DOI: 10.1002/adsc.200600521

An Efficient and Practical Method for Highly Chemoselective Hydrogenation of Nitrobenzylamines to Aminobenzylamine Hydrochlorides

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Received: October 11, 2006; Revised: March 15, 2007

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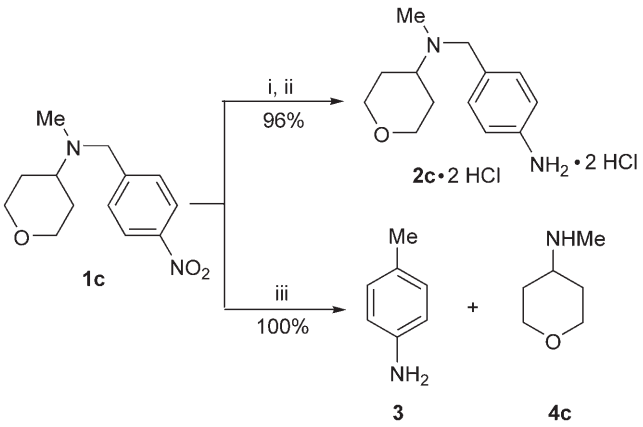
Abstract: Aqueous hydrochloric acid proved to be a very reliable modulator for adjusting the reactivity of palladium on carbon. Thus an efficient and practical method for the highly chemoselective hydrogenation of *N,N*-dialkylnitrobenzylamines to amino-*N,N*-dialkylbenzylamine hydrochlorides was established. The method features convenient performance, easy work-up and high efficiency.

Keywords: amines; chemoselectivity; hydrogenation; palladium; reduction

Introduction

Palladium-catalyzed chemoselective hydrogenations have played an important role in modern organic synthesis, such as the well-known Rosenmund reduction and Lindlar reduction. Palladium on carbon (Pd-C) is a commercially available catalyst featured by a low price and easy regeneration. Pd-C-catalyzed hydrogenations have been widely employed in numerous organic transformations with high efficiency in both academic and industrial laboratories. Prominent among them are the catalytic hydrogenation of aromatic nitro groups[1] and the catalytic hydrogenolysis of *N,N*-dialkylbenzylamines.[2] Since these two transformations occur under very similar conditions (room temperature and atmospheric hydrogen pressure), low chemoselectivity was observed between them.[3] In fact, no general and practical protocol by catalytic hydrogenation exists for this purpose to date, even though many efforts have been made to develop chemoselective Pd-C-catalyzed hydrogenations.[4]

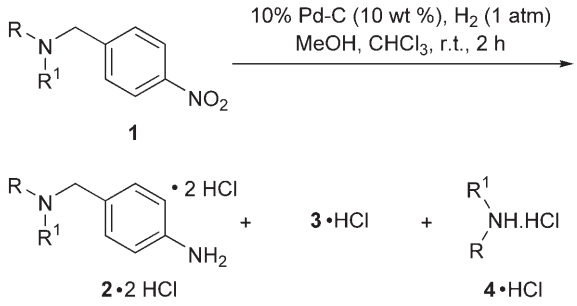
In past decades, amino-*N,N*-dialkylbenzylamines (**2**) have been gaining increasing importance in medicinal chemistry and organic chemistry.[3,5,6] The most convenient preparations of them are the chemoselective reduction of the corresponding *N,N*-dialkylnitrobenzylamines (**1**). For example, TAK-779 was reported as the first small-molecule, non-peptide CCR5 antagonist with highly potent and selective anti-HIV-1 activity.[7] *N*-[(4-Aminophenyl)methyl]tetrahydro-*N*-methyl-2*H*-pyran-4-amine (**2c**) was recognized as both a key pharmacophore and an intermediate for the synthesis of TAK-779. As shown in Scheme 1, compound **2c** was prepared smoothly by a chemoselective reduction of *N*-[(4-nitrophenyl)methyl]tetrahydro-*N*-methyl-2*H*-pyran-4-amine (**1c**) with a stoichiometric amount of $SnCl_2$ in aqueous HCl and was then converted into **2c**·2 HCl for easy purification. Unfortunately, the Pd-C- or Raney-Ni-catalyzed hydrogenation of **1c** was non-selective and led to hydrogenolyzed products **3** and **4c**.[3a,b]



Scheme 1. *Conditions:* i) $SnCl_2$, aqueous HCl, 20–40 °C, 1 h; ii) aqueous HCl, *i*-PrOH; iii) Pd-C or Raney-Ni, H_2, room temperature.

