Unexpected Reduction of *N*-Hydroxyphthalimides to Phthalimides – Orthogonal Reduction of Functionalized *N*-Hydroxyphthalimides

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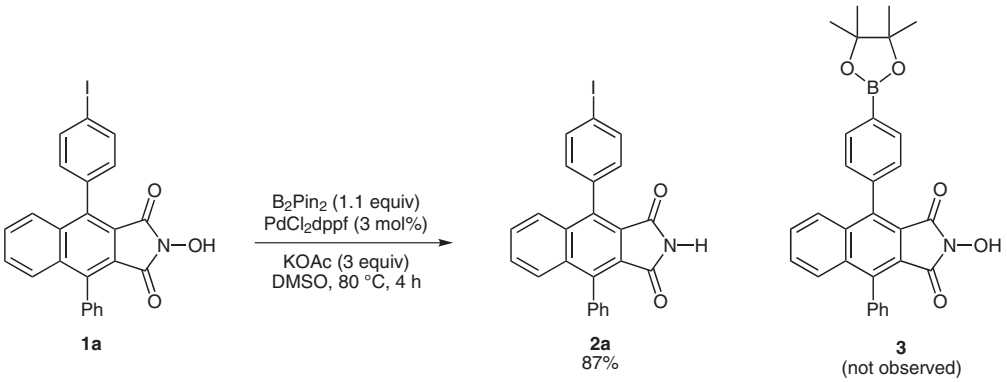
Abstract: A chemoselective reduction of *N*-hydroxyphthalimides to phthalimides under mild conditions has been discovered. It involves reaction of an *N*-hydroxyimide with bis(pinacolato)diboron in the presence of a base. Other easily reducible functional groups, such as iodo, nitro, or azido groups are unaffected. Alternatively, such functional groups may be selectively reduced without affecting the *N*-hydroxyimide moiety using a set of classical conditions.

Key words: chemoselective reduction, bis(pinacolato)diboron, *N*-hydroxyphthalimides, phthalimides, mild conditions

N-Hydroxyphthalimide (NHPI) is a valuable organocatalyst allowing aerobic oxidation reactions to be performed under mild conditions.[1] A broad variety of NHPI analogues has also been prepared, with the aim of developing more effective or more selective catalysts.[2] Moreover, we found recently that some functionalized polycyclic NHPI analogues posses promising biological activities.[3] In order to prepare rapidly functionally diverse NHPI analogues, we became interested in synthetic methods allowing functional-group transformations to be performed in the presence of an unprotected *N*-hydroxyimide moiety. Thus, C-borylation of iodinated NHPI analogue **1a** was attempted, using conditions developed by Miyaura et al.: Compound **1a** was reacted with bis(pinacolato)diboron (B_2Pin_2) in the presence of potassium acetate and a catalytic amount of $PdCl_2$dppf in DMSO at 80 °C.[4] Unexpectedly, no C-borylated product was obtained but compound **2a**, still iodinated but having lost its hydroxy group, was isolated in 87% yield (Scheme 1). A similar reaction was observed with NHPI, which was smoothly reduced to phthalimide under the same conditions.

Intrigued by this result, we investigated the reaction conditions more in detail. Without palladium catalyst, the reaction proceeded equally well. No reaction occurred when potassium acetate was omitted, but potassium acetate could be replaced effectively by other bases such as sodium acetate, sodium hydrogenocarbonate, or potassium triphosphate. Finally, DMSO could be advantageously replaced by methanol. Under the new set of conditions (1.1 equiv B_2Pin_2, 3 equiv KOAc, in MeOH at 50 °C for 2 h) NHPI was reduced to phthalimide in 88% isolated yield (Table 1, entry 1). Under such conditions, many easily reducible functional groups are unaffected, as shown by the chemoselective reduction of NHPI analogues bearing iodo, nitro, or azido functional groups (Scheme 2, Table 1). As expected, iodinated NHPI analogues **1e** and **1f** gave the corresponding phthalimides **2e** and **2f** in 81% and 56% isolated yields (Table 1, entries 4 and 5). Periodinated NHPI analogue **1h** was found to be hardly soluble in methanol, so the reaction was performed in DMSO at 80 °C, giving the expected phthalimide **2h** in good yield (Table 1, entry 7). In the case of the nitro analogue **1c** the reaction was slower, and **2c** was obtained in only 13% yield (Table 1, entry 2). Nevertheless, other nitro NHPI analogues, including polycyclic compounds **1i–l**, gave medium to high yields of the corresponding imides (Table 1, entries 3 and 8–11). Finally, even the fragile azi-



