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Reduction of *N*-(alkoxy(aryl)methyl)benzamide Compounds by a Hantzsch Ester 1,4-Dihydropyridine Using Pd/C as a Catalyst

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Abstract Pd/C-catalyzed transfer hydrogenation with Hantzsch ester1,4-dihydropyridine was found to be very effective for the selective reduction of *N*-(alkoxy(aryl) methyl) benzamide compounds to the corresponding benzamides. The reaction conditions, solvent effects, and reaction mechanism were discussed in the present work.

Keywords *N*-(alkoxy(aryl)methyl)benzamide compounds · Palladium on carbon · Reduction · Hantzsch ester 1,4-dihydropyridine

1 Introduction

The development of new reduction procedures using safe and practically useful reducing agents is of great importance. Existing reducing agents such as H_2 (gas), $NaBH_4$, $LiAlH_4$ and DIBAL-H, although efficient in producing good yields of the desired products, require precautions in handling. The title reagent, namely, Hantzsch ester. 1,4-dihydropyridine (HEH) is being investigated as a safe, easy-to-handle, cheap and environmentally benign reagent for the reduction of organic functional groups. Hantzsch ester 1,4-dihydropyrindine, a well-known model compound of co-enzyme nicotinamide adenine dinucleotide (NADH), has been found to be an attractive biomemetic reducing agent for a variety of useful organic transformations. Many studies have been conducted concerning the mechanism of its reduction of various electron-deficient functional groups [1–5]. Recently, there has been much interest in finding an application for HEH as a biomimetic reducing agent in synthetically useful organic transformations [6], such as organocatalytic and enantioselective reduction of α,β-unsaturated aldehydes [7–10], α,β-unsaturated ketones [11, 12], nitroolefins [13], conjugated olefins [14], α-Ketoesters [15] and Imines [16, 17], reduction of tertiary amides [18], reductive amination of carbonyl compounds [19–25], reductive cyclization of electron-deficient double bonds [26], and cascade asymmetric synthesis of Wieland–Miescher ketone analogs [27]. Actually, we also expended some useful HEH-based synthetic methods [28–30].

It is well-known that Pd/C is a cost-efficiency heterogeneous catalyst and is used extensively in organic chemistry [31–34]. Hayashi and his co-workers have reported an efficient dehydrogenative method using a catalytic amount of Pd/C under an ethylene atmosphere [35–38]. The dramatic catalytic ability of Pd/C was shown vividly in oxidative aromatization of HEH and it is analogs [39]. The facile and effective catalyst activity of Pd/C intrigued our interest in developing it is further application for HEH-based synthetic methods. Benzamides have been found to be an attractive bioactivity [40]. Reductive dealkoxylation of *N*-(alkoxy (aryl)methyl)benzamide compounds have been reported by reducing agents such as $NaBH_3CN$ [41], $LiAlH_4$ [42] and Et_3SiH [43]. Herein we report a new and efficient method for the reduction of *N*-(alkoxy(aryl)methyl)benzamide compounds using HEH in the presence of Pd/C as a catalyst.

2 Experimental Procedures

To the CH_3CN solution (20 mL) of *N*-(alkoxy(aryl) methyl)benzamide compounds [44, 45] (1.0 mmol) were

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added HEH [46] (1.0 mmol) and Pd/C (10 wt% of 3), and the mixture was refluxed under stirring and argon atmosphere for the given time. After completion of the reaction as monitored by TLC, the solvent was filtered and the filtrate was concentrated under reduced pressure. The corresponding benzamides 4 were isolated in excellent yield by a column chromatography (silica gel) and identified by comparing its ^{1}H NMR, ^{13}C NMR and EI–MS spectral data with those reported in the literature.

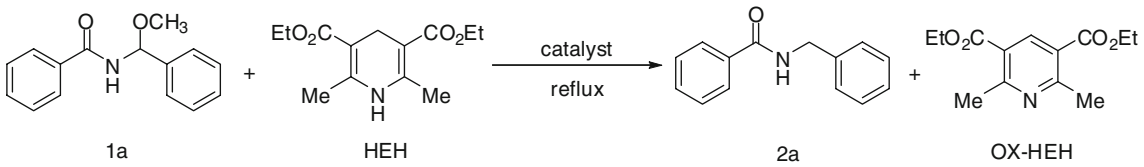
N-Benzylbenzamide: white solid; mp 105–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.66 (2H, d, $J = 6.0$ Hz), 6.46 (1H, s), 7.53–7.29 (8H, m), 7.80 (2H, dd, $J = 1.8$, 1.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 43.9$, 126.9, 127.4, 127.8, 128.5, 128.6, 131.4, 134.3, 138.2, 167.4. MS (EI) *m/z* (%) 211 $[M]^{\bullet+}$ (69.4), 105 (100), 77 (53.6).

