One-pot Reduction of Nitrostyrenes to Phenethylamines using Sodium Borohydride and Copper(II) chloride

Laura D'Andrea[a#*] and Jesper L. Kristensen[a]

[a]Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, 2100 København Ø, Denmark

Present addresses:

[#]Department of Chemistry and Bioscience, Aalborg University, Fredrik Bajers Vej 7H, 9220 Aalborg, Denmark

*E-Mail: laurad@bio.aau.dk

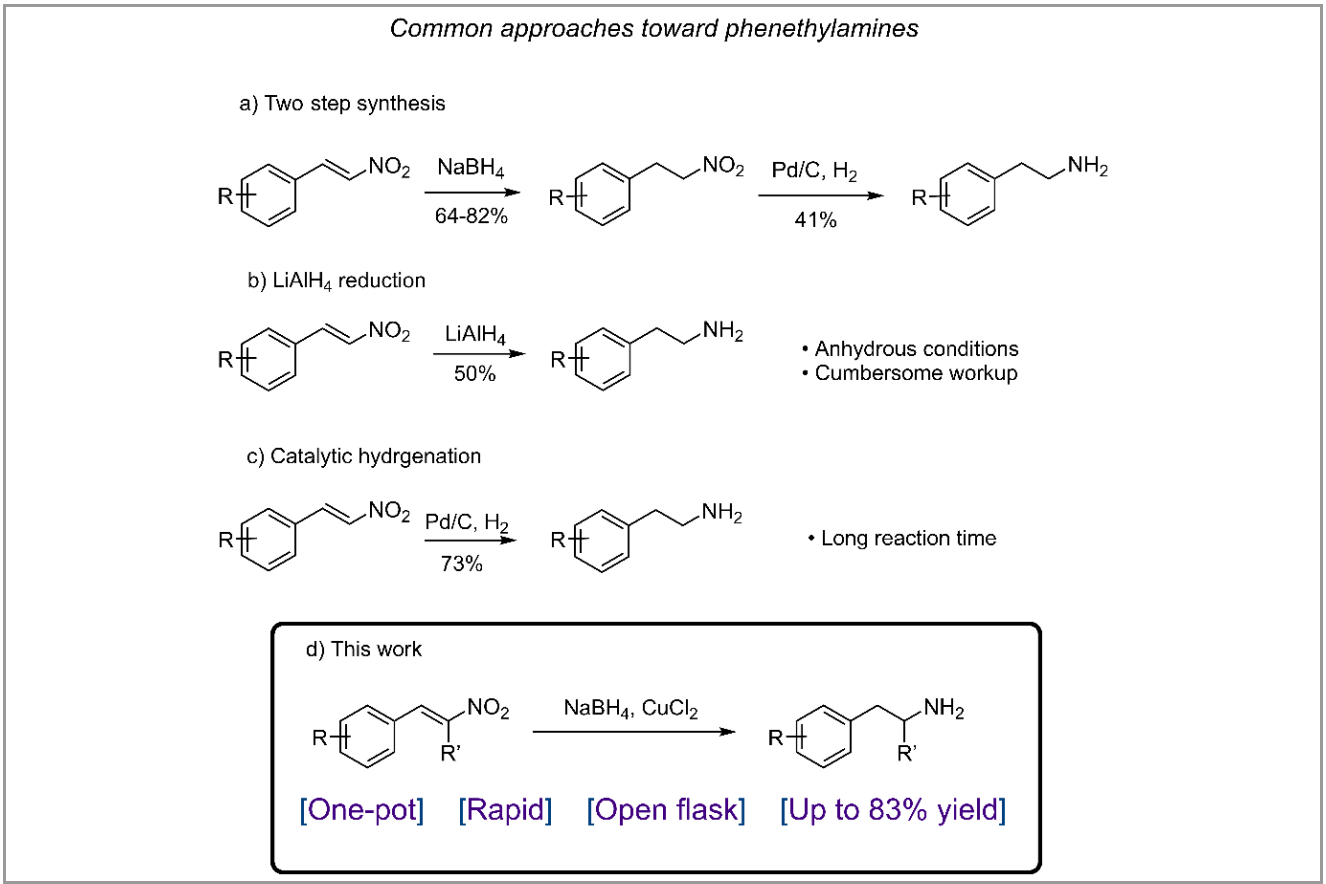
ABSTRACT

The preparation of phenethylamines and phenylisoproylamines of scientific relevance can be achieved with a $NaBH_4/CuCl_2$ system in 10 to 30 minutes via reduction of substituted β-nitrostyrenes. The method also reduces nitrobenzene and methyl benzoate in 92 to 97% yields, respectively, while has no effect on benzoic acid, benzamide, and aromatic halides. This one-pot procedure allows the isolation of substituted β-nitrostyrene scaffolds up to 83% yield under mild conditions, without the need for special precautions, inert atmosphere, and time-consuming purification techniques.

Keywords: phenethylamine, $NaBH_4$, β-nitrostyrene, 2C-X, $CuCl_2$, reduction, amphetamine

The phenethylamine scaffold represents a recurring motif among natural and synthetic drug molecules. The latter are mainly constituted by a varied class of substituted phenylethylamines exhibiting psychoactive properties, and typically employed for medical and recreational use.[1] Representative examples include CNS stimulants (amphetamine), antidepressants and antiparkinson's agents (e.g., L-deprenyl)[2], hallucinogens and entactogens (e.g., 2,5-dimethoxy4-iodoamphetamine (DOI) and 3,4-methylenedioxy-N-methylamphetamine (MDMA)),[3] nasal decongestants (e.g., levomethamphetamine) and appetite suppressants (e.g. phentermine).[4]

