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A Novel Iodide-Catalyzed Reduction of Nitroarenes and Aryl Ketones with H_3PO_2 or H_3PO_3: Its Application to the Synthesis of a Potential Anticancer Agent

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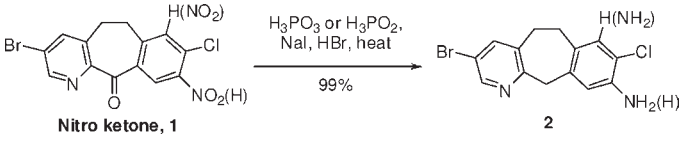
ABSTRACT



A novel iodide-catalyzed reduction method using hypophosphorous and/or phosphorus acids was developed to reduce both diaryl ketones and nitroarenes chemoselectively in the presence of chloro and bromo substituents in high yield. This efficient and practical method has been successfully applied to a large scale production of a potential anticancer agent.

In the synthesis of a potential anticancer agent, Lonafarnib, we needed to reduce both a nitro group and an aromatic ketone in the presence of chloro and bromo subsituents on aromatic rings as shown in Scheme 1.

A number of methods including hydrogenation, modified hydrides, metals or metal derivatives (Sn, SnX_2, $TiCl_3$, Zn), sulfides (Na_2S, $Na_2S_2O_4$), and enzymes are known to reduce nitro groups to the corresponding amines.[1] The first three methods (hydrogenation, hydrides, and metals) are also capable of reducing ketones to the CH_2 group under certain conditions.[1b] However, most of the methods also reduce bromo and chloro substituents, thus generating dehalogenated impurities. On an industrial scale, it can be extremely difficult to separate relatively small amounts of dehalogenated impurities from the desired product to meet the strict purity requirements of active pharmaceutical ingredients. Various methods have been developed to reduce nitro and ketone groups while minimizing the undesired dehalogenation,[2] but most of the reported methods have limited scope and/or utilize complex procedures.[3] Furthermore, bromo and iodo substituents do not survive those conditions.[4] Recently, this group has reported a novel ZnX_2-modulated Pd/C and Pt/C method for chemoselective hydrogenation and hydrogenolysis of halogen-substituted nitroarenes, alkenes, benzyl ethers, and aromatic ketones.[5] However, these procedures only reduce an aromatic ketone to its corresponding alcohol and not to the desired methylene group. We now report a novel iodide-catalyzed chemoselective reduction of nitroarenes to anilines and diaryl ketones to

(1) (a) Larock, R. C. *Comprehensive Organic Transformations*, John Wiley & Sons: New York, 1999; Chapter 7, pp 821−827. (b) For ketone reduction, see ref 1a, pp 61−64.

(2) (a) Mallat, T.; Baiker, A. *Appl. Catal., A* **2000**, *200*, 3 and references cited therein. (b) Baumeister, P.; Studer, M.; Roessler, F. In *Handbook of Heterogeneous Catalysis*, Vol. 5; Ertl, G., Knzinger, H., Weitkamp, J., Eds.; VCH: Weinheim, 1997; p 2186. (c) Straz, A. M. In *Catalysis of Organic Reactions*; Kosak, J. R., Ed.; Marcel Dekker: New York, 1984; p 335.

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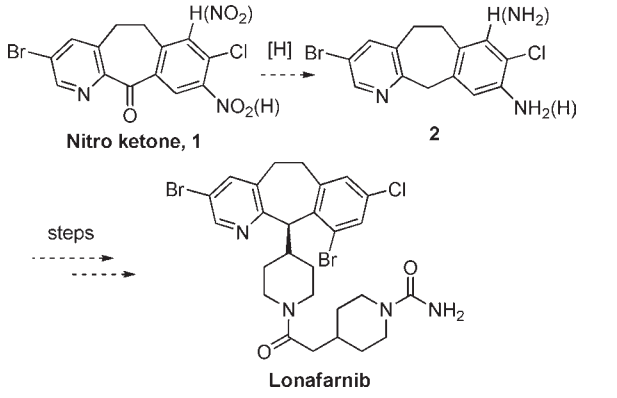
methylene groups using either hypophosphorous acid or a combination of hypophosphorous and phosphorus acids. Furthermore, we report a successful application of this novel method to the synthesis of an arylhalogen-containing anticancer agent, Lonafarnib.