N-(4-Chlorobenzyl)benzamide: white solid; mp 137–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.60 (2H, d, $J = 6.0$ Hz), 6.80 (1H, s), 7.52–7.22 (7H, m), 7.78 (2H, d, $J = 9.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 43.2$, 127.8, 128.5, 128.8, 129.1, 131.6, 133.2, 134.1, 136.8, 167.4. MS (EI) *m/z* (%) 245 $[M]^{\bullet+}$ (23.0), 211 (33.2), 105 (100), 77 (33.5).

N-(4-Methylbenzyl)benzamide: white solid; mp 133–134 C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (3H, s), 4.57 (2H, d, $J = 5.4$ Hz), 6.68 (1H, s), 7.24–7.13 (4H, m), 7.50–7.37 (3H, m), 7.78 (2H, d, $J = 8.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 21.0$, 43.8, 126.9, 127.8, 128.4, 129.3, 131.4, 134.3, 135.1, 137.1, 167.3. MS (EI) *m/z* (%) 225 $[M]^{\bullet+}$ (57.2), 105 (100), 77 (40.2).

N-(4-Methoxybenzyl)benzamide: white solid; mp 93–94 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (3H, s), 4.62 (2H, d, $J = 5.1$ Hz), 6.61 (1H, s), 6.86 (2H, d, $J = 8.1$ Hz), 7.25 (2H, d, $J = 8.7$ Hz), 7.50–7.36 (3H, m), 7.77 (2H, d, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 43.5$, 55.2, 114.0, 126.9, 128.5, 129.2, 130.3, 131.4,

Table 1 Catalytic activity of Lewis acid in the reduction of *N*-(methoxy(phenyl) methyl)benzamide 1a using HEH



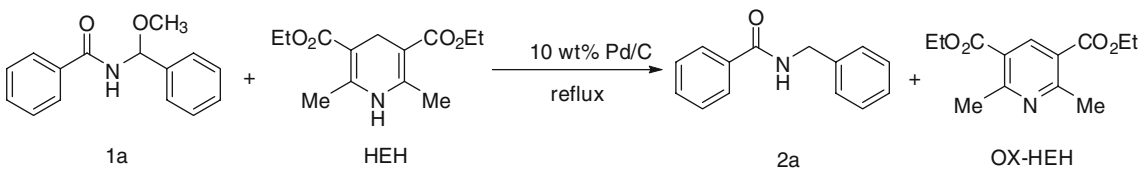
1a HEH 2a OX-HEH

Acid(10 mol%)	None	$AlCl_3$	PTSA	$ZrCl_4$	$BF_3{\cdot}Et_2O$	Pd/C[a]
Time (h)	5	5	5	5	5	5
Yield (%)[b]	N. R.	N. R.	N. R.	N. R	N. R	94%

[a] 10 wt% Pd/C of 1a was used as the catalyst

[b] Isolated yields

Table 2 Effect of solvent loading on the the reduction of *N*-(methoxy(phenyl) methyl)benzamide 1a using HEH in the presence of Pd/C as a catalyst

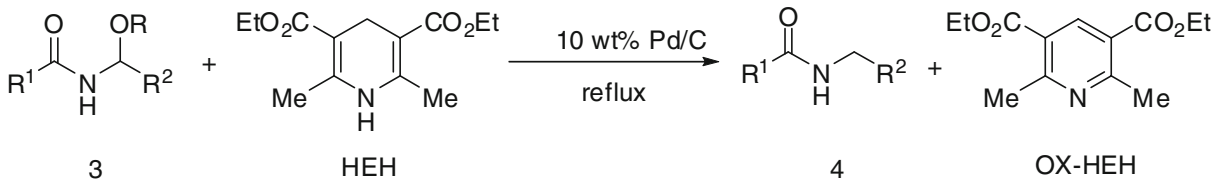


1a HEH 2a OX-HEH

Entry	Solvent	Time (h)	Yield (%)[a]
1	THF	8	81
2	EtOH	10	73
3	CH_3OH	10	70
4	$PhCH_3$	6	90
5	PhH	6	90
6	DMF	7	75
7	CH_3CN	5	94