Scheme 1 Unexpected reduction of the *N*-hydroxyphthalimide function to the phthalimide

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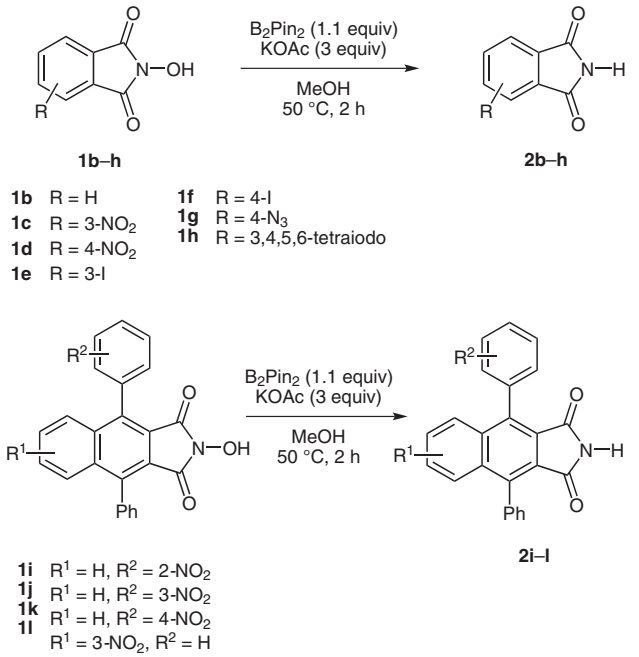


Scheme 2 Selective reduction of the *N*-hydroxyphthalimide function to the phthalimide

Table 1 Selective Reduction of the *N*-Hydroxyphthalimide **1** Function to the Phthalimide **2**

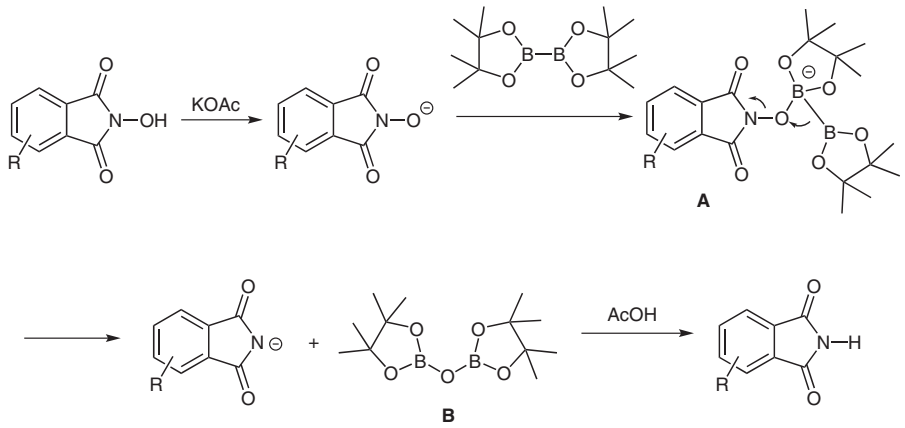
Entry	Reactant	Product	Yield (%)[a]
1	**1b**	**2b**	88
2[b]	**1c**	**2c**	13
3	**1d**	**2d**	56
4[c]	**1e**	**2e**	81
5	**1f**	**2f**	56
6	**1g**	**2g**	50
7[d]	**1h**	**2h**	80
8	**1i**	**2i**	90
9	**1j**	**2j**	56
10	**1k**	**2k**	68
11	**1l**	**2l**	82

[a] Reaction conditions: **1** (0.1–0.5 mmol), B_2Pin_2 (1.1 equiv), KOAc (3 equiv), MeOH (0.017 M), 50 °C, 2h; isolated yields.
[b] Reaction time was 5 h.
[c] Reaction time was 3.5 h.
[d] Reaction performed in DMSO at 80 °C.

do NHPI analogue **1g** could be transformed into the corresponding azidophthalimide **2g** in a satisfactory isolated yield (Table 1, entry 6).