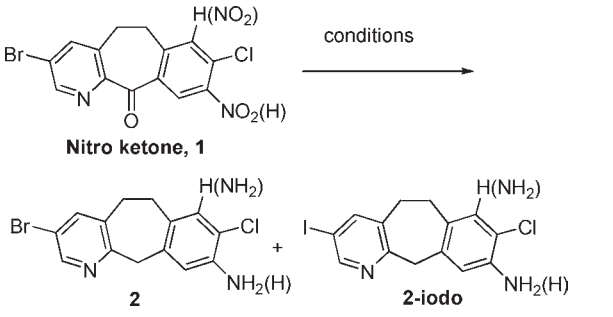
Scheme 1. Proposed Synthesis of Lonafarnib



Recently, Fry reported a chemoselective reduction of aryl ketones in the presence of bromo substituents with a combination of H_3PO_2 and I_2 in refluxing HOAc.[6] This method is safer than a previously reported procedure using red phosphorus and HI under refluxing conditions.[7] However, similar conditions are not known to reduce nitroarenes.[9] Thus, we initially planned a two-stage reduction: first reducing the aryl ketone with the H_3PO_2-based method and then the nitro group with our ZnX_2-modulated Pd/C catalyst.[5] In light of safety considerations, we focused our effort on H_3PO_2-based reducing agents, rather than the red phosphorus. To our suprise, the first reaction with 11 equiv of H_3PO_2 and 4 equiv of HI in refluxing water not only reduced the ketone group to a methylene group but also reduced the nitro group to the corresponding aniline; both the bromo and chloro substituents were largly preserved. To the best of our knowledge, this is the first example of nitroarene reduction with the HI−H_3PO_2 system. This method can be complementary to the current methods such as hydrogenation, hydride, and metal-based procedures. However, there were two issues associated with this procedure: (1) a major byproduct was observed at about the 5% level; and (2) a severe foaming at the beginning of the reduction. The byproduct was identified as the 3-iodo analogue of **2**, apparently derived from an iodo replacement of the 3-bromo substituent on the pyridine ring, and was very difficult to remove to a pharmaceutically acceptable level. Thus, we undertook additional studies to optimize the reaction conditions to minimize the byproduct and improve the operability on a large scale. A number of experiments were carried out, and the results are listed in Table 1.

As indicated by entry 2 of Table 1, reducing the amount of H_3PO_2 and replacing HI with NaI did not reduce the level of the byproduct. Use of less potent reducing agents such as H_3PO_3 (entry 3) or NaH_2PO_3 (entry 4) in the presence of 2 equiv of NaI and aqueous HBr completed the reduction with a longer reaction time. However, neither of the conditions prevented the formation of the iodo byproduct. We thought that the level of the iodo displacement byproduct should be proportional to the concentration of iodide and that the less the iodide concentration, the lower the byproduct. To our delight, reducing the amount of NaI from 2 to 0.1 equiv suppressed the formation of the byproduct to an undetectable level. However, use of a catalytic amount of NaI (0.1 equiv) also slowed the desired reductions. For example, use of 3.5 equiv of H_3PO_2 and 0.1 equiv of NaI (entry 5) completely reduced the diaryl ketone, but only partially reduced the nitro group. On the other hand, a mixture of 8 equiv of H_3PO_3 and 0.1 equiv of NaI (entry 6) reduced the nitro group quickly, but the carbonyl group very slowly. Concentrated HCl was not tested in this study.

Table 1. A Novel Reduction of Nitroarenes and Aryl Ketones[a]



entry	reducing agents (equiv)	catalyst (equiv)	solvents	**2:2-iodo**	comments
1	H_3PO_2 (11)	HI (4)	H_2O	95:5	Complete
2	H_3PO_2 (3.5)	NaI (2)	HBr/H_2O	95:5	Complete
3	H_3PO_3 (8)	NaI (2)	HBr/H_2O	95:5	Complete
4	NaH_2PO_2 (11)	NaI (2)	HBr/H_2O	95:5	Complete
5	H_3PO_2 (3.5)	NaI (0.1)	HBr/H_2O	100:0	Nitro remain
6	H_3PO_3 (8)	NaI (0.1)	HBr/H_2O	100:0	Ketone remain
7	H_3PO_2 (2)/ H_3PO_3 (3.5)	NaI (0.1)	HBr/H_2O	100:0	Complete

[a] All reactions were carried out at 115 °C for 1 to 16 h.

