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Exploration of relative chemoselectivity in the hydrodechlorination of 2-chloropyridines

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ABSTRACT

The chemoselectivity of hydrodechlorination in 2-chloropyridine derivatives possessing reduction-sensitive functionalities is examined. The reaction conditions employed tolerate a variety of functionalities illustrating highly chemoselective hydrodechlorination in the presence of nitrile, allyl, terminal olefin, and nitroamine functionalities in excellent yield. Chemoselective deprotection of carboxybenzyl ethers is illustrated in moderate yield.

The use of palladium on charcoal (Pd/C) under an atmosphere of hydrogen in organic synthesis is commonplace. The conditions are employed in a myriad of transformations, often being the agent of choice for the reduction of olefins,[1] alkynes,[2] nitro,[1] and nitrile[3] functionalities, and the deprotection of benzyl ethers,[4] allyl ethers,[5] and carboxybenzyl amines[2] by catalytic hydrogenation. The conditions are also utilized to undertake hydrodehalogenation, the reduction of a carbon–halogen bond, as a rapid and simple method to remove halogens from aromatic rings.[6]

2-Chloropyridine derivatives are key synthetic intermediates for many pharmaceutical and commercially-relevant products such as the non-opioid analgesic flupirtine (**1**),[7] epibatidine (**2**),[8] and its synthetic derivative ABT-594 (**3**).[9] The neurotoxin imidacloprid (**4**) is the worlds best-selling insecticide, yet has been linked to bee colony collapse disorder and is toxic to mammals. Removal of the 2-chlorine moiety renders the compound inactive, providing for a potential route of safe disposal (Fig. 1).[10] The ability of 2-chloropyridines to undergo substitution reactions catalyzed by microsomal glutathione *S*-transferease 1 indicates the general lability of this moiety both metabolically and chemically[11].

The ability to selectively hydrodechlorinate 2-chloropyridines in the presence of reduction-sensitive protecting groups or other functionalities is essential for continued synthetic manipulation.[12] Conversely, the orthogonal deprotection of multiple groups, or more rarely, synthetic manipulation at different functionalities using one reagent is a coveted strategy to improve overall reaction yields and streamline organic synthesis.[13] Despite the importance of chemoselective hydrodechlorination to 2-chloropyridines there is a paucity of literature available to allow prediction of chemoselectivity. The chemoselective hydrodechlorination of 2-methyl-3-nitro-5-cyano-6-chloropyridine and 4,6-dimethyl-5-nitro-3-cyano-2-chloropyridine has previously been reported.[14] However, the method resulted in extremely low yields, probably due to the harsh conditions of elevated pressure and equal quantities of 5% Pd/C employed compared with the substrate. Thus it is questionable if

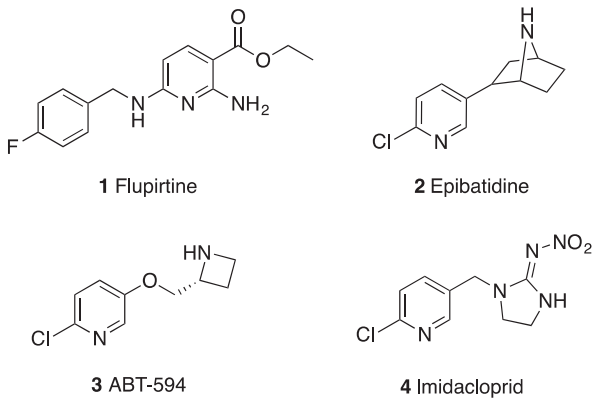

Figure 1. Examples of bioactive molecules synthesized through 2-chloropyridine intermediates.

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0040-4039/

true chemoselectivity was achieved and the large amounts of Pd/C employed represent a significant safety hazard. The synthesis of deuterated pyridines via hydrogenation of dichloropyridine-N-oxides employing Pd/C, D_2O, and K_2CO_3 at 190 °C has been reported but with no investigation of chemoselectivity.[15] Chelucci reported chemoselectivity in hydrodehalogenation of pyridine and quinolone derivatives using $NaBH_4$, TMEDA, PPh_3 and a variety of palladium catalysts including $Pd(OAc)_2$, $PdCl_2$(dppf), and $PdCl_2$ at a range of temperatures from 25 °C to 60 °C and reaction times up to three days.[16] Under these conditions 4-chloro-2-cyanopyridine was hydrodechlorinated without concomitant reduction of the cyano group. The methodology was also extended to a range of halogenated heterocycles.[17]