In our research project on the chemical biology, a series of amino-*N,N*-dialkylbenzylamines (**2**) derivatives was chosen as synthetic targets. The literature shows that the most reliable methods for the chemoselective transformation of **1** to **2**, in practice, are those using reducing metals in acidic media, such as Fe, Sn or $SnCl_2$ in aqueous HCl.[3,6] But, these methods are unavoidably associated with tedious work-ups and release of a large amount of hazardous wastes to the environment. Therefore, there is a great need to find a chemoselective catalytic hydrogenation method as an alternative. We report herein a novel method to accomplish this goal, which is characterized by adding a suitable amount of aqueous HCl to the conventional Pd-C-catalyzed system in MeOH. The method features convenient performance, easy work-up and high efficiency.

Table 1. Effect of the size of substituents on the chemoselectivity.



1, 2, 4	R	R^1	2·2 HCl [%]	3·HCl [%]	4·HCl [%]
a	Me	Me	97	3	3
b	Et	Et	85	15	15
c	Me	4-THP	19	81	81
d	*i*-Pr	*i*-Pr	0	100	100

Results and Discussion

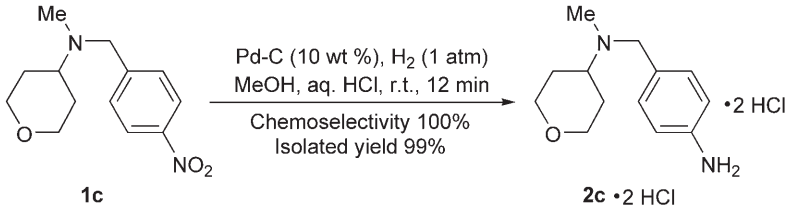
It is well known that: (1) the hydrogenation ability of the Pd-C catalyst is enhanced by a catalytic amount of HCl, but retarded with an excess amount of HCl (over 1 equivalent) due to the unproductive occupation of Pd-C catalytic sites by HCl molecules.[8] (2) The Pd-C-catalyzed hydrogenation of nitrobenzene in the presence of $CHCl_3$ produced aniline hydrochloride in excellent yields, in which the hydrochloride came from the Pd-C-catalyzed hydrodechlorination of $CHCl_3$.[9] These results strongly imply that the Pd-C-catalyzed hydrogenation of *N,N*-dialkylnitrobenzylamines (**1**) in the presence of $CHCl_3$ could be a possible method to chemoselectively obtain amino-*N,N*-dialkylbenzylamines (**2**•2 HCl), because the catalytic ability of the Pd-C catalyst will be certainly retarded by the HCl produced from the dehydrochlorination of $CHCl_3$.

As was expected, when *N,N*-dimethyl-4-nitrobenzylamine (**1a**) was hydrogenated with Pd-C catalyst under 1 atmosphere hydrogen pressure at room temperature for 2 h in the presence of $CHCl_3$ (2 mL), the desired 4-amino-*N,N*-dimethylbenzylamine dihydrochloride (**2a**·2 HCl) was obtained as white crystals in 97% yield. Only a 3% yield of hydrogenolyzed products **3**·HCl and **4a**•HCl were detected. Unfortunately, the chemoselectivity of this method sharply decreased with increasing size of the substituents on the benzylamine (Table 1). When **1c** was employed as a substrate, the undesired hydrogenolyzed products were obtained in 81% yields.

Control experiments proved that the undesired hydrogenolyzed products were produced totally in the first 5 min of the hydrogenation. During that period, just a small amount of HCl was released from the dechlorohydrogenation of $CHCl_3$. Thus, HCl actually enhanced rather than weakened the catalytic ability of the Pd-C catalyst.

Many attempts have been made to avoid the hydrogenolysis occurring at the beginning of the hydrogenation. By using compound **1c** as a model substrate, we observed that the addition of anhydrous HCl made the catalyst lose its reactivity completely, while HOAc and TFA accelerated the hydrogenolysis of **1c** significantly. Luckily, when a few drops of concentrated aqueous HCl were added to the hydrogenation system, the chemoselectivity for the conversion of **1c** to **2c**·2 HCl was significantly improved to 78%. When $CHCl_3$ was replaced completely by the same amount of concentrated aqueous HCl (2 mL), the hydrogenation finished within 12 min and gave **2c**·2 HCl as the single product in almost quantitative yield (Scheme 2).

