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Hydrodehalogenation of halogenated pyridines and quinolines by sodium borohydride/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine under palladium catalysis

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ABSTRACT

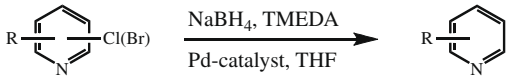
A protocol for the hydrodehalogenation of halogenated pyridines and quinolines by the sodium borohydride/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine ($NaBH_4$–TMEDA) system under palladium catalysts is reported. Catalytic amounts of [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) in combination with $NaBH_4$–TMEDA rapidly hydrodehalogenate chloro(bromo)-pyridines and -quinolines at room temperature in quantitative yields. Chemoselective reduction of 4,7-dichloroquinoline affords 7-chloroquinoline as the sole product in almost quantitative yield. Moreover, palladium(II) acetate-triphenylphosphine and $NaBH_4$–TMEDA are able to reduce efficiently reactive bromo-pyridines and -quinolines.

Removal of halogen from an aromatic ring is an important chemical transformation in organic synthesis. A wide variety of hydrodehalogenating systems have been used over the years and this subject has recently been reviewed in detail.[1] Reduction is usually mediated by a transition metal catalyst (Ni, Pd, Rh, Pt) and is performed with molecular hydrogen, metal hydrides or hydrogen sources such as formic acid and its salts, hydrazine or alkoxides possessing a β-hydrogen.[1]

However, the application of these methodologies to halogenated heterocycles is rather sporadic, most often accomplished by catalytic hydrogenation on metal catalyst, Pd–C[2] or Raney nickel[3] and halogen–metal exchange reaction.[4] These processes are often troublesome to execute since the former ignites easily and the latter requires a dehydrated condition and a low reaction temperature. For safety and simplicity of operation, a liquid-phase process without using molecular hydrogen is more advantageous.

Interestingly, some alternative methods have been recently described. Cristau and co-workers indicated that the hydrogenolysis of aryl halides with catalytic Pd/C in the presence of hydrazine hydrochloride led to the corresponding hydrodehalogenation products with high selectivity, but only two cases of heteroaryl halides (2-bromothiophene and 3-bromopyridine) were included in this work.[5] Tanji et al. reported that the indium-mediated dehalogenation of haloheteroaromatics in water is a facile and safe method, but gives good results only with iododerivatives.[6] The reduction at room temperature of chloroarenes in high yield by catalytic amounts of palladium(II) acetate [$Pd(OAc)_2$] in combination with polymethylhydrosiloxane and aqueous KF has been reported.[7] However, among chloroarenes that were examined there is only one example of haloheterocycle, namely the three regioisomers of chloropyridine. Nolan et al. have described a general system, involving the use of catalytic *N*-heterocyclic carbene–palladacycle complex and NaO*t*-Bu in 2-propanol, that displays very high activity for dehalogenation reactions of activated and unactivated aryl chlorides, but also in this case the 3-chloropyridine is the sole reported example of heterocycle.[8] More recently, in a related study 2- and 3-bromopyridine and 2-bromothiophene have been dehydrohalogenated in 43–72% yields.[9] Thus, the development of a facile and general method for the dehalogenation of heteroaromatic halides is still of great value.

About ten years ago, Hor and co-workers reported the reductive debromination of highly brominated benzenes using a variety of metal complexes, reducing agents and bases.[10] Palladium complexes served as the most effective catalysts, while sodium borohydride ($NaBH_4$) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) were the best reductant and base, respectively. Notwithstanding the excellent results obtained in this study, to our knowledge, no systematic study on the use of this method for the hydrodehalogenation



Scheme 1.

