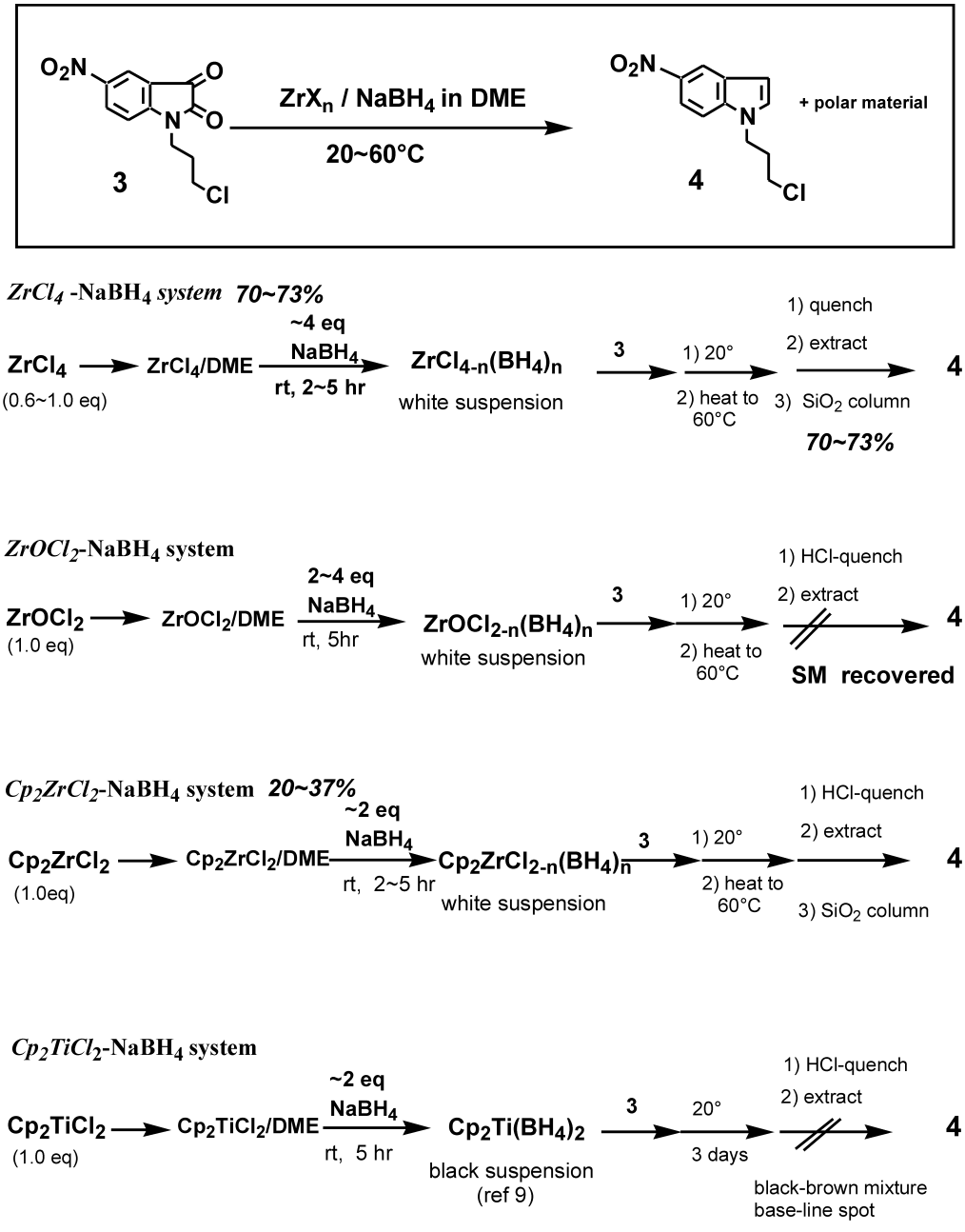
Scheme 1. Initial study.

This was due to the instability of the active reducing species. Thus, $ZrCl_4/NaBH_4$ system offered a rapid and reliable conversion to indole nucleus.

In the representative procedure, we prepared a suspension of $ZrCl_4$ (1 mM) and $NaBH_4$ (4 mM) in DME at room temperature, to which the nitroisatin (**3**, 1 mM) was added in one portion. After the exothermic process subsided, the mixture was stirred at room temperature (20 °C) for 2 h, before heating at around 60 °C for 1 h to complete the reduction. After checking the consumption of **3**, the reaction mixture was diluted with AcOEt–H_2O in an ice-bath temperature and worked up as usual.[6] Purification of the crude product by column chromatography afforded the product **4** as a solid material, identical with authentic material prepared from 5-nitroindole.[10]

Additionally, a direct reduction of 5-nitro-*NH*-isatin (**2**) was investigated again with $ZrCl_4/NaBH_4$. With various amounts of $ZrCl_4/NaBH_4$, the desirable 5-nitroindole was obtained only in a low isolated yield (~30%). Slightly less than 1 equiv of $NaBH_4$ afforded a cleaner mixture albeit with incomplete conversion. This is partly due to the undesirable side reaction (probably over-reduction of the nitro group). To circumvent these troubles, it is recommendable to use temporally *N*-protected isatin derivatives. Selection of the proper nitrogen protecting group of isatins and further survey of the *N*-protected isatin are now in progress.

In summary, we have disclosed the utility of $ZrCl_4/NaBH_4$ in the reduction of labile isatins (**3**) as an alternative to the traditional BH_3 reagents. The present system could produce an active species ($ZrCl_{4-n}(BH_4)_n$/



Scheme 2.

DME) which is stable at room temperature and thus offered rapid and direct conversion of isatin to indole nucleus. Comparison with other reducing agents indicated the superiority of the present system. This study along with our previous report[5c] indicated the usefulness of the mild reagent $ZrCl_4$/DME in the manipulation of the nitrogen ring systems.

It is interesting to note that the very recent report by Iyenger described an efficient conversion of aromatic and aliphatic nitro compounds into primary amines using $ZrCl_4/NaBH_4$ in THF.[11] Our results thus indicated the usefulness of Zr-based reduction protocol for chemoselective reduction in multifunctional molecules. Narashimhan has also noted another chemoselective reaction with $ZrCl_4/NaBH_4$ in THF.[5e] In our tentative assessment, $ZrCl_{n-4}(BH_4)_n$/DME is milder than Red-Al but stronger than DIBAL-H. Long shelf life as a safe reagent and presumed stability of the active species are the key natures of $ZrCl_4$ for further application.[12]

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7. Preliminary survey on the *N*-alkylation revealed the following results. Same reaction with K_2CO_3/DMF or NaH/DMF gave slightly inferior results (55–65% product). Reaction with Cs_2CO_3/DMF was as effective as the Cu/Cs system. Furthermore, effective *N*-alkylation and even *N*-arylation of *NH*-lactam was successfully carried out using this combination [$CuCO_3/Cs_2CO_3$] under heating (~130 °C) in DMF or DMA. As a solvent choice, CH_3CN, DMEm dioxane and toluene did not give any more satisfactory conversion than in DMF. A partial conversion of the bromide to the alcohol was observed in wet solvent system. Details of the progress in $CuCO_3/Cs_2CO_3$ promoted *N*-alkylation will be presented elsewhere.
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