One of the most studied and inexpensive routes to synthesize substituted phenylethylamines involves the reduction of their α,β-unsaturated nitroalkene analogue (β-nitrostyrene), where both the double bond and the nitro group need to be reduced to deliver the corresponding primary amine. Their reduction can be accomplished via catalytic hydrogenation, involving stepwise reactions and workup, use of additional reagents, and reaction time between 3 and 24 hours.[5] Most commonly, metal hydrides are employed, typically lithium aluminium hydride[6,7], requiring inert atmosphere, special precautions, and with yields up to ca. 60 %.[6] Due to the formation of side products, final purification of the amino products requires using either multiple separation techniques, chromatography, or distillation. [6c,7,8] (Scheme 1)



Scheme 1: Comparison between some examples of traditional synthetic routes for the preparation of substituted phenethylamines from β-nitrostyrene scaffolds and our work.

Sodium borohydride is non-pyrophoric and, therefore, easy-to-handle reducing agent. Since the first attempts in 1967, $NaBH_4$ has been employed to reduce β-nitrostyrenes scaffolds to the corresponding nitroalkanes.[9] For this reason, several catalysts have been tested over the decades with $NaBH_4$ to facilitate full reduction to the phenethylamine, but to date no effective method for converting α,β-unsaturated nitroalkenes into aminoalkanes have been developed using $NaBH_4$ as reducing agent.[9c, 10]

Herein, we demonstrate that $NaBH_4$ in combination with a catalytic amount of $CuCl_2$ is a simple and higher yielding method to synthesize phenethyl- and phenylisoproylamines from the corresponding nitroalkenes.[6c] Representative substituted β-nitrostyrene analogues were reduced via this method, including β-methyl-β-nitrostyrene **3a**, precursor of amphetamines, and 2,5-dimethoxy-β-nitrostyrene **4a**, precursor of most of the hallucinogenic 2C-X family and its derivatives.[7a,11] (Table 1)