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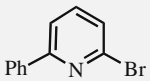
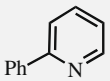
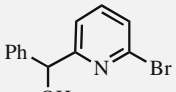
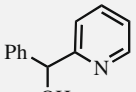
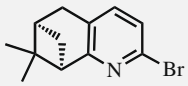
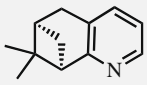
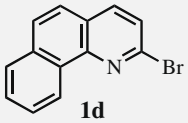
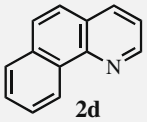
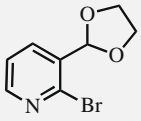
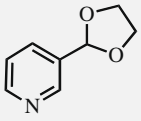
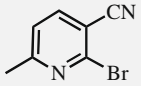
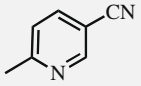
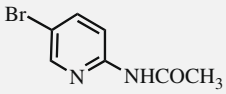
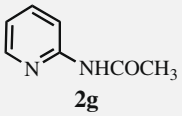
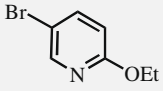
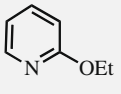
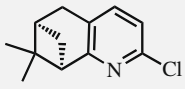
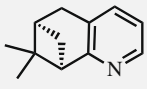
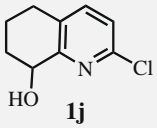
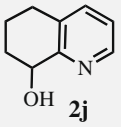
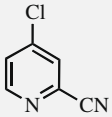
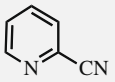
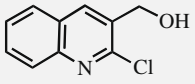
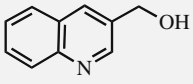
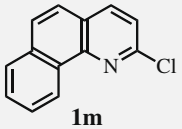
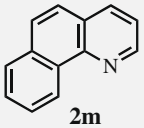
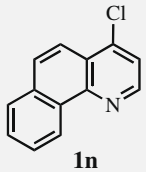
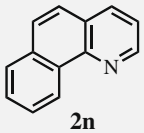
Table 1
Hydroalogenation of halogenated pyridines and quinolines (Scheme 1)

Entry	Halo-heterocycle	Product	Method[a]	Temp (°C)	Time (h)	Conversion[b] (%)	Yield[c] (%)
1	 **1a**	 **2a**	A	25	0.5	100	95
2	 **1b**	 **2b**	A	25	0.5	100	95
3	 **1c**	 **2c**	A	25	6	100	95
4	 **1d**	 **2d**	A	25	0.5	100	95
5	 **1e**	 **2e**	A	25	1.5	100	95
6	 **1f**	 **2f**	A B B C	25 25 60 25	48 48 72 6	0 0 30 100	– – nd 95
7	 **1g**	 **2g**	A A C	25 60 25	24 1 2	35 100 100	nd 85 95
8	 **1h**	 **2h**	A A C	25 60 25	24 1 2	30 100 100	nd 83 95
9	 **1i**	 **2i**	B B D	25 60 25	48 72 6	0 30 100	– nd 95
10	 **1j**	 **2j**	A B C	25 60 25	48 18 0.5	40 100 100	nd 85 95
11	 **1k**	 **2k**	D	25	2	100	95
12	 **1l**	 **2l**	A A B C	25 60 60 25	24 24 24 3	40 100 100 100	nd 65 76 92
13	 **1m**	 **2m**	D	25	6	100	95

(*continued on next page*)

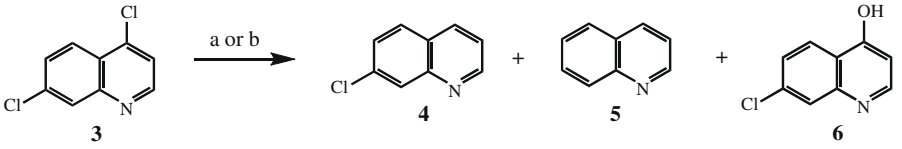
Table 1 (*continued*)

Entry	Halo-heterocycle	Product	Method[a]	Temp (°C)	Time (h)	Conversion[b] (%)	Yield[c] (%)
14	 **1n**	 **2n**	D	25	2	100	95

[a] Method: A = heterocycle (0.66 mmol), $Pd(OAc)_2$ (5.0 mol %), PPh_3 (20.0 mol %), $NaBH_4$ (1.7 equiv), TMEDA (1.7 equiv), THF (13.2 mL). B = heterocycle (0.66 mmol), $Pd(OAc)_2$ (10.0 mol %), PPh_3 (40.0 mol %), $NaBH_4$ (3.4 equiv), TMEDA (3.4 equiv), THF (13.2 mL). C = heterocycle (0.66 mmol), $PdCl_2$(dppf) (5.0 mol %), $NaBH_4$ (1.7 equiv), TMEDA (1.7 equiv), THF (13.2 mL). D = heterocycle (0.66 mmol), $PdCl_2$(dppf) (5.0 mol %), $NaBH_4$ (3.4 equiv), TMEDA (3.4 equiv), THF (13.2 mL).

