

Tetrahedron Letters 42 (2001) 167-170

Chemoselective reductions of nitroarenes: bromoethanol-assisted phthalocyanatoiron/NaBH₄ reductions

H. Scott Wilkinson, Gerald J. Tanoury,* Stephen A. Wald and Chris H. Senanayake*

Chemical Research and Development, Sepracor Inc., 111 Locke Drive, Marlborough, MA 01752, USA

Received 25 August 2000; revised 23 October 2000; accepted 26 October 2000

Abstract—Porphyrinatoiron/NaBH₄ and a novel phthalocyanatoiron/NaBH₄ catalyst systems were investigated for the reductions of nitroarenes. The phthalocyanatoiron/NaBH₄ system was superior to the porphyrinatoiron/NaBH₄ system. The reductions were performed in good yields and excellent chemoselectivities. The rate of reduction by the PcFe/NaBH₄ system increased upon the addition of 2-bromoethanol. © 2000 Elsevier Science Ltd. All rights reserved.

The use of transition metal complexes to effect the reduction of a nitroarene to the corresponding aniline is a well-known process.¹ The most common methods employ a heterogeneous Pd/C or Pt/C catalyst,² or a homogeneous ruthenium- or rhodium-based catalyst³ and a hydrogen source (hydrogen gas or transfer hydrogenation). Methods also exist for transition-metalcatalyzed hydride reductions, and one of the most promising methods employs NaBH₄ as the hydride source. The types of homogeneous catalysts used for these NaBH₄-mediated reductions vary widely from simple metal chlorides and oxides⁴ to metallochelate systems.⁵ Of the metallochelate systems studied to date, metalloporphyrins have garnered considerable attention, mainly due to their applicability to biological systems. However, metalloporphyrin complexes remain expensive and are prone to reaction of the porphyrin ligand. The closely analogous metallophthalocyanine complexes, however, have not been studied in this context, are less expensive, possess a more stable ligand, and provide a novel method for the reduction of nitroarenes under metal-catalyzed hydride transfer conditions. With a need to obviate the use of hydrogen gas in performing the chemoselective reduction of 1 to 2 (Eq. 1), a key step in the total synthesis of (R,R)-formoterol, and with an opportunity to develop a new synthethic method for the reduction of nitroarenes, studies were commenced to develop and extent the application of the metallochelate reduction methodology. Reported herein is the discovery of a novel phthalocyanatoiron(II)/NaBH₄ catalytic system for the chemoselective reduction of nitroarenes and the use of 2-bro-

moethanol to increase the activity of the catalytic system.



Initially, studies on the reduction of **1** focused on the use of palladium- and platinum-based heterogeneous catalysts under hydrogen transfer conditions.⁶ Using 2–5 mol% of 10% Pd/C or 5% Pt/C catalyst in the presence of several hydrogen transfer reagents (formic acid, ammonium formate, cyclohexene, limonene and terpene) resulted in <13% formation of **2**. Pt/C systems afforded only starting material and Pd/C systems gave <5% consumption of **1** with formic acid as the transfer reagent and <13% of **2** with ammonium formate as the transfer reagent. Due to the poor reactivity of these systems, and a need to perform the transformation under hydride transfer conditions, attention was focused on the application of metallochelate-catalyzed nitro reductions.

Investigation of the literature indicated that the use of NaBH₄ as the hydride source in the presence of transition metal complexes were promising conditions for the development of a new method for the conversion of 1 to $2.^7$ Initial studies using CoCl₂ or Fe(acac)₃ with NaBH₄ resulted in a combination of epoxide formation (3), debromination (4), and/or nitroreduction (5). Compound 2 was not observed. We then turned our attention to the use of metalloporphyrins to catalyze the

^{*} Corresponding authors.

^{0040-4039/01/\$ -} see front matter @ 2000 Elsevier Science Ltd. All rights reserved. PII: S0040-4039(00)01920-1



Table 1. Comparison of reduction of 1 with	(TPP)FeCl and PcFe(II)/(III) catalyst systems ^a
--------------------------------------------	------------------------------------------------------------

Entry	Catalyst (mol%)	NaBH ₄ (equiv.)	Time (h)	1 (%)	2 (%)	5 (%)
1	(TPP)FeCl (0.4)	1.0	4	54	29	13
2	(TPP)FeCl (0.4)	2.0	4	3	37	13
3	(TPP)FeCl (1.5)	1.5	1	0	36	20
4	PcFe(II) (2.0)	2.0	2	1	57	29
5	PcFe(III)Cl (2.0)	2.0	2	1	58	31

