$NaBH_4$, CH_3CO_2H, Pd/C as a reagent system to hydrogenate activated alkenes without *O*-or *N*-debenzylation

Nuha Al Soom, Thies Thiemann

Department of Chemistry, United Arab Emirates University, Al Ain, Abu Dhabi, United Arab Emirates
E-mail: nuhalsoom@hotmail.com

Abstract — $NaBH_4$, CH_3CO_2H, Pd/C has been described as a reagent system to hydrogenate alkenoates and alkenones. Here, we show that *O*-debenzylation does not occur under the conditions, making it possible to hydrogenate a double bond under Pd/C catalysis without *O*-debenzylation or *N*-debenzylation.

Keywords— double bond hydrogenation, benzyl ether protective group

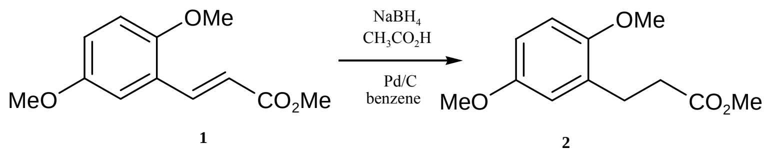
I. INTRODUCTION

Protective groups in synthetic organic chemistry are a valuable tool [1]. A functional group that is sensitive in a chemical transformation is first converted to a protected functional group. Thereafter, the actual chemical transformation is carried out with the molecule, and at some point later, the protective group is removed. One of the common protective groups for the alcohol (OH) function and for the carboxylic acid (CO_2H) function is the benzyl moiety in form of an *O*-benzyl ether (OCH_2Ph) and *O*-benzyl ester (CO_2CH_2Ph). Often, both can be removed by hydrogenolysis when using a palladium on carbon (Pd/C) catalyst [2]. Also, an *N*-function, such as in an amide, can be protected with a benzyl group, where the group is subsequently removed by Pd-catalysed hydrogenation. Under the conditions of the reductive debenzylation, double bonds can also be hydrogenated. If the actual desired transformation is to be the hydrogenation of a double bond in the substrate, then one risks losing the benzyl functions as protective groups in the molecule at the same time.

In the following, the authors present reaction conditions under which an activated double bond can be hydrogenated using Pd/C as a catalyst, but benzyl ethers, benzyl esters and *N*-benzyl amides are not converted to alcohols, acids, and amides respectively.

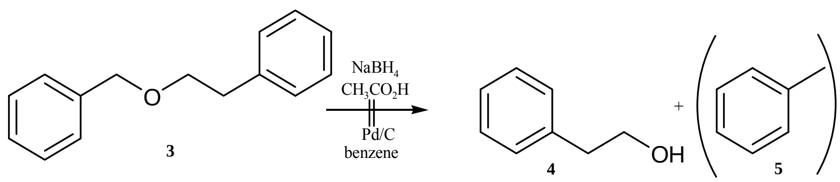
II. RESULTS AND DISCUSSION

Because of the danger of working with H_2 in our laboratory when hydrogenating alkenes, we looked for a reaction system that would generate H_2 *in situ*. Recently, A.T. Russo et al. [3,4] have published a reaction conditions ($NaBH_4$, CH_3CO_2H, Pd/C) that would achieve this. We could utilize this system, *eg.*, in the hydrogenation of **1** to **2** (Scheme 1), where **2** is a precursor to quinones linked to a carrier. As solvent we exchanged the published toluene to the more easily removable benzene.



Scheme 1. Olefin hydrogenation with $NaBH_4$, CH_3CO_2H, Pd/C

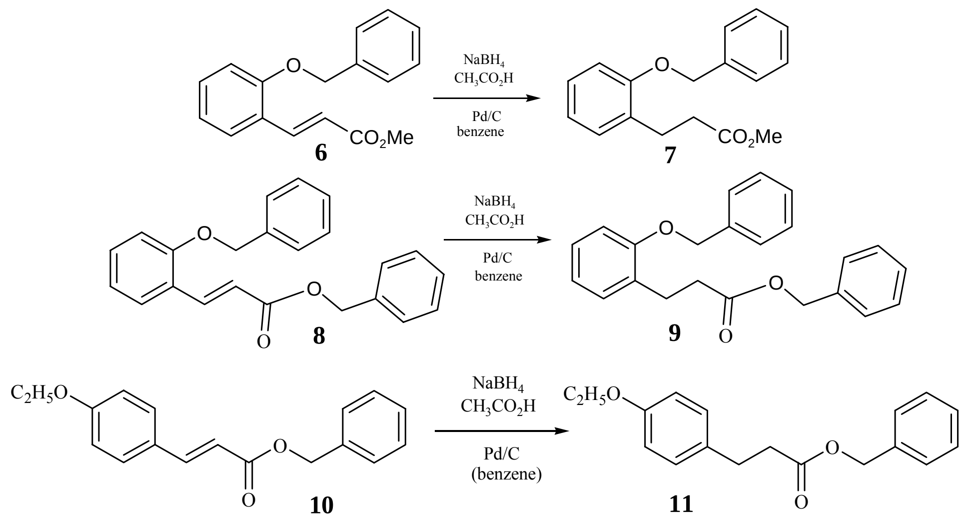
The reagent system was also noted to be effective in C-Cl dechlorination reactions. However, when we tried to used $NaBH_4$, CH_3CO_2H, Pd/C in *O*-debenzylation reactions, the *O*-debenzylation, *eg.* from **3** to **4**, did not proceed, even with an excess of reagent (Scheme 2).