We found that water is essential to control the catalytic ability of Pd-C catalyst when HCl was used as an inhibitor. For example, when anhydrous HCl (2.5



Scheme 2.

equivalents) was used in the Scheme 2, no hydrogenation occurred in 30 min. However, the hydrogenation finished within 15 min to give **2c**·2 HCl in 99 % yield after 1.0 mL of H_2O was added. Thus, we supposed that the occupation of Pd-C catalytic sites by HCl in the presence of H_2O may be a reversible process. Therefore, the catalytic ability of Pd-C catalyst with aqueous HCl is partially weakened to enable reduction of the aromatic nitro group, while the *N,N*-dialkylbenzylamine stays intact under these conditions.

Further experiments proved that at least 2.5 equivalents of aqueous HCl were required to guarantee the chemoselectivity (entry 3 in Table 2). Two equivalents of aqueous HCl are necessary for the formation of the product **2c**·2 HCl and 0.5 equivalents of aqueous HCl are enough to maintain the reactivity of Pd-C catalyst. The chemoselectivity is so good that the theoretical amount of hydrogen was absorbed exactly even with prolonged reaction time. More than 2.5 equivalents of aqueous HCl proved to have no negative effect (entry 4). However, less than 2.0 equivalents of aqueous HCl not only led to a cloudy endpoint of the hydrogenation (entry 1), but also dramatically affected the chemoselectivity with extended reaction time (entry 2). Clearly, these problems must have occurred at the end of the hydrogenation because two equivalents of aqueous HCl were completely captured as product **2c**·2 HCl was formed. Thus, the Pd-C catalyst was re-activated to lead to hydrogenolysis of the products. The effects of the amount of Pd-C catalyst on the hydrogenation are shown in entries 5 and 6. The excellent chemoselectivity was obtained even with 20 wt % of Pd-C catalyst, while a satisfactory hydrogenation speed was maintained by using 5 wt % Pd-C catalyst.

As shown in Table 3, a wide range of concentrations of aqueous HCl can be used in the reaction. However, a dilute solution of aqueous HCl made the formation of the hydrochloride salt difficult because more water was brought into the reaction system (entries 2 and 3).

Table 2. Effect of amount of aqueous HCl on the chemoselective hydrogenation of **1c**.[a]

Entry	10 % Pd-C [wt %]	aq. HCl[b] [mol equiv]	Time[c] [min]	**2c**·2 HCl [%][d]	**3**·HCl [%][d]	**4c**·HCl [%][d]
1	10	2.0	9 (+10)	83	16	16
2	10	2.0	9 (+60)	50	49	49
3	10	2.5	12 (+60)	99	0	0
4	10	5.0	12 (+60)	99	0	0
5	20	2.5	5 (+30)	99	0	0
6	5	2.5	15 (+30)	99	0	0

[a] Hydrogenation was performed in MeOH at room temperature and 1 atmosphere pressure of H_2.
[b] 37 % aqueous HCl was used.
[c] The number in parenthesis is the extended time after the absorption of the theoretical amount of hydrogen.
[d] Isolated yields are given and the ratios were determined by ^{1}H NMR.

Table 3. Effect of concentration of aqueous HCl on the chemoselective hydrogenation of **1c**.[a]

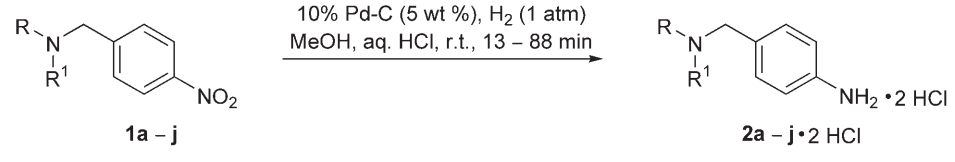
Entry	Concentration of aqueous HCl [%]	Volume [mL]	Time [min]	**2c**·2 HCl [%][b]	**3**·HCl [%][b]	**4c**·HCl [%][b]
1	37	0.63	12	99	0	0
2	18.5	1.25	10	98	0	0
3	9.25	2.50	10	98	0	0