^a Reactions were conducted in diglyme as solvent at room temperature. Ratios were determined by HPLC analysis.

reduction of nitroarenes to anilines.8 The reports indicated that tetraphenylporphyrinatoiron(III) chloride ((TPP)FeCl) reduced nitroaromatics to the corresponding anilines in high yield in the presence of NaBH₄ using diglyme as solvent. This system was extended to the reduction of 1, as shown in Table 1.9 With diglyme as solvent, the product ratios (1:2:5) were found to be a function of the number of equivalents of NaBH₄ and the catalyst loading. At 0.4 mol% (TPP)FeCl, the extent of reaction after 4 h at room temperature rose from 46% conversion with 1.0 equiv. of NaBH₄ to 97% conversion with 2.0 equiv. of NaBH₄ (entries 1 and 2). In both cases, the product mixture contained no debrominated by-products, but 13% of 5 and only 29-37% of 2 were observed. Raising the catalyst loading to 1.5 mol% resulted in complete consumption of 1 after 1 h at room temperature with 1.5 equiv. of $NaBH_4$ present (entry 3). Although the amount of 2 in the product mixture was 36%, and no debromination was observed, 5 was present at a level of 20%. The related phthalocyanatoiron complexes were evaluated as potential catalysts to effect the conversion of 1 to 2. To our knowledge, these complexes have never been used to catalyze the reduction of nitroarenes. Also, the phthalocyanine systems are more practical than the porphyrin complexes due to their lower cost and greater availability. In the presence of 2 mol% of PcFe(II) or PcFe(III)Cl, 1 was converted to 2 and 5 in 57 and 28% yields, respectively. Even though mixtures of 2 and 5 were obtained, the reaction was cleaner than the TPP systems, and both Fe(II) and Fe(III) performed the reduction with identical results, indicating the active catalyst was a Fe(II) species.¹⁰ The reactions were successful with 1.8 equiv. of NaBH₄ in diglyme at room temperature in 2 h. Due to the consistently superior reactivity and selectivity of the PcFe(II)/(III) system, our attention focused on the development of this catalyst.

The new catalytic system was investigated in greater detail by studying the conversion of *rac*-4 to 6 (Eq. (2)). Unexpectedly, the rate of reduction of *rac*-4 was less than one-tenth the rate of reduction of 1: after 2 h at room temperature only 10% of *rac*-4 was consumed and converted to 6, while 1 was converted to 2 and was

99% consumed after 2 h at room temperature with 2 mol% catalyst (Table 2, entries 4 and 5). The slow rate of reduction of *rac*-4 compared to 1, and the concomitant formation of epoxide 5 during the rapid reduction of 1 indicated that the generation of HBr during the formation of 5 could account for the faster rate of reduction of 1.



To determine the effect of HBr on the nitroarene reduction with PcFe(II), *rac-4* was reduced in the presence of various amounts of HBr, or HBr equivalents, and the data are shown in Table 2. In the presence of 2.5 mol% PcFe(II), and no HBr, 77% of *rac-4* remained after 2 h at room temperature (entry 1). With the addition of 5 and 10 mol% HBr, 46 and 62% of *rac-4* remained after 1 h of reaction (entries 2 and 3). At a level of 40 mol% HBr, the rate of reaction increased dramatically, and only 2% of *rac-4* remained after 1 h (entry 4). This corresponded to a 16:1 ratio of HBr:PcFe(II). Nearly identical results were obtained with 100 mol% HBr (entry 5). Due to the safety issues associated with handling large quantities of HBr, a

Table 2. Reduction of *rac*-4 with PcFe(II) as catalyst with various amounts of HBr^{a}

Entry	Acid additive (mol%)	Time (h)	Rac-4 (%)	6 (%)
1	HBr (0)	2	77	23
2	HBr (5)	1	62	35
3	HBr (10)	1	46	46
4	HBr (40)	1	2	85
5	HBr (100)	1	3	86
6	2-Bromoethanol (100)	2	0	87

^a Reactions were conducted in diglyme at 2.5 mol% PcFe(II) and 1.8 equiv. of NaBH₄ at room temperature. Ratios were determined by HPLC analysis.