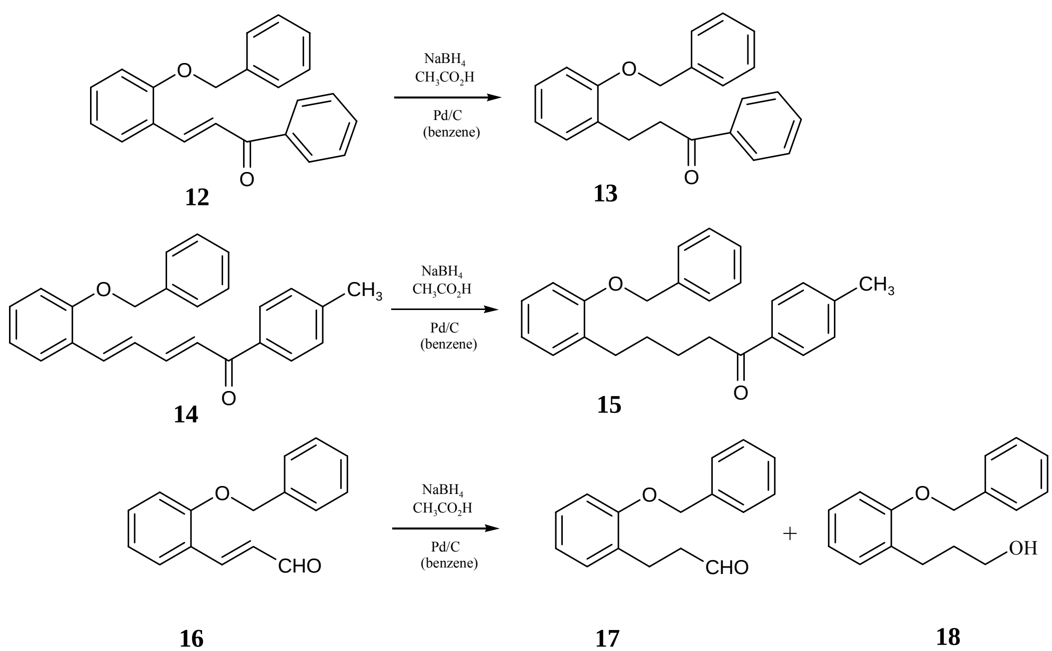
Scheme 2. *O*-Debenzylation of **3** does not proceed under the conditions

This gave us a reaction system that would allow us to hydrogenate double bonds in the presence of benzyl ether (eg., **6** to **7**) and benzyl ester (eg., **8** to **9**) functions, that would not be affected under the normal reaction conditions used (Scheme 3). Both of these reactions proceeded in excellent yield. Prolonged reaction times, and periodic addition of further acetic acid, however, led to the debenzylated acids, so that careful monitoring of the reaction progress is a must.

Multiple double bonds in a substrate are completely hydrogenated under the conditions as can be seen in the transformation of **14** to **15**. Ketones are not reduced with $NaBH_4$, CH_3CO_2H, (cat.) Pd/C, evident in the conversions of **12**/**14** to **13**/**15**. Upon careful handling, even a carbaldehyde-function can be retained in the reaction as can be seen in the transformation of 2-benzyloxycinnamaldehyde (**16**) to 2-benzyloxyphenylpropionaldehyde (**17**) with only relatively small amounts of 2-benzyloxyphenylpropanol (**18**) evident as by-product (Scheme 4).

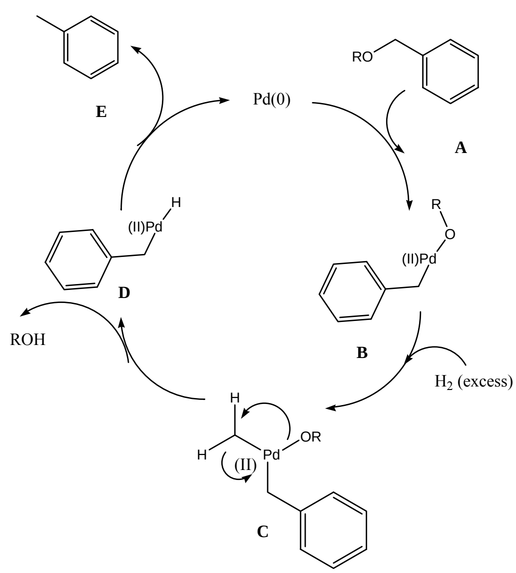


Scheme 3. Hydrogenation of cinnamates in the presence of benzyl ether and benzyl ester moieties.

