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One-pot reductive monoalkylation of nitro aryls with hydrogen over Pd/C

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Abstract

A range of different nitro aryls were converted in one-pot to the corresponding secondary alkyl amino aryls in good to excellent yields by using aldehydes as alkyl source and hydrogen over Pd/C (10%) as reducing agent. In all examples, but one, the secondary amine was the sole alkylation product isolated. When formaldehyde was used as the alkyl source, substantial amount of the corresponding tertiary amine was isolated, however, by altering the reaction conditions slightly the corresponding secondary amine could be isolated in superb yield.

Keywords: One-pot; Reductive monoalkylation; Nitro aryls; Secondary alkyl amino aryls; Pd/C

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1. Introduction

The nitro group is a versatile moiety in organic synthesis.[1] Especially, aromatic nitro compounds are frequently used in synthesis, mostly due to their ease of formation and their subsequent efficient conversion to aromatic amines.[2] Primary aromatic amines in their place are vital starting materials for further elaboration to secondary amines, which for example, are important pharmacophores in numerous biologically active compounds.[3] However, preparing secondary amines and obtaining them in good yields with high selectivity still remain a challenge.[3]

There have been a few reports describing the one-pot reductive monoalkylation of aromatic nitro compounds using hydrogen and Raney nickel,[4] decaboran,[5,6] hydrogen and Pd/C (10%),[7] ammonium formate and Pd/C (5%)[8] or polymethylhydrosiloxane, and $Pd(OH)_2/C$ (20%)[9] as the reducing agent and ethanol [acetaldehyde is the actual alkyl source (ethanol is oxidized under the reaction conditions to give acetaldehyde)],[4] carbonyls,[5,6] or nitriles[7–9] as the alkyl source. Conversion of nitro aryls to the corresponding carbamates (Boc and CO_2Et) using Sn/NH_4Cl and Boc_2O or $ClCO_2Et$ in one-pot has also been reported.[10] Herein we report a simple one-pot procedure for the reductive monoalkylation of nitro aryls with aldehydes using hydrogen over Pd/C (10%) as the reducing agent.[11]

2. Results and discussion

The work presented herein was prompted by an interesting finding during the conversion of nitro aryl **1** to primary amine **2**, required as an intermediate for the synthesis of the corresponding aryl azide.[12] We observed that prolonged reaction time (48 h) provided a significant amount (41%) of secondary amine **3a** (Scheme 1). Interestingly no trace of the corresponding tertiary amine was formed under these conditions.

The alkylation agent in the forgoing reaction is most likely the corresponding aldehyde, viz. acetaldehyde, which is formed in low quantity during the reaction by the dehydrogenation of the solvent upon reaction with Pd.[13]

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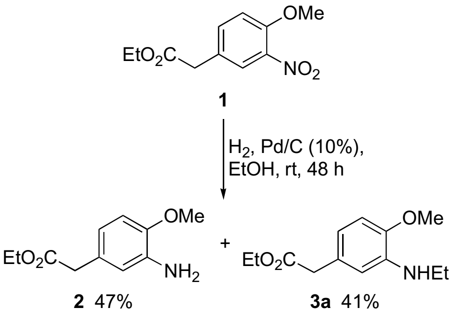


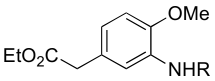
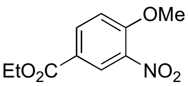
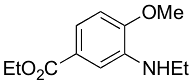
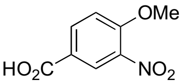
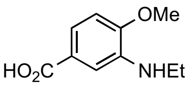
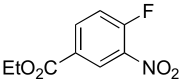
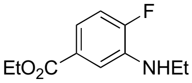
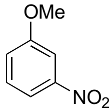
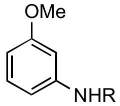
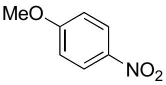
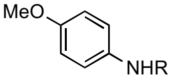
Scheme 1. Initial finding.

Indeed, when a control experiment was performed where 1.1 equiv of acetaldehyde was added to the reaction mixture from the start, it resulted in quick conversion of compound **1** to the corresponding secondary amine **3a** (98% isolated yield) in the course of 3 h (Table 1, entry 1) (no trace of the tertiary amine could be detected by ^{1}H NMR).