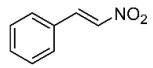
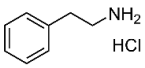
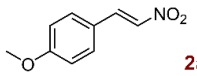
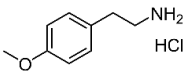
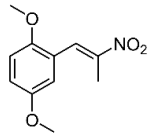
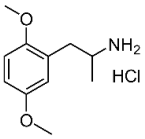
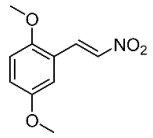
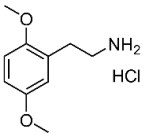
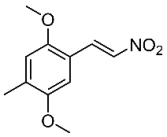
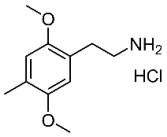
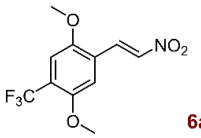
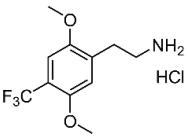
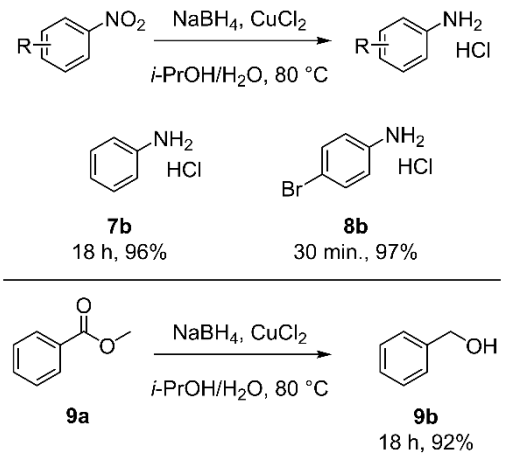
Substrate	Product	Time (min.)	Yield (%)
 1a	 1b	30	83
 2a	 2b	10	82
 3a	 3b	30	62
 4a	 4b	10	82
 5a	 5b	30	65
 6a	 6b	30	71

Table 1: The β-nitrostyrene scaffolds with their corresponding products, reaction times and their yields.

The method was also tested on other types of scaffolds to investigate its potential general applications and effects on other substituents. As sodium borohydride per se does not reduce ester nor nitro functionalities,[6c,12] the presence of the copper salt results in overcoming this issue, leading to yields of their reduced derivatives above 90% (**7**-**9**). (Scheme 2)



Scheme 2: Additional products obtained via this method: nitrobenzene and methyl benzoate are reduced in excellent yields, while dehalogenation of haloarenes does not occur.

Therefore, the $NaBH_4/CuCl_2$ system was proved to work on aromatic ester, nitro, and α,β-unsaturated nitroalkenes functionalities.

Our studies demonstrate that, up to 24 hours, the method shows some degree of functional group tolerance, as the amido and carboxylic acid functionalities of benzamide and benzoic acid, respectively, were left untouched, and the starting materials were finally fully recovered.

1-Bromo-4-nitrobenzene **8a** and 3-chlorophenol were used to test the potential effects on halogenated aromatic structures and no dehalogenation was detected up to 24 hours stirring. The retainment of halogens atoms on aryl halides distinguishes this procedure from traditional techniques, such as those involving $LiAlH_4$, causing dehalogenation.[13]

The role of the $CuCl_2$ salt is pivotal to the success of the method. Studies on the reduction of $CuCl_2$ by $NaBH_4$ suggest that copper(II) is promptly reduced to free Cu(0), composing up to 96% of the products. The remaining 4% consists of Cu_2O and negligible amounts of other copper species.[14] Consistently, once the chloride is added, the reduction to free Cu(0) is visually indicated by the immediate disappearance of the blue color of the copper(II) solution, and the formation of a fine suspended black powder. The latter, as metallic copper particles, acts as the actual catalyst.

Time seems to be a key factor for the phenethylamine structures, as the yields decrease over time after reaching their maxima, which are indicated in Table 1. Once 2-propanol is evaporated, the products can also

be isolated as free amines by dissolving the residue in ether, decanting it into another flask, and concentrating *in vacuo*.

In summary, the presented procedure represents a scalable, higher-yielding, and faster alternative to the conventional reductive methods used to date for the synthesis of substituted phenethylamines from their α,β-unsaturated nitroalkene analogues. Furthermore, the $NaBH_4/CuCl_2$ system is effective at reducing nitro and ester functionalities on aromatic structures, while leaving intact benzoic acid, amido- and halogenated aromatic compounds.

Acknowledgment

L.D.A. and J.L.K. acknowledge the EU Horizon 2020, Innovative Training Network SAFER (765657).

Supporting Information

The Supporting Information is available and contains the NMR ^{1}H and ^{13}C spectra of the synthesized compounds.