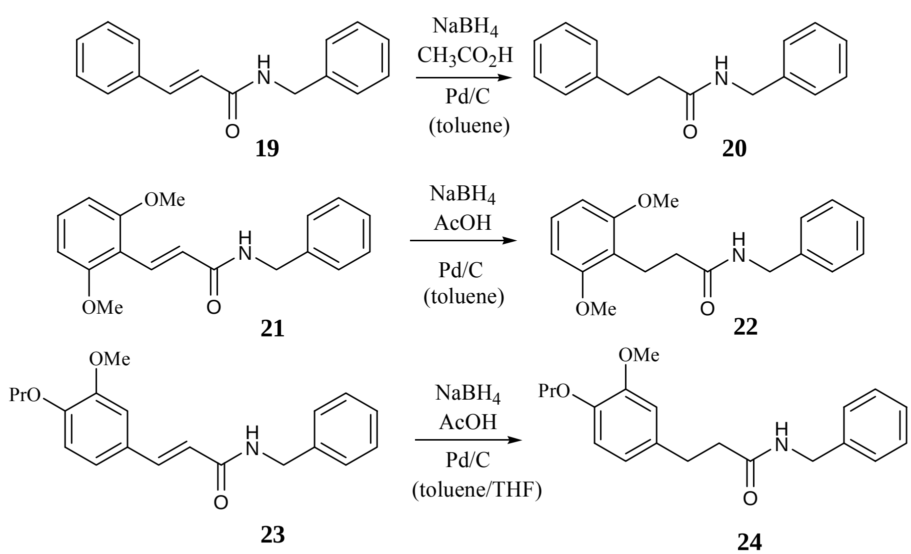


Scheme 4. Hydrogenation of enones and enaldehydes in the presence of an *O*-benzyl function

It is known that also ammonia, ammonium acetate and pyridine suppress reductive *O*-debenzylation with hydrogen in the presence of Pd/C, while the hydrogenation of alkenes proceeds under the conditions [5]. Also, amines have been noted to suppress the reductive cleavage of benzyl ethers [6-8]. Momentarily, the mechanistic reasoning behind the suppression of the *O*-debenzylation in our case is not clear. The accepted mechanism for the Pd(0) hydrogenative *O*-debenzylation is shown in Scheme 5. It must be noted that the reaction is taken place under heterogeneous conditions, while the mechanism does not take this into account. It is believed that the reductive step **D** to **E** is significantly important to determine the character of the “Pd(0)” species and may depend on the reactive system.

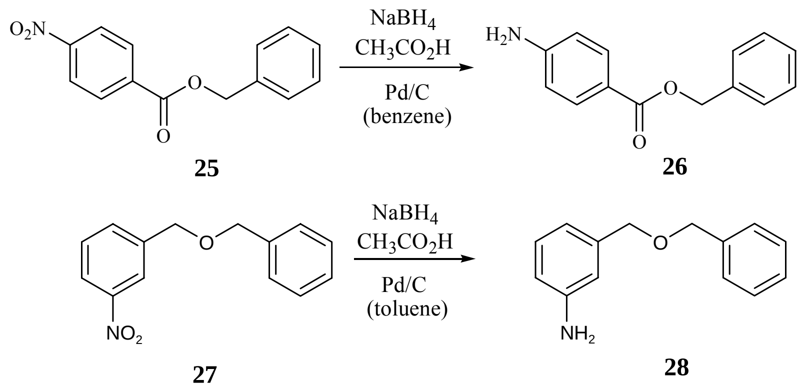


Scheme 5. Accepted mechanism for Pd(0) catalysed hydrogenative *O*-debenzylation.



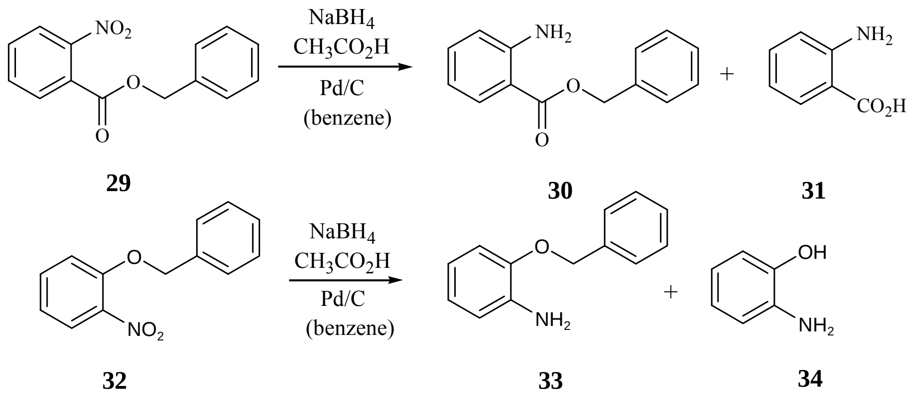
Scheme 6. Hydrogenation of *N*-benzyl cinnamides to N-benzyl phenylpropionamides

Also, *N*-benzyl cinnamides **19**, **21**, and **23** were subjected to hydrogenation with $NaBH_4$, CH_3CO_2H in the presence of cat. Pd/C to afford the corresponding *N*-benzyl phenylpropionamides **20**, **22**, and **24** (Scheme 6). Due to the poor solubility of **23** in toluene or benzene, its hydrogenation was carried out in a mixture of toluene and THF (1/1 *v*/*v*). No *N*-debenzylation was observed in the reactions. Overall, the stability of the benzyl protective group (Bzl) was found to be -NHBzl; $-CH_2OCH_2Ph$ > $PhOCH_2Ph$ > $-CO_2CH_2Ph$, under the reaction conditions used.



