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Chemoselective reduction of aromatic nitro compounds (*o-nitro*phenol derivatives) using simple borane-THF without transition metal catalysts, additives, or ligands

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A R T I C L E I N F O

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A B S T R A C T

Chemoselective reduction of aromatic nitro compounds (*ortho*-nitrophenol derivatives) using Borane in THF (BH_3-THF) at room temperature, without using an additional metal catalyst is reported. Interestingly, nitroarenes containing two or three groups, a selective reduction of the nitro group adjacent to the hydroxy group is observed which happens to be the first Chemoselective reduction protocol for nitro groups using BH_3-THF. The presence of the phenolic hydroxyl group is found to be the key that aids in hydrogen transfer to the nitro group through a cyclic transition step.

Chemoselective conversions are very important in organic synthesis as they help in synthesizing molecules exclusively with selected functionalities. One of the reactions is the reduction of nitro groups. Nitro group is a versatile functionality that can be easily introduced and subsequently can be converted to other important groups. The reduction of nitro groups is one among the interesting conversions for which many established protocols are available in the literature [1]. Problems are encountered with molecules having either multiple nitro groups or other sensitive functional groups which may get affected during reduction. While selective reduction of the nitro group in the presence of other functional groups is known [2], challenges are faced with molecules with multiple nitro groups.

Attempts to reduce nitro group in the presence of multiple nitro functionalities usually result in the formation of diamino compounds. Herein we report the preliminary results of the first use of simple BH_3-THF for the reduction of hydroxy nitroarenes without additional metal catalysts. Nitro groups present in meta and para positions are unaffected. Importantly, only one nitro group is reduced in molecules having two nitro groups adjacent to hydroxyl groups (e.g., 2,6-dinitro phenol). Additionally, this protocol tolerates the presence of a diverse array of functional moieties and protecting groups.

Normally, boranes are inert towards nitro groups due to the weakly polarized boron-hydrogen bond. Bond activation is required to ease the proper transfer of hydrogens from BH_3-THF to nitro group. Borane B–H activation is well-known with transition metals both via oxidative addition and metal–ligand interactions [3].

Among the traditional reducing agents, Hydrazine hydrate [4] and sodium borohydride ($NaBH_4$) are known to promote nitro group reduction efficiently with the help of transition metal salts e.g., Co [5], Fe [6], Sn [7], Cu [8] and Ni [9]. A metal-free protocol was developed by Behzad *et.al.,* where activated charcoal was used in place of metals [10]. Although the exact mechanism and role of charcoal was not reported, it was assumed that an interaction between borane and charcoal liberates hydrogen gas which is utilized for the reduction. Recently ammonia-borane reagents [11], particularly amine-Boranes are gaining importance due to high hydrogen content and ease of handling.

Chemoselective nitro reduction has also been reported with various reagents [12]. However, all these protocols involve the activation of Borane or Hydrazine by an additional metal or ligands.

In one of our studies targeting the synthesis of a key metabolite of an agrochemical, we attempted the use of BH_3-THF to reduce the carboxylic acid group in **compound 1** (Scheme 1). Spectroscopic analysis of the

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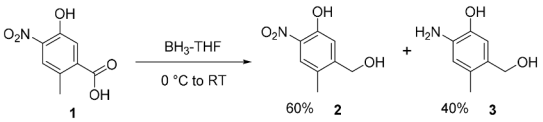


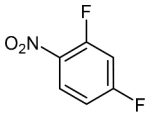
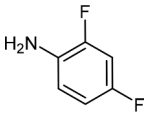
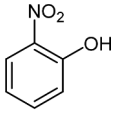
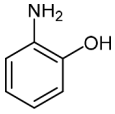
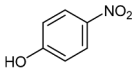
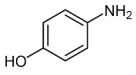
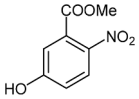
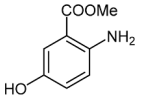
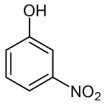
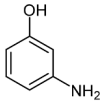
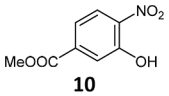
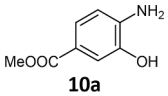
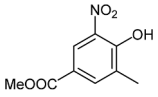
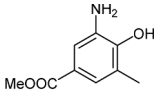
Scheme 1. Reduction of carboxylic acid using BH_3-THF.

isolated material revealed that the product is a mixture of both alcohol and amine. One of the nitro groups adjacent to the hydroxy group was also reduced along with carboxylic acid. Surprised and intrigued by this finding, we performed multiple reactions with varying borane ratios and temperatures and the results indicate the partial reduction of nitro group to amine & complete reduction of both acid & nitro group with higher equivalents of borane.

We contemplated that this amazing reactivity finding should not remain as such but should be explored in detail with various substrates to understand the mechanism of action.

