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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

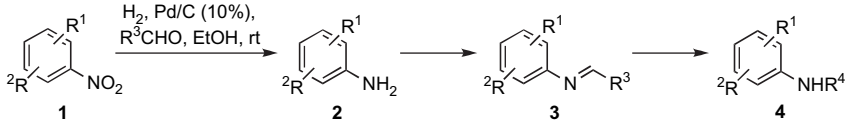
One-pot reactions, where several steps are performed in the same reaction vessel, are gaining popularity as we strive towards conducting our profession in a more sustainable fashion.[1] Development of such reactions is therefore of paramount importance as chemists aim at minimizing reagent and solvent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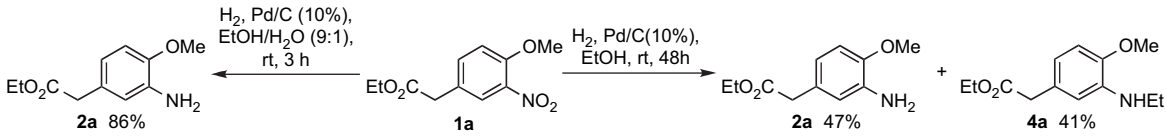


Scheme 2. Formation of secondary amine **4a** during reduction of nitro aryl **1a** under an atmosphere of H_2 over Pd/C (10%) in ethanol.

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

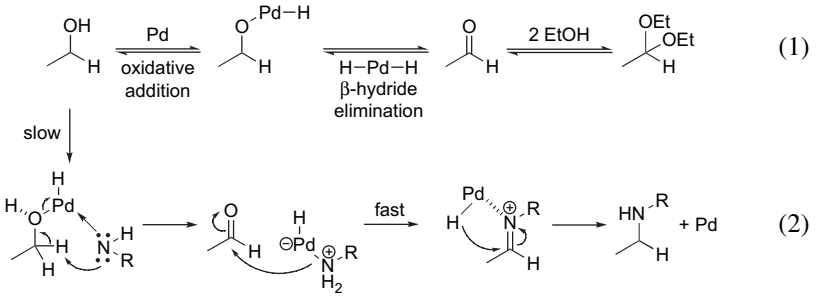
Entry	Solvent	Time (days)	Temperature (°C)	R^{4a} (compound)	**2a**/**4**[b]
1	EtOH	5	rt	Et (**4a**)[6]	25:75
2	EtOH	2	50	Et (**4a**)[6]	65:35[c]
3[d]	EtOH	4	rt	Et (**4a**)[6]	33:67
4[e]	EtOH	5.5	rt	Et (**4a**)[6]	28:72
5	MeOH	5	rt	Me (**4b**)[6]	58:42
6	*n*-BuOH	5	rt	*n*-Bu (**4c**)	82:18
7	*i*-PrOH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

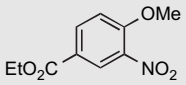
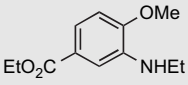
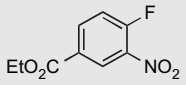
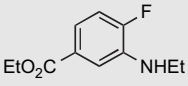
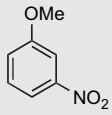
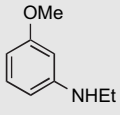
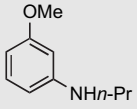
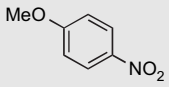
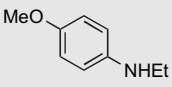
We then became interested in testing if a similar oxidation/alkylation reaction would occur when the reaction was conducted in other alcohols such as methanol, *n*-butanol, *i*-propanol and 2,2,2-trifluoroethanol. When the reaction was performed in methanol it resulted in the formation of the corresponding 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%).

Table 2
Comparative survey of *i*-propanol (methanol and 2,2,2-trifluoroethanol) versus ethanol as solvent for the reductive monoalkylation reaction

Entry	SM	Solvent	Carbonyl (equiv)	Time (h)	Product (secondary amine)	Ratio **2**/**4**[a]	Isolated yield using EtOH as solvent[b,c,6]
1	 **1b**	*i*-PrOH	CH_3CHO (1.7)	24	 **4e**[6]	16:84	99% (6 h)
2	 **1c**	*i*-PrOH	CH_3CHO (1.1)	36	 **4f**[6]	42:58	84% (7 h)
3	 **1d**	*i*-PrOH	CH_3CHO (1.1)	23	 **4g**[6]	23:77	96% (8 h)
4	**1d**	*i*-PrOH	CH_3CH_2CHO (1.6)	24	 **4h**[6]	44:56	99% (6.5 h)
5	 **1e**	*i*-PrOH	CH_3CHO (1.1)	24	 **4i**[6]	35:65	79% (5 h)
6	**1e**	MeOH	CH_3CHO (1.1)	24	**4i**[6]	32:68	79% (5 h)
7	**1e**	TFE[d]	CH_3CHO (1.1)	24	**4i**[6]	62:38	79% (5 h)

[a] Ratio primary amine **2**/secondary amine **4**.
[b] Isolated yield of the product when the reaction was conducted in ethanol (see Ref. 6).
[c] Reaction time in ethanol in brackets.
[d] The reduction of the nitro group was completed in <1 h; SM=starting material; TFE=2,2,2-trifluoroethanol.