Given the synthetic advantages of retaining reduction-sensitive functionality and protecting groups in pyridine intermediates obtained from hydrodechlorination of 2-chloropyridine moieties we wished to establish the relative chemoselectivity of reduction-sensitive functionalities commonly encountered in synthetic routes to bioactive molecules. Successful hydrodechlorination of unfunctionalized 2-chloropyridines using catalytic quantities of 10% w/w Pd/C, hydrogen gas, and elevated pressures (2–3 atms) has been reported.[18] Reasoning that elevated pressure would increase the rate of both hydrodechlorination and reduction, 2-chloro-5-nitro-6-aminopyridine was stirred at 1 atmosphere for 24 h with Pd/C and hydrogen gas. These conditions succeeded in fully reducing the aromatic ring, the nitro group, and the chlorine–carbon bond. The effect of solvent in catalytic hydrogenations is known to have a significant influence on rate of reaction[19] therefore to eliminate this variable methanol was employed as the solvent in all reactions. Similar conditions, utilized with a triethylamine additive, have been reported to be a mild and general procedure to achieve hydrodechlorination with no concomitant loss of aromaticity in a variety of phenyl and naphthyl chlorides.[20]

Initial investigation into optimal conditions for hydrodechlorination employed 2,6-dichloro-3-nitropyridine (**5**) as the substrate (Table 1), reasoning that conditions that would remove two equivalents of chlorine would be efficient for all subsequent substrates. Reaction of **5** in the presence of 10 mol % Pd/C for 4 h provided complete conversion to amine **6** (Table 1: entry 1). Decreasing the molar percentage of the catalyst by 20-fold provided a 75% conversion to amine **6** with unreacted starting material remaining (Table 1: entry 2). Setting the catalyst loading at 1 mol % we next investigated the effect of reduced reaction time. 2 h stirring provided a 100% conversion to **6** (Table 1: entry 3), while 1 h stirring again resulted in 25% isolation of chlorinated starting material (Table 1: entry 4).

To ensure that hydrochloric acid produced as a byproduct in this reaction was not acting to deactivate the Pd/C catalyst we used stoichiometric $NaHCO_3$, relative to the produced HCl, as a basic additive to counter the acid. While other reports cite $NaHCO_3$ as acting as a poison at low catalyst loading we observed no such effect.[21] Results with this additive were identical to those without after 1 and 2 h(s) reaction times (Table 1: compare entries 5 and 6 to 3 and 4), although a pleasing improvement in sharpness of the NMR spectra was observed attributed to the prevention of the acid salt formation. Finally, the use of palladium on barium sulfate (Pd/$BaSO_4$) was investigated to ascertain if poisoning the catalyst would result in observable chemoselectivity (Table 1: entry 7). However, analysis of the product by NMR revealed a large number of degradation products. Based on this collection of experiments we set the conditions for hydrodechlorination as 1 mol % Pd/C with $NaHCO_3$ additive for 2 h. It is also evident that no chemoselectivity exists between hydrodechlorination and reduction of the nitro group within **5** with the reaction rates for both processes apparently equal.

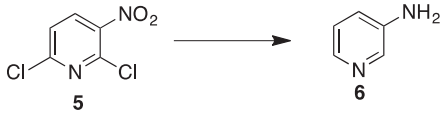
A series of 2-chloropyridine derivatives was assembled through commercial sources and standard synthetic procedures as substrates to examine the relative chemoselectivity of hydrodechlorination under these conditions (Table 2). In all the scope experiments the aromatic ring of the substrate was not reduced, attributed to the mild conditions employed. However, it is notable that a recent report describing the use of these exact conditions with a $ClCH_2CHCl_2$ additive did result in full hydrogenation of the aromatic ring to the corresponding piperidine.[22]

To ensure hydrodechlorination was achievable we began by exposing 2-chloropyridine (**7**) (Table 2, entry 1) to the reaction conditions, as expected after 2 h complete conversion to pyridine was obtained. In order to investigate if selectivity of hydrodechlorination is preferred at the 2-position we next exposed 2,3-dichloropyridine (**9**) to the reaction conditions (Table 2, entry 2). Complete conversion to pyridine (**8**) in quantitative yield demonstrated that no positional selectivity was evident. Indeed, carefully following the reaction by NMR provided no evidence of the 3-chloropyridine product that would be expected if the 2-chloro position is hydrodechlorinated at a faster rate.