[a] Isolated yields

Table 3 Reductive dealkoxylation of *N*-(alkoxy(aryl)methyl)benzamide compounds using HEH in the presence of Pd/C as a catalyst



3 HEH 4 OX-HEH

$R = -CH_3, -CH_2CH_3$

$R^1 = -Ph, -p\text{-}Cl\text{-}Ph, -p\text{-}CH_3\text{-}Ph$

$R^2 = -Ph, -p\text{-}Cl\text{-}Ph, -p\text{-}CH_3\text{-}Ph, -p\text{-}OCH_3\text{-}Ph$

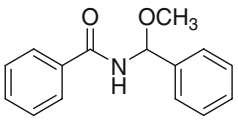
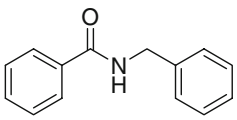
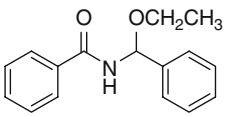
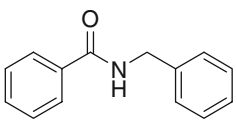
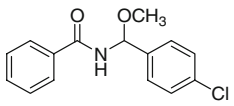
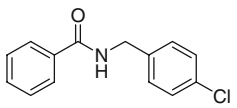
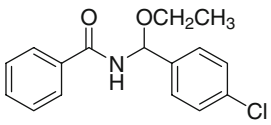
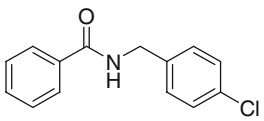
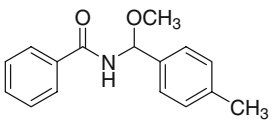
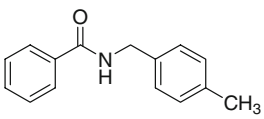
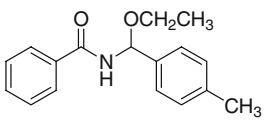
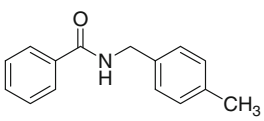
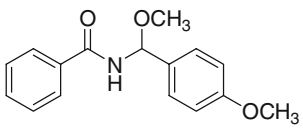
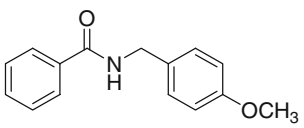
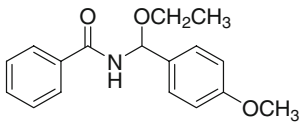
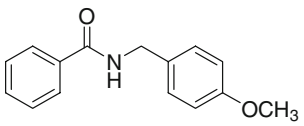
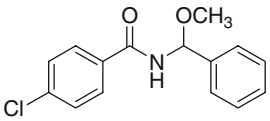
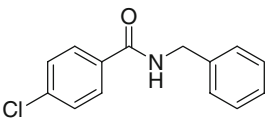
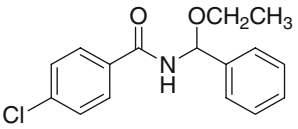
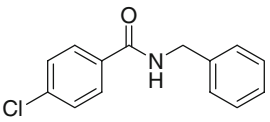
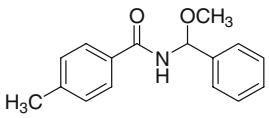
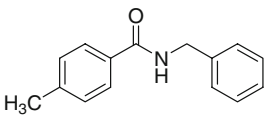
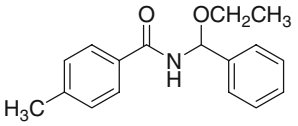
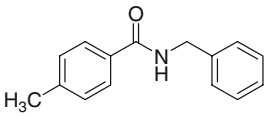
Entry	Substrate	Product	Time (h)	Yield (%)[a]
1[b]			First 5 Second 5 Third 5	First 94[c] Second 93 Third 94
2			5	92
3			5.5	92
4			5.5	90
5			4.5	95
6			5	94
7			4	96

Table 3 continued

Entry	Substrate	Product	Time (h)	Yield (%)[a]
8			4.5	94
9			5	92
10			5.5	90
11			4	94
12			4.5	93

[a] Isolated yields. All products are known compounds and were characterized by EI-MS, ^{1}H NMR and ^{13}C NMR[13]

[b] 10 wt% Pd/C of 3 was reused three times

[c] The yield was determined by GC–MS

134.4, 159.0, 167.2. MS (EI) *m/z* (%) 241 $[M]^{\bullet+}$(71.5), 136 (43.4), 121 (26.7), 105 (100), 77 (45.2).