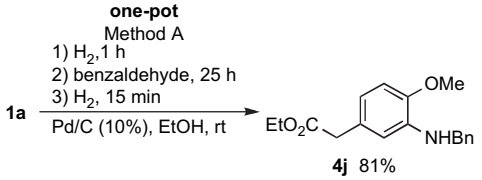
R-alkyl is not the same as ROH). However, due to cost *i*-propanol would probably be a preferred candidate in this case, despite the fact that 2,2,2-trifluoroethanol can be quite easily recycled.[15] A few experiments were performed in order to establish if *i*-propanol could replace ethanol as solvent in the reductive monoalkylation reaction. The findings from these experiments are outlined in Table 2.

In all experiments conducted in *i*-propanol (Table 2, entries 1–5) the reactions proceed much slower compared with the same reaction performed in ethanol. None of the reactions had reached completion within 24 h as judged by TLC analysis and crude ^{1}H NMR analysis. To be precise, the initial reduction of the nitro functionality was complete in all cases; however, the concomitant imine formation proceeded rather slowly in this solvent. The same was found when methanol and 2,2,2-trifluoroethanol (entries 6 and 7) were used as solvent. Furthermore, of the solvents tested 2,2,2-trifluoroethanol was found to be the least suitable solvent for this conversion. Judging from the results obtained with 2,2,2-trifluoroethanol we can conclude that this solvent nicely facilitates the initial reduction of the nitro group to the primary amine (Table 1, entry 8), however, the following imine formation proceeds sluggishly in this solvent (Table 2, entry 7). Based on these findings we concluded that the reaction is best conducted in ethanol despite the fact that small amounts of the secondary ethylamine could be formed over time in this solvent.

2.2. Reductive monobenzylation of nitro aryls

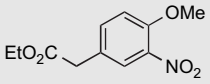
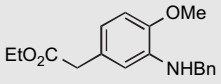
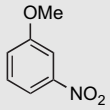
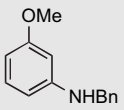
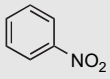
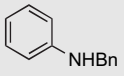
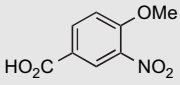
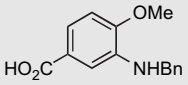
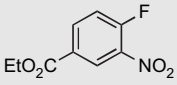
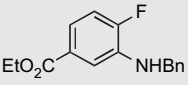
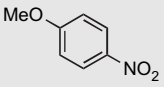
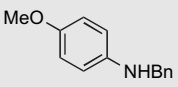
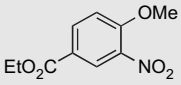
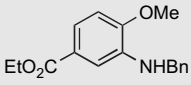
A useful extension of the reductive monoalkylation chemistry, which we recently reported,[6] would be if benzaldehyde could be used as the alkyl source in order to generate the corresponding benzyl protected amine from the corresponding nitro aryl in one-pot. But there is one caveat, hydrogen over Pd/C is also the most utilized method for cleaving benzyl groups in benzylamines.[16] However, the deprotection reaction often proceeds slowly[17] so we envisaged that by fine tuning the reaction conditions it would be possible to acquire the desired benzyl protected amines in good yield via this method. After some experimentation using nitro aryl **1a** as substrate we arrived at conditions that allowed us to conduct this transformation in one-pot. The reaction conditions are essentially the same as the optimized conditions used in order to convert nitro aryl **1a** to the corresponding secondary methyl amine in our previous work.[6] These conditions involve conducting the initial reduction reaction with hydrogen over Pd/C (10%) without benzaldehyde present. Benzaldehyde (a slight excess) was then added once the primary amine was formed and the reaction mixture was then stirred under an atmosphere of air or argon[18] 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 a short period of time, thus resulting in the formation of the benzyl protected aryl amine **4j** (Scheme 4, method A).

By utilizing these conditions we were able to convert nitro aryls **1a** (Scheme 3), **1d** and **1f** to the corresponding benzyl protected aryl



Scheme 4. Synthesis of benzylamine **4j** using method A.

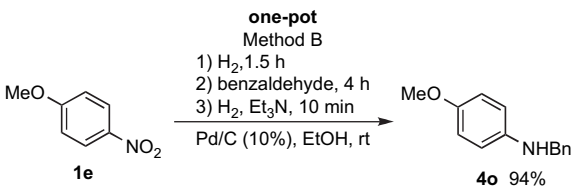
Table 3
One-pot synthesis of benzyl protected aryl amines

Entry	SM	Equivalents of benzaldehyde	Method	Solvent	Reaction time[a]	Product	Isolated yield (%)
1	 **1a**	1.4	A	EtOH	1 h+25 h+15 min	 **4j**	81
2	 **1d**	1.2	A	EtOH	2 h+18 h+15 min	 **4k**	86
3	 **1f**	2.6	A	EtOH	2 h+48 h+45 min	 **4l**	99
4	 **1g**	1.3	A	EtOH	2 h+4.5 h+15 min	 **4m**	58
5	 **1c**	3.9	A	EtOH	2 h+18 h+5 min	 **4n**	0
6	 **1e**	1.2	A	EtOH	2 h+5 h+15 min	 **4o**	0
7	**1e**	1.2	A	EtOH	2 h+5 h+2 min	**4o**	21
8	**1e**	1.2	B	EtOH	1.5 h+4 h+10 min	**4o**	94
9	**1e**	1.2	B	*i*-PrOH	1.5 h+4 h+10 min	**4o**	71
10	**1c**	3.8	B	EtOH	2.5 h+45.5 h[b]+10 min	**4n**	43
11	 **1b**	3.9	B	EtOH	1.5 h+96 h[b]+10 min	 **4p**	41