Conflict of Interest

The authors declare no conflict of interest.

References and Notes

(1) **(a)** Shulgin A. T. in *Hallucinogens: a forensic drug handbook*. Academic Press, **2003**, 67. **(b)** Chackalamannil, S., Rotella, D., & Ward, S., *Comprehensive medicinal chemistry III*. Elsevier, **2017**.
(2) Youdim, M. B., & Bakhle, Y. S., *Monoamine oxidase: isoforms and inhibitors in Parkinson's disease and depressive illness.* British journal of pharmacology, **2006**, *147*(S1), S287-S296.
(3) **(a)** Nichols, D. E., *Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens.* Journal of psychoactive drugs, 18.4, **1986**, 305-313. **(b)** Nichols, D. E., *Hallucinogens*. Pharmacology & therapeutics, 101.2, **2004**, 131-181.
(4) Silverstone, T., *Appetite suppressants: a review*. Drugs, 43.6, **1992**, 820-836.
(5) **(a)** Coutts, R. T., & Malicky, J. L., *The Synthesis of Four Possible in vitro Metabolites of the Hallucinogen 1-(2, 5-Dimethoxy-4-methylphenyl)-2-aminopropane (DOM).* Canadian Journal of Chemistry 52.3, **1974**, 395-399. **(b)** Phillips, B. *Catalytic Transfer Hydrogenation of Nitroalkenes to Primary Amines*, **2016**. (c) Kohno, M., Sasao, S., & Murahashi, S. I., *Synthesis of phenethylamines by hydrogenation of β-nitrostyrenes.* Bulletin of the Chemical Society of Japan, 63.4, **1990**, 1252-1254.
(6) **(a)** Guy, Michelle, et al. *The Henry reaction: spectroscopic studies of nitrile and hydroxylamine by-products formed during synthesis of psychoactive phenylalkylamines.* Central European Journal of

Chemistry 6 (2008): 526-534. **(b)** Oberlender, Robert A., et al. *Substituent branching in phenethylamine-type hallucinogens: a comparison of 1-[2, 5-dimethoxy-4-(2-butyl) phenyl]-2-aminopropane and 1-[2, 5-dimethoxy-4-(2-methylpropyl) phenyl]-2-aminopropane.* Journal of medicinal chemistry 27.6 (1984): 788-792. **(c)** d'Andrea, Laura. *Design and synthesis of beta-Arrestin-biased 5HT2AR agonists.* (2023).

(7) **(a)** Shulgin, Alexander, and A. Shulgin. *PiHKAL*. Berkeley. (1991). **(b)** Kupriyanova, Olga V., et al. *Synthesis and determination of analytical characteristics and differentiation of positional isomers in the series of N-(2-methoxybenzyl)-2-(dimethoxyphenyl) ethanamine using chromatography–mass spectrometry*. Drug testing and analysis 12.8 (2020): 1154-1170.

(8) Giannis, A., and K. Sandhoff. *LiBH4 (NaBH4)/Me3SiCl, an unusually strong and versatile reducing agent.* Angewandte Chemie International Edition in English 28.2 (1989): 218-220.

(9) **(a)** Meyers, Albert I., and J. C. Sircar. *Reduction of nitroalkenes to nitroalkanes with aqueous sodium borohydride*. The Journal of Organic Chemistry 32.12 (1967): 4134-4136. **(b)** Varma, Rajender S., and George W. Kabalka. *Selective reduction of a, β-unsaturated nitrocompounds with sodium borohydride in methanolic solutions: a facile route to nitroalkenes*. Synthetic Communications 15.2 (1985): 151-155. **(c)** Kabalka, G. W.; Varma R. S. *Comprehensive Organic Synthesis* 8 (1991): 363-379.

