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Self-modulated highly chemoselective direct-reductive-amination (DRA) of benzaldehydes straightforward to *N*-monosubstituted benzylamine hydrochlorides

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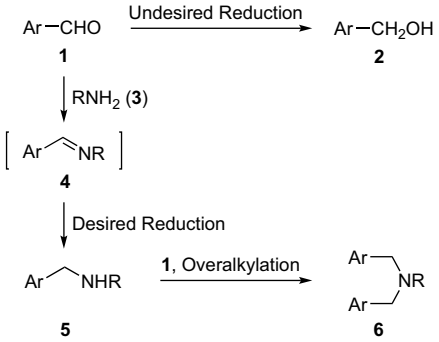
ABSTRACT

An unprecedented efficient and chemoselective DRA of benzaldehydes and primary amines was developed to directly yield *N*-monosubstituted benzylamine hydrochlorides as single products in practically quantitative yields. The method was characterized by simply adding a few milliliters of $CHCl_3$ in the conventional Pd–C catalytic hydrogenation system at atmospheric pressure and room temperature. A self-modulated system and a four-stage cyclic pathway were proposed.

1. Introduction

One-step direct-reductive-amination (DRA) is a powerful tool to synthesize higher order amine from a carbonyl compound and an amine in the presence of a reducing agent, which proceeds through the formation of an imine intermediate followed by an in situ reduction. Since benzaldehyde (**1**) has much higher reactivity than aliphatic aldehyde, its DRA for preparation of *N*-monosubstituted benzylamine (**5**) suffered from two serious drawbacks (Scheme 1): (a) undesired competitive reduction of **1** to benzenemethanol (**2**); (b) overalkylation of **5** to tertiary amine **6**.[1,2] Thus, DRA of benzaldehyde (**1**) was normally associated with very tedious separation and low yields. The literature also showed that two-step indirect-reductive-amination (IDRA) has been the major method to serve for this purpose, where the imine intermediate (**4**) was prepared first followed by a reduction.[3,4] In fact, highly efficient preparation of *N*-monosubstituted benzylamines by DRA still remains a formidable synthetic challenge.

N-Benzyl aminoaldehyde acetals [**5**, R=$-(CH_2)_nCH(OR)_2$] are significantly versatile precursors in the syntheses of many biologically important 5–7 membered heterocycles[3,5] and alkaloids.[4,6]



Scheme 1.

In our recent research project on chemical biology, a variety of them were chosen as synthetic targets. Unfortunately, we observed that the drawbacks of DRA were remarkably magnified in the syntheses of those compounds because the aminoaldehyde acetals [**3a**, $H_2NCH_2CH(OMe)_2$; **3b**, $H_2NCH_2CH_2CH(OEt)_2$] are weak nucleophiles, no matter when the DRA was performed with hydride reducing agents or under catalytic hydrogenations. When some typical hydride reducing agents [such as $NaBH_3CN$ or $NaBH(OAc)_3$] were used under acidic conditions, the decompositions of **3a**–**b** were observed.

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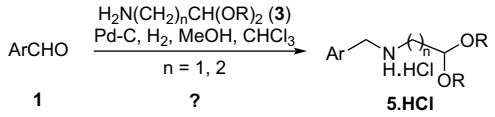
Recently, two excellent procedures of catalytic hydrogenation DRA were reported with mild homogeneous catalyst $[Ir(cod)_2]BF_4$[7] or $Pd(PhCN)_2Cl_2$-BQC[8] under 30–50 atmospheric pressures, by which *N*-monosubstituted benzylamines were obtained with high yields and chemoselectivity. For a long time, it was believed that the reactivity of heterogeneous catalyst was difficult to modulate, even though the well-known Rosenmund and Lindlar hydrogenations have been widely used. Herein, we report a novel heterogeneous catalytic hydrogenation DRA procedure, which is characterized by simply adding a few milliliters of $CHCl_3$ to a conventional Pd–C catalytic hydrogenation system. By using this procedure, an unprecedented efficient DRA of benzaldehydes (**1**) and primary amines (**3**) was achieved to directly yield *N*-monosubstituted benzylamine hydrochlorides (**5**·HCl) at room temperature and atmospheric pressure.