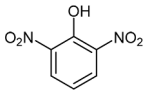
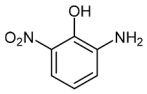
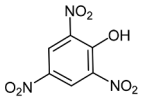
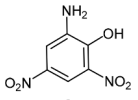
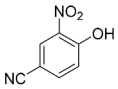
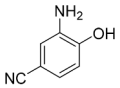
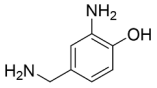
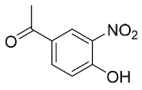
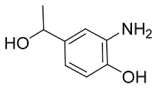
To begin with, simple nitro arene like nitrobenzene & 2,4-difluoro nitrobenzene (**4** & **5**) were tested and found to be unreactive with BH_3-THF (See Table 1). However, nitrobenzene with *ortho*-hydroxy group (**6**) underwent smooth reduction to provide the corresponding amine in moderate yields. Other differentially substituted hydroxy

Table 1
Substrate scope for reduction of nitroarenes using BH_3-THF.

Entry	Substrate	Time (h)	Product	%Yield[b]
1	 **4**	30	 **4a**	No reaction
2	 **5**	24	 **5a**	No reaction
3	 **6**	20	 **6a**	55
4	 **7**	30	 **7a**	No reaction
5	 **8**	30	 **8a**	No reaction
6	 **9**	30	 **9a**	No reaction
7	 **10**	18	 **10a**	50
8	 **11**	20	 **11a**	82

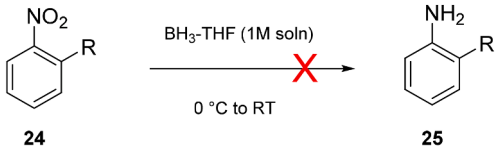
(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	Time (h)	Product	%Yield[b]
9	 **12**	15	 **12a**	90
10	 **13**	8	 **13a**	90
11	 **14**	40	 **14a**	50
12	**14**	8[c]	 **14b**	55
13	 **15**	24	 **15a**	70

[a] All reactions were carried out using 10 mmol of substrate, 10 equivalent BH_3-THF (1 M solution), dry THF (10 vol), under N_2 atmosphere, monitored by TLC. [b] Isolated yields, [c] at 70 °C.

To a Stirred solution of picric acid (500mg, 2.18mmol) in dry THF (5.0ml), was added BH_3·THF (1M soln) (21.8ml, 21.8mmol) slowly at 0 °C for 30 mins. After complete addition, the temperature of the reaction was increased to 25 – 28 °C and stirred for 6 – 8h. The reaction was monitored by TLC (EtOAc: Hexane 7:3).The reaction mixture was quenched with methanol (15ml) slowly at 0 °C. The temperature was raised to 25 – 28 °C and stirred for 30 mins. Solvents were removed in rotary evaporator to get 480 mg of crude 2-amino-4,6-dinitrophenol as brown solid. Crude 2-amino-4,6-dinitrophenol (480mg) was purified by flash column chromatography eluted with 30% ethyl acetate in hexane. Fractions were concentrated using rotary evaporator to get pure 2-amino-4,6-dinitrophenol (395mg, 90%) as pale red powder.



Scheme 2. Investigation of other proton sources.

nitroarenes like para (**7** & **8**) & meta (**9**) did not undergo reduction like *ortho*-substituted arenes. As expected, the ester group (**8**) was unaffected in this transformation. Different *ortho*-hydroxy substituted nitroarenes (**10** – **15**) were tested and found to undergo reduction smoothly in BH_3-THF. Interestingly, a highly facile & Chemoselective reduction was observed with molecules containing two or three nitro groups (**12** & **13**). Only one nitro group was reduced among the two *ortho*-substituted nitro groups. This may be due to the anchimeric assistance of the hydroxy group in the reduction process, probably assisting in generating an active borane species.

While nitrile group (**14**) was found to be inert during the reduction process under standard conditions, the same was reduced with higher temperatures in BH_3-THF. Along with nitro group, Ketone (**15**) underwent smooth reduction to provide amino alcohol.

Other proton donors such as $–NH_2$, –COOH, CH_2OH (**24a**, **b**, **c** resp, Scheme 2) were tested which were found to be inert in activating the borane for hydride transfer. In the case of **24b**, reduction of carboxylic acid was observed giving rise to corresponding benzyl alcohol.

The importance of *ortho*-hydroxy group is further confirmed by *ortho*-methoxy derivative **24d** where the reaction did not proceed at all. *ortho*-Hydroxy group appears to be critical for the transformation.

The protocol requires around 8 – 10 eq of BH_3-THF reagent and the rate of reaction is drastically reduced with lesser equivalents of reagent. Mechanistically, 3 equivalents are consumed in the reaction and the need for additional quantities needs to be examined.