[a] The times given correspond to the following reactions: reduction+imine formation+reduction.
[b] The reaction was not completed; SM=starting material.

amines in 81, 86 and 99% yield, respectively (Table 3, entries 1–3). The conversion of compound **1g**, possessing a free carboxylic acid, proceeded rather sluggishly and gave the desired product in only 58% yield (entry 4). However, this method failed to yield the corresponding benzylamine when substrates **1c** and **1e** were treated under the exact same conditions (entries 5 and 6). Only the corresponding primary amine could be isolated in these two examples resulting from over-reduction. A small amount of benzylamine **4o** could be isolated when the exposure time to hydrogen was reduced from 15 to 2 min for the final reduction step, viz. reduction of the imine. However, this also failed to give the desired product in a synthetically useful yield (21%) (entry 7).

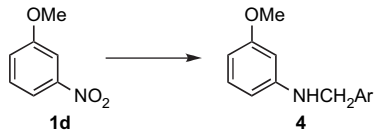
Sajiki and Hirota reported some time ago that using nitrogen containing bases (e.g., ammonia, triethylamine, pyridine and ammonium acetate) as catalyst poison in Pd/C catalyzed hydrogenation reactions resulted in selective reduction of a double bond in the presence of *O*-benzyl ether.[19] It occurred to us that a similar strategy might be possible to utilize for the final reduction of the imine. Gratifyingly, when 0.5 equiv (compared to nitro aryl) of triethylamine was added before the final imine reduction it resulted in the isolation of benzylamine **4o** in 94% yield (Scheme 5, method B; Table 3, entry 8).

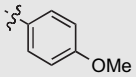
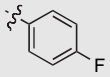
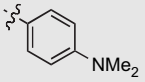
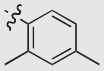
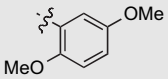


Scheme 5. Synthesis of benzylamine **4o** using method B.

Subjecting nitro aryl **1e** to the same conditions as used in entry 8, but changing the solvent to *i*-propanol resulted in the formation of the desired product **4o** in a reduced yield (71%) (Table 3, entry 9), thus providing further evidence that ethanol is the solvent of choice for this reaction. The reduced yield when *i*-propanol was used as solvent is due to the fact that there still was unreacted primary amine left in the reaction mixture at the stage of the final hydrogenation reaction. Treating ethyl 4-fluoro-3-nitrobenzoate (**1c**) under these revised conditions (method B) resulted in a moderate yield of the desired product **4n** (entry 10). A similar outcome was also the case when compound **1b** was used as substrate (entry 11). The low yield is mostly due to the lack of conversion in the imine formation step and the reaction was subjected to the final hydrogenation while there still was a significant amount of unreacted primary amine left in the reaction mixture as evident from TLC analysis. The slow formation of the imine in these two examples is probably due to steric hindrance caused by the adjacent fluorine and methoxy groups, respectively.

Table 4
One-pot synthesis of substituted benzyl amino aryls



Entry	Aldehyde	Equivalents of aldehyde	Method	Solvent	Reaction time[a]	Product	Isolated yield (%)
1	*p*-Anisaldehyde	1.2	B	EtOH	1.5 h+21.5 h+10 min	 **4q**	67
2	*p*-Fluorobenzaldehyde	1.2	B	EtOH	1.5 h+22.5 h+10 min	 **4r**	71
3	*p*-Dimethylaminobenzaldehyde	1.2	B	EtOH	1.5 h+48 h+10 min	 **4s**	19[b]
4	*p*-Dimethylaminobenzaldehyde	1.2	B	EtOH	1.5 h+144 h+10 min	**4s**	28[b]
5	2,4-Dimethylbenzaldehyde	1.2	B	EtOH	1.5 h+89 h+20 min	 **4t**	54[b]
6	2,5-Dimethoxybenzaldehyde	1.3	B	EtOH	1.5 h+66 h[b]+10 min	 **4u**	5[c]
7	2,4-Dimethylbenzaldehyde	1.2	C	Benzene	7 h+23 h[d]+30 min	**4t**	68
8	*p*-Dimethylaminobenzaldehyde	1.3	C	Benzene	7 h+21 h[d]+15 min	**4s**	41[b]
9	2,5-Dimethoxybenzaldehyde	1.05	C[e]	Benzene	7 h+24 h[d]+15 min	**4u**	54[c]
10	2,4-Dimethylbenzaldehyde	1.2	D	EtOH/benzene (1:1)	3 h+26 h[d]+30 min	**4t**	58

[a] The times given correspond to the following reactions: reduction+imine formation+reduction.
[b] Imine formation was not finalized before the reaction mixture was subjected to the final hydrogenation.
[c] Yield based on HPLC analysis (see Section 4.6.2 for details).
[d] Reflux with removal of water with a Dean–Stark trap.
[e] Triethylamine was not used as catalyst poison in this reaction.

The remarkable difference in reactivity in the final imine reduction between the corresponding imine of 3-nitroanisole and 4-nitroanisole entries 2 and 6, respectively, is most likely due to the electron-donating effect of the methoxy group. When the methoxy group is in *para* position it results in a more electron rich imine and benzylamine (after reduction) compared with the corresponding *meta* intermediate, which results in a quicker reduction and deprotection.