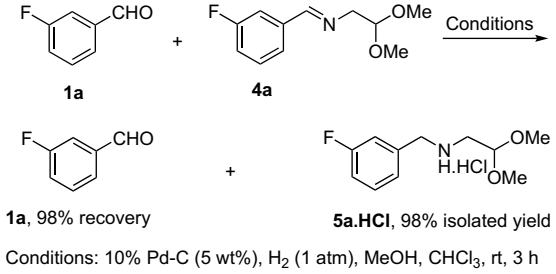
2. Results and discussion

Palladium on carbon (Pd–C) is the most often used and commercially available palladium-based catalyst featured with cheap price and easy regeneration. Since the hydrogenation of benzaldehyde (**1**) into benzenemethanol (**2**) proceeded under very mild conditions, Pd–C catalytic hydrogenation was not used often in the DRA of benzaldehyde (**1**). In our recent work, the reactivity of Pd–C was modulated in the presence of $CHCl_3$ to achieve a chemoselective hydrogenation of 4-$NO_2C_6H_4CH_2NMe_2$ directly to 4-$NH_2C_6H_4CH_2NMe_2\cdot 2HCl$ in 97% yield.[9] This resulted from the fact that Pd–C catalyst was partially poisoned[10] by HCl molecules released in situ from the Pd–C catalyzed hydrodechlorination[11] of $CHCl_3$. Therefore, Pd–C catalytic hydrogenation DRA of benzaldehydes (**1**) and aminoaldehyde acetals (**3**) in the presence of $CHCl_3$ may be expected to chemoselectively yield *N*-benzyl aminoaldehyde acetal hydrochlorides (**5**·HCl) (Scheme 2).



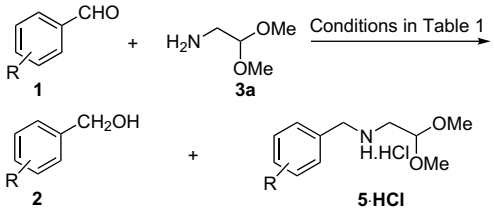
Scheme 2.

In the control experiments, we observed that 3-fluoro-benzaldehyde (**1a**) was smoothly reduced into 3-fluoro-benzenemethanol (**2a**, 90%) under the conventional hydrogenation conditions [10% Pd–C (5 wt %), 1 atm, rt, 2 h]. However, when the mixture of **1a** and *N*-(2,2-dimethoxylethyl)-3-fluorobenzylideneamine (**4a**) was hydrogenated in the presence of $CHCl_3$, **1a** was recovered in 98% yield, while *N*-(2,2-dimethylethyl)-3-fluoro-benzylamine hydrochloride (**5a**·HCl) was collected in 98% yield as a white crystal (Scheme 3). This result strongly suggested that Pd–C catalytic hydrogenation with $CHCl_3$ may well meet the requirements of DRA because the imine was reduced selectively over the carbonyl group. It also



Scheme 3.

Table 1
Pd–C catalytic hydrogenation DRA of **1** and **3a**[a,b]



a. R = 3-F
b. R = 3,4,5-trimethoxy

Entry	**1** (**1**:**3a**)	Additive	Time (h)	Yield of **2** (%)	Yield of **5** (%)	Yield of **3a**·HCl (%)
1	**1a** (1:0)	None	2	**2a** (21)	**5a** (76)	None
2	**1a** (1:0)	$CHCl_3$	10	**2a** (0)	**5a**·HCl (98)	(0)
3	**1a** (1:2)	$CHCl_3$	10	**2a** (0)	**5a**·HCl (98)	(0)
4	**1b** (1:0)	$CHCl_3$	5	**2b** (9)	**5a**·HCl (89)	(9)
5	**1b** (1:5)	$CHCl_3$	5	**2b** (9)	**5a**·HCl (97)	(0)

[a] The reaction proceeded in 5 mmol scale with 10% Pd–C (10 wt %) in MeOH (30 mL) and $CHCl_3$ (2 mL) under H_2 (1 atm) at room temperature.
[b] Isolated yields were obtained.

indicated that the acetal group was well tolerated in the reaction conditions because **5a**·HCl was isolated as a stable crystal.

