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Reductive monoalkylation of nitro aryls in one-pot

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ABSTRACT

The scope of the serendipitous reductive monoalkylation of ethyl (4-methoxy-3-nitrophenyl) acetate taking place during reduction of the nitro functionality to the corresponding primary amine when treated with hydrogen (1 atm) over Pd/C (10%) in ethanol is investigated. Upon prolonged reaction time the reaction conducted in ethanol and methanol yields significant amount of the corresponding secondary amines, while when performed in *n*-butanol and *i*-propanol it only resulted in the formation of a small amount of the corresponding secondary amines. Further development of the reductive monoalkylation reaction provided conditions that facilitate conversion of a range of different nitro aryls in one-pot to the corresponding secondary benzyl amino aryls in mostly good to excellent yields. This is accomplished by using hydrogen (1 atm) over Pd/C (10%) as reducing agent and benzaldehyde as the benzyl source combined with a stepwise reaction sequence. This chemistry was further extended to the formation of substituted benzyl amino aryls. The yields of the latter products varied dramatically depending on the substitution patterns associated with the benzaldehyde. However, by altering the reaction conditions it was possible to improve the yields of the benzylated products.

1. Introduction

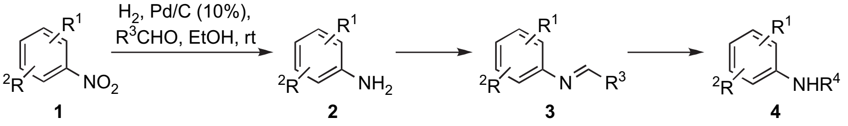
One-pot reactions, where several steps are performed in the same reaction vessel, are gaining popularity as we strive towards conducting our profession in a more sustainable fashion.[1] Development of such reactions is therefore of paramount importance as chemists aim at minimizing reagent and solvent use, as well as reducing isolation steps.

Compounds containing a nitro group are valuable substrates in organic synthesis.[2] In particular, nitro aryls are important due to their ready formation from a range of aromatic starting materials[3] and their easy conversion to aromatic amines.[4] Primary aryl amines are in its place vital starting materials for numerous products of great importance, such as pharmaceuticals.[5] Often these aryl amines are taken through several steps where the use of protection groups is essential in order to secure the desired outcome. In a recent communication we reported a simple one-pot procedure for reductive monoalkylation of nitro aryls using aliphatic aldehydes as alkyl source and H_2 (1 atm) over Pd/C (10%) as reducing agent (Scheme 1).[6,7] This procedure afforded exclusively the secondary amines even when excess amount of aldehyde was used. Herein we report on the further development of this chemistry for the synthesis of benzyl protected aryl amines and substituted benzyl aryl amines.

2. Results and discussion

2.1. Solvent effects

Recently we reported that secondary amine **4a** was formed in a reasonable yield (41%) together with the desired primary amine **2a** (47%) when the reduction of nitro aryl **1a** was run for a prolonged period of time (48 h) in ethanol (Scheme 1).[6] However, upon



Scheme 1. General outline of the one-pot reductive monoalkylation reaction (intermediates are shown; amine **2** and imine **3**).

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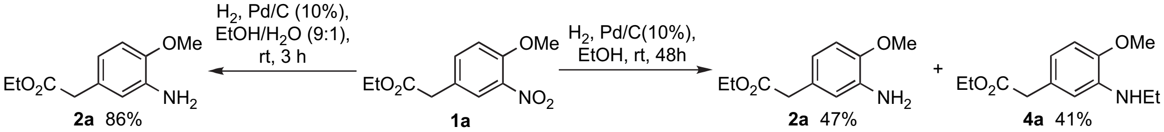


Scheme 2. Formation of secondary amine **4a** during reduction of nitro aryl **1a** under an atmosphere of H_2 over Pd/C (10%) in ethanol.

modification of the reaction conditions, adding small amounts of water to the solvent (ethanol/water 9:1) and stirring for 3 h (Scheme 2) or reducing the reaction time to 1 h (reaction conditions not shown in Scheme 2), we were able to obtain compound **2a** cleanly in good yield.[8]

We found the aforementioned formation of compound **4a** intriguing, in particular due to the fact that the corresponding tertiary amine was not formed under these conditions. This prompted us to conduct a few experiments in order to verify if it would be possible to obtain alkyl amine **4a** in a synthetic useful yield via this method. The efforts directed towards this end are summarized in Table 1. Indeed, by leaving the reaction for 5 days at room temperature improved the ratio of compounds **2a**/**4a** to 1:3 (Table 1, entry 1), thus approaching a useful conversion. However, the reaction time exceeded by far what would be regarded as synthetically useful.

Heating the reaction mixture at 50 °C (entry 2) did not improve matters; the reaction mixture was now contaminated by small amounts of unidentified byproducts, which increased in concentration upon prolonged heating. In addition, the ratio between amines **2a**/**4a** did not seem to improve (**2a**/**4a**=65:35) compared to entry 1 when the reaction was conducted at room temperature. Doubling the amount of catalyst (entry 3) or utilizing Pd/alumina (10%) as catalyst (entry 4) gave the same outcome as obtained in entry 1.