Although the foaming was manageable on laboratory scales by adjusting both the agitation and the addition rate, it would not be easy to operate in plant production. Careful observations indicated that the severe foaming takes place only at the beginning of the reaction. We speculated that a

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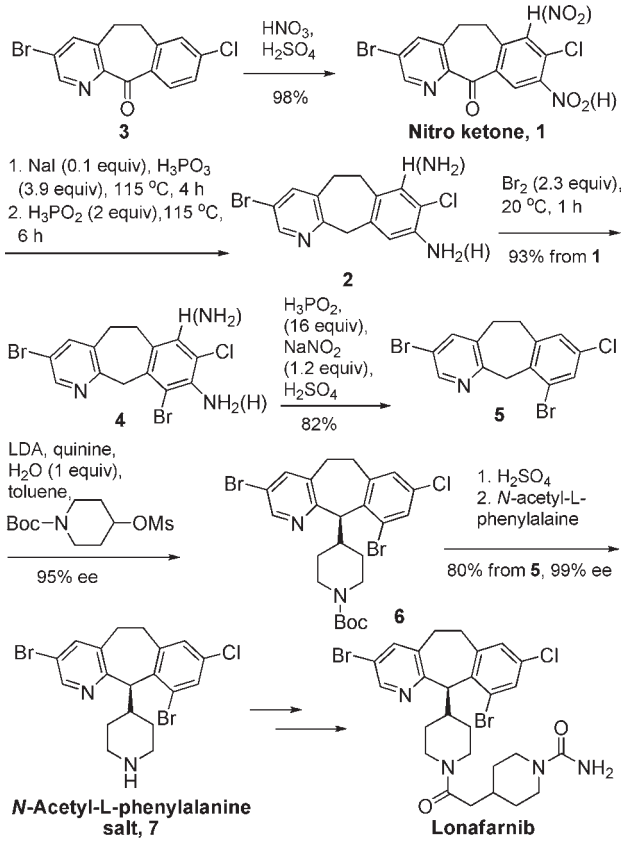
(9) (a) Wu, G. G.; Wong, Y.; Poirier, M. *Org. Lett.* **1999**, *1*, 745. (b) Bernard, C. F.; Casey, M.; Chen, F. X.; Grogan, D. C.; Poirier, M.; Williams, R. P.; Wong, Y.; Wu, G. U.S. Patent 6,495,689, December 17, 2002.

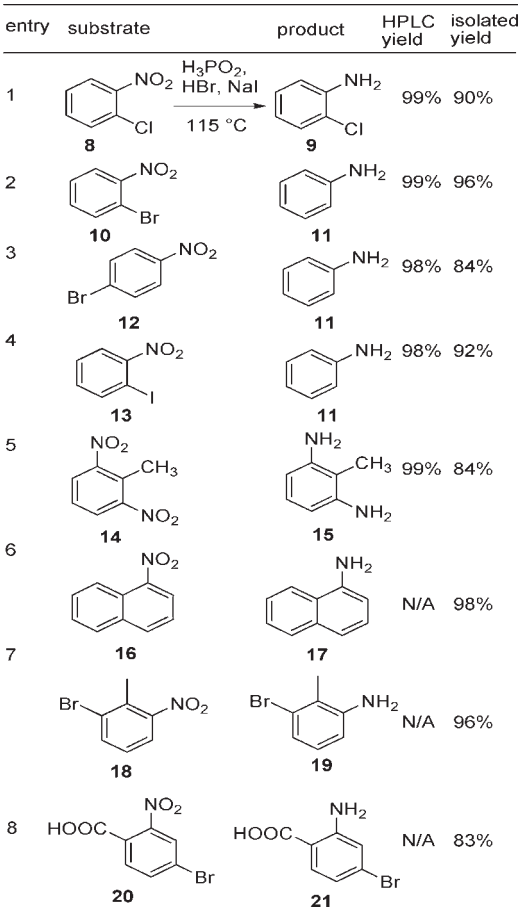
fast initial reaction rate with H_3PO_2 may account for the foaming and use of a less potent reducing reagent such as H_3PO_3 could reduce the foaming. Indeed, replacing H_3PO_2 with H_3PO_3 did minimize the foaming at the beginning of the reduction. Based on this observation and the results from entries 5 and 6 in Table 1, we decided to do a sequential reduction of the nitro group first and then the aryl ketone group by using a stepwise addition of H_3PO_3 and H_3PO_2. Thus, nitro ketone **1** was first treated with H_3PO_3 and 0.1 equiv of NaI in aqueous HBr at 115 °C to reduce the nitro group followed by an addition of H_3PO_2 to reduce the carbonyl group. As shown by entry 7 in Table 1, this combination method gave a complete reduction of both the nitro and the ketone groups while minimizing the iodo byproduct to below the detection limit (0.03%). In addition, operational hazardous evaluation indicated that this procedure is suitable for production.