Scheme 7. Reductive transformation of nitroarenes to anilines with $NaBH_4$, AcOH, cat. Pd/C.

Finally, the use hydrogen in presence of Pd/C is an often used method to convert nitroarenes to anilines.[9] Other hydrogen sources such as formic acid and decaborane with Pd/C have been used in the transformation.[10,11] It was found that nitroarenes are reduced to anilines also with the system $NaBH_4$ and CH_3CO_2H in the presence of cat. Pd/C. Here, benzyl 4-nitrobenzoate (**25**) could be converted cleanly to benzyl 4-aminobenzoate (**26**). Furthermore, benzyl 3-nitrobenzyl ether (**27**) could be transformed to 3-aminobenzyl benzyl ether (**28**) (Scheme 7). However, in the case of both benzyl 2-nitrobenzoate (**29**) and benzyl 2-nitrobenzyl ether (**32**), the benzyl group was removed reductively to give mixtures of anthranilic acid (**31**) and benzyl 2-aminobenzoate (**30**) and of 2-aminobenzyl benzyl ether (**33**) and 2-aminophenol (**34**), respectively (Scheme 8). Here, close proximity of the nitro group to the benzyl function leads to partial reductive cleavage of the latter. While the reduction of the nitro group can pass through a number of intermediates and can be mechanistically complex, it is believed that a reactive intermediate along the pathway from nitro- to amino-function leads to the reductive cleavage of the benzyl ether in **33** and benzyl ester in **30**.



Scheme 8. Reductive transformations of nitroarenes with benzyl functions in close proximity to the nitro group.

III. CONCLUSIONS

With $NaBH_4$, AcOH in the presence of catalytic amounts of Pd/C, a simple reactive system was utilized to hydrogenate alkenes in the presence of *O*-benzyl ether and benzyl ester protective groups, which are not affected by the reaction. It was found that an aromatic nitro function is reduced to amino group by $NaBH_4$, AcOH, cat. Pd/C. Here a benzyl ether or a benzyl ester function can then be retained, when in the substrate the nitro group and the benzyl function are positioned adequately far apart.

IV. EXPERIMENTAL

Melting points were measured on a Stuart SMP 10 melting point apparatus and are uncorrected. Infrared spectra were measured with a Thermo/Nicolet Nexus 470 FT-IR ESP Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian 400 NMR (^{1}H at 395.7 MHz, ^{13}C at 100.5 MHz) and a Varian 200 MHz NMR spectrometer (^{1}H at 200.0 MHz, ^{13}C at 50.3 MHz). The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). Mass spectra were measured with a JMS-01-SG-2 spectrometer. CHN-analysis was performed on a LECO TruSpec Micro instrument. Column chromatography was carried out on silica gel (60 A, 230 – 400 mesh, Sigma-Aldrich).

5w% Palladium on carbon (Aldrich, 205680) was used in all experiments. $NaBH_4$ and acetic acid were acquired commercially. Benzene, toluene and THF were used without prior purification. Benzyl esters **6**, **8**, **10**, **25**, and **29** were prepared from the corresponding acids (benzyl alcohol, PPh_3, $BrCCl_3$, CH_2Cl_2) following a known procedure. Also, *N*-benzyl amides **19**, **21**, and **23** were synthesized from the corresponding acids (benzylamine, PPh_3, $BrCCl_3$, CH_2Cl_2). Substituted dibenzyl ethers **27** and **32** were obtained by Wilkinson-type etherification ($ArCH_2OH$, benzyl chloride, KOH, DMSO) as was 2-benzyloxycinnamaldehyde (**16**) (2-hydroxycinnamaldehyde, benzyl chloride, KOH, DMSO). **12** and **14** were prepared by Wittig olefination, starting from 2-benzyloxybenzaldehyde and benzoylmethylidenetriphenylphosphorane and from 2-benzyloxycinnamaldehyde (**16**) and toluoylmethylidenetriphenylphosphorane.

Caution: In the presence of dry palladium on carbon, hydrogen enflames upon contact with air. Therefore, it is advisable to purge the reaction flasks with an inert gas before use in the described hydrogenation. Also, where filtrating the reaction mixture directly, especially when using a paper filter, it must be noted that the filter cake upon drying can enflame due to the fact that unreacted sodium borohydride slowly hydrolyses with air moisture, thereby releasing hydrogen. Therefore, after diligent washing with chloroform, the filter and filter cake should be immersed in water.