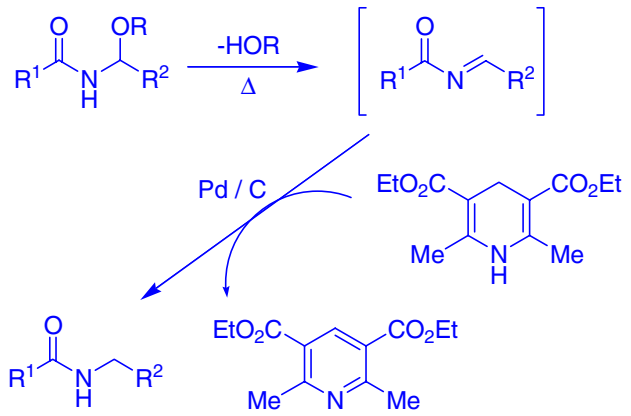
N-Benzyl-4-chlorobenzamide: white solid; mp 165–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.59 (2H, d, $J = 6.0$ Hz), 6.66 (1H, s), 7.37–7.29 (7H, m), 7.71 (2H, d, $J = 8.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 44.1$, 127.6, 127.8, 128.4, 128.8, 131.6, 132.7, 137.7, 137.9, 166.3. MS (EI) *m/z* (%) 245 $[M]^{\bullet+}$(77.0), 139 (100), 91 (38.9), 77 (28.5).

N-Benzyl-4-methylbenzamide: white solid; mp 133–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (3H, s), 4.58 (2H, d, $J = 5.7$ Hz), 6.61 (1H, s), 7.70–7.18 (7H, m), 7.68 (2H, d, $J = 8.1$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.4$, 44.0, 126.9, 127.4, 127.8, 128.7, 129.1, 131.5, 138.3, 141.8, 167.3. MS (EI) *m/z* (%) 225 $[M]^{\bullet+}$(66.8), 119 (100), 91 (39.5).

3 Results and Discussion

To test the reactivity of *N*-(alkoxy(aryl)methyl)benzamide compounds, we chose the reaction of *N*-(Methoxy(phenyl) methyl)benzamide 1a in the presence of various catalytic systems. Thus, the catalytic effect of several Lewis acids on the reaction was investigated, and the results are summarized in Table 1. As shown in Table 1, in the absence of acidic catalysts, the reaction did not proceed. With $AlCl_3$, *p*-methylbenzenesulfonic acid (PTSA), $ZrCl_4$ or $BF_3{\cdot}Et_2O$ as the catalyst, the reaction did not also proceed. The best result (94% yield, 5 h) was obtained when 10 wt% Pd/C of 1a was used as the catalyst.

Various solvents such as THF, EtOH, CH_3OH, $PhCH_3$, PhH, DMF and CH_3CN were also screened for this



Scheme 1 Plausible Mechanism of the reduction of *N*-(alkoxy(aryl)methyl)benzamide compounds using HEH in the presence of Pd/C as a catalyst

reaction, and the results are summarized in Table 2. As shown in Table 2, the best results were observed under CH_3CN conditions.

With this initial success, the scope of this protocol was examined for other substrates. As shown in Table 3. using HEH in the presence of Pd/C as a catalyst, excellent yields were obtained for the direct reduction of *N*-(alkoxy (aryl)methyl)benzamide. Pd/C was found to be compatible with various substituents (electron withdrawing as well as donating substituents) such as OMe, Cl, and Me and the resultant products were obtained in good to excellent yields in short reaction times.

Based on the above results and literature reports [47, 48], a plausible mechanism could be drawn for the reduction of *N*-(alkoxy(aryl)methyl)benzamide compounds, as illustrated in Scheme 1. The corresponding benzamides would directly afford from *N*-(alkoxy(aryl)methyl)benzamide compounds probably through *N*-acylimines as intermediates, which have been isolated by refluxing *N*-(alkoxy(aryl)methyl)benzamides without HEH and Pd/C in anhydrous toluene [44].

4 Conclusions

We have demonstrated that HEH is a versatile reducing agent for reduction of *N*-(alkoxy(aryl)methyl)benzamide compounds. We believe that the reagent system described herein may find wide applicability in organic synthesis due to its efficiency, economy, simplicity and safety.

Acknowledgments We thank the National Natural Science Foundation of China (Grant No. 20702023) and special fund for doctoral program from the Ministry of Education of China (Grant No. 20070730040) for financial support.

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