[b] Determined by ^1H NMR.

[c] Isolated yields after flash chromatography.



a: $Pd(PPh_3)_2Cl_2$ (1.0 mol%), Et_3SiH (1.4 equiv), MeCN, 70 ºC, 18 h, 92% conversion, **4** (85%), **5** (5%), **6** (8%).

b: $PdCl_2(dppf)_2$ (5.0 mol%), $NaBH_4$ (3.4 equiv), TMEDA (3.4 equiv), THF, 25 ºC, 6 h, 100% conversion, **4** (95%).

Scheme 2. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$ (1.0 mol %), Et_3SiH (1.4 equiv), MeCN, 70 °C, 18 h, 92% conversion, **4** (85%), **5** (5%), **6** (8%); (b) $PdCl_2(dppf)_2$ (5.0 mol %), $NaBH_4$ (3.4 equiv), TMEDA (3.4 equiv), THF, 25 °C, 6 h, 100% conversion, **4** (95%).

of other substrates and in particular of haloheterocycles has appeared in the literature.

Thus, we decided to examine the scope and limitations of this methodology for the hydrodehalogenation of heteroaromatic halides, reporting in this occasion the reductive removal of halogroup from halogenated pyridines and quinolines by means of couple $NaBH_4$–TMEDA under palladium catalysis (Scheme 1).

Starting our investigation to optimize the reaction conditions, the reductions were carried out with 2-bromo-6-phenylpyridine **1a**. After a careful examination of various reaction conditions, we concluded that the best results for the intended hydrodehalogenation were achieved using 5 mol % $Pd(OAc)_2$ with 20 mol % PPh_3 as the catalyst, 1.7 equiv of $NaBH_4$ and TMEDA as the reducing system and THF as the solvent (Method A).[11] Under these conditions the substitution of the bromine with hydrogen in **1a** was complete at room temperature in less than 30 min giving the dehalogenated pyridine **2a** in almost quantitative yield (Table 1, entry 1). Similar results were obtained with the (6-bromopyridin-2-yl)phenylmethanol **1b** and 2-bromobenzo[*h*]quinoline **1d** (entries 2 and 4). The more sterically hindered bromide in pyridines **1c** and **1e** (entries 3 and 5) was also removed quantitatively at room temperature, albeit after a somewhat extended reaction time (6 and 1.5 h, respectively). These reaction conditions failed to reduce 2-bromo-3-cyano-6-methylpyridine **1f** (entry 6), and even increasing the number of equivalents (from 1.7 to 3.4) of the couple $NaBH_4$–TMEDA (Method B) was unproductive. Whereas partial conversion of the starting material was obtained when the reaction was carried out at 60 °C for 72 h. Impressively, this transformation could take place when [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) [$PdCl_2$(dppf)] was used as the catalyst. Thus, 5 mol % of $PdCl_2$(dppf), $NaBH_4$ (1.7 equiv) and TMEDA (1.7 equiv) (Method C) converted **1f** in the related hydroalogenated pyridine **2f** in excellent yield (95%) after 6 h at room temperature. For the hydrodehalogenation of *meta*-bromopyridines **1g** and **1h** (entries 7 and 8), method A was successful only when the reaction was carried out at 60 °C, giving the reduced products in good yield. However, the results were also in this case improved using $PdCl_2$(dppf) (Method C). As expected, chloropyridines resulted less reactive than the related bromoheterocycles. Thus, for instance, chloropyridine **1i** was unreactive under the conditions in which the related bromoropyridine **1c** was smoothly reduced (entry 9 vs 3). Fortunately, also in this case, the use of $PdCl_2$(dppf) was beneficial, allowing the tetrahydroquinoline **2i** to be obtained in excellent yield (95%) after 6 h. In this circumstance, to speed up the reaction, 3.4 equiv of the couple $NaBH_4$–TMEDA (Method D) was employed. The use of $PdCl_2$(dppf) resulted also essential for the rapid and high yielding reduction of a variety of chloro-pyridines and -quinolines (entries 10–14).

