Rapid and Convenient Microwave-Assisted Synthesis of Primary Amines via Reductive N-Alkylation of Methyl Carbamate with Aldehydes

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Abstract: Microwave-assisted reductive alkylation of methyl carbamate with a range of aldehydes provides, after basic work-up, an experimentally simple, one-pot method for rapid functional group interconversion of structurally diverse aldehydes into primary amines. The method has several advantages over more traditional methods of carrying out this transformation and is particularly amenable to high-throughput synthesis.

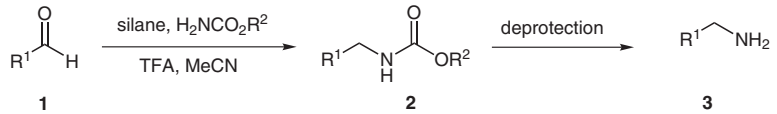
Key words: aminations, aldehydes, reductive alkylation, carbamates, amines, microwave synthesis

As part of a medicinal chemistry program aimed at the discovery of new antagonists of the melanin-concentrating hormone receptor (MCH1R), we required rapid and parallel synthetic access to novel benzylamine derivatives from a diverse set of proprietary aldehydes. The conversion of aldehydes into primary amines by reductive amination using ammonia can often be problematic since the resulting amine, once formed, is usually more nucleophilic than ammonia itself.[1] Consequently, secondary and tertiary amines are commonly formed by over-alkylation. Additionally, traces of the alcohol are often formed by reduction of the unreacted aldehyde. An alternative approach sometimes used to carry out this transformation is via the corresponding oxime derivative, which is then reduced to furnish a primary amine.[2] The latter method has several drawbacks, firstly, hydroxylamine itself is extremely toxic and, secondly, reductive cleavage of the intermediate oxime can sometimes be problematic or incompatible with other functionalities. Moreover, reduction of the oxime can often involve the use of toxic heavy metals. Other alternatives, such as reduction of an aldehyde to the corresponding alcohol, followed by formation of phthalamido-derivatives and subsequent removal with hydrazine, or even conversion of the alcohols into azides followed by reduction, are indirect procedures and have similar shortcomings to those described above.[3,4]

We were interested in a recent report by Dube and Scholte outlining an efficient method for reductively alkylating benzyl- or *tert*-butyl carbamate with various aldehydes in the presence of triethylsilane and trifluoroacetic acid (Scheme 1).[5] The resulting carbamate derivatives **2** may be converted into the corresponding primary amines **3** by either hydrogenolysis or acid-catalysed Boc-cleavage. A later report outlining similar reductive alkylations of methyl carbamate in the presence of trichlorosilane appeared in the patent literature.[6] The resulting methyl carbamates **2** can be easily hydrolysed under basic conditions to furnish the desired primary amines **3**.

A survey of recent literature showed that, despite its potential appeal, this methodology has received surprisingly little attention to date.[7] A drawback these methods suffer from is the relatively long reaction times, often requiring one or two days for the synthesis of simple amines. We considered that development of a rapid, one-pot, microwave-assisted protocol would be ideally suited to our needs, potentially affording an efficient and general synthetic method which would be appropriate for in-house high-throughput parallel synthesis. We herein report results from these studies.

Conversion of 4-bromobenzaldehyde (**4**) into the corresponding methyl carbamate **5** was initially investigated using five different silanes, in the presence of trifluoracetic acid, using acetonitrile as solvent (Scheme 2). Triethylsilane (**6**), triisopropylsilane (**7**) and trichlorosilane (**8**) all furnished the expected product **5**, however, *tert*-butyldimethylsilane (TBDMSH; **9**) gave the corresponding methyl carbamate **5** in highest yield and overall purity. To our knowledge, use of this silane has not been previously



silane = triethylsilane or trichlorosilane, R^2 = benzyl, *tert*-butyl or methyl

Scheme 1

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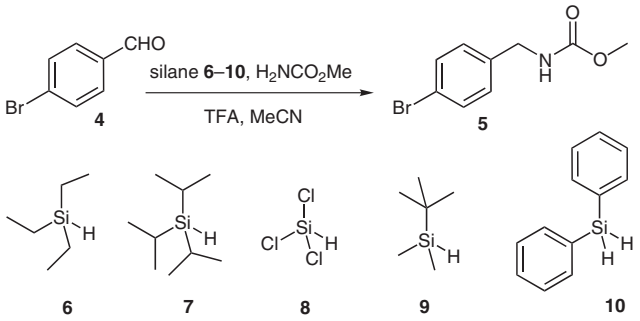


Scheme 2 Initial optimisation of reaction conditions using different silanes. *tert*-Butyldimethylsilane (**9**) afforded highest yields and purity.

reported in this context. Interestingly, use of diphenylsilane (**10**) gave only unreacted starting material.