Itsuno et al. and Corey et al. reported oxazaborolidine-catalyzed asymmetric borane reduction of achiral ketones [13], which is unique among asymmetric reductions. The reagent acts in multiple ways (Lewis basic nitrogen and Lewis acidic boron) in promoting the reduction of carbonyl groups. The proximity of these two groups helps in holding the ketone and promoting the hydride transfer in a controlled and specific manner. In our case, we speculate that the presence of oxygen from the hydroxyl group and nitrogen from the nitro group could act in the same manner as depicted for CBS reduction.

Based on this idea, we speculate a mechanism that involves the attack of borane with substrate **13** affording oxyborane intermediate **18** (figure 1). This intermediate undergoes intramolecular transfer of hydride from the borane group to the nitro group, giving intermediate **19**. An intramolecular attack of nitrogen to borane forms a nitrogen-borate cyclic intermediate which upon elimination of borinic acid (with 2nd equivalent of borane) leads to the formation of **20**.

Transfer of hydride from boron to amine followed by the formation of amine borate complex with 3rd equivalent of borane results in

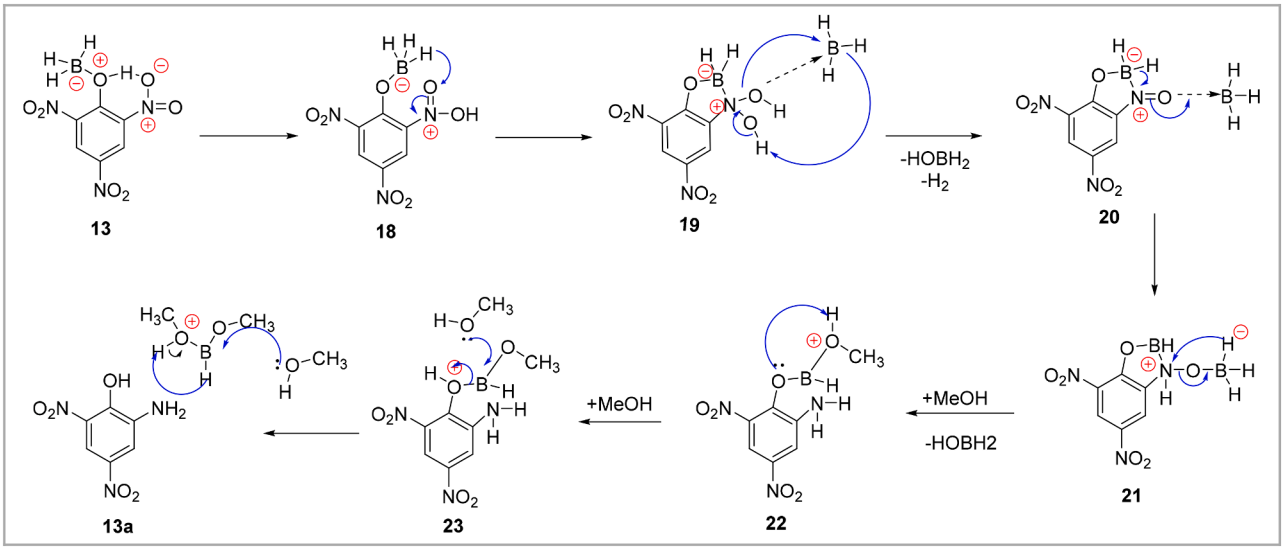


Fig. 1. A tentative mechanism for hydroxy group assisted borane-promoted reduction of the nitro group.

intermediate **21**. Following the same sequence, a second mole of borinic acid is eliminated followed by a hydride transfer that generates **22** which, under mild work-up conditions [quenching with methanol] provide amine as the product.

The formation of cyclic intermediate **19** is the rate-determining step as well as the key transition step which aids the Chemoselective reduction of dinitro substrates.

A close reaction monitoring using LC-MS/MS technique revealed the formation of two key intermediates **18** & **20** with their respective *m/z* ions *viz* 243 & 225 respectively. The observed mass values indicate the possibility of thermodynamically stable intermediates. The other intermediate species were not detectable by LC-MS/MS. The mechanism demonstrates the participation of the neighboring hydroxy group in the activation of borane and transfer of hydrogen to the nitro group.

A detailed substrate scope, functional group tolerance, and confirmative studies on the mechanism are underway and will be communicated shortly.

CRediT authorship contribution statement

Suryakant R. Rode: Conceptualization. **Prashant Mahajan:** Investigation. **Bhavik Dadhaniya:** Investigation. **Mahesh K. Shirsath:** Investigation. **Ravi Thakur:** Investigation. **Rajesh Doss:** Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. **Nadeem A. Khan:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2023.154899.

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