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Selective Nitro Reduction of Ester Substituted Nitroarenes by $NaBH_4$-$FeCl_2$

Zi-Hong Zhou[1,2] Yong-Bo Xu[1] Shu-Ming Wu[1,3] Wei-Jian Ling[1] Lei Zhang[2] Zhong-Qing Wang[1,3,4*]

[1] Department of Process Research and Development, HEC Pharm Group, Dongguan, People's Republic of China
[2] School of Biology and Biological Engineering, South China University of Technology, Guangzhou, People's Republic of China
[3] State Key Laboratory of Anti-Infective Drug Development, Sunshine Lake Pharma Co., Ltd., Dongguan, People's Republic of China
[4] School of Pharmacy, Xiangnan University, Chenzhou, People's Republic of China

Address for correspondence Zhong-Qing Wang, PhD, Department of Process Research and Development, HEC Pharm Group, 368 Zhenan Road, Dongguan 523871, People's Republic of China (e-mail: WangZhongqing@hec.cn).

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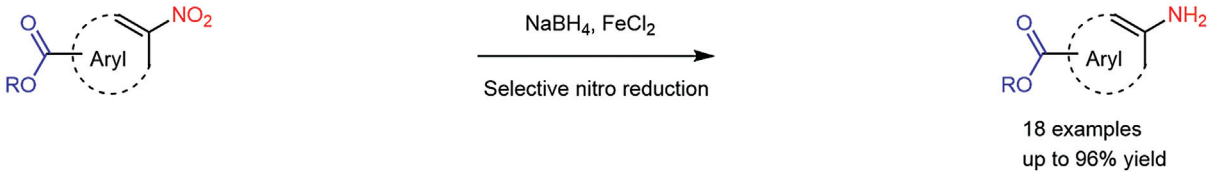

Abstract

This work aimed to explore a novel protocol for selective reduction of the nitro group on the aromatic ring while remaining the ester group unaffected. In this study, $NaBH_4$-$FeCl_2$ was disclosed as a key reductant in the process. $NaBH_4$-$FeCl_2$-mediated reduction showed high chemoselectivity, gave the desired products in magnificent yield (up to 96%), and was applied to synthesize a key intermediate of vilazodone (an antidepressant drug) on a hectogram scale in a total yield of 81% (two steps). The protocol is practical, and capable of synthesis of a range of aromatic amines, especially those with ester substituted in the ring.

Keywords
- ester
- nitroarene
- selectivity reduction
- sodium borohydride
- vilazodone

Introduction

Amino is a ubiquitous functional group that has been widely used in the synthesis of many natural products, pharmaceuticals, agrochemicals, and biologically active compounds.[1–3] Currently, nitro reduction is the predominant strategies applied for the synthesis of amino compounds.[3] Traditional methodologies for nitroarene reduction mainly include direct metal reduction such as Béchamp reduction,[4–11] hydrogenation,[4,12–19] and silyl hydride reduction.[4,20] Under these conditions, most ester groups would not be affected. However, these protocols suffer from drawbacks such as high economic cost, functional group incompatibility, reagent or environmental hazardousness, and high-pressure equipment dependence. Hence, a benign, green, and efficient method for nitro reduction is still required.

Compared with traditional reducing agents, sodium borohydride ($NaBH_4$) is mild, homogenous, inexpensive and environmental-friendly for applications in a wide range of reduction processes.[21] However, for the reduction of some less-electronphilic functional groups, the reducibility of