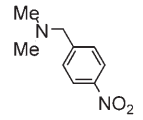
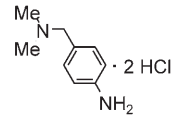
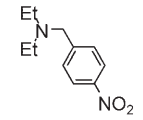
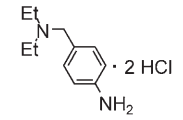
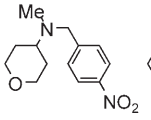
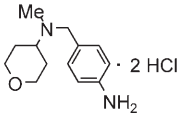
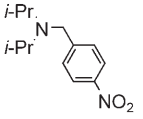
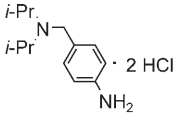
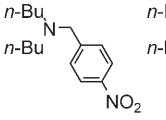
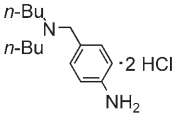
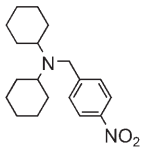
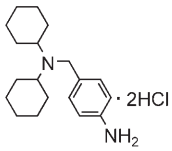
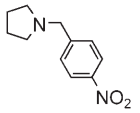
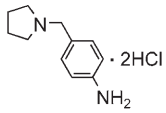
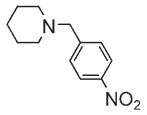
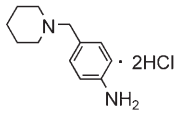
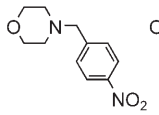
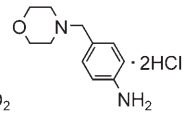
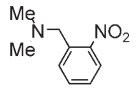
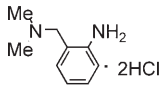
[a] 2.5 mmol of **1c** and 10 % Pd-C (10 wt %) were used in MeOH at room temperature and 1 atmosphere pressure of H_2.
[b] Isolated yields are given.

To generalize this highly chemoselective protocol, different *N,N*-dialkylnitrobenzylamines (**1a–l**) were tested. As shown in Table 4, they all gave the corresponding amine hydrochlorides (**2a–l**·*n* HCl) as single products in excellent yields. The hydrogenation of substrates with acyclic amines (**1a–f**) normally was completed within a few minutes, while those with cyclic amines (**1g–i**) took a little longer. Substrates **1g–i** were reported to be converted into **2g–i** in 43 %, 75 % and 1.9 % yields, respectively, in conventional Pd-C catalyzed hydrogenations.[3c] However, they were obtained as **2g–i**·2 HCl using our protocol in 97 %, 95 % and 96 % isolated yields, respectively. This method is so efficient that the bulky *N,N*-dicyclohexylbenzylamine (**1f**) also gave **2f**·2 HCl in excellent chemoselectivity and yield. When **1k** was employed as the substrate and 3.5 equivalents of aqueous HCl were used, the corresponding trihydrochloride **2k**·3 HCl (Figure 1) was obtained smoothly. It is noteworthy that **2l**·4 HCl (Figure 1), which could be an attractive dendrimeric core molecule, was obtained from **1l** in excellent yield under extremely convenient conditions.

To explore the chemoselectivity of this method with other functional groups, the mixture of **1c** with chlorobenzene, bromobenzene or octadec-1-ene was hydrogenated (Scheme 3). As a result, highly chemoselectivity between the aryl nitro group and the chlorobenzene was observed. The chlorobenzene was recovered in quantitative yield while **2c**·2 HCl was obtained in 98 % yield. Unfortunately, the method had

Table 4. Chemoselective hydrogenation of *N,N*-dialkylnitrobenzylamines (**1a–j**).



1,2	Substrate (**1**)	Product (**2** · 2 HCl)	Time [min]	Yield [%]
a			17	98
b			15	99
c			15	99 (0)[a]
d			13	99
e			17	99
f			14	99
g			65	97 (43)[b]
h			88	95 (75)[b]
i			63	96 (1.9)[b]
j			33	96

[a] 2.5 mmol of **1c** and 10% Pd-C (10 wt%) were used in MeOH at room temperature and 1 atmosphere pressure of H_2.
[b] Isolated yields are given.[a] Isolated as **2c**, see ref.[3a]
[b] Isolated as **2g**, **2h** and **2i**, see ref.[3c]