Very recently, Zacuto and Hirner have demonstrated the versatility of 7-chloroquinoline as a synthetic intermediate for the synthesis of more complex 7-mono- and 2,7-di-substituted quinolines.[12] For this purpose they have developed a practical synthesis of 7-chloroquinoline **4** via a chemoselective reduction of 4,7-dichloroquinoline **3** (Scheme 2). Under their best reaction conditions that resulted in an optimal balance between conversion (92%) and chemoselectivity [$Pd(PPh_3)_2Cl_2$ (1.0 mol %), Et_3SiH (1.4 equiv), MeCN, 70 °C, 18 h], reduced compound **4** was obtained in 85% yield with the over reduction byproduct quinoline **5** (5%) and 7-chloro-4-hydroxyquinoline **6** (8%), which appeared to result from a reaction between **3** and water in the reaction solution or in the quench.

On this basis, we decided to examine the chemoselective reduction of 4,7-dichloroquinoline **3** using our protocol. We were delighted to find that under method D, dichloro compound **3** was completely converted after 6 h at room temperature, giving the 7-chloroquinoline as the sole product in 95% isolated yield (Scheme 2).

As pointed out by Hor and co-workers[10], the effect of TMEDA is suggested to be threefold: (a) weak coordination to the electronically unsaturated intermediate and hence stabilization of the catalyst; (b) capturing of BH_3 from BH_4^-, thus providing an extra drive for the hydride transfer to the Pd centre and (c) facilitating an alternative debromination pathway through the elimination of HBr.

In summary, the pair $NaBH_4$–TMEDA and catalytic $PdCl_2$(dppf) in THF is a mild and efficient system for the hydrodehalogenation of halopyridine derivatives. Under these conditions, a variety of chloro(bromo)-pyridines and -quinolines are hydrodehalogenated at room temperature in excellent yields. Reactive bromo-pyridines and -quinolines can also be efficiently reduced using $Pd(OAc)_2$-PPh_3 as the catalyst. Moreover, chemoselective reduction of 4,7-dichloroquinoline affords 7-chloroquinoline as the sole product in almost quantitative yield. Further studies on this subject are currently in progress.

Acknowledgements

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11. *Typical procedure for the hydrodehalogenation of halogenated pyridine derivatives.* Method A: A mixture of the halogenated heterocycle (0.66 mmol) in anhydrous THF (13.2 mL) was degassed by bubbling argon for few minutes. Then, $Pd(OAc)_2$ (7.2 mg, 0.033 mmol, 5 mol %), PPh_3 (17.7 mg, 1.132 mmol, 20 mol %), TMEDA (0.130 g, 1.122 mmol, 1.7 equiv) and finally $NaBH_4$ (42.4 mg, 1.122 mmol, 1.7 equiv) were introduced in sequence. The mixture was stirred at room temperature or heated at 60 °C under argon for the specific time. The residue was taken up in brine and extracted with ethyl acetate. The organic phase was separated, dried (Na_2SO_4), the solvent was evaporated and the residue was purified by flash chromatography (mixtures of petroleum ether and ethyl acetate) to give pure hydrodehalogenated heterocycles.
Method C: A mixture of the halogenated heterocycle (0.66 mmol) in anhydrous THF (13.2 mL) was degassed by bubbling argon for few minutes. Then, $PdCl_2$(dppf)·CH_2Cl_2 (27.0 mg, 0.033 mmol, 5.0 mol %), TMEDA (0.130 g, 1.122 mmol, 1.7 equiv) and finally $NaBH_4$ (42.4 mg, 1.122 mmol, 1.7 equiv) were introduced in sequence. The mixture was stirred at room temperature under argon for the specific time and then worked up as described above.
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