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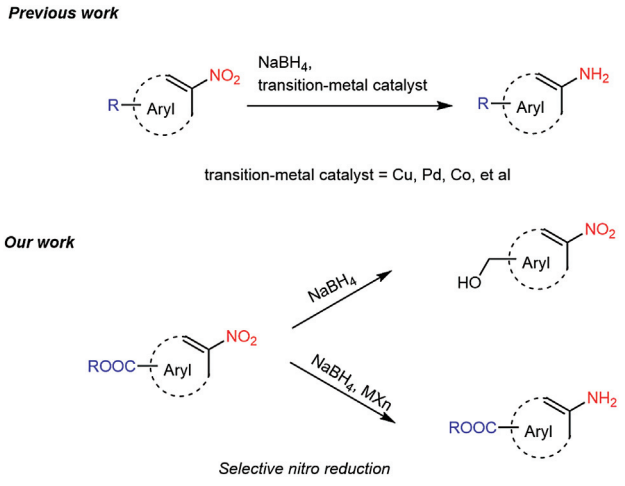
$NaBH_4$ needed to be enhanced by combining with transition metal catalysts.[22–30] Indeed, $NaBH_4$ combined transition metal such as Fe,[31–33] Co,[34,35] Ni[36,37] and Cu[38,39] are available for reducing nitroaromatics to the corresponding aromatic amines, nevertheless, these metal catalysts are associated with one or more problems such as necessity of using metal nanoparticles and was not commercially available, no assess the substrate scope, and poor selectivity, as it did in the case of the process development of vilazodone, of which the key intermediate ethyl 5-nitrobenzofuran-2-carboxylate (**1a**) is envisioned to be reduced by $NaBH_4$ during our project development.

Although in some transition-metal catalyzed protocols, ester groups were reported compatible,[40–45] the selectivity of nitro group over ester group can still be improved. To verify method applicability in our project, ester substituted nitroarene **1a** was subjected to the aforementioned $NaBH_4$-involved approaches (►**Scheme 1**).[45,46] Disappointingly, **1a** was reduced to quite a small amount of the desired aniline compound **1b**, yet, (5-nitrobenzofuran-2-yl)methanol (**1c**), the corresponding primary alcohol with intact nitro group, was the major product. Furthermore, the control experiment (with only $NaBH_4$) confirmed that only **1c** was generated when no other additives were present. Thus, it is still desirable to develop a new methodology for the highly-selective reduction of ester substituted nitroarenes not only in this situation.

As mentioned before, we hypothesize that the selectivity could be improved by adding transition metal salts, because $NaBH_4$ can reduce transition metal salts to zero valence, and the zero valence metals can selectively reduce nitro to amino under special conditions. In addition, the previously reported[47] procedure utilizing $CuSO_4$ in solvent with $NaBH_4$ afforded conversion of **1a** to the desired product **1b** with very low impurity levels, and a large number of **1c** was obtained. However, these results also suggest that ester reduction could be inhibited by some salts. Inspired by the previous results, we wonder whether other metal salts could realize the selective reduction of ester substituted aromatic nitro compounds with high conversion.



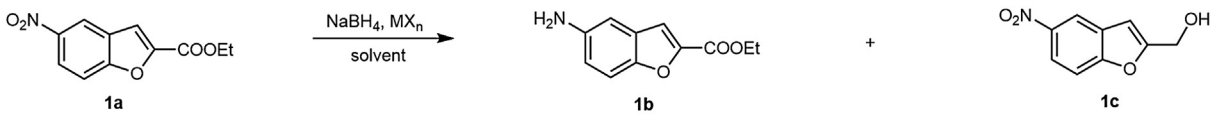
Scheme 1 Comparison of $NaBH_4$-involved approaches of selective nitro reduction.