Encouraged by those primary results, Pd–C catalytic hydrogenation DRA of **1a** and aminoacetaldehyde dimethylacetal (**3a**) was tested. As shown in Table 1, the mixture of **1a** and **3a** was hydrogenated without $CHCl_3$ to yield a mixture of **2a** (21%) and **5a** (76%) (entry 1). To our great surprise, **5a**·HCl was obtained as a single product in 98% yield in the presence of $CHCl_3$ and its work-up procedure was as simple as a filtration (entry 2).

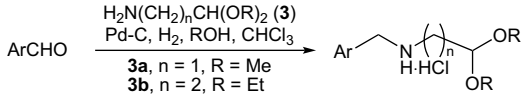
However, when the active 3,4,5-trimethoxybenzaldehyde (**1b**) was used as a substrate, a crystalline mixture of *N*-(2,2-dimethoxylethyl)-3,4,5-trimethoxybenzylamine hydrochloride (**5b**·HCl, 89%) and aminoacetaldehyde dimethylacetal hydrochloride (**3a**·HCl, 9%) was collected, while **2b** was also separated in 9% yield from the filtrate (entry 4). This result suggested that 1.0 equiv of **1b** was not enough to exhaust 1.0 equiv of **3a** and the excess of **1b** was required. When 1.5 equiv of **1b** was used, pure crystalline **5b**·HCl was collected in 97% yield (entry 5). Although the unreacted **1b** and byproduct **2b** were found in the filtrate, they did not have any bad effect on the work-up procedure.

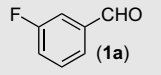
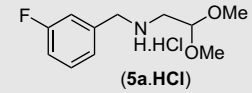
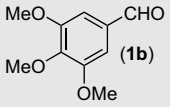
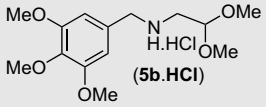
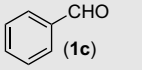
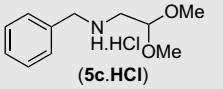
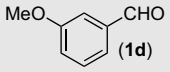
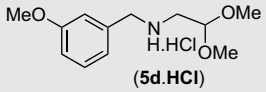
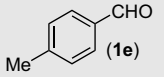
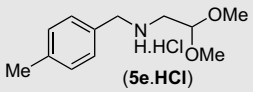
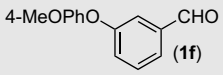
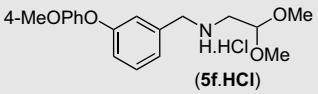
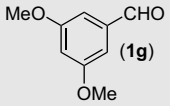
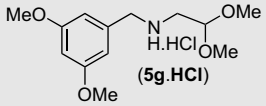
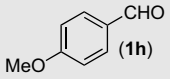
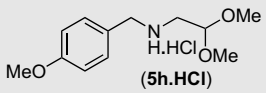
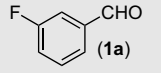
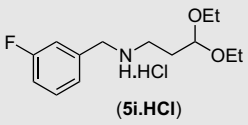
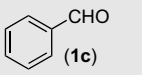
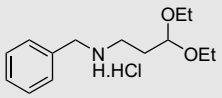
To generalize the application of this novel procedure, different benzaldehydes **1a**–**h** were tested. As shown in Table 2, the corresponding DRA products **5a**–**j** were obtained in excellent yields. In most cases, 1.2 equiv of benzaldehydes were good enough to achieve excellent yields and chemoselectivity. However, a little higher proportion of active benzaldehydes was essential in entry 2 and entry 8. When 3-aminopropionaldehyde diethylacetal (**3b**) was used, similar successful results were achieved (entries 9 and 10).