We next wanted to examine possible selectivity between halogens. It has been reported that the rate of hydrodehalogenation increases with increasing electronegativity (I < Br < Cl).[23,24] Methodology similar to the investigated hydrodechlorination conditions, but using a 6.4-fold excess of $NaHCO_3$ has been reported to allow the selective reduction of phenyl bromines over phenyl chlorines.[23] Intrigued by this apparent conflict within the literature we investigated the chemoselectivity of hydrodechlorination conditions on 5-bromo-2-chloro-3-nitropyridine (**10**) (Table 2, entry 3) which resulted in an 80% yield of 3-nitropyridine (**11**). The other product isolated was a 20% yield of 3-aminopyridine (**6**). Interestingly, when two equivalents of $NaHCO_3$ are employed to counter both halogens a 1:1 mixture of the nitro and amino pyridine products are obtained. In both cases no isolation of any 3-bromopyridine or 2-chloropyridine indicates no selectivity between the two halogens. It is possible that the adjacent pyridine nitrogen plays a role in withdrawing electron density from the 2-chloro group reducing electronegativity to a value comparable to that of bromine, thus accounting for the lack of selectivity between the two halogens.

It is intriguing to note that the major product of this reaction is the non-reduced 3-nitropyridine. The quantity of catalyst used in the reaction conditions is sufficient to reduce all three groups (Table 1). It would appear that the presence of bromine within

Table 1
Optimization of reaction conditions for hydrodechlorination

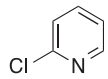
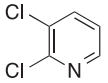
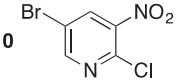
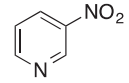
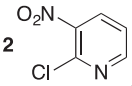
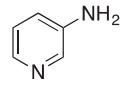
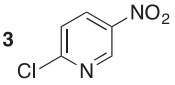
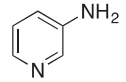
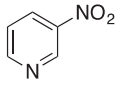
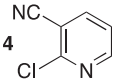
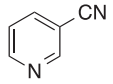
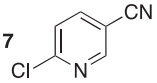
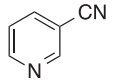
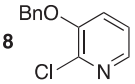
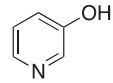
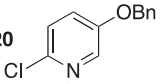
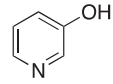
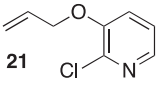
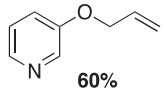
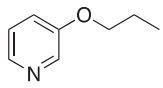
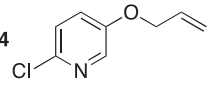
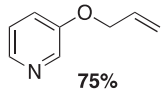
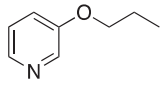
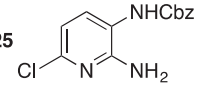
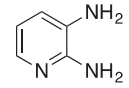
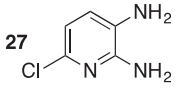
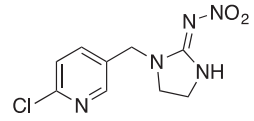
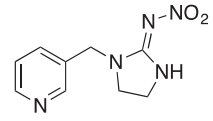


5 6

Entry	Pd source	Pd mol %	Additive	Time (min)	Conversion (%)
1	10% Pd/C	10	n/a[1]	240	100
2	10% Pd/C	0.5	n/a	240	75:25 (P/SM)[2]
3	10% Pd/C	1	n/a	120	100
4	10% Pd/C	1	n/a	60	75:25 (P/SM)
5	10% Pd/C	1	$NaHCO_3$ (2 equiv)	60	75:25 (P/SM)
6	10% Pd/C	1	$NaHCO_3$ (2 equiv)	120	100
7	5% Pd/$BaSO_4$	1	n/a	240	Degradation products

[1] n/a = not applicable.
[2] P = product; SM = starting material.

Table 2
Scope and relative chemoselectivity of 2-chloropyridine derivatives

Entry	Substrate	Product	Ratio	Yield[1]
1	**7** 	**8** 	n/a[2]	Quant.
2	**9** 	**8** 	n/a	Quant.
3	**10** 	**11** 	n/a	Quant.[3]
4	**12** 	**80%** **6** 	n/a	Quant.
5	**13** 	**6**  **11** 	3:1	Quant.
6	**14** 	**15** 	n/a	Quant.
7	**17** 	**80%** **15** 	n/a	Quant.
8	**18** 	**80%** **19** 	n/a	Quant.
9	**20** 	**19** 	n/a	80%
10	 **21**	**22**  **23** 	3:2	Quant.[1]
11	**24** 	**60%** **22**  **23** 	3:1	Quant.[1]
12	**25** 	**75%** **26**  **27** 	1:1	87%
13	**4** 	**45%** **28**  **42%**	n/a	Quant.