Results and Discussion

The screening of reduction conditions was conducted in ►**Table 1**. We began our exploration with **1a** as the model substrate. Initially, the reaction was performed in the presence of 1.0 equiv. of MX_n and 2.5 equiv. of $NaBH_4$ under nitrogen atmosphere in THF at 28°C. The process proceeded slowly to furnish the desired product **1b** only in 10.9% conversion when $CuSO_4$ was used, but 9.41% of **1c** was formed (►**Table 1**, entry 1). In addition, the large amount of **1c** was obtained when $AlCl_3$ or LiCl was used, and the conversions up to 36.1% and 20.2%, respectively (►**Table 1**, entries 2, 3). Surprisedly, when 1.0 equiv. of $FeCl_3$ was used, only a small amount of **1c** was observed (►**Table 1**, entry 4, 0.5%). This finding indicated that the reduction of ester group might be suppressed by some metal salts or the reaction proceeded differently. Then, several kinds of ferrous salts were evaluated. Fortunately, we found that $FeCl_2$ was suitable for this reaction, achieving at high **1b** conversion (up to 92.8%), and only 0.1% of **1c** was detected, while the others gave poor conversion of **1b** (less than 30%, ►**Table 1**, entries 5–8). Subsequently, we attempted to lower the equiv. of $NaBH_4$ but found that the conversion decreased seriously when the $NaBH_4$ loading was cut down from 2.5 equiv. to 1.5 or 1.1 equiv. (►**Table 1**, entries 9–11). Furthermore, testing various amounts of $FeCl_2$ revealed that 1.0 equiv of $FeCl_2$ was the best, and the decrease in equiv. of $FeCl_2$ caused an obvious increase in the content of **1c** (►**Table 1**, entries 12–14). The solvent had a great impact on this reaction. It was found that aprotic solvents contribute to the high conversion, however, in a polar protic solvent (EtOH), poor conversion was provided (►**Table 1**, entries 6, 15–16). Thus, THF was selected as the optimized solvent for further studies. Finally, we assess the effect of reaction temperature on the conversion. When we lower the reaction temperature, the conversion of **1b** was decreases while the content of **1c** was increased (►**Table 1**, entry 17). As such, we tried to improve the reaction rate by raising the temperature from 28 to 40°C. Unexpectedly, the conversion was still low (►**Table 1**, entry 18). Above all, 2.5 equiv. of $NaBH_4$, 1.0 equiv. of $FeCl_2$, THF as the solvent, and reaction temperature at 28°C were set as the optimal reaction conditions.

To assess the substrate scope, a full set of ester group substituted aromatic nitro compounds were reduced under the optimized conditions. Examination of the results listed in ►**Table 2** shows that the reaction proceeded well in most cases. For a better understanding, the substrates were divided into different groups depending on the relative position of the nitro and ester groups on the phenyl ring. In group 1, the ester group was located in a *meta*-position of the nitro group in substrates **2a**-**2d** (►**Table 2**, entries 1–4), giving **3a**-**3d** in excellent yields (91–96%). In group 2, a series of *para*-ester nitroarene derivatives were investigated. At first, methyl 4-nitrobenzoate (**2e**) showed good conversion and obtained the desired product in 93% yield. And the substrates

Table 1 Optimization of the reaction conditions[a]



Entry	MX_n (equiv.)	$NaBH_4$ (equiv.)	Solvent	Conv. (%)[b]	
				1b	1c
1	$CuSO_4$ (1.0)	2.5	THF	10.9	9.41
2	$AlCl_3$ (1.0)	2.5	THF	31.1	36.1
3	LiCl (1.0)	2.5	THF	2.6	20.2
4	$FeCl_3 \cdot 6H_2O$ (1.0)	2.5	THF	3.6	0.5
5	$FeSO_4 \cdot 7H_2O$ (1.0)	2.5	THF	24.0	14.2
6	$FeCl_2$ (1.0)	2.5	THF	92.8 (91.3[c])	0.1
7	$FeBr_2$ (1.0)	2.5	THF	trace	1.5
8	$FeC_2O_4 \cdot 2H_2O$ (1.0)	2.5	THF	12.6	36.7
9	$FeCl_2$ (1.0)	2.0	THF	81.9	0.6
10	$FeCl_2$ (1.0)	1.5	THF	60.0	0.3
11	$FeCl_2$ (1.0)	1.1	THF	17.2	0.1
12	$FeCl_2$ (0.8)	2.5	THF	85.5	0.4
13	$FeCl_2$ (0.5)	2.5	THF	71.4	1.2
14	$FeCl_2$ (0.2)	2.5	THF	36.3	10.3
15	$FeCl_2$ (1.0)	2.5	MeCN	77.7	0.2
16	$FeCl_2$ (1.0)	2.5	EtOH	16.5	2.0
17[d]	$FeCl_2$ (1.0)	2.5	THF	22.6	1.0
18[e]	$FeCl_2$ (1.0)	2.5	THF	33.6	0.5

[a]Reaction conditions: 3.8 mmol of **1a**, respective mmol of MX_n and $NaBH_4$ were added into 10 mL of solvent, and the mixture was stirred under nitrogen atmosphere at 25–28 oC for 12 hours.
[b]Conversion was determined by HPLC.
[c]Yield of isolated product after flash column chromatography on silica gel.
[d]Reaction temperature is 15°C.
[e]Reaction temperature is 40°C.