This novel procedure is a one-pot multi-step reaction, in which each step proceeded with extremely high orderliness and efficiency. We hypothesized that the procedure proceeded in a self-modulated system and a possible four-stage cyclic pathway was proposed in Scheme 4.

In stage 1, 'active Pd–C catalyst' preferentially catalyzed the hydrodechlorination of $CHCl_3$ to release HCl. Then Pd–C catalyst was poisoned immediately by HCl until it could not further catalyze the hydrodechlorination. At that time, 'active Pd–C catalyst' was converted into 'mild Pd–C catalyst', which has a high selectivity to reduce imine over carbonyl group. In stage 2, benzaldehyde (**1**) and amine (**3**) underwent an efficient condensation to yield benzylideneamine (**4**) catalyzed by HCl produced in stage 1. In stage 3, benzylideneamine (**4**) was hydrogenated selectively to yield benzylamine (**5**) catalyzed by 'mild Pd–C catalyst'. In the end of the

Table 2
Pd–C catalytic hydrogenation DRA of **1a–j** in the presence of $CHCl_3$[a,b]



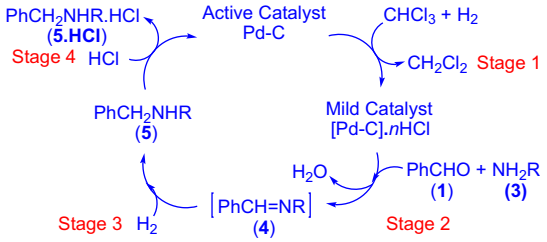
Entry	1	3	5·HCl	Time (h)	Yield (%)
1	 (**1a**)	**3a**	 (**5a**.**HCl**)	10	98
2	 (**1b**)	**3a**	 (**5b**.**HCl**)	5	97[c]
3	 (**1c**)	**3a**	 (**5c**.**HCl**)	10	97
4	 (**1d**)	**3a**	 (**5d**.**HCl**)	8	96
5	 (**1e**)	**3a**	 (**5e**.**HCl**)	9	97
6	 (**1f**)	**3a**	 (**5f**.**HCl**)	7	96
7	 (**1g**)	**3a**	 (**5g**.**HCl**)	8	98
8	 (**1h**)	**3a**	 (**5h.HCl**)	7	96[c]
9	 (**1a**)	**3b**	 (**5i.HCl**)	10	97[d]
10	 (**1c**)	**3b**	 (**5j.HCl**)	10	97[d]

[a] The reaction proceeded with **1** (6 mmol), **3** (5 mmol), and 10% Pd–C (10 wt %) in MeOH (30 mL) and $CHCl_3$ (2 mL) under H_2 (1 atm) at room temperature.
[b] Isolated yields were obtained.
[c] 1.5 equiv of **1b** or **1h** was used.
[d] EtOH was used as a solvent.

cycle (stage 4), benzylamine (**5**) captured an HCl molecule from the reaction system to form benzylamine hydrochloride (**5**·HCl), by which the 'mild Pd–C catalyst' was reactivated to be an 'active Pd–C catalyst' again. Clearly, the 'mild Pd–C catalyst' can be maintained steadily if there is enough $CHCl_3$ in the system.

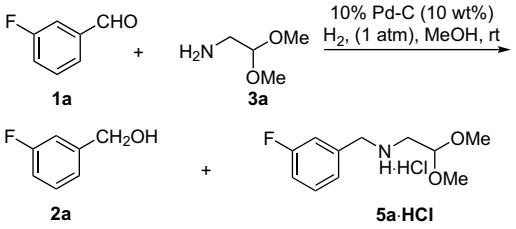
In this novel procedure, the HCl molecule in situ generated from the hydrodechlorination of $CHCl_3$ played a critical role for the selectivity and efficiency. Further experiments with **1a** and **3a** proved that $CHCl_3$ cannot be replaced by other chloroalkanes. As shown in Table 3, both CH_2Cl_2 and CH_3CCl_3 gave a mixture of **2a**, **3a**·HCl, and **5a**·HCl because they could not release enough excess HCl to poison Pd–C catalyst to a desired level (entries 1 and 2). On the contrary, the hydrodechlorination of CCl_4 was too easy to be controlled, where Pd–C catalyst was completely poisoned by the excess HCl within a few minutes. Thus, the DRA stopped quickly and the unreacted **3a** captured HCl molecule to form **3a**·HCl (entry 3).