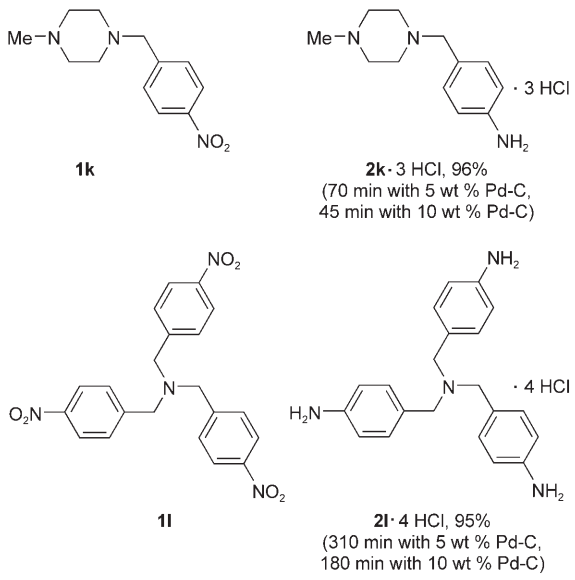
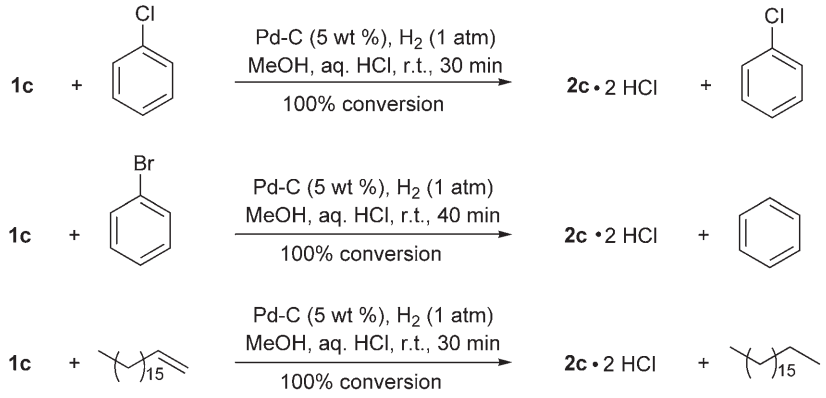


Figure 1.

no chemoselectivity between an aryl nitro group and aryl bromobenzene or octadec-1-ene, which was hydrogenated completely to give the corresponding benzene or octadecane.

Conclusions

We found that aqueous HCl is a very reliable modulator for adjusting the reactivity of the Pd-C catalyst. By addition of a suitable amount of aqueous HCl to a routine Pd-C-catalyzed hydrogenation system, an efficient and practical method for highly chemoselective hydrogenation of *N,N*-dialkylnitrobenzylamines to amino-*N,N*-dialkylbenzylamine hydrochlorides was established. The method features convenient performance, easy work-up and high efficiency. It is likely that the replacement of the routine procedures (using reducing metals in acidic media) by this method will also significantly reduce the release of hazardous wastes to the environment.



Scheme 3.

Experimental Section

Typical Procedure for the Hydrogenation of *N*-[(4-Nitrophenyl)methyl]tetrahydro-*N*-methyl-2*H*-pyran-4-amine (1c)

A mixture of **1c** (626 mg, 2.5 mmol), 10% Pd-C (31.3 mg), and aqueous HCl (37%, 800 mg, *ca.* 8 mmol) in MeOH (30 mL) was stirred under H_2 at ambient temperature and atmospheric pressure until the absorption of hydrogen ceased (15 min). After the catalyst was filtered off, the filtrate was evaporated and Et_2O (20 mL) was added. The desired product **2c**·2 HCl was collected by filtration as yellowish crystals; yield: 726 mg (99%); mp 177–179 °C (MeOH-Et_2O, lit.[3a] 177–179 °C); IR: $\nu = 3429$, 2951, 2858, 1611, 1575 cm^{-1}; ^1H NMR (D_2O): $\delta = 7.71$ (d, $J = 8.6$ Hz, 2H), 7.46 (d, $J = 8.6$ Hz, 2H), 4.58 (d, $J = 13.1$ Hz, 1H), 4.18 (d, $J = 13.1$ Hz, 1H), 4.01 (d, $J = 11.3$ Hz, 2H), 3.48–3.64 (m, 1H), 3.38 (t, $J = 12.4$ Hz, 2H), 2.64 (s, 3H), 2.06 (t, $J = 10.9$ Hz, 2H), 1.77–1.94 (m, 2H); ^{13}C NMR (D_2O): $\delta = 133.4$, 132.9, 131.1, 124.1, 66.2, 62.9, 55.8, 35.3, 28.0, 27.0; MS: *m*/*z* (%) = 221 (M+1, 2.4), 220 (M^+, 18.0), 106 (100.0); anal. calcd. for $C_{13}H_{22}Cl_2N_2O$: C 53.25, H 7.56, N 9.55; found: C 53.23, H 7.57, N 9.54.