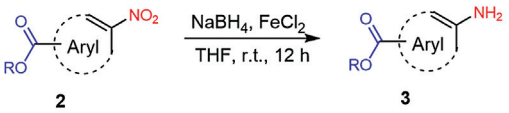
containing an electron-donating group (**2f**) or an electron-withdrawing group (**2g**, **2h**) also gave desired products in high yield (92–95%). Generally, unlike *meta*- or *para*-ester substituted nitro compounds, the *ortho*-effect of ester and nitro group in **2i**-**2k** (group 3; ►**Table 2**, entries 9–11) made the selective nitro-reduction more challenging. To our delight, satisfying results were also observed. In contrast, *ortho*-disubstituted substrate **2j** showed an obvious decrease of yield (83%) even under optimized conditions, which was probably due to the steric effect. Meanwhile, we also examined aliphatic ester substrate (►**Table 2**, entry 12) and acquired the corresponding aniline (**3i**) in 85% yield.

Heterocycles are prevalent in many pharmacologically important core structures. Selectivity of the nitro group over the ester group in pyridine systems, which were common in pharmaceutical molecules, was also demonstrated by the reduction of **2m** and **2n**, which proceeded smoothly to provide **3m** and **3n** in 89% and 92% yield, respectively. To further expand the substrate scope, the substrates bearing nitro and acid groups such as 2-nitrobenzoic acid and 5-fluoro-2-nitrobenzoic acid were also investigated, disappointingly, no more than 10% conversions were detected. This result maybe due to that $NaBH_4$ was a high energy material that easy decomposed by reacting with carboxy group on the substrates.

Other types of nitro compounds (**2o**-**2q**) were also tested under optimized conditions (►**Table 2**, entries 15–17). Excellent halide compatibility was observed from the above results, and interestingly, cyano group was also observed relatively stable under the same conditions (►**Table 2**, entry 15). Pleasingly, 4,6-dichloro-5-nitro-2-(propylthio)pyrimidine (**2p**) and 2-bromo-6-nitrobenzo[*d*] thiazole (**2q**) could be reduced with good results (93% and 94% yield, respectively). The corresponding products are important skeletons present in bioactive compounds, such as ticagrelor,[48] and some potential anti-hepatitis C or anti-Alzheimer's disease drugs.[49–52]

The synthetic utility of this methodology was confirmed in the synthesis of vilazodone. As shown in ►**Scheme 2**,

Table 2 Substrate scope[a]