[1] Determined by NMR.
[2] Not applicable.
[3] One equivalent $NaHCO_3$.

the substrate has an effect of deactivating the catalyst, preventing further reduction of the nitro group.

With the 80% yield of unreduced nitropyridine obtained in entry 3 indicating the enticing prospect of obtaining chemoselectivity at the 2-chloro position over the nitro group we next investigated if the reaction conditions could affect this transformation (Table 2, entries 4 and 5). In the case of 2-chloro-3-nitropyridine (**12**) (Table 2, entry 4) a quantitative yield of 3-aminopyridine was isolated. However, 2-chloro-5-nitropyridine (**13**) (Table 2, entry 5) proceeded to provide a 25% yield of 3-nitropyridine indicating a substitution pattern effect on chemoselectivity. Substrates with *ortho* substituents appear to show less chemoselectivity than substrates with *para* substituents (an observation also repeated with allyl protected alcohols, Table 2, entries 10 and 11). This may perhaps be explained by the simultaneous hydrodechlorination and reduction occurring on the palladium metal surface made possible when the two functionalities are in close proximity.

Application of hydrodechlorination conditions to 2-chloro-3-cyanopyridine (**14**) (Table 2, entry 6) and 2-chloro-5-cyanopyridine (**17**) (Table 2, entry 7) resulted in excellent chemoselectivity to the hydrodechlorinated product over the nitrile group with an 80% yield of 3-cyanopyridine (**15**) in both cases.

We next investigated the chemoselectivities of common reduction-sensitive protecting groups. Protection of 2-chloro-hydroxypyridine derivatives as their benzylethers proceeded in good yield to provide 2-chloro-3-hydroxybenzylpyridine (**18**)[25] (Table 2,

entry 8) and 2-chloro-5-hydroxybenzylpyridine (**20**)[26] (Table 2, entry 9). Application of the reaction conditions provided complete removal of both the chlorine and benzyl protecting group. An effect not observed in hydrodeiodination reactions; in the presence of a benzyl ether, iodine can be chemoselectively removed from phenyl rings.[23] The previously noted effect of pyridine to prevent hydrogenolysis of the benzyl ether was not observed.[27]

Allyl ethers are common protecting groups for alcohols and are know to be easily cleaved by conditions similar to the reaction conditions used herein.[5] In addition, the olefin moiety in these ethers presents another opportunity for possible chemoselectivity. 2-Chloro-3-hydroxyallylpyridine (**21**) and 2-chloro-5-hydroxyallylpyridine (**24**) were synthesized following a reported procedure.[28] Application of hydrodechlorination conditions to **21** (Table 2, entry 10) provided good chemoselectivity over allyl deprotection and surprisingly, olefin hydrogenation. The hydrodechlorinated product 3-hydroxyallylpyridine (**22**) was obtained as the major product in good yield (60%) over the 40% yield of 3-hydroxypropylpyridine (**23**). No trace of the deprotected hydroxy product was detected. When the same conditions were applied to the 2-chloro-5-hydroxyallylpyridine derivative (**24**) an even higher chemoselectivity was obtained with 75% of the hydrodechlorinated product **22**.

Exposure of the Cbz protected amine **25** (Table 2, entry 12) to hydrodechlorination conditions resulted in a partial 45% yield of diamine **26**, demonstrating deprotection of the carboxybenzyl group along with full hydrodechlorination. Surprisingly a 42% yield of the carboxybenzyl deprotected 2-chloropyridine compound **27** was isolated. This is the only such compound that failed to result in full hydrodechlorination under the conditions applied. This observation may be attributed to the extreme lability of the Cbz protecting group to hydrogenation[29] and intimates that chemoselective deprotection of a carboxybenzyl ether in the presence of a chlorine is possible, albeit in a 1:1 ratio with the expected fully reduced product.

Application of the reaction conditions to the insecticide **4** (Table 2, entry 13) resulted in complete chemoselective hydrodechlorination to yield **28** wherein the nitroamine functionality is retained. This method could potentially be employed in neutralizing the neurotoxic effects of this compound without further structural fragmentation.[30]

In summary we demonstrate that highly chemoselective hydrodechlorination of 2-chloropyridines can be achieved in the presence of cyano, allyl, terminal olefin and nitroamine groups in excellent yield and that hydrodehalogenation of 2-chloro-3-bromopyridine can be achieved in the presence of a nitro functionality in good yield. This study provides for the first time a guide to synthetic chemists wishing to affect the chemoselective hydrodechlorination of 2-chloropyrdine derivatives possessing reduction-sensitive functional groups in the synthesis of pharmacologically active compounds.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.008.

References and notes

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