As we previously concluded, the alkylation agent under these conditions is acetaldehyde, which is formed in a small amount from ethanol during the course of the reaction (Scheme 3).[6,9] We previously proposed that the mechanism outlined in Scheme 3, Eq. 1 is operating in order to generate acetaldehyde.[6] This mechanism is based on the proposal put forward by Sajiki et al.[10] in order to explain the formation of ketones (in some examples in good yield) from secondary alcohols when treated under an atmosphere of hydrogen over Pd/C (10%) in D_2O at elevated temperature (reflux) over a 24 h period. Acetaldehyde thus formed might then react further with 2 equiv of ethanol forming the corresponding acetal,[11] or react with the primary amine giving rise to the corresponding imine. However, due to the slight acidity of Pd/C[12] the equilibrium between acetaldehyde and the acetal is most likely situated towards the left, thus favouring the aldehyde. It is also possible that the reaction outlined in Eq. 2 (Scheme 3) is operating together with the mechanism depicted in Eq. 1 (Scheme 3). The latter mechanism would be a palladium variation of the combination of a Meerwein–Ponndorf–Verlay reduction and Oppenauer oxidation.[13]

Table 1
Solvent and reaction condition survey conducted with nitro aryl **1a** as starting material

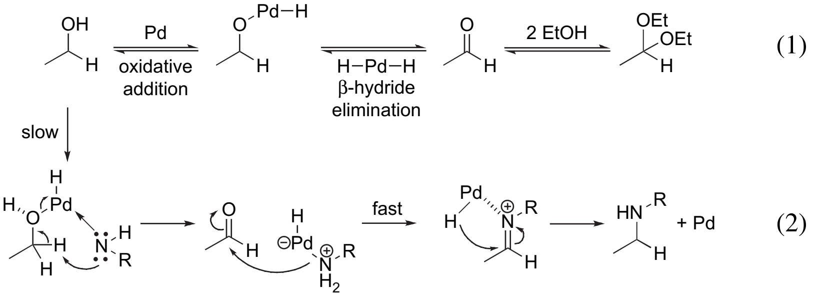
Entry	Solvent	Time (days)	Temperature (°C)	R^4[a] (compound)	**2a**/**4**[b]
1	EtOH	5	rt	Et (**4a**)[6]	25:75
2	EtOH	2	50	Et (**4a**)[6]	65:35[c]
3[d]	EtOH	4	rt	Et (**4a**)[6]	33:67
4[e]	EtOH	5.5	rt	Et (**4a**)[6]	28:72
5	MeOH	5	rt	Me (**4b**)[6]	58:42
6	*n*-BuOH	5	rt	*n*-Bu (**4c**)	82:18
7	*i*-PrOH	2	rt	*i*-Pr (**4d**)	92:8
8	TFE	5[f]	rt	CF_3CH_2	>99:<1[g]

[a] R^4 in compound **4** Scheme 1, R^1=*o*-OMe and R^2=*m*-CH_2CO_2Et.
[b] Based on ^1H NMR integration of the crude reaction mixture.
[c] The reaction mixture also contained small amounts of unidentified byproducts.
[d] Double amount of catalyst was used.
[e] Pd/alumina (10%) was used as catalyst.
[f] The reduction of the nitro group was completed in <1 h.
[g] Alkylation product was not detected by ^1H NMR of the crude reaction mixture; TFE=2,2,2-trifluoroethanol.

In an attempt to verify the extent of the formation of acetaldehyde and/or the corresponding acetal we stirred a mixture of Pd/C (10%) in ethanol under an atmosphere of hydrogen at room temperature for 5 days. The filtered reaction mixture[14] was then subjected to GC–MS analysis, however, this analysis failed to reveal the formation of acetaldehyde or the corresponding acetal. This finding verifies our previous speculation that the aldehyde is formed in extremely small quantities and that the first equilibrium in Scheme 3, Eq. 1 is orientated far to the left. However, in the presence of a primary amine, which removes acetaldehyde from the reaction mixture, the two first equilibriums depicted (Scheme 3, Eq. 1) are slowly driven towards the right.

We then became interested in testing if a similar oxidation/alkylation reaction would occur when the reaction was conducted in other alcohols such as methanol, *n*-butanol, *i*-propanol and 2,2,2-trifluoroethanol. When the reaction was performed in methanol it resulted in the formation of the corresponding secondary amine in moderate yield after 5 days (Table 1, entry 5). However, in *n*-butanol (entry 6) and *i*-propanol (entry 7) only small amounts of compounds **4c** and **4d** could be detected by crude ^1H NMR analysis, while 2,2,2-trifluoroethanol (entry 8) resulted in clean conversion of the nitro aryl to the primary amine **2a**. Even after prolonged reaction time (5 days) no trace of the corresponding secondary amine could be detected (TLC and ^1H NMR analyses). It is also worth noting that no trans-esterification was observed in these experiments.

The aforementioned results indicate that 2,2,2-trifluoroethanol potentially could be an ideal solvent for our one-pot reductive monoalkylation of nitro aryls. Under such conditions the potential contamination of the product by the adduct resulting from oxidation of the solvent would be minimized to zero (given that



Scheme 3. Proposed mechanism for the formation of acetaldehyde from ethanol when treated with hydrogen (1 atm) over Pd/C (10%).