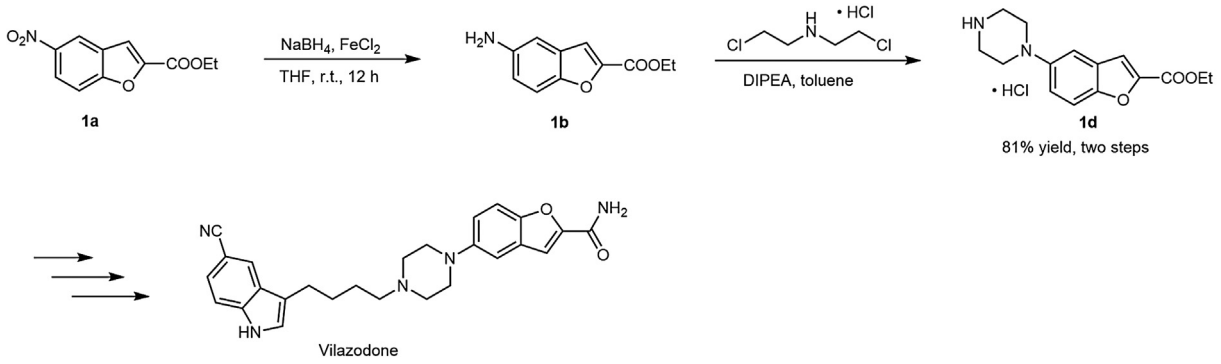


2 **3**

Entry	Substrate **2**	Product **3**	Yield (%)[b]
1	**2a**, X = Br, Y = H, R = H	**3a**, X = Br, Y = H, R = H	92%
2	**2b**, X = F, Y = H, R = H	**3b**, X = F, Y = H, R = H	94%
3	**2c**, X = H, Y = H, R = Br	**3c**, X = H, Y = H, R = Br	96%
4	**2d**, X = H, Y = Br, R = H	**3d**, X = H, Y = Br, R = H	91%
5	**2e**, X = H, Y = H	**3e**, X = H, Y = H	93%
6	**2f**, X = OMe, Y = H	**3f**, X = OMe, Y = H	92%
7	**2g**, X = F, Y = H	**3g**, X = F, Y = H	95%
8	**2h**, X = H, Y = Br	**3h**, X = H, Y = Br	94%
9	**2i**, X = H, Y = H, R = Cl	**3i**, X = H, Y = H, R = Cl	96%
10	**2j**, X = OMe, Y = H, R = H	**3j**, X = OMe, Y = H, R = H	83%
11	**2k**, X = H, Y = OMe, R = OMe	**3k**, X = H, Y = OMe, R = OMe	94%
12	**2l**	**3l**	85%
13	**2m**, X = H, R = Me	**3m**, X = H, R = Me	89%
14	**2n**, X = Cl, R = Et	**3n**, X = Cl, R = Et	92%
15	**2o**	**3o**	81%
16	**2p**	**3p**	93%
17	**2q**	**3q**	94%

[a]Reaction conditions: 3.8 mmol of **2**, 3.8 mmol of $FeCl_2$, and 9.5 mmol of $NaBH_4$ were added into 10 mL of THF, and the mixture was stirred under a nitrogen atmosphere at 25–28°C for 12 hours.
[b]Yield of isolated product after flash column chromatography on silica gel.

under the optimized conditions, a hectogram scale of **1a** was selectivly reduced to give **1b**, which was extracted with ethyl acetate, concentrated, and used to produce **1d** directly (81% yield, two steps).[53] **1d** is the key intermediate for the construction of vilazodone, and proceed to synthsize the target product according to a reported study.[54]



Scheme 2 Synthesis of vilazodone. The starting material **1a** was used at 100 g-scale. **1d** was obtained from **1b** according to Jayaraman et al's method,[53] and then participated the process for producing vilazodone according to a reported study.[54]

Conclusion

In summary, it has been demonstrated that the introduction of $FeCl_2$ into the $NaBH_4$ reduction system brings significant benefits for selective nitro reduction. Through this protocol, a range of multi-substituted aromatic amino compounds could be synthesized with excellent yield. Especially, utilization of this method enabled an efficient synthesis of the ester substituted amino compounds. In addition, $NaBH_4$-$FeCl_2$-promoted nitro reduction provided a useful synthetic strategy for the synthesis of a key intermediate of the antidepressant drug vilazodone. Further applications of this protocol are currently being explored and will be disclosed in due course.

Experimental section

General Procedure for the Synthesis of 1b, 3a-3q

To a stirred solution of **1a** (3.8 mmol) in THF (10 mL) was added $FeCl_2$ (3.8 mmol) at r.t., then the $NaBH_4$ (9.5 mmol) was added under nitrogen atmosphere, the resulting solution was stirred for 12 hours at 25–28°C. Water (20 mL) was added to the reaction mixture. The mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were washed with water (20 mL) and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel using ethyl acetate/*n*-hexane mixture to afford **1b.**

Ethyl 5-aminobenzofuran-2-carboxylate (1b): Yellow solid. 91% yield. mp 58–60°C. ESI-HRMS (*m/z*): calcd. for $[M+H]^+$ 206.0812, found 206.0810. ^{1}H NMR (400 MHz, DMSO) δ 7.51 (s, 1H), 7.38 (d, J = 9.4 Hz, 1H), 6.82 (d, J = 6.9 Hz, 2H), 5.22 (s, 2H), 4.32 (dd, J = 14.1, 7.0 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.82, 148.66, 145.09, 144.77, 127.34, 117.25, 113.65, 111.98, 104.41, 60.86, 14.12.

Full experimental detail for the synthesis of **3a-3q**, and the ^{1}H and ^{13}C NMR spectra can be found in **Supporting Information** of this article's webpage.

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Conflict of Interest

All authors declare no conflict of interest.

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