2.3. Synthesis of substituted benzyl amino aryls

Next we tested if these conditions were suitable when substituted benzaldehydes were used as the alkyl source together with 3-nitroanisole (**1d**) as substrate. The reaction worked reasonably well when the substituent on benzaldehyde was methoxy or fluorine positioned in the *para* position (Table 4, entries 1 and 2). However, for *para*-dimethylaminobenzaldehyde the yield was very low (entries 3 and 4). Not surprisingly the yield was also dramatically reduced when the substituents were placed closer to the aldehyde functionality (entries 5 and 6). This represents a big drawback and a revised strategy was sought.

In an attempt to address this issue the reaction was conducted in benzene with reflux of the reaction mixture and simultaneous removing of water azeotropically by means of a Dean–Stark trap during the imine forming step (method C). Pd/alumina (10%)[20] was chosen as catalyst for these experiments due to its increased stability over Pd/C at elevated temperatures.[21] Although the initial reduction of the nitro group proceeded much slower in benzene compared to in ethanol, presumably due to poor solubility of hydrogen gas in benzene, the overall reaction time could be cut in half (Table 4, entry 7) compared with the same reaction using method B (entry 5). By such means compound **4t** could be isolated in 68% yield after column chromatography. Subjecting *p*-dimethylaminobenzaldehyde and 2,5-dimethoxybenzaldehyde to these revised conditions, viz. method C, resulted in improved yields in both cases (entries 8 and 9). Keeping the reaction conditions the same but switching solvent to a mixture of ethanol and benzene (1:1) (method D) resulted in a quicker reduction of the nitro group compared to the same reaction run in pure benzene, however, the overall yield of the reaction dropped slightly (entry 10).

An attempt to conduct the benzylation reaction on aliphatic nitro compounds has thus far not been successful. Although the desired compound was formed, as evident from crude ^{1}H NMR analysis, it was never formed in a synthetically useful yield and was always accompanied by several other products. This is possibly due to the fact that aliphatic amines are more basic compared to aromatic amines and therefore forms the corresponding ammonia

compound,[22] which is not reactive enough to form the corresponding imine upon exposure to aldehyde.

3. Conclusion

We found that the best solvent for performing the one-pot monoalkylation reaction is ethanol, however, when the imine forming step proceeds slowly, benzene and heating the reaction mixture at reflux were found to be the conditions of choice. The current work demonstrates that the reductive monoalkylation reaction is useful for the formation of benzyl protected amines in one-pot starting from nitro aryls. Further improvement of this methodology also resulted in development of a useful approach for the preparation of substituted benzyl amino aryls.

4. Experimental

4.1. General experimental

NMR chemical shifts were recorded as δ values in parts per million (ppm) using tetramethylsilane (δ=0.00 ppm) as internal standard for proton (^{1}H) NMR and residual chloroform (δ=77.0 ppm) as internal standard for carbon (^{13}C) NMR. Fluorine (^{19}F) NMR spectra were referenced externally to 1,1,1-trifluorotoluene at δ=0.00 ppm. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel coated glass plates 60F$_{254}$ using UV light as visualizing agent and basic $KMnO_4$ solution followed by heating as developing agent. Silica gel 60 (particle size 0.063–0.2 mm ASTM) was used for flash chromatography. Elemental analyses were performed at the Analytical Laboratory, Bioagricultural Sciences, Nagoya University. Non-commercial starting materials were prepared according to literature methods (compounds **1a**,[8] **1b**,[23] **1c**[8]).

4.2. General procedure for reductive monoalkylation without addition of carbonyl, as exemplified for ethyl 3-(ethylamino)-4-methoxyphenyl acetate (4a) (Table 1, entry 1)

Pd/C (10%) (7.5 mg, 7.05 μmol) was added to a stirred solution of nitro aryl **1a** (16.1 mg, 0.0673 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 (balloon) for 5 days. The reaction mixture was then diluted with ethanol (10 mL), filtered through a plug of Celite® and washed after with ethanol (3×5 mL). After concentration under reduced pressure the resulting product mixture was analyzed by ^{1}H NMR.

Signals associated with compound **4a** and **4b** in the respective ^{1}H NMR spectra were in full agreement with the data previously reported.[6]

*4.2.1. Ethyl 3-(butylamino)-4-methoxyphenyl acetate (**4c**) (Table 1, entry 6)*

Compound **4c** was obtained in 11% yield as a light yellow oil by flash chromatography (silica, hexane→hexane/Et$_2$O 3:2 elution) R_f 0.5 (in hexane/Et$_2$O 3:2). IR ν_{max} 3426, 2957, 2928, 2858, 1735, 1602, 1524, 1461, 1445, 1366, 1248, 1225, 1163, 1033, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.68 (d, J=8.0 Hz, 1H), 6.55–6.52 (m, 2H), 4.14 (q, J=7.2 Hz, 2H), 3.82 (s, 3H), 3.51 (s, 2H), 3.11 (t, J=7.2 Hz, 2H), 1.64 (quintet, J=7.2 Hz, 2H), 1.56 (s, 1H), 1.45 (quintet, J=7.2 Hz, 2H), 1.25 (t, J=7.2 Hz, 3H), 0.96 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.2, 145.8, 138.5, 127.0, 116.5, 110.5, 109.2, 60.7, 55.5 (CH_3), 43.3, 41.3, 31.6, 20.4, 14.2, 14.0; MS (EI$^+$) m/z 265 (M$^{+\bullet}$, 92%), 250 (16), 222 (100), 207 (7), 192 (14), 134 (18); HRMS (EI$^+$) Found: M$^{+\bullet}$, 265.1683 $C_{15}H_{23}NO_3$ requires M$^{+\bullet}$, 265.1678.