Methyl 3-[2-benzyloxyphenyl]propionate (7).[12] – To a solution of methyl *o*-benzyloxycinnamate (**6**, 188 mg, 0.70 mmol) in benzene (10 mL) is given Pd/C (70 mg, 5 wt%) and acetic acid (AcOH, 100 mg). Thereafter, is added portionwise $NaBH_4$ (128 mg, 3.38 mmol). After 3h at rt, further AcOH (50 mg) and $NaBH_4$ (60 mg, 1.58 mmol) are added successively, and the resulting mixture is stirred at rt for 12h. Thereafter, half conc. aq. HCl is added dropwise until there is no futher gas evolution. H_2O (30 mL) is added and the mixture is extracted with CH_2Cl_2 (3 X 20 mL). The combined organic phase is dried over anhydrous $MgSO_4$, concentrated *in vacuo* and the residue is subjected to column chromatography on silica gel (CH_2Cl_2) to give **7** (175 mg, 93%) as a colorless oil; ν_{max} (neat/cm^{-1}) 3064, 3033, 2950, 1736, 1601, 1588, 1493, 1453, 1436, 1381, 1290, 1241, 1193, 1162, 1025, 752; δ_H (400 MHz, $CDCl_3$) 2.65 (2H, t, ^3J = 7.6 Hz), 3.01 (2H, t, ^3J = 7.6 Hz), 3.64 (3H, s, OCH_3), 5.09 (2H, s, OCH_2), 6.87 – 6.92 (2H, m), 7.16 – 7.46 (8H, m); δ_C (100.5 MHz, $CDCl_3$) 26.2 (CH_2), 34.0 (CH_2), 51.5 (OCH_3), 69.7 (OCH_2), 111.5 (CH), 120.7 (CH), 127.0 (2C, CH), 127.6 (CH), 127.8 (CH), 128.6 (2C, CH), 129.1 (C_{quat}), 130.1 (CH), 137.2 (C_{quat}), 156.5 (C_{quat}), 173.8 (C_{quat}, CO); MS (EI, 70 eV) m/z (%) 270 (M^+, 85).

Benzyl 3-[2-benzyloxyphenyl]propionate (9). – colorless oil; ν_{max} (neat/cm^{-1}) 3064, 3033, 2933, 1735, 1601, 1588, 1491, 1450, 1382, 1232, 1110, 1009, 910, 853, 742, 696; δ_H (400 MHz, $CDCl_3$) 2.71 (2H, t, ^3J = 7.6 Hz), 3.05 (2H, t, ^3J = 7.6 Hz), 5.09 (4H, s), 6.87 – 6.89 (2H, m), 7.15 – 7.42 (12H, m); δ_C (100.5 MHz, $CDCl_3$) 26.3 (CH_2), 34.2 (CH_2), 66.1 (OCH_2), 69.7 (OCH_2), 111.6 (CH), 120.8 (CH), 127.0 (2C, CH), 127.6

(CH), 127.7(5) (CH), 128.1 (2C, CH), 128.5 (3C, CH), 128.5(5) (2C, CH), 129.1 (C_{quat}), 130.1 (CH), 136.1 (C_{quat}), 137.2 (C_{quat}), 156.6 (C_{quat}), 173.2 (C_{quat}, CO); MS (EI, 70 eV) m/z (%) 346 (M^+, 73).

Benzyl 3-[4-ethoxyphenyl]propionate (**11**). - colorless oil; ν_{max} (KBr/cm^{-1}) 3065, 3033, 2979, 2930 1736, 1612, 1512, 1454, 1383, 1297, 1242, 1150, 1116, 1048, 923, 825, 737, 698; δ_H (400 MHz, $CDCl_3$) 1.40 (3H, t, ^3J = 7.2 Hz), 2.64 (2H, t, ^3J = 7.6 Hz), 2.90 (2H, t, ^3J = 7.6 Hz), 3.99 (2H, q, ^3J = 7.2 Hz, OCH_2), 5.10 (2H, s, OCH_2), 7.29 (2H, d, ^3J = 7.6 Hz), 7.34 (2H, d, ^3J = 7.6 Hz), 6.79 (2H, d, ^3J = 8.8 Hz), 7.08 (2H, d, ^3J = 8.8 Hz); δ_C (100.5 MHz, $CDCl_3$) 14.9 (CH_3), 30.1 (CH_2), 36.2 (CH_2), 63.4 (OCH_2), 66.2 (OCH_2), 114.4 (2C, CH), 128.2 (2C, CH), 128.5 (2C, CH), 129.2 (2C, CH), 132.3 (CH), 135.9 (C_{quat}), 138.9 (C_{quat}), 157.5 (C_{quat}), 172.8 (C_{quat}, CO); MS (EI, 70 eV) m/z (%) 284 (M^+, 43).