Table 3. Reduction of nitroarenes with PcFe(II)/NaBH₄/2-bromoethanol system^a



^aReactions were conducted on a 2 mmol scale in 11 mL of diglyme with 2 mol % PcFe(11), 2.0 equiv. of NaBH₄, and 1.0 equiv. of 2-bromoethanol at room temperature. Yields were determined by isolation of the final product, unless otherwise noted.

more easily manipulated and readily available HBr equivalent was investigated: 2-bromoethanol. As shown in entry 6, 100 mol% of 2-bromoethanol afforded a rapid reduction of **6** in high yield: 87% after 2 h at room temperature.¹¹ Extending these new reaction conditions to the TPPFeCl system resulted in consumption of *rac-4* but with <50% of **6** present. Also, no rate acceleration was observed for the (TPP)FeCl system upon addition of 2-bromoethanol or HBr. Again, the PcFe(II)/NaBH₄/2-bromoethanol catalyst system was superior to the corresponding (TPP)FeCl system.

To determine the generality of the 2-bromoethanol-mediated reduction of rac-4 with PcFe(II) and NaBH₄, the scope and utility of the reaction was studied on numerous substrates.¹² From the data shown in Table 3, an electron-withdrawing ester group attached to the aryl ring underwent reduction ten times slower than the parent nitrobenzene (entries 1 and 2). For iodobenzene, the carbon-iodine bond, highly reactive under Pd/C and Pt/C hydrogenation conditions, was stable to the reaction conditions (entry 3),13 as were nitriles and benzyl-protected anilines (entries 4 and 5). The result shown in entry 6 demonstrated that CBZ protecting group, removed under standard Pd/C-catalyzed hydrogenation conditions, remained intact during reduction of the nitro group using the PcFe(II)/NaBH₄/2-bromoethanol conditions. The stability of a CBZ-protected amine to the reaction conditions should allow for these reduction conditions to be applied to solid phase synthesis. Enantiopure 1 was subjected to the optimized reaction conditions (entry 7) and was found to convert rapidly to 2 in 67% isolated yield without loss of enantiomeric purity.

The results presented here have demonstrated that $PcFe(II)/NaBH_4/2$ -bromoethanol is a novel, efficient,

and practical catalytic system for the reduction of nitroarenes. The presence of HBr, generated in a controlled manner from 2-bromoethanol, has been shown to be crucial for a rapid and chemoselective reduction. The reductions can be conducted in the presence of other labile functionality, and the PcFe(II) complex (or PcFe(III)Cl) is a readily available and inexpensive catalyst. The ability of the PcFe(II) complex to catalyze the reduction, while the corresponding (TPP)FeCl system was troublesome, remains unclear. This new catalyst/ reagent combination will prove to be valuable in the arsenal of the synthetic chemist. Further studies are underway to better understand the differences between the porphyrin and phthalocyanine systems, and the cause of the rate increase upon addition of HBr or an HBr equivalent.

Acknowledgements

We thank Professor Peter Wipf for helpful discussions.

References

- For a review, see: Tafesh, A. M.; Weiguny, J. Chem. Rev. 1996, 96(6), 2035. Also, see: (a) Reetz, M. T.; Frombgen, C. Synthesis 1999, 1555. (b) Wang, X.; Xu, M.; Lian, H.; Pan, Y.; Shi, Y. Synth. Commun. 1999, 29, 3031.
- For palladium- and platinum-catalyzed heterogeneous systems, see: (a) Bae, J. W.; Cho, Y. J.; Lee, S. H.; Yoon, C. M. *Tetrahedron Lett.* 2000, 41, 175. (b) Chen, F.; Yan, Q.; Shao, L.; Liu, M. *Lizi Jiaohuan Yu Xifu* 1999, 15, 572. (c) Kantam, M. L.; Bandyopadhyay, T.; Rahman, A.; Reddy, N. M.; Choudary, B. M. J. Mol. Catal. A: Chem. 1998, 133, 293. (d) Islam, S. M.; Bose, A.; Palit,

B. K.; Saha, C. R. J. Catal. **1998**, 173, 268. (e) Yu, Z.; Liao, S.; Xu, Y.; Yang, B.; Yu, D. J. Mol. Catal. A: Chem. **1997**, 120, 247.