*4.2.2. Ethyl 3-(isopropylamino)-4-methoxyphenyl acetate (**4d**) (Table 1, entry 7)*

Compound **4d** was obtained in 7% yield as a light yellow oil by flash chromatography (silica, hexane/Et$_2$O 3:2 elution) R_f 0.5. IR ν_{max} 3415, 2965, 2933, 1735, 1601, 1523, 1465, 1444, 1428, 1256, 1225, 1175, 1033 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.68 (d, J=8.0 Hz, 1H), 6.53–6.51 (m, 2H), 4.14 (q, J=7.2 Hz, 2H), 4.05 (br s, 1H), 3.81 (s, 3H), 3.62 (app. quintet, J=6.4 Hz, 1H), 3.50 (s, 2H), 1.28–1.22 (m, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.2, 145.9, 137.4, 126.9, 116.3, 111.1, 109.4, 60.6, 55.4, 43.7, 41.3, 22.9, 14.2; MS (EI$^+$) m/z 251 (M$^{+\bullet}$, 52%), 236 (100), 222 (7), 208 (10), 178 (12), 162 (9), 148 (9); HRMS (EI$^+$) Found: M$^{+\bullet}$, 251.1529 $C_{14}H_{21}NO_3$ requires M$^{+\bullet}$, 251.1521; Anal. Found: C 66.90, H 8.45, N 5.59%. $C_{14}H_{21}NO_3$ requires: C 66.91, H 8.42, N 5.57%.

4.3. General procedure for reductive monoalkylation of nitro aryls in *i*-propanol with addition of aldehyde, as exemplified for ethyl 3-(ethylamino)-4-methoxybenzoate (4e)

Pd/C (10%) (3.6 mg, 3.38 μmol) was added to a stirred solution of nitro aryl **1b** (17.4 mg, 0.0773 mmol) and acetaldehyde (0.30 mL of ca. 2% solution in DMF, ca. 0.129 mmol) in *i*-propanol (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 (balloon) for 24 h. The reaction mixture was then diluted with ethanol (10 mL), filtered through a plug of Celite® and washed after with ethanol (3×5 mL). After concentration under reduced pressure the resulting product mixture was analyzed by ^{1}H NMR.

Signals associated with compounds **4e**, **4f**, **4g**, **4h**, and **4i** in the respective ^{1}H NMR spectra were in full agreement with the data previously reported.[6]

4.4. Method A: general procedure for reductive monobenzylation of nitro aryls, as exemplified for ethyl 3-(benzylamino)-4-methoxyphenyl acetate (4j)

Pd/C (10%) (5.6 mg, 5.26 μmol) was added to a stirred solution of nitro aryl **1a** (16.9 mg, 0.0707 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 (balloon) for 2 h. The H_2 atmosphere was then replaced with air and the reaction mixture was stirred vigorously for 5 min before benzaldehyde (10.0 μL, 0.098 mmol) was added. The resulting reaction mixture was stirred for 25 h 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$_2$O/Et$_3$N 90:9.95:0.05→80:19.95:0.05→60:39.95:0.05 gradient elution) and concentration of the relevant fractions (R_f 0.3 in hexane/Et$_2$O) gave the desired compound **4j** (17.1 mg, 81%) as a light yellow oil. IR ν_{max} 3423, 2925, 2851, 1734, 1600, 1523, 1452, 1252, 1225, 1142, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.32 (m, 4H), 7.29–7.27 (m, 1H), 6.71 (d, J=8.0 Hz, 1H), 6.58 (dd, J=2.0 and 8.0 Hz, 1H), 6.53 (d, J=2.0 Hz, 1H), 4.58 (br s, 1H), 4.34 (s, 2H), 4.10 (q, J=7.2 Hz, 2H), 3.82 (s, 3H), 3.48 (s, 2H), 1.21 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.1, 145.9, 139.4, 138.1, 128.6, 127.6, 127.1, 126.9, 117.1, 110.8, 109.3, 60.6, 55.5, 48.0, 41.2, 14.2; MS (EI$^+$) m/z 299 (M$^{+\bullet}$, 6%), 226 (11), 211 (11), 134 (16), 104 (33), 91 (100), 77 (16), 65 (32); HRMS (EI$^+$) Found: M$^{+\bullet}$, 299.1541 $C_{18}H_{21}NO_3$ requires M$^{+\bullet}$, 299.1521; Anal. Found: C 72.23, H 7.13, N 4.68%. $C_{18}H_{21}NO_3$ requires: C 72.22, H 7.07, N 4.68%.

*4.4.1. N-Benzyl-3-methoxyaniline (**4k**) (Table 3, entry 2)*

Compound **4k**[24] was obtained in 86% yield as a light yellow oil by flash chromatography (silica, hexane/Et$_2$O/Et$_3$N 90:9.95:0.05→60:39.95:0.05 gradient elution) R_f 0.7 (in hexane/Et$_2$O 60:40). ^{1}H

NMR ($CDCl_3$, 400 MHz) δ 7.38–7.31 (m, 4H), 7.29–7.26 (m, 1H), 7.07 (t, J=8.0 Hz, 1H), 6.29–6.24 (m, 2H), 6.19 (t, J=2.2 Hz, 1H), 4.31 (s, 2H), 4.03 (br s, 1H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 160.8, 149.6, 139.3, 130.0, 128.6, 127.5, 127.2, 106.0, 102.7, 98.9, 55.1, 48.3.