2-(2'-Benzyloxyphenyl)ethyl phenylketone (13). – colorless oil; ν_{max} (KBr/cm^{-1}) 3063, 2929, 1682, 1598, 1495, 1450, 1240, 1111, 1021, 740; δ_H (400 MHz, $CDCl_3$) 3.09 (2H, t, ^3J = 7.2 Hz), 3.27 (2H, dt, ^3J = 7.2 Hz, ^4J = 1.2 Hz), 5.11 (2H, s, OCH_2), 6.89 – 6.95 (2H, m), 7.17 – 7.25 (2H, m), 7.30 – 7.53 (8H, m), 7.90 (2H, d, ^3J = 7.6 Hz); δ_C (100.5 MHz, $CDCl_3$) 26.1 (CH_2), 39.1 (CH_2), 69.9 (OCH_2), 111.6 (CH), 120.9 (CH), 127.3 (2C, CH), 127.5 (CH), 127.9 (CH), 128.1 (2C, CH), 128.5 (2C, CH), 128.6 (2C, CH), 129.8 (C_{quat}), 130.4 (CH), 132.8 (CH), 136.8 (C_{quat}), 137.2 (C_{quat}), 156.6 (C_{quat}), 200.1 (C_{quat}, CO).

1-Benzyloxy-2-[4-(4-methylbenzoyl)butyl]benzene (15). - colorless oil; ν_{max} (KBr/cm^{-1}) 3062, 3032, 2927, 2858, 1680, 1606, 1493, 1451, 1379, 1290, 1238, 1180, 1112, 1025, 752, 696; δ_H (400 MHz, $CDCl_3$) 1.61 – 1.82 (4H, m), 2.40 (3H, s, CH_3), 2.72 (2H, t, ^3J = 7.2 Hz), 2.93 (2H, t, ^3J = 7.2 Hz), 5.07 (2H, s, OCH_2), 6.88 – 6.91 (2H, m), 7.13 – 7.44 (9H, m), 7.83 (2H, d, ^3J = 8.0 Hz); δ_C (100.5 MHz, $CDCl_3$) 21.6 (CH_3), 24.3 (CH_2), 29.6 (CH_2), 30.1 (CH_2), 38.3 (CH_2), 69.8 (OCH_2), 111.6 (CH), 120.7 (CH), 126.9 (CH), 127.1 (2C, CH), 127.7 (CH), 128.2 (2C, CH), 128.5 (2C, CH), 129.2 (2C, CH), 130.0 (CH), 131.1 (C_{quat}), 134.6 (C_{quat}), 137.5 (C_{quat}), 143.5 (C_{quat}), 156.5 (C_{quat}), 200.2 (C_{quat}, CO).

3-(2-Benzyloxyphenyl)propionaldehyde (17).[13] - colorless oil; ν_{max} (KBr/cm^{-1}) 2929, 1722, 1600, 1493, 1452, 1382, 1238, 1118, 1019, 748; δ_H (400 MHz, $CDCl_3$) 2.75 (2H, dt, ^3J = 7.6 Hz, ^4J = 1.6 Hz), 3.00 (2H, t, 3J = 7.6 Hz), 5.08 (2H, s), 6.87 – 6.92 (2H, m), 7.13 – 7.20 (2H, m), 7.30 – 7.43 (5H, m), 9.78 (1H, t, ^3J = 1.6 Hz); δ_C (100.5 MHz, $CDCl_3$) 23.5 (CH_2), 43.9 (CH_2), 69.8 (OCH_2), 111.6 (CH), 120.8 (CH), 127.1 (2C, CH), 127.7 (CH), 127.9 (CH), 128.6 (2C, CH), 128.9 (C_{quat}), 130.1 (CH), 137.1 (C_{quat}), 156.5 (C_{quat}), 202.4 (CHO); MS (EI, 70 eV) *m/z* (%) 240 (M^+, 13).

3-(2-Benzyloxyphenyl)propan-1-ol (18).[13] – colorless oil; ν_{max} (KBr/cm^{-1}) 3351 (broad, OH), 3064, 3033, 2933, 2864, 1600, 1587, 1493, 1452, 1381, 1239, 1041, 910, 751, 696; δ_H (400 MHz, $CDCl_3$) 1.86 (2H, tt, ^3J = 7.2 Hz, ^3J = 6.0 Hz, CH_2), 2.78 (2H, t, ^3J = 7.2 Hz, CH_2), 3.60 (2H, t, ^3J = 6.0 Hz, OCH_2), 5.08 (2H, s, OCH_2), 6.90 – 6.94 (2H, m), 7.15 – 7.20 (2H, m), 7.31 – 7.45 (5H, m); δ_C (100.5 MHz, $CDCl_3$) 26.0 (CH_2), 33.0 (CH_2), 61.9 (OCH_2), 70.1 (OCH_2), 111.7 (CH), 121.0 (CH), 127.2 (CH), 127.3 (2C, CH), 128.0 (CH), 128.6 (2C, CH), 130.3 (CH), 130.4 (C_{quat}), 137.0 (C_{quat}), 156.6 (C_{quat}); MS (EI, 70 eV) *m/z* (%) 240 (M^+, 25).