(10) **(a)** Satoh, Toshio, et al. *Reduction of organic compounds with sodium borohydride-transition metal salt systems: Reduction of organic nitrile, nitro and amide compounds to primary amines.* Tetrahedron Letters 10.52 (1969): 4555-4558. **(b)** Heinzman, Stephen W., and B. Ganem. *Mechanism of sodium borohydride-cobaltous chloride reductions.* Journal of the American Chemical Society 104.24 (1982): 6801-6802. **(c)** N. Astuko, and T. Kudo. *Studies of Reduction with the Sodium Borohydride-Transition Metal Boride System. I.: Reduction of Nitro and the Other Functional Groups with the Sodium Borohydride-Nickel Boride System.* Chemical and pharmaceutical bulletin 36.4 (1988): 1529-1533. **(d)** J. O. Osby, and B. Ganem. *Rapid and efficient reduction of aliphatic nitro compounds to amines.* Tetrahedron letters 26.52 (1985): 6413-6416. **(e)** G. Sujata, D. Prajapati, and J. S. Sandhu. *A New and Efficient Method for the Selective Reduction of Nitroarenes: Use of Ammonium Sulphate-Sodium Borohydride*. Chemistry letters 8 (1995): 725-726.

(11) Hansen, M. et al. *Synthesis and structure–activity relationships of N-benzyl phenethylamines as 5-HT2A/2C agonists.* ACS chemical neuroscience 5.3 (2014): 243-249.

(12) Smith, M. *Organic synthesis*. Academic Press, (2016): 7.4.

(13) Smith, M.B. *Organic synthesis*. Academic Press, (2016): 7.6.2.1.

(14) **(a)** Hohnstedt, L. F., B. O. Miniatas, and Sr M. C. Waller. *Aqueous Sodium Borohydride Chemistry. The Colnage Metals, Copper, Silver, and Gold.* Analytical Chemistry 37.9 (1965): 1163-1164. **(b)** Glavee, George N., et al. *Borohydride reduction of nickel and copper ions in aqueous and nonaqueous media. Controllable chemistry leading to nanoscale metal and metal boride particles.* Langmuir 10.12 (1994): 4726-4730.

(15) Hansen, M. *Design and Synthesis of Selective Serotonin Receptor Agonists for Positron Emission Tomography Imaging of the Brain: PhD Thesis. Faculty of Pharmaceutical Sciences*, University of Copenhagen (2010).

(16) Williamson, K. L., and K. M. Masters. *Macroscale and microscale organic experiments.* Cengage Learning (2016).

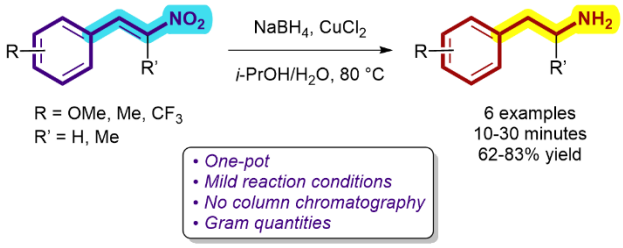
Experimental section

NMR spectra were recorded on Bruker Avance 400 MHz or Bruker Avance III HD 600 MHz spectrometers. Residual solvent peaks ($CDCl_3$, D_2O, CD_3OD, $(CD_3)_2SO$) were used as internal standard (7.26, 4.79, 3.31, and 2.50 ppm for ^1H, and 77.16, 49, and 39.52 ppm for ^{13}C, respectively). UPLC-MS analyses were performed on a Waters Acquity H-class UPLC with a Sample Manager FTN and a TUV dual wavelength detector coupled to a QDa single quadrupole analyser using electrospray ionization (ESI). UPLC separation was achieved with a C18 reversed-phase column (Acquity UPLC BEH C18, 2.1 mm × 50 mm, 1.7 µm) operated at 40 °C, using a linear gradient of the binary solvent system of buffer A (milliQ H_2O:MeCN:formic acid, 95:5:0.1 v/v%) to buffer B (MeCN:formic acid, 100:0.1 v/v%) from 0 to 100% B in 3.5 min, then 1 min at 100%B, Flow rate: 0.8

ml/min. Data acquisition was controlled by MassLynx ver. 4.1 and data analysis was done using Waters OpenLynx browser ver. 4.1.
Solvents were commercial HPLC grade and used without further purification. The substrates 2a, 7a, and 8a were commercially available and used without further purification. The substituted β-nitrostyrenes 1a and 3a-6a were prepared by use of literature.[15] 9a was prepared by modification of literature.[16]