*4.4.2. N-Benzylaniline (**4l**) (Table 3, entry 3)*

Compound **4l**[25] was obtained in 99% yield as a white solid, mp 33–34 °C, lit.[25] mp 35–38 °C, by flash chromatography (silica, hexane/Et_2O/Et_3N 90:9.95:0.05→80:19.95:0.05 gradient elution) R_f 0.8 (in hexane/Et_2O 60:40). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70–7.33 (m, 7H), 6.91–6.77 (m, 3H), 4.46 (s, 2H), 4.07 (br s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 148.1, 139.4, 129.2, 128.5, 127.4, 127.1, 117.4, 112.8, 48.2.

*4.4.3. 3-(Benzylamino)-4-methoxybenzoic acid (**4m**) (Table 3, entry 4)*

Compound **4m** was obtained in 58% yield as light yellow oil by flash chromatography (silica, Et_2O/hexane/Et_3N 59.9:40:0.1 elution) R_f 0.3 (in Et_2O/hexane 60:40). IR ν_{max} 3382 (broad), 2926, 2853, 1625, 1519, 1451, 1227 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.37–7.16 (m, 5H), 6.65 (d, J=8.4 Hz, 1H), 6.10 (d, J=2.8 Hz, 1H), 6.03 (dd, J=2.8 and 8.4 Hz, 1H), 4.25 (s, 2H), 3.77 (s, 3H), 3.73–3.59 (br s, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 143.3, 140.4, 139.9, 137.2, 128.5, 127.5, 127.1, 112.5, 102.5, 101.2, 56.4, 49.1; MS (EI$^+$) m/z 257 (M$^{+\bullet}$, 8%), 228 (99), 213 (52), 91 (100); HRMS (EI$^+$) Found: M$^{+\bullet}$, 257.1049. $C_{15}H_{15}NO_3$ requires M$^{+\bullet}$, 257.1052.

4.5. Method B: general procedure for reductive monobenzylation of nitro aryls, as exemplified for *N*-benzyl-4-methoxyaniline (4o) (Table 3, entry 8)

Pd/C (10%) (6.2 mg, 5.83 μmol) was added to a stirred solution of 4-nitroanisole (**1e**) (48.1 mg, 0.314 mmol) in ethanol (2.0 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 (balloon) for 1.5 h. The H_2 atmosphere was then replaced with air and the reaction mixture was stirred vigorously for 5 min before benzaldehyde (38.9 μL, 0.382 mmol) was added. The resulting reaction mixture was stirred for 4 h before triethylamine (22.0 μL, 0.157 mmol) was added to the reaction mixture. The resulting reaction mixture was subjected to three cycles of vacuum followed by flush with H_2 before being stirred vigorously under an atmosphere of H_2 (balloon) for 10 min. The crude reaction mixture was subjected to flash chromatography (silica, hexane/Et_2O/Et_3N 80:19.95:0.05 elution) and concentration of the relevant fractions (R_f 0.4 in hexane/Et_2O 80:20) gave the desired compound **4o**[26] (63.0 mg, 94%) as a light yellow solid, mp 45–46 °C, lit.[26] mp 48 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.20 (m, 5H), 6.76 (d, J=9.0 Hz, 2H), 6.58 (d, J=9.0 Hz, 2H), 4.26 (s, 2H), 3.75 (br s, 1H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 152.2, 142.4, 139.7, 128.5, 127.5, 127.1, 114.9, 114.1, 55.7, 49.2.

*4.5.1. Ethyl 3-(benzylamino)-4-fluorobenzoate (**4n**) (Table 3, entry 10)*

Compound **4n** was obtained in 43% yield as a light yellow oil by flash chromatography (silica, hexane/Et_3N 99.95:0.05→hexane/Et_2O/Et_3N 80:19.95:0.05 gradient elution) R_f 0.4 (in hexane/Et_2O 80:20). IR ν_{max} 3417, 2925, 1741, 1618, 1523, 1437, 1296, 1254, 1188, 1103 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.26 (m, 7H), 7.00 (dd, J=8.4 and 11.2 Hz, 1H), 4.40 (s, 2H), 4.32 (q, J=7.2 Hz, 2H), 1.56 (br s, 1H), 1.36 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 166.3, 154.2 (d, J_{C-F}=248 Hz), 138.4, 136.5 (d, J_{C-F}=12 Hz), 128.8, 127.6 (3), 127.5 (7), 127.1 (d, J_{C-F}=3 Hz), 119.0 (d, J_{C-F}=8 Hz), 114.2 (d, J_{C-F}=20 Hz), 113.3 (d, J_{C-F}=5 Hz), 60.9, 47.8, 14.3; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −66.9; MS (EI$^+$) m/z 273 (M$^{+\bullet}$, 48%) 205 (100), 196 (79), 168 (63), 138 (35), 136 (31), 91 (76), 77 (21); HRMS (EI$^+$) Found: M$^{+\bullet}$, 273.1195. $C_{16}H_{16}FNO_2$ requires M$^{+\bullet}$, 273.1165; Anal. Found: C 70.37, H 5.63, N 5.29%. $C_{16}H_{16}FNO_2$ requires: C 70.31, H 5.90, N 5.12%.