***N*-Benzyl 3-phenylpropionamide (20). –** To a mixture of *N*-benzyl cinnamide (335 mg, 1.41 mmol) and Pd/C (70 mg, 5 w%) in toluene (8 mL) was added acetic acid (210 mg) and subsequently $NaBH_4$ (185 mg). After the mixture was stirred for 14h, it was filtered, and the filter cake was washed with $CHCl_3$ (3 X 15 mL). The combined organic phase was concentrated *in vacuo*, and the residue was subjected to column chromatography on silica gel (ether/$CHCl_3$/hexane 2:2:1) to give **20** (315 mg, 95%) as a colorless solid, mp. 90 - 93 °C; ν_{max} (KBr/cm^{-1}) 3292 (s, NH), 3061, 3026, 2924, 1639, 1543, 1495, 1453, 1227, 1029, 741, 694; δ_H (400 MHz, $CDCl_3$) 2.51 (2H, t, ^3J = 7.6 Hz), 2.99 (2H, t, ^3J = 7.6 Hz), 4.38 (2H, d, ^3J = 5.6 Hz), 5.66 (1H, bs, NH), 7.12 – 7.29 (10H, m); δ_C (100.5 MHz, $CDCl_3$) 31.7 (CH_2), 38.5 (CH_2), 43.6 (CH_2), 126.3 (CH), 127.5 (CH), 127.7 (2C, CH), 128.4 (2C, CH), 128.6 (2C, CH), 128.7 (2C, CH), 138.1 (C_{quat}), 140.7 (C_{quat}), 171.9 (C_{quat}, CO).

***N*-Benzyl 3-(2,5-dimethoxyphenyl)propionamide (22). –** as a colorless solid, mp. 154 - 155 °C; ν_{max} (KBr/cm^{-1}) 3311, 3063, 2948, 2839, 1638, 1593, 1541, 1474, 1255, 1161, 1113, 774; δ_H (400 MHz, $CDCl_3$) 2.61 (2H, t, ^3J = 7.2 Hz), 2.95 (2H, t, ^3J = 7.2 Hz), 3.67 (2C, 2 OCH_3), 6.42 (1H, s, NH), 6.48 (2H, d, ^3J = 8.4 Hz), 7.13 (1H, dd, ^3J = 8.4 Hz, ^3J = 8.4 Hz), 7.15 – 7.20 (2H, m), 7.26 - 7.33 (3H, m); δ_C (100.5 MHz, $CDCl_3$) 18.6 (CH_2), 35.5 (CH_2), 43.7 (CH_2), 55.4 (2C, 2 OCH_3), 103.6 (2C, CH), 116.5 (C_{quat}), 127.4 (2C, CH), 128.0 (2C, CH), 128.6 (2C, CH), 138.2 (C_{quat}), 157.9 (2C, C_{quat}), 173.1 (C_{quat}, CO).

***N*-Benzyl 3-(3-methoxy-4-propoxyphenyl)propionamide (24).** – as a colorless solid; mp. 127 °C; ν_{max} (KBr/cm^{-1}) 3292 (NH), 3057, 3028, 2962, 2934, 2874, 1640, 1550, 1515, 1453, 1256, 1227, 1136, 1025, 803, 741, 697; δ_H (400 MHz, $CDCl_3$) 1.02 (3H, t, ^3J = 7.6 Hz, CH_3), 1.85 (2H, qt, CH_2, ^3J = 7.6 Hz, ^3J = 6.8 Hz), 2.49 (2H, t, ^3J = 7.6 Hz, CH_2), 2.92 (2H, t, ^3J = 7.6 Hz, CH_2), 3.80 (3H, s, OCH_3), 3.92 (2H, t, ^3J = 6.8 Hz, OCH_2), 4.38 (2H, d, ^3J = 1.2 Hz, CH_2), 5.69 (1H, bs, NH), 6.69 (1H, dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz), 6.71 (1H, d, ^4J = 2.0 Hz), 6.76 (1H, d, ^3J = 8.0 Hz), 7.24 – 7.31 (5H, m); δ_C (100.5 MHz, $CDCl_3$) 10.5 (CH_3), 22.5 (CH_2), 31.4 (CH_2), 38.8 (CH_2), 43.6 (NCH_2), 55.9 (OCH_3), 70.5 (OCH_2), 112.1 (CH), 113.0 (CH), 120.2 (CH), 127.5 (CH), 127.7 (2C, CH), 128.7 (2C, CH), 133.3 (C_{quat}), 138.1 (C_{quat}), 147.0 (C_{quat}), 149.3 (C_{quat}), 172.0 (C_{quat}, CO).