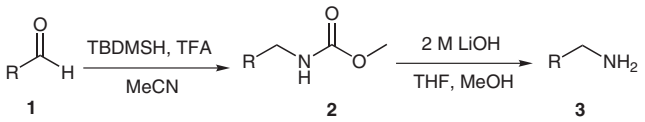
Further optimisation of reaction conditions using TBDMSH as reductant was carried out with four different benzaldehydes; the effects of both reaction temperature and reaction time on yield and purity were investigated. Optimal conversion into the corresponding methyl carbamates was achieved by heating at 150 °C for 15 minutes (inferred by LC-MS analysis of the crude reaction mixtures).

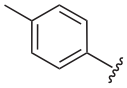
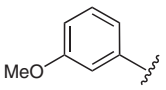
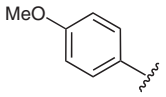
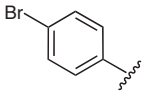
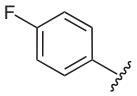
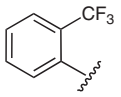
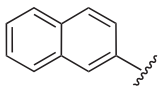
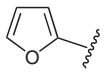
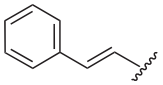
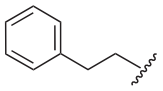
Using the optimised reaction conditions, the synthetic scope was then probed in a high-throughput setting by using a diverse set of alkyl, vinyl, benzylic and heterocyclic aldehydes (Table 1). In all cases, excellent conversion into the expected methyl carbamates **2** was observed by LC-MS analysis of the crude reaction mixtures. Rather than isolate these carbamates, we carried out their hydrolysis using a one-pot procedure. Thus, after removal of solvent from the crude reaction mixtures by evaporation, the carbamates were heated at 120 °C for 10 minutes in a mixture of 2 M lithium hydroxide, THF and methanol. Amines **3a–j** were conveniently isolated as their hydrochloride salts in high yields and with chemical purities generally well above 90% by using a simple acid-base work-up.

In conclusion, we have developed a rapid, chemically robust, one-pot, microwave-based synthesis of primary amines. Use of TBDMSH for reductive alkylation of methyl carbamate was superior to other previously reported alternatives. Using a simple acid-base work-up, pure products could be obtained in very short reaction times. The methodology we developed will be applied to the high-throughput synthesis and biological evaluation of novel MCH1R antagonists, details of which will be published elsewhere.

^{1}H NMR spectra were recorded on a Bruker Advance DPX 400 spectrometer at 400 MHz. All spectra were recorded using residual solvent or TMS as internal standard. Electrospray mass spectrometry (MS) were obtained using an Agilent MSD mass spectrometer. Compounds used in Table 1, entries **3a–h** were obtained from Aldrich. Methyl carbamate and *tert*-butyldimethylsilane (**9**; TBDMSH) were purchased from Aldrich. All solvents were of standard reagent grade. Microwave irradiation was carried out using a Smith Synthesizer™ instrument (Biotage) using 2–5 mL Smith Process vials fitted with aluminum caps and septa.

Table 1 One-Pot Conversion of Aldehydes into Primary Amines via the Corresponding Methyl Carbamates



Entry	R	Yield (%)[a]	Purity (%)[b]
3a		89	99
3b		75	99
3c		93	99
3d		72	99
3e		96	95
3f		66	99
3g		93	99
3h		77	90
3i		95	90
3j		87	98

[a] Isolated yield of hydrochloride salt.
[b] Determined by LC-MS and/or NMR analysis.