General procedure
The desired substrate (**1a**-**9a**) (2 mmol, 1 eq.) was added in small portions to a stirring suspension of $NaBH_4$ (15 mmol, 7.5 eq.) in *i*-PrOH/H_2O (8:4ml). 0.1 ml of a freshly prepared $CuCl_2$ 2M solution were added dropwise but rapidly to the vessel. The reaction was monitored by TLC and refluxed at 80 °C in either oil bath or heating mantle for the time indicated in Table 1.
*General workup procedure of the amino products (**1-8**):* Once cooled to room temperature, 35% solution of NaOH (10 ml) was added under stirring. The mixture was extracted with *i*-PrOH (3 x 10 ml), and the organic extracts were combined, thoroughly dried over $MgSO_4$, and filtered.
(I) The residue was concentrated under reduced pressure and dissolved in a large amount of diethyl ether. The amino products were precipitated under stirring with an excess of HCl 2N in diethyl ether solution and the vessel was cooled to 5 °C. The solid was filtered, washed with cold diethyl ether, and dried under reduced pressure as the amine hydrochloride salt derivative.
(II) An excess of HCl 4N in dioxane solution was added and the filtrate was stirred for 30 minutes. The residue was concentrated under reduced pressure, suspended in dry cold acetone, and stirred vigorously for 1 hour. The suspension was filtered and washed with minimum amount of cold acetone to deliver the product as hydrochloride salt.
2-phenylethan-1-amine hydrochloride (**1b**) - The product was isolated by use of (II) as a as a colorless amorphous solid (83%).
^{1}H-NMR (600 MHz, CD_3OD) δ 2.97 (2H, q, *J* = 5.18 Hz), 3.18 (2H, q, *J* = 5.24 Hz), 7.28 (3H, q, *J* = 4.28 Hz), 7.35 (2H, t, *J* = 7.59 Hz); ^{13}C-NMR (151 MHz, CD_3OD) δ 34.55, 41.98, 128.26, 129.77, 129.99, 137.92.
MS (ESI): 121,1; Found $[M+1]^+$: 121,0.
Mp: 220-221 ˚C
2-(4-methoxyphenyl)ethan-1-amine hydrochloride (**2b**) - The product was isolated by use of (I) as a as a white solid (82%).
^{1}H-NMR (600 MHz, CD_3OD) δ 2.89 (2H, t, *J* = 7.7 Hz), 3.13 (2H, t, *J* = 7.7 Hz), 3.78 (s, 3H), 6.91 (2H, q, *J* = 2.9 Hz), 7.19 (2H, q, *J* = 2.9 Hz); ^{13}C-NMR (151 MHz, CD_3OD) δ 33.75, 42.14, 55.71, 115.43, 129.60, 130.78, 160.47.
MS (ESI): 151,1; Found $[M+1]^+$: 152,1.
Mp: 214-216 ˚C
1-(2,5-dimethoxyphenyl)propan-2-amine hydrochloride (**3b**) - The product was isolated by use of (II) as a as a colorless solid (62%).
^{1}H-NMR (600 MHz, CD_3OD) δ 1.26 (3H, d, *J* = 6.60 Hz), 2.82 (1H, q, *J* = 6.92 Hz), 2.95 (1H, q, *J* = 6.60 Hz), 3.56 (1H, q, *J* = 6.76 Hz), 3.75 (3H, s), 3.81 (3H, s), 6.79 (1H, d, *J* = 2.94 Hz), 6.84 (1H, q, *J* = 3.76 Hz), 6.93 (1H, d, *J* = 8.94 Hz); ^{13}C-NMR (151 MHz, CD_3OD) δ 18.56, 36.85, 49.22, 56.12, 56.24, 112.81, 114.06, 118.63, 126.24, 153.17, 115.14.
MS (ESI): 135,1; Found $[M+1]^+$: 136,2.
Mp: 115-117 ˚C
2-(2,5-dimethoxyphenyl)ethan-1-amine hydrochloride (**4b**) - The product was isolated by use of (I) as a as a white solid (82%).
^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ 6.92 (d, *J* = 8.9 Hz, 1H), 6.81 (q, *J* = 4.0 Hz, 1H), 6.78 (d, *J* = 3.1 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 2.97 (t, *J* = 7.8 Hz, 2H), 2.81 (t, *J* = 7.8 Hz, 2H). ^{13}C-NMR (151 MHz, $(CD_3)_2SO$) δ 28.14, 38.65, 55.32, 55.79, 111.78, 112.18, 116.45, 126.03, 151.25, 153.05.
MS (ESI): 181.1; Found $[M+1]^+$: 182.1.
Mp: 138-140 ˚C