Benzyl 4-aminobenzoate (26). – colorless needles, mp. 97°C; ν_{max} (KBr/cm^{-1}) 3456, 3359, 3223, 2937, 1683, 1632, 1572, 1517, 1436, 1380, 1310, 1278, 1170, 1116, 974, 846, 771, 730, 691; δ_H (400 MHz, $CDCl_3$) 4.06 (2H, bs, NH_2), 5.31 (2H ,s, OCH_2), 6.62 (2H, d, ^3J = 8.8 Hz), 7.30 – 7.44 (5H, m), 7.88 (2H, d, ^3J = 8.8 Hz); δ_C (100.5 MHz, $CDCl_3$) 66.1 (OCH_2), 113.8 (2C, CH), 119.6 (C_{quat}), 128.0 (2C, CH), 128.5 (2C, CH), 131.8 (3C, CH), 136.6 (C_{quat}), 150.9 (C_{quat}), 166.5 (C_{quat}, CO).

3-Aminobenzyl benzyl ether (28).[14] – as a pale yellow oil; ν_{max} (KBr/cm^{-1}) 3500 (bs, NH), 3369 (NH), 3029, 2855, 1619, 1493, 1358, 1299, 1068; δ_H (400 MHz, $CDCl_3$) 4.48 (2H, OCH_2), 4.55 (2H, OCH_2), 6.62 – 6.64 (1H, m), 6.73 – 6.77 (2H, m), 7.14 (1H, dd, ^3J = 8.0 Hz, ^3J = 8.0 Hz), 7.25 – 7.39 (5H, m); δ_C (100.5 MHz, $CDCl_3$) 70.0 (OCH_2), 70.1 (OCH_2), 111.5 (CH), 114.5 (CH), 116.2 (CH), 117.6 (CH), 127.8 (2C, CH), 128.4 (2C, CH), 129.3 (CH), 138.3 (C_{quat}), 139.5 (C_{quat}), 146.2 (C_{quat}).

Anthranilic acid benzyl ester (30). – To a mixture of benzyl 2-nitrobenzoate (**29**, 361 mg, 1.4 mmol), Pd/C (100 mg, 5w%) and AcOH (210 mg) in benzene (10 mL) is slowly added $NaBH_4$ (185 mg, 4.87 mmol), and the resulting reaction mixture is stirred at rt for 14h. Thereafter, the mixture is filtrated and the filter cake is washed with $CHCl_3$ (2 X 20 mL). Column chromatography on silica gel (ether/CH_2Cl_2 1:10 → ethyl acetate/hexane 1:1) gave **30** (225 mg, 71%) as a pale yellow oil; ν_{max} (KBr/cm^{-1}) 3033, 2950, 1693, 1615, 1487, 1455, 1378, 1291, 1243, 1161; δ_H (400 MHz, $CDCl_3$) 5.34 (2H, s OCH_2), 6.62 – 6.68 (2H, m), 7.24 – 7.41 (4H, m), 7.44 (2H, d, ^3J = 8.8 Hz), 7.93 (1H, d, ^3J = 8.0 Hz); δ_H (400 MHz, $CDCl_3$) 66.0 (OCH_2), 110.7 (C_{quat}), 116.4 (CH), 116.7 (CH), 128.0 (2C, CH), 128.1 (CH), 128.6 (2C, CH), 131.3 (CH), 134.2 (CH), 136.3 (C_{quat}), 150.5 (C_{quat}), 167.9 (C_{quat}, CO) and **31** (38 mg, 20%).

Anthranilic acid (31). – To a mixture of benzyl 2-nitrobenzoate (**29**, 361 mg, 1.4 mmol), Pd/C (100 mg, 5w%) and AcOH (210 mg) in benzene (10 mL) is slowly added $NaBH_4$ (185 mg, 4.87 mmol), and the resulting reaction mixture is stirred at rt for 14h. Then, additional AcOH (105 mg) and $NaBH_4$ (100 mg, 2.63 mmol) were added, and the reaction was stirred at rt for an additional 10h. Thereafter, half-conc. aq HCl is added dropwise. Subsequently, water (25 mL) is added, and the mixture is extracted with ethyl acetate (3 X 20 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (ethyl acetate – hexane 1:1) to give anthranilic acid (**31**, 163 mg, 85%) as a beige-colored solid, mp. 144-146 °C (Lit. 146-147 °C[15]); ν_{max} (KBr/cm^{-1}) 3472 (NH), 3373 (NH), 3040 – 2350 (bs, OH), 1672, 1617, 1588, 1563, 1485, 1419, 1301, 1247, 1161, 916, 753, 659; δ_H (400 MHz, $CDCl_3$) 6.65 – 6.69 (2H, m), 7.29 – 7.33 (1H, m), 7.92 (1H, dd, ^3J = 8.4 Hz, ^4J = 1.6 Hz); δ_H (400 MHz, $CDCl_3$) 109.5 (C_{quat}), 116.5 (CH), 116.8 (CH), 132.1 (CH), 135.1 (CH), 151.1 (C_{quat}), 173.1 (C_{quat}, CO); MS (EI, 70 eV) m/z (%) 137 (M^+, 64), 119 (100), 92 (81, M^+-CHO_2).

Benzyl 3-nitrobenzyl ether (33). – as a pale yellow oil; ν_{max} (KBr/cm^{-1}) 3031, 2861, 1528, 1349, 1071, 1028, 804, 731, 669; δ_H (400