A similar procedure was used to convert the substrates **1a–j** chemoselectively to **2a–j**.

4-[(4-Methyl-1-piperazinyl)methyl]benzenamine Trihydrochloride (2k·3 HCl)

Using as similar procedure as that above and 3.5 equivalents of aqueous HCl, compound **2k**·3 HCl; mp 139–141 °C (MeOH-Et_2O). IR: $\nu = 3341$, 2986, 2897, 1615 cm^{-1}; ^1H NMR (D_2O): $\delta = 7.74$ (d, $J = 6.5$ Hz, 2H), 7.43 (d, $J = 6.5$ Hz, 2H), 4.46 (s, 2H), 3.50–3.70 (m, 8H), 2.91 (s, 3H); ^{13}C NMR (D_2O): $\delta = 140.2$, 129.3, 123.1, 50.1, 42.8, 41.0; MS: *m*/*z* (%) = 206 (M+1, 9.9), 205 (M^+, 79.0), 106 (100.0); anal. calcd. for $C_{11}H_{22}Cl_3N_3$: C 45.80, H 7.05, N 13.35; found: C 45.91, H 7.04, N 13.57.

Tris-(4-nitrobenzyl)amine (1l)

A mixture of 4-nitrobenzyl bromide (1.62 g, 7.5 mmol) and aqueous ammonia solution (25%, 5 mL) in anhydrous MeOH (2.5 mL), was heated in a sealed tube at 100 °C for 4 h. Then it was cooled to room temperature and poured into H_2O (20 mL). The resulting mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. Removal of the solvents yielded a yellow solid, which was recrystallized in EtOAc to give **1l** as a light yellow crystal; yield: 0.72 g (68%); mp 170 °C (lit.[10] 168 °C); ^1H NMR ($CDCl_3$): $\delta = 8.20$ (d, $J = 8.6$ Hz, 6H), 7.58 (d, $J = 8.6$ Hz, 6H), 3.70 (s, 6H); ^{13}C NMR ($CDCl_3$): $\delta =$ 147.4, 146.0, 129.2, 123.8, 57.7.

Tris-(4-aminobenzyl)amine Tetrahydrochloride (2l·4 HCl)

A mixture of tris(4-nitrobenzyl)amine (**1l**, 634 mg, 1.5 mmol), 10% Pd-C (31.7 mg), and aqueous HCl (37%, 3.0 g) in MeOH (30 mL) was hydrogenated at ambient temperature and atmospheric hydrogen pressure for 310 min. After the catalyst was filtered off and MeOH was evaporated, the residue was dissolved in anhydrous ethanol (10 mL). Removal of ethanol (as an azeotropic mixture with water) yielded a light yellow solid, which was washed with anhydrous diethyl ether to give pure **2l**·4 HCl; yield: 680 mg (95%); mp >250 °C (MeOH); IR: $\nu = 3412$, 2857, 1616, 1573 cm^{-1}; ^1H NMR (D_2O): $\delta = 7.56$ (d, $J = 8.6$ Hz, 6H), 7.42 (d, $J = 8.6$ Hz, 6H), 4.30 (s, 6H); ^{13}C NMR (D_2O): $\delta = 131.7$, 131.6, 131.5, 123.8, 50.0; MS *m*/*z* (%): 227 (5.4), 122 (55.1), 121 (86.4), 107 (26.3), 106 (100.0), 94 (28.1); anal. calcd. for $C_{21}H_{28}Cl_4N_4$: C 52.74, H 5.90, N 11.71; found: C 52.86, H, 5.89, N 11.80.

Supporting Information

Characterization data and ^1H NMR and ^{13}C NMR spectra for products **2a–l** are given in the Supporting Information.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (20025204, 20272023) and the Key Subject Foundation from Beijing Department of Education (XK100030514).

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