- For rhodium-catalyzed reductions, see: (a) Nomura, K.; Ishino, M.; Hazama, M. Bull. Chem. Soc. Jpn. 1991, 64, 2624. (b) Nomura, K.; Ishino, M.; Hazama, M. J. Mol. Catal. 1991, 66, L11–L13. (c) Nomura, K.; Ishino, M.; Hazama, M. J. Mol. Catal. 1991, 65, L5–L7. (d) Nomura, K.; Ishino, M.; Hazama, M. J. Mol. Catal. 1993, 78, 273. For ruthenium-catalyzed reductions, see: (a) Nomura, K. Chem. Lett. 1991, 1679. (b) Nomura, K. J. Mol. Catal. 1992, 73, L1–L4. (c) Nomura, K.; Ishino, M.; Hazama, M. J. Mol. Catal. 1993, 78, 273. For other types of conditions, see: (a) Moody, C. J.; Pitts, M. R. Synlett 1998, 1028; (b) Fischer, B.; Sheihet, L. J. Org. Chem. 1998, 63, 393.
- Yanada, K.; Yanada, R.; Meguri, H. *Tetrahedron Lett.* 1992, 33, 1463.
- (a) Suzuki, H.; Manabe, H.; Inouye, M. Chem. Lett. 1985, 1671. (b) Yanada, K.; Yanada, R.; Meguri, H. Tetrahedron Lett. 1992, 33, 1463. (c) Vizi-Orosz, A.; Marko, L. Transition Met. Chem. 1991, 16(2), 215. (d) Cho, J. G.; Potter, W. T.; Sublette, K. L. Appl. Biochem. Biotechnol. 1994, 2273.
- Another method for the conversion of 1 to 2 is described in: Wilkinson, H. S.; Tanoury, G. J.; Senanayake, C. H.; Wald, S. A. Org. Proc. Res. Dev. 2000, 4, 567.
- (a) Aoyama, Y.; Fujisawa, T.; Watanabe, T.; Toi, H.; Ogoshi, H. J. Am. Chem. Soc. 1983, 86, 943. (b) Barley, M.; Takeuchi, K.; Meyer, T. J. Am. Chem. Soc. 1983, 86, 5876. (c) Aoyama, Y.; Midorikawa, K.; Toi, H.; Ogoshi, H. Chem. Lett. 1987, 1651.
- (a) Cho, J. G.; Potter, W. T.; Sublette, K. L. Appl. Biochem. Biotechnol. 1994, 2273. (b) Sakai, L.; Mitarai, S.; Ohkubo, K. Chem. Lett. 1991, 195.
- 9. Ru(TPP) and Ni(TPP) catalysts were also used. With both catalysts, under an atmosphere of Ar or air, and

with diglyme as solvent, 28-33% of 1 was converted to 4 in 30 min.

- 10. The reduction of Fe(III) to Fe(II) can be visually observed by the change in color from green to deep blue upon addition of $NaBH_4$. This color change occurred prior to reduction of 1.
- 11. (a) The corresponding conversion without 2-bromoethanol was 15% after 2 h with 2.0 mol% PcFe(II) and 1.8 equiv. of NaBH₄. (b) The conversion of **4** to **6** occurred without racemization of the benzylic carbon atom (determined by HPLC analysis). (c) The use of HCl and 2-chloroethanol as additives had no observable effect on the reaction rate or product distribution. Using 40 mol% HCl, 51% of **4** remained after 1 h, and 48% of **4** remained after 7 h.
- 12. A typical procedure is as follows: 4-(Aminophenyl)acetonitrile from 4-(nitrophenyl)acetonitrile. To a solution of 4-nitrophenylacetonitrile (162 mg, 1.0 mmol) in diglyme (1 mL) was added Fe(II)-phthalocyanine (12 mg, 0.02 mmol, 0.02 equiv.), followed by addition of 2-bromoethanol (124 µL, 1.0 mmol, 1 equiv.) at 22°C. The mixture was stirred at room temperature for 3 min, followed by addition of sodium borohydride (0.5 M, 4 mL, 2 equiv.). The reaction mixture was stirred at room temperature until the starting material was consumed (monitored by HPLC). Ethyl acetate (30 mL) and water (40 mL) were added and the reaction mixture was poured into a separatory funnel and the aqueous layer was discarded. The organic layer was washed with water (2×20 mL) and concentrated in vacuo to yield the product as a blue oil. Purification by flash chromatography on silica gel (eluent: EtOAc:hex 1:4) yielded the desired product (130 mg, 98% yield) as a yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 3.75 (s, 2H), 4.83 (s, 2H), 6.73 (d, 2H), 7.07 (d, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 22.81, 116.80, 120.46, 120.80, 129.90, 148.71.
- 13. No products corresponding to dehalogenation of the haloarenes were observed by HPLC and NMR analysis.