2-(2,5-dimethoxy-4-methylphenyl)ethan-1-amine hydrochloride (**5b**) - The product was isolated by use of (II) as a as a colorless solid (65%).
^{1}H-NMR (600 MHz, CD_3OD) δ 2.18 (3H, s), 2.92 (2H, t, *J* = 7.38 Hz), 3.12 (2H, t, *J* = 7.38 Hz), 3.79 (6H, d, *J* = 10.02 Hz), 6.76 (1H,s), 6.81 (1H,s); ^{13}C-NMR (151 MHz, CD_3OD) δ 16.27, 29.81, 41.07, 56.33, 56.48, 114.24, 114.96, 123.38, 127.73, 152.65, 153.22.
MS (ESI): 195.1; Found $[M+1]^+$: 196.2.
Mp: 213-215 ˚C
2-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)ethan-1-amine hydrochloride (**6b**) - The product was isolated by use of (II) as a as a colorless solid (71%).
^{1}H-NMR (400 MHz, CD_3OD) δ 3.03 (2H, t, *J* = 7.38 Hz), 3.18 (2H, m, *J* = 3.76 Hz), 3.87 (6H, d, *J* = 4.52 Hz), 7.10 (1H, s), 7.16 (1H, s); ^{13}C-NMR (151 MHz, CD_3OD) δ 155.24, 153.15, 126.84, 117.99, 113.87, 113.86, 112.74, 56.26, 56.11, 40.85, 29.96.
MS (ESI): 249.1; Found $[M+1]^+$: 250.1.
Mp: 260-261 ˚C
aniline hydrochloride (**7b**) - The product formation was monitored by TLC using Hex:EtOAc:TEA (3:7:0.1). The product was isolated by use of (I) as a white solid (96%).
^{1}H-NMR (600 MHz, D_2O) δ 7.40 (2H, q, *J* = 2.96 Hz), 7.51 (1H, m, *J* = 1.66 Hz), 7.56 (2H, m, *J* = 1.79 Hz); ^{13}C-NMR (151 MHz, D_2O) δ 109.59, 122.50, 128.67, 130.07.
MS (ESI): 93.1; Found $[M+1]^+$: 94,2.
Mp: 196-197 ˚C
***p*-bromo-aniline hydrochloride** (**8b**) - The product formation was monitored by TLC using pure pentane. The product was isolated by use of (I) as a bright white powder (97%).
^{1}H-NMR (600 MHz, D_2O) δ 6.87 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H); ^{13}C-NMR (151 MHz, D_2O) δ 132.11, 119.07, 109.58.
MS (ESI): 171,0; Found $[M+1]^+$: 171.1.
Mp: 190-191 ˚C
benzyl alcohol (**9b**) - The product formation was monitored by TLC using Hex:EtOAc (6:1). Once cooled to room temperature, the mixture was acidified with HCl 20% solution and extracted with DCM (3 x 15 ml). The organic extracts were combined, dried over $MgSO_4$, and concentrated under reduced pressure to deliver **9b** as colorless liquid (92%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.87 (br, 1H), 4.69 (s, 2H), 7.31 (1H, m, *J* = 2.67 Hz), 7.37 (4H, d, *J* = 4.56 Hz); ^{13}C-NMR (151 MHz, $CDCl_3$) δ 65.48, 127.12, 127.79, 128.69, 140.97.
MS (ESI): 108.1; Found $[M+1]^+$: 109.1.



For Table of Contents Only