We then attempted to extend this novel procedure to the normal amines **3c–j** other than aminoaldehyde acetals **3a–b**, in which



Scheme 4. A self-modulated system with a four-stage cyclic pathway.

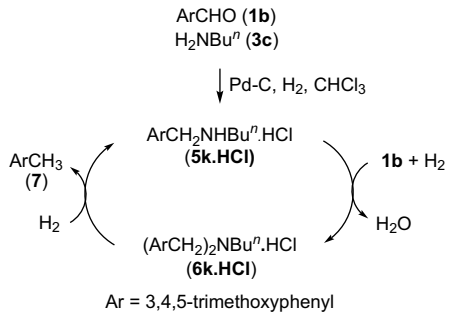
Table 3
Effect of chloroalkanes on Pd–C catalytic hydrogenation DRA[a]



Entry	Additive	Time (h)	Yield of **2a** (%)	Yield of **3a**·HCl (%)	Yield of **5a**·HCl (%)
1	CH_2Cl_2	2	80	82	16
2	CH_3CCl_3	3	58	60	39
3	$CHCl_4$	1	0	90	9
4	$CHCl_3$	10	0	0	98

[a] Isolated yields were obtained.

1b and *n*-$BuNH_2$ (**3c**) were used as model substrates (Scheme 5). As was expected, 1.2 equiv of **1b** was good enough to give *N*-butyl-3,4,5-trimethoxyl-benzylamine hydrochloride (**5k**·HCl) in 97% yield because **3c** has higher nucleophilic reactivity than **3a**–**b**. Interestingly, we also observed that 3,4,5-trimethoxy-benzene-methane (**7**, 4%) was the only byproduct instead of expected **2b**. To understand this phenomenon, the hydrogenation at the end of 2.5 h was stopped and the reaction mixture was separated to get an overalkylation intermediate *N*,*N*′-di(3,4,5-trimethoxybenzyl)butyl-amine hydrochloride (**6k**·HCl). When **6k**·HCl was hydrogenated under DRA conditions, it was *N*-debenzylated to give **5k**·HCl and **7** in almost quantitative yields.



Scheme 5. The formation of the byproduct **7**.

As shown in Scheme 5, we hypothesized that the DRA of **1b** and **3c** first yielded the desired product **5k**·HCl, which then underwent a second DRA with **1b** to yield **6k**·HCl. Since **6k**·HCl is a tertiary benzylamine and susceptible toward hydrogenolysis, it carried out a Pd–C catalytic N-debenzylation to give **5k**·HCl and **7**. As a result, **5k**·HCl was collected as a single product without any contamination of **6k**·HCl.

As shown in Table 4, the DRA of different benzaldehydes **1b**–**j** and amines **3c**–**j** gave the corresponding products **5k**–**x** in excellent yields and selectivity. Compared with **3a**–**b**, amines **3c**–**j** benefited the reaction with lower Pd–C loading (5 wt%), less equivalents of benzaldehydes and shorter reaction time. The hydroxyl groups in aminoalcohols **3h**–**i** stayed intact to give **1v**·HCl and **1w**·**HCl** in excellent yields (entries 12 and 13). In the cases of pyridine-3-yl-methylamine (**3g**) and *N*,*N*-dimethylethane-1,2-diamine (**3j**), the corresponding dihydrochlorides **1u**·2HCl and **1x**·2HCl were formed automatically (entries 11 and 14).