*4.5.2. Ethyl 3-(benzylamino)-4-methoxybenzoate (**4p**) (Table 3, entry 11)*

Compound **4p** was obtained in 41% yield as a yellow oil by flash chromatography (silica, hexane/Et_3N 99.95:0.05→hexane/Et_2O/Et_3N 80:19.95:0.05 gradient elution) R_f 0.2 (in hexane/Et_2O 80:20). IR ν_{max} 3423, 2931, 1707, 1599, 1523, 1454, 1294, 1252, 1223, 1106, 1026, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (m, 7H), 6.77 (d, J=8.4 Hz, 1H), 4.59 (br s, 1H), 4.38 (s, 2H), 4.31 (q, J=7.2 Hz, 2H), 1.36 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 167.0, 150.4, 139.1, 137.7, 128.6, 127.8, 127.3, 123.4, 119.5, 110.5, 108.4, 60.5, 55.6, 48.0, 14.4; MS (EI$^+$) m/z 285 (M$^{+\bullet}$, 14%), 223 (55), 208 (100), 180 (82), 164 (44), 150 (32), 135 (36), 104 (36), 91 (56), 77 (67); HRMS (EI$^+$) Found: M$^{+\bullet}$, 285.1373. $C_{17}H_{19}NO_3$ requires M$^{+\bullet}$, 285.1365; Anal. Found: C 71.57, H 6.87, N 4.77%. $C_{17}H_{19}NO_3$ requires: C 71.56, H 6.71, N 4.91%.

*4.5.3. N-(4-Methoxybenzyl)-3-methoxyaniline (**4q**) (Table 4, entry 1)*

Compound **4q**[27] was obtained in 67% yield as a clear oil by flash chromatography (silica, hexane/Et_3N 99.95:0.05→hexane/Et_2O/Et_3N 80:19.95:0.05 gradient elution) R_f 0.2 (in hexane/Et_2O 80:20). IR ν_{max} 3412, 2954, 2933, 2834, 1614, 1512, 1463, 1302, 1248, 1210, 1162, 1036, 825, 758, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (d, J=8.8 Hz, 2H), 7.08 (t, J=8.0 Hz, 1H), 6.89 (d, J=8.8 Hz, 2H), 6.30–6.25 (m, 2H), 6.20 (t, J=2.2 Hz, 1H), 4.25 (s, 2H), 3.96 (br s, 1H), 3.81 (s, 3H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 160.8, 158.9, 149.6, 131.3, 130.0, 128.8, 114.0, 106.0, 102.7, 98.9, 55.3, 55.1, 47.8; MS (EI$^+$) m/z 243 (M$^{+\bullet}$, 43%), 121 (100), 91 (22); HRMS (EI$^+$) Found: M$^{+\bullet}$, 243.1250. $C_{15}H_{17}NO_2$ requires M$^{+\bullet}$, 243.1259; Anal. Found: C 74.06, H 6.91, N 5.89%. $C_{15}H_{17}NO_2$ requires: C 74.05, H 7.04, N 5.76%.

*4.5.4. N-(4-Fluorobenzyl)-3-methoxyaniline (**4r**) (Table 4, entry 2)*

Compound **4r** was obtained in 71% yield as a clear oil by flash chromatography (silica, hexane/Et_3N 99.95:0.05→hexane/Et_2O/Et_3N 80:19.95:0.05 gradient elution) R_f 0.2 (in hexane/Et_2O 80:20). IR ν_{max} 3413, 2931, 1612, 1508, 1219, 1159, 823 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.30 (m, 2H), 7.09–6.99 (m, 3H), 6.29 (ddd, J=0.6, 2.4, 8.0 Hz, 1H), 6.24 (ddd, J=0.8, 2.4, 8.0 Hz, 1H), 6.17 (t, J=2.48 Hz, 1H), 4.27 (s, 2H), 4.01 (br s, 1H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 162.1 (d, J_{C-F}=251 Hz), 160.8, 149.3, 135.0 (d, J_{C-F}=3 Hz), 130.0, 129.0 (d, J_{C-F}=8 Hz), 115.4 (d, J_{C-F}=21 Hz), 106.0, 102.8, 99.0, 55.0, 47.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −52.9; MS (EI$^+$) m/z 231 (M$^{+\bullet}$, 60%), 205 (100), 136 (40), 109 (94), 93 (24), 80 (32), 77 (25); HRMS (EI$^+$) Found: M$^{+\bullet}$, 231.1018. $C_{14}H_{14}FNO$ requires M$^{+\bullet}$, 231.1059; Anal. Found: C 72.73, H 6.16, N 6.10%. $C_{14}H_{14}FNO$ requires: C 72.71, H 6.10, N 6.06%.