Synthesis of 4-Methylbenzylamine Hydrochloride (3a); Typical Procedure

4-Methylbenzaldehyde (24 mg, 0.2 mmol), methyl carbamate (30 mg, 0.4 mmol), TFA (91 mg, 0.8 mmol) and TBDMSH (114 mg, 0.8 mmol) were dissolved in MeCN (4.0 mL) and heated to 150 °C for 15 min in a Smith Synthesizer™ microwave apparatus. The mixture was concentrated in vacuo and the residue was dissolved in a mixture of THF, MeOH and 2M LiOH (1:1:1, 4 mL) and heated at 120 °C for 10 min in a Smith Synthesizer™. EtOAc (4 mL) and 1M NaOH (4 mL) were added and the phases were separated. The organic phase was extracted with 1M HCl (2 × 4 mL) and the aqueous extract was evaporated to afford 4-methylbenzylamine as its hydrochloride salt (28 mg, 89%). The purity of this material was at least 99% as determined by LC-MS.

4-Methylbenzylamine Hydrochloride (3a)
^{1}H NMR (400 MHz, CD_3OD): δ = 2.37 (s, 3 H), 4.09 (s, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.38 (d, *J* = 8.0 Hz, 2 H).

MS (ES+): *m*/*z* = 122 $[M + H]^+$.

3-Methoxybenzylamine Hydrochloride (3b)
^{1}H NMR (400 MHz, CD_3OD): δ = 3.84 (s, 3 H), 4.12 (s, 2 H), 7.01 (dd, *J* = 2.2, 8.0 Hz, 1 H), 7.05–7.11 (m, 2 H), 7.36 (app t, *J* = 8.0 Hz, 1 H).

MS (ES+): *m*/*z* = 138 $[M + H]^+$.

4-Methoxybenzylamine Hydrochloride (3c)
^{1}H NMR (400 MHz, CD_3OD): δ = 3.72 (s, 3 H), 3.96 (s, 2 H), 6.89 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H).

MS (ES+): *m*/*z* = 138 $[M + H]^+$.

4-Bromobenzylamine Hydrochloride (3d)
^{1}H NMR (400 MHz, CD_3OD): δ = 4.12 (s, 2 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 8.0 Hz, 2 H).

MS (ES+): *m*/*z* = 186, 188 $[M + H]^+$.

4-Fluorobenzylamine Hydrochloride (3e)
^{1}H NMR (400 MHz, CD_3OD): δ = 4.03 (s, 2 H), 7.07 (app t, *J* = 8.0 Hz, 2 H), 7.31 (dd, *J* = 2.0, 8.0 Hz, 2 H).

MS (ES+): *m*/*z* = 126 $[M + H]^+$.

2-(Trifluoromethyl)benzylamine Hydrochloride (3f)
^{1}H NMR (400 MHz, CD_3OD): δ = 4.25 (s, 2 H), 7.54 (t, *J* = 7.28 Hz, 1 H), 7.62–7.75 (m, 3 H).

MS (ES+): *m*/*z* = 176 $[M + H]^+$.

2-Naphthylmethylamine Hydrochloride (3g)
^{1}H NMR (400 MHz, CD_3OD): δ = 4.32 (s, 2 H), 7.47–7.66 (m, 3 H), 7.82–8.08 (m, 4 H).

MS (ES+): *m*/*z* = 158 $[M + H]^+$.

2-Furfurylmethylamine Hydrochloride (3h)
^{1}H NMR (400 MHz, CD_3OD): δ = 4.19 (s, 2 H), 6.48 (d, *J* = 7.5 Hz, 1 H), 6.58–6.61 (m, 1 H), 7.62 (d, *J* = 6.8 Hz, 1 H).

MS (ES+): *m*/*z* = 98 $[M + H]^+$.

(*E*)-Cinnamylamine Hydrochloride (3i)
^{1}H NMR (400 MHz, CD_3OD): δ = 3.33 (d, *J* = 6.9 Hz, 2 H), 6.35 (dd, *J* = 16.0, 6.9 Hz, 1 H), 6.84 (d, *J* = 16.0 Hz, 1 H), 7.27–7.41 (m, 3 H), 7.49 (d, *J* = 7.0 Hz, 2 H).

MS (ES+): *m*/*z* = 134 $[M + H]^+$.

3-Phenylpropylamine Hydrochloride (3j)
^{1}H NMR (400 MHz, CD_3OD): δ = 2.00 (quin, *J* = 7.78 Hz, 2 H), 2.74 (t, *J* = 7.78 Hz, 2 H), 2.95 (t, *J* = 7.80 Hz, 2 H), 7.16–7.35 (m, 5 H).

MS (ES+): *m*/*z* = 136 $[M + H]^+$.

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