3. Conclusions

In conclusion, an unprecedented efficient and chemoselective DRA of benzaldehyde and primary amine was developed to directly yield *N*-monosubstituted benzylamine hydrochloride. This novel procedure was characterized by simply adding a few milliliters of $CHCl_3$ into a conventional Pd–C catalytic hydrogenation system. The Pd–C catalyzed hydrodechlorination of $CHCl_3$ to release HCl was the key step and the released HCl molecules played three roles: (a) it converted the 'active Pd–C catalyst' into the 'mild Pd–C catalyst'; (b) it catalyzed the condensation of aldehyde and amine to form imine efficiently; (c) it was captured by amine product to yield amine hydrochloride. We hypothesized that the procedure proceeded in a self-modulated system and a possible four-stage cyclic pathway was proposed. The procedure works quite general for a wide range of benzaldehydes and primary amines, by which *N*-monosubstituted benzylamine hydrochloride was prepared constantly as a single product in practically quantitative yields. Since the procedure directly yielded amine hydrochloride, it offered an extremely convenient work-up procedure as simple as a filtration.

4. Experimental section

4.1. A typical procedure for preparation of *N*-(2,2-dimethoxyethyl)benzylamine hydrochloride (5c·HCl) by Pd–C catalytic hydrogenation DRA

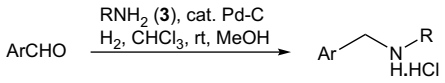
The suspension of benzaldehyde (**1c**, 12.73 g, 0.12 mol), aminoacetaldehyde dimethylacetal (**3a**, 10.51 g, 0.10 mol), 10% Pd–C (1.273 g, 10 wt%) in MeOH (150 mL), and $CHCl_3$ (10 mL) was hydrogenated (2 atm, on a Parr hydrogenator) at room temperature until the absorption of hydrogen ceased (10 h). After the Pd–C catalyst was filtered off, solvent was removed on a rotavapor. The residue was diluted with diethyl ether (100 mL) and **5c**·HCl (22.47 g, 97%) was collected as a white crystal by filtration. Usually, the product was pure enough for any analytical purposes. It had mp 108–110 °C (CH_3OH–Et_2O); IR: ν 3417, 2936, 1593, 1455, 1390 cm^{-1}; ^1H NMR: δ 7.44–7.42 (m, 5H), 4.65 (t, J=4.80 Hz, 1H), 4.20 (s, 2H), 3.38 (s, 6H), 3.12 (d, J=4.80 Hz, 2H); ^{13}C NMR: δ 130.3, 130.1, 129.9, 129.4, 100.4, 55.7, 51.3, 47.4; MS m/z (%): 195 (M−HCl, 0.80), 91 (100). Anal. Calcd for $C_{11}H_{18}ClNO_2$ (231.72): C, 57.02; H, 7.83; N, 6.04. Found: C, 56.88; H, 7.72; N, 5.96.

The similar procedure was used to convert the substrates **1a**–**h** efficiently to the corresponding products **5a**–**j**·HCl.

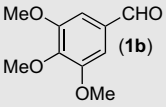
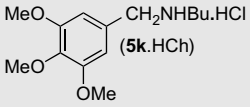
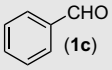
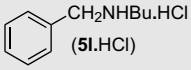
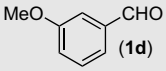
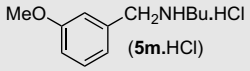
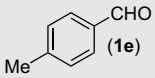
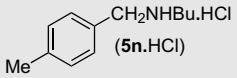
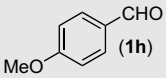
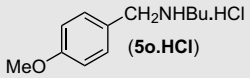
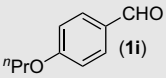
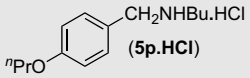
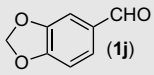
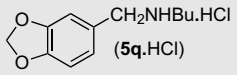
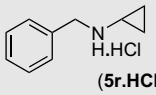
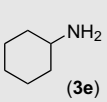
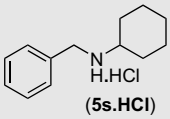
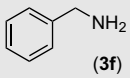
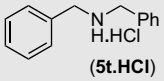
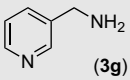
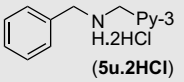
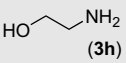
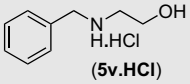
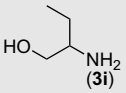
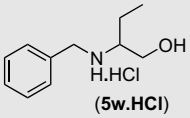
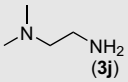
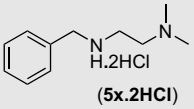
4.2. A typical procedure for preparation of *N*-butylbenzylamine hydrochloride (5l·HCl) by Pd–C catalytic hydrogenation DRA