4.6. Method C: general procedure for reductive monobenzylation of nitro aryls, as exemplified for *N*-(2,4-dimethylbenzyl)-3-methoxyaniline (4t) (Table 4, entry 7)

Pd/alumina (10%) (6.6 mg, 6.20 μmol) was added to a stirred solution of 3-nitroanisole (**1d**) (32.6 mg, 0.213 mmol) in benzene (2.0 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 (balloon) for 7 h. The H_2 atmosphere was then replaced with air and the reaction mixture was stirred vigorously for 5 min before 2,4-dimethylbenzaldehyde (35.6 μL, 0.255 mmol) was added. The resulting reaction mixture was stirred at reflux with azeotropic removal of water with a Dean–Stark trap for 23 h. Triethylamine (14.9 μL, 0.107 mmol) was added to the reaction mixture and the resulting reaction mixture was subjected to three cycles of vacuum followed by flush with H_2 before being stirred vigorously under an atmosphere of H_2 (balloon)

for 30 min. The crude reaction mixture was subjected to flash chromatography (silica, hexane/Et_3N 99.95:0.05→hexane/EtOAc/Et_3N 95:4.95:0.05→90:9.95:0.05 gradient elution) and concentration of the relevant fractions (R_f 0.2 in hexane/EtOAc 90:10) gave the desired compound **4t** (34.8 mg, 68%) as a clear oil. IR ν_{max} 3410, 2920, 1614, 1502, 1460, 1209, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.19 (d, J=7.6 Hz, 1H), 7.07 (t, J=8.2 Hz, 1H), 7.01 (s, 1H), 6.97 (d, J=7.6 Hz, 1H), 6.27 (dd, J=2.2 and 8.2 Hz, 1H), 6.24 (dd, J=2.2 and 8.2 Hz, 1H), 6.18 (t, J=2.2 Hz, 1H), 4.20 (s, 2H), 3.76 (br s, 1H), 3.75 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 160.9, 149.7, 137.1, 136.2, 133.9, 131.2, 130.0, 128.5, 126.7, 105.8, 102.4, 98.7, 55.0, 46.1, 21.0, 18.8; MS (EI^+) m/z 241 ($M^{+\bullet}$, 63%), 119 (100), 91 (22); HRMS (EI^+) Found: $M^{+\bullet}$, 241.1452. $C_{16}H_{19}NO$ requires $M^{+\bullet}$, 241.1467; Anal. Found: C 79.59, H 8.16, N 5.87%. $C_{16}H_{19}NO$ requires: C 79.63, H 7.94, N 5.80%.

4.6.1. *N-(4-(N,N-Dimethylamino)-benzyl)-3-methoxyaniline (**4s**) (Table 4, entry 8)*

Compound **4s** was obtained in 41% yield as a light yellow oil by flash chromatography (silica, hexane/Et_3N 99.95:0.05→hexane/Et_2O/Et_3N 80:19.95:0.05→60:39.95:0.05 gradient elution) R_f 0.3 (in hexane/Et_2O 60:40). IR ν_{max} 3411, 2921, 1612, 1520, 1460, 1342, 1205, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.23 (d, J=8.6 Hz, 2H), 7.07 (t, J=8.2 Hz, 1H), 6.72 (d, J=8.6 Hz, 2H), 6.28–6.25 (m, 2H), 6.21 (t, J=2.2 Hz, 1H), 4.18 (s, 2H), 3.88 (br s, 1H), 3.76 (s, 3H), 2.94 (s, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 160.8, 150.1, 149.8, 129.9, 128.8, 127.0, 112.8, 106.0, 102.5, 98.7, 55.1, 48.0, 40.7; MS (EI^+) m/z 256 ($M^{+\bullet}$, 33%), 147 (26), 134 (99), 118 (100), 95 (49), 91 (39), 77 (27), 65 (19); HRMS (EI^+) Found: $M^{+\bullet}$, 256.1532. $C_{16}H_{20}N_2O$ requires $M^{+\bullet}$, 256.1576; Anal. Found: C 74.98, H 7.61, N 10.85%. $C_{16}H_{20}N_2O$ requires: C 74.97, H 7.86, N 10.93%.

4.6.2. *N-(2,5-Dimethoxybenzyl)-3-methoxyaniline (**4u**) (Table 4, entry 9)*

Compound **4u**[28] was obtained in 54% yield as evident from HPLC analysis. A pure sample of the product for spectroscopic analysis was obtained by preparative HPLC [Cosmosil 5C18-AR (10×250 mm i.d.), CH_3CN, 2 mL/min]. Concentration of the relevant fraction (t_R 7.9 min) gave the desired product **4u** as a yellow oil. IR ν_{max} 3412, 2938, 2834, 1613, 1497, 1464, 1277, 1215, 1162, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.06 (t, J=8.0 Hz, 1H), 6.91 (d, J=2.8 Hz, 1H), 6.81 (d, J=8.8 Hz, 1H), 6.75 (dd, J=2.8 and 8.8 Hz, 1H), 6.29–6.26 (m, 2H), 6.22 (t, J=2.4 Hz, 1H), 4.29 (s, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 160.8, 153.7, 151.6, 149.8, 129.9, 128.6, 115.4, 112.3, 111.3, 106.3, 102.6, 99.1, 55.9, 55.7, 55.1, 43.5; MS (EI^+) m/z 273 ($M^{+\bullet}$, 94%), 151 (100), 121 (46), 91 (19), 77 (23); HRMS (EI^+) Found: $M^{+\bullet}$, 273.1353. $C_{16}H_{19}NO$ requires $M^{+\bullet}$, 73.1365.

4.7. Method D: general procedure for reductive monobenzylation of nitro aryls, as exemplified for *N*-(2,4-dimethylbenzyl)-3-methoxyaniline (4t) (Table 4, entry 10)

The reaction was conducted as in method C take for the use of ethanol/benzene 1:1 as solvent. The crude product was purified as given above in method C. Concentration of the relevant fractions gave 58% yield of the desired compound **4t**, which was identical in all respects with the product obtained via method C.

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Supplementary data

Copies of ^1H and ^{13}C NMR spectra of all new compounds are included as supplementary materials. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.077.

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