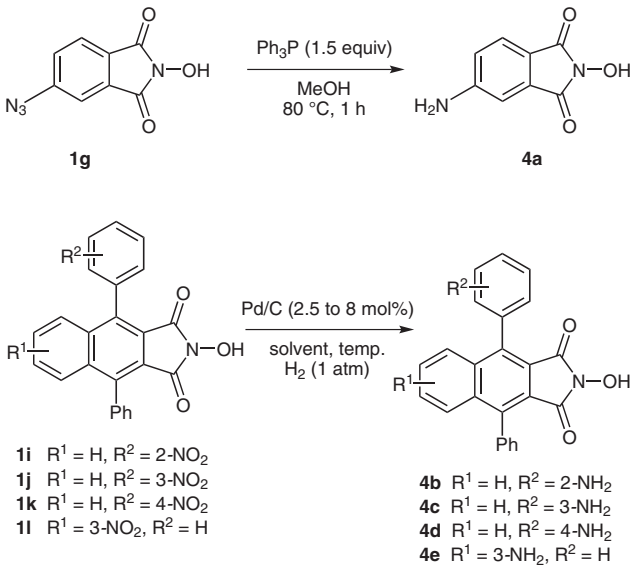
The mechanism of this reduction may tentatively be asset as follows (Scheme 3): owing to their low p*K*a (p*K*a of NHPI itself in water is 6.1)[5], NHPI analogue can be deprotonated even by weak bases such as potassium acetate. This deprotonation can in fact be easily visualized by the formation of a deeply red colored NHPI anion. This anionic species could add to one of the boron atom of B_2Pin_2 to give intermediate **A**. Nitrogen–oxygen bond cleavage, accompanied by boron migration from boron to oxygen, would then furnish deprotonated phthalimide along with boron species **B**.[6] The progress of the reaction can be monitored by progressive fading of the deeply red colored reaction medium.

Although the nitrogen–oxygen bond cleavage of *N*-hydroxyphthalimides occurs under particularly mild conditions by the method disclosed above, this bond proved to be quite resistant to a set of other reductive conditions. Thus, it was also possible to perform the selective reduction of some of the previous functional groups without affecting the *N*-hydroxyimide moiety (Scheme 4, Table 2). The selective reduction of 4-nitro NHPI **1d** into 4-amino NHPI **4a** has already been reported using palladium on charcoal under pressure of hydrogen (Table 2, entry 1).[7] We found that in this case, it is important to control the amount of hydrogen consumed during the reaction, to avoid complete reduction into 4-aminophthalimide. We also applied the catalytic hydrogenation procedure to polycyclic NHPI analogues bearing nitro groups **1i–l**, obtaining good isolated yields of the corresponding amino NHPI analogues **4b–e** (Table 2, entries 3–6). In these cases no fully reduced compounds were obtained. When



Scheme 3 Proposed mechanism of the B_2Pin_2 reduction of *N*-hydroxyphthalimides to phthalimides

applied to 4-azido-*N*-hydroxyphthalimide (**1g**) catalytic hydrogenation procedure led only to the fully reduced 4-aminophthalimide. Nevertheless **1g** could smoothly be transformed into 4-amino NHPI **4a**, using the Staudinger reaction (Table 2, entry 2).



Scheme 4 Selective reduction of the function on the *N*-hydroxyphthalimide

Table 2 Selective Reduction of the Substituent of *N*-Hydroxyphthalimide **1** to give *N*-Hydroxyphthalimide **4**

Entry	Reactant	Product	Time (h)	Yield (%)
1[a]	**1d**	**4a**	0.75	70
2[b]	**1g**	**4a**	1	74
3[c]	**1i**	**4b**	4	88
4[c]	**1j**	**4c**	4	72
5[d]	**1k**	**4d**	6	55
6[d]	**1l**	**4e**	6	64

[a] Reaction described in the literature.[7,]
[b] Staudinger reaction was used.
[c] Reaction conditions: **1** (0.1 mmol), Pd/C (5–8 mol%), EtOH (3 mL), 70 °C, 4 h, isolated yields.
[d] Reaction conditions: **1** (0.1 mmol), Pd/C (2.5 mol%), EtOAc (2.5 mL), 50 °C, 6 h, isolated yields.

In summary we developed the first selective reduction of *N*-hydroxyphthalimides to phthalimides under very mild conditions. This reaction is tolerant toward many fragile functional groups like iodo, nitro, or azido groups. We also showed that it is possible to reduce selectively some functional groups present on the *N*-hydroxyphthalimide backbone, keeping the *N*-hydroxyimide moiety unchanged. Such orthogonal functional-group manipulation could find interesting applications, as phthalimide and *N*-hydroxyphthalimide moieties can be found in many biologically active compounds.[3,8]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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