Scheme 2. An Efficient Synthesis of Lonafarnib



We have applied this method to the synthesis of Lonafarnib shown in Scheme 2, which we have performed on a 100 kg scale. Thus, nitration of tricyclic compound **3**[9] with HNO_3 and H_2SO_4 gave nitro ketone **1** as a mixture of two regioisomers (7-nitro and 9-nitro) in a 3:7 ratio and 98% isolated yield.[10] Under the newly discovered reduction conditions, nitro ketone **1** was converted to **2**, which was directly brominated to give dibromo **4** in one pot in 93% overall isolated yield. Afterward, the amino group in compound **4** was removed under standard conditions with $NaNO_2$ and H_3PO_2 in H_2SO_4 in 82% isolated yield. The introduction of the doubly benzylic chiral center was previously reported in 95% ee using a chiral alkylation method with LDA and quinine.[11] The ee was further enhanced to 99% through a salt formation with *N*-acetyl-L-phenylalanine.[11] With these achievements, we have accomplished an efficient and practical synthesis of Lonafarnib.

Table 2. Reduction of Nitroarenes[a]



[a] Conditions: reactions were carried out with 4 equiv of H_3PO_3 and 2 equiv of NaI in aqueous HBr and HOAc at 115 °C.

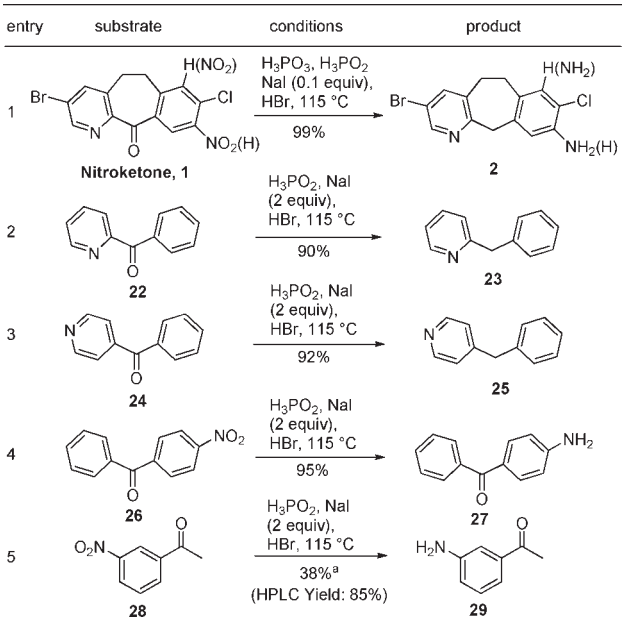
Next, we subjected a number of nitroarenes to this novel reducing method, and our results are summarized in Table 2. In all 8 entries, the nitro goup was completely reduced to the corresponding anilines in 83 to 98% isolated yields. The chemoselectivity for the chloro nitroarenes is excellent as shown by substrates **1** and **8**. On the other hand, the chemoselectivity is good for meta-substituted bromo

(10) Chen, F. X.; Wong, Y.; Eckert, J. M.; Liang, F.; Zou, N.; Kim-Meade, A. S.; Poirer, M.; Thiruvengadam,, T. K.; Wu, G. G. U.S. Patent 7,049,440, May 23, 2006.