The suspension of benzaldehyde (**1c**, 637 mg, 6 mmol), *n*-$BuNH_2$ (**3c**, 366 mg, 5 mmol), 10% Pd–C (36 mg, 5 wt%) in MeOH (30 mL), and $CHCl_3$ (2 mL) was hydrogenated (1 atm, on an atmospheric pressure hydrogenator) at room temperature until the absorption

Table 4
Pd–C catalytic hydrogenation DRA in the presence of $CHCl_3$[a,b]



1 **5.HCl**

Entry	1	3	5·HCl	Time (h)	Yield (%)
1	 (**1b**)	$BuNH_2$ (**3c**)	 (**5k**.HCh)	2	97
2	 (**1c**)	**3c**	 (**5l**.HCl)	5	98
3	 (**1d**)	**3c**	 (**5m**.HCl)	4	96
4	 (**1e**)	**3c**	 (**5n**.HCl)	4	95
5	 (**1h**)	**3c**	 (**5o.HCl**)	2	98
6	 (**1i**)	**3c**	 (**5p.HCl**)	4	95
7[c]	 (**1j**)	**3c**	 (**5q**.HCl)	4	98
8	**1c**	 (**3d**)	 (**5r.HCl**)	5	98
9	**1c**	 (**3e**)	 (**5s.HCl**)	10	97
10	**1c**	 (**3f**)	 (**5t.HCl**)	2	96
11	**1c**	 (**3g**)	 (**5u.2HCl**)	3	98
12	**1c**	 (**3h**)	 (**5v.HCl**)	8	97
13	**1c**	 (**3i**)	 (**5w.HCl**)	10	97
14	**1c**	 (**3j**)	 (**5x.2HCl**)	6	98

[a] The reaction proceeded with **1** (6 mmol), **3** (5 mmol), and 10% Pd–C (5 wt %) in MeOH (30 mL) and $CHCl_3$ (2 mL) under H_2 (1 atm) at room temperature.
[b] Isolated yields were obtained.
[c] Compound **1J** (1.5 equiv) was used.

of hydrogen ceased (5 h). After the Pd–C catalyst was filtered off, solvent was removed on a rotavapor. The residue was diluted with diethyl ether (20 mL) and **5l**·HCl (979 mg, 98%) was collected as a white crystal by filtration. Usually, it was pure enough for any analytical purposes. It had mp 164 °C (decomposed); IR: ν 3439, 2954, 1583, 1475 cm^{-1}; ^1H NMR: δ 7.44–7.42 (m, 5H), 4.15 (s, 2H), 2.99 (d, J=7.89 Hz, 2H), 1.63–1.57 (m, 2H), 1.34–1.27 (m, 2H), 0.85 (t, J=7.56 Hz, 3H); ^{13}C NMR: δ 130.9, 129.8, 129.7, 129.3, 50.9, 46.9, 27.5, 19.2, 12.8; MS m/z (%): 163 (M−HCl, 1.8), 91 (100). Anal. Calcd for $C_{11}H_{18}ClN$ (199.72): C, 66.15; H, 9.08; N, 7.01. Found: C, 65.82; H, 8.96; N, 6.92.

The similar procedure was used to convert the substrates **1b–j** efficiently to the corresponding products **5k–x**·nHCl.

Acknowledgements

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Supplementary data

Experiments, characterization, ^1H, and ^{13}C NMR spectra for all products **5a–x**·nHCl are give in the Supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.072.

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