Acetaldehyde is most likely formed from ethanol via a similar mechanism to the one recently proposed by Sajiki et al. to explain the formation of ketones (in some cases in high yield) from secondary alcohols when treated with hydrogen in D_2O at elevated temperature over Pd/C (Scheme 2).[14]

Based on our investigation post these initial results it seems that in the case of ethanol the equilibrium is located far to the left. However, due to the presence of the primary amine, which removes the aldehyde from the reaction mixture forming the corresponding imine, and eventually the secondary amine after reduction, and the prolonged reaction

Table 1
Reductive monoalkylation of nitro aryls

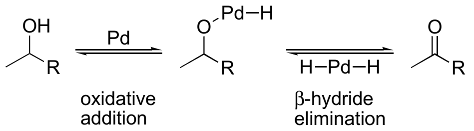
Entry	Starting material	Aldehyde (equiv)	Time (h)	Product	Isolated yield[a] (%)
1	**1a**	CH_3CHO (ca. 1.1)[b]	3	 **3a**, R = Et	98
2	**1a**	HCHO (1.0)[c]	3	**3b**, R = Me	61[d]
3	**1a**	CH_3CH_2CHO (1.6)	4	**3c**, R = *n*-Pr	95
4	 **1b**	CH_3CHO (ca. 1.7)[b]	6	 **3d**	99
5	 **1c**	CH_3CHO (ca. 1.6)[b]	16	 **3e**	90
6	 **1d**	CH_3CHO (ca. 1.1)[b]	7	 **3f**	84
7	 **1e**	CH_3CHO (ca. 1.6)[b]	8	 **3g**, R = Et	96
8	**1e**	CH_3CH_2CHO (1.6)	6.5	**3h**, R = *n*-Pr	99
9	 **1f**	CH_3CHO (ca. 1.1)[b]	5	 **3i**, R = Et	79
10	**1f**	CH_3CH_2CHO (1.6)	6.5	**3j**, R = *n*-Pr	87

[a] All compounds had characterization data consistent with the assigned structure.

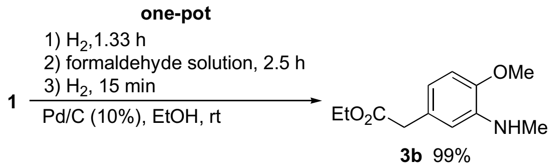
[b] Acetaldehyde is supplied as a ca. 2% solution in DMF.

[c] Formaldehyde solution was used (37 wt % in water).

[d] Ethyl-(3-dimethylamino-4-methoxyphenyl)acetate (**4**) (16%) and ethyl-(3-amino-4-methoxyphenyl)acetate (**2**)[12] (17%) were also isolated.



Scheme 2. Mechanism proposed by Sajiki et al.[14] for the formation of ketones from secondary alcohols under an atmosphere of H_2 in the presence of Pd/C (10%).



Scheme 3. Optimized reaction conditions for the formation of compound **3b**.

time results in the formation of the secondary amine in reasonable yield after 48 h. It should be noted that primary amine **2** is formed cleanly with no traces of compound **3a** being detected as evident by crude ^{1}H NMR analysis, when the reaction is conducted for 1 h under the same conditions as given in Scheme 1 (the reaction is normally complete after 1 h) or when 10% water is added to the reaction mixture.

The fact that the secondary amine was formed in these reactions without a trace of the corresponding tertiary amine was intriguing and bears the potential to be a useful method for the direct conversion of nitro aryls to secondary alkyl amino aryls. To test this theory we treated a range of nitro aryls in ethanol in the presence of various aldehydes (1.0–1.7 equiv) under an atmosphere of hydrogen gas (balloon) over Pd/C (10%) (3–5 mol %) (see Table 1).[15] Under these conditions the corresponding secondary amines could mostly be isolated in high yield and excellent purity after a simple purification, which in many cases only consisted of filtration through a pad of Celite® (see Supplementary data for details). For reactions that were proceeding slowly an excess of the aldehyde was applied in order for the reaction to go to completion. These conditions also worked well for the conversion of the nitro aryl to the corresponding secondary aryl ethyl amine, even in the case when the nitro aryl possessed a free acid group (Table 1, entry 5).

All examples, but one, only gave the secondary amine as the sole isolable amine from these reactions, even when close to two equivalents of the aldehyde was used. The exception occurred when formaldehyde was used as the alkylation agent. In this case the amount of formaldehyde had to be restricted to one equivalent to diminish the formation of the corresponding tertiary amine, viz. ethyl-(3-dimethylamino-4-methoxyphenyl)acetate (**4**). By such means the secondary amine **2b** could be isolated in 61% yield after purification by flash chromatography (Table 1, entry 2), however, the yield of compound **2b** could be further improved by altering the reaction conditions slightly.