(11) Kuo, S. C.; Chen, F. X.; Hou, D.; Kim-Meade, A.; Bernard, C.; Liu, J.; Levy, S.; Wu, G. G. *J. Org. Chem.* **2003**, *68*, 4984.

nitroarenes such as substrates **1**, **18**, and **20**, but poor for other substrates (**10** and **12**). This method is not chemoselective for iodonitroarene (**13**). Apparently, additional studies are required to understand the chemoselectivity better.

Table 3. Reduction of Aryl Ketones and Nitroarenes



Finally, we studied the reduction of those substrates bearing aryl ketones or bifunctional groups, and our results are summarized in Table 3. As discussed earlier, a combination of H_3PO_3 and H_3PO_2 in the presence of 0.1 equiv of NaI effectively reduced both the diaryl ketone and the nitro groups in nitro ketone **1** (entry 1). For the rest of the substrates in Table 3, only H_3PO_2 along with 2 equiv of NaI was used since the foaming was manageable on laboratory scales. As indicated by entries 2 and 3, this procedure reduced substrates **22** and **24** in 90% and 92% isolated yields, respectively. However, it only reduced the nitro group in the less activated substrates (**26**, **28**). Apparently, the electon-withdrawing pyridine ring in substrates **1**, **22**, and **24** played a role in the reduction of the diaryl ketone group. The lower recovery yield in entry 5 was due to an intermolecular imine formation during pH adjustment in workup. It is worth noting that use of more potent red phosphorus and HBr has been shown to reduce benzophenone chemoselectively in the presence of a bromo group.[7] In addition, use of iodine as a catalyst instead of NaI effectively reduces diaryl ketones.[6]

Fry has postulated a mechanism for the reduction of aryl ketones with HI, H_3PO_2, and refluxing HOAc.[6] HI was speculated to be the direct reducing agent for the carbonyl group to give CH_2 and one "I^+" species, which combines with "I^-" to produce iodine. Iodine is then reduced by H_3PO_2 back to HI in the presence of acid. Similarly, we speculated a two-stage process for the reduction of the nitro group. NaI reacts with HBr to produce a small amount of HI. HI reduces Ar$-NO_2$ first to Ar$-$NO and then quickly to $ArNH_2$. Both H_3PO_2 and H_3PO_3 can reduce iodine back to HI. In both reductions, H_3PO_2 or H_3PO_3 is the ultimate reducing agent.

In summary, we have discovered a novel and practical iodo-catalyzed reduction of nitroarenes with H_3PO_2 or H_3PO_3. This method can reduce some aryl ketone groups in the presence of chloro and bromo substituents. It can be complementary to the current reduction methods including hydrogenation, hydrides, and metal reagents. Furthermore, we have successfully applied this method to the synthesis of a potential anticancer agent.

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Supporting Information Available. Experimental procedures,[12] full characterization data, and ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Representative Experimental Procedure: To a 1-L three-necked flask equipped with a mechanical stirrer, a thermometer, and a condenser were charged, under nitrogen, 50 g (0.14 mol) of nitro ketone **1**, 2 g of NaI (13.3 mmol), 45 g of H_3PO_3 (0.55 mol), 250 mL of hydrobromic acid (48%), and 50 mL of water. The resulting suspension was heated to about 115 °C and stirred at this temperature for 4 h. The reaction mixture was cooled to 60 °C, and 40 mL (0.30 mol) of 50% H_3PO_2 were added. The reaction mixture was heated to 115 °C for another 6 h. After cooling to 20 °C, the reaction mixture was transferred into a solution of 200 mL of ammonium hydroxide and 100 mL of MeOH. The pH was adjusted to 5 with ammonium hydroxide, and the resulting suspension was stirred for 1 h. The solid was filtered, washed with water, and dried at 60 °C to give 46.9 g (99% yield) of **2** as a mixture of 7- and 9-amino isomers.