As alluded to, the yield of amine **3b** could be dramatically improved by slightly changing the reaction conditions. The conditions implemented conducting the initial reduction reaction with hydrogen over Pd/C (10%) without formaldehyde present in the reaction mixture. Formaldehyde was then added once the primary amine was formed, and the resulting reaction mixture was then stirred under an atmosphere of air at room temperature until the imine formation had reached completion. Finally, the resulting imine was reduced by stirring the reaction mixture under an atmosphere of hydrogen for 15 min (Scheme 3).[16] Under these conditions nitro aryl **1a** could be converted to the secondary amine **3b** in 99% yield.

In summary, we have developed a simple one-pot procedure for the conversion of nitro aryls to the corresponding secondary amines using aldehydes as alkyl source and hydrogen over Pd/C as reducing agent.

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Supplementary data

Supplementary data (isolation procedures for all compounds and characterization data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.030.

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15. General procedure for the reductive monoalkylation of nitro aryls as exemplified for compound **3a**: Pd/C (10%) (4.0 mg, 3.76 μmol) was added to a stirred solution of nitro aryl **1a** (18.3 mg, 0.0765 mmol) and acetaldehyde (0.20 mL of a ca. 2% solution in DMF, ca. 0.0863 mmol) in ethanol (1.3 mL). The resulting reaction mixture was then subjected to three cycles of vacuum followed by flush with H_2 before being stirred vigorously under an atmosphere of H_2 for 3 h. The resulting reaction mixture was then filtered through a plug of Celite® and washed afterwards with ethanol. Concentration of the filtrate gave the desired secondary amine **3a** (17.7 mg, 98%) as a light yellow oil. IR ν_{max} 3411, 2923, 2856, 1730, 1599, 1521, 1439, 1103, 935 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.68 (d, $J = 7.8$ Hz, 1H), 6.55 (dd, $J = 1.8$ and 8.1 Hz), 6.52 (d, $J = 1.8$ Hz, 1H), 4.14 (q, $J = 7.2$ Hz, 2H), 3.82 (s, 3H), 3.51 (s, 2H), 3.16 (q, $J = 7.2$ Hz, 2H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.25 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 172.2, 145.8, 138.3, 126.9, 116.7, 110.6, 109.2, 60.6, 55.4, 41.3, 38.1, 14.8, 14.2; MS (EI+) *m/z* 237 (M^+, 88%), 222 (100), 194 (14), 164 (28), 134 (29); HRMS (EI+) found: M^+, 237.1347. $C_{13}H_{19}NO_3$ requires M^+, 237.1365; Anal. found: C, 65.91; H, 8.16; N, 5.94. $C_{13}H_{19}NO_3$ requires: C, 65.80; H, 8.07; N, 5.90.
16. Improved synthetic procedure for the synthesis of compound **3b**: Pd/C (10%) (2.9 mg, 2.73 μmol) was added to a stirred solution of nitro aryl **1a** (22.7 mg, 0.0949 mmol) in ethanol (1.5 mL). The resulting reaction mixture was then subjected to three cycles of vacuum followed by flush with H_2 before being stirred vigorously under an atmosphere of H_2 for 1.33 h. The H_2 atmosphere was then replaced with air and the reaction mixture was stirred vigorously for 5 min before formaldehyde solution (8.5 μL of a 37 wt % in water solution, 0.105 mmol) was added. The resulting reaction mixture was stirred for 2.5 h at room temperature before being subjected to three cycles of vacuum followed by flush with H_2 before being stirred vigorously under an atmosphere of H_2 for 15 min. The crude reaction mixture was subjected to flash chromatography (silica, hexane/Et_2O/Et_3N 60:39.95:0.05 elution) and concentration of the relevant fractions (R_f 0.4 in hexane/Et_2O 60:40) gave the desired compound **3b** (21.0 mg, 99%) as a light yellow oil. IR ν_{max} 3428, 2925, 1732, 1603, 1524, 1262, 1225, 1168, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.69 (d, $J = 8.0$ Hz, 1H), 6.56 (dd, $J = 2.0$ and 8.0 Hz, 1H), 6.51 (d, $J = 2.0$ Hz, 1H), 4.22 (br s, 1H), 4.14 (q, $J = 7.2$ Hz, 2H), 3.82 (s, 3H), 3.52 (s, 2H), 2.85 (s, 3H), 1.25 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.2, 146.0, 139.4, 127.0, 116.7, 110.2, 109.1, 60.6, 55.5, 41.3, 30.3, 14.2; MS (EI+) *m/z* 223 (M^+, 100%), 208 (44), 150 (17), 135 (15); HRMS (EI+) found: M^+, 223.1222 $C_{12}H_{17}NO_3$ requires M^+, 223.1208; Anal. found: C, 64.55; H, 7.51; N, 6.31. $C_{12}H_{17}NO_3$ requires: C, 64.55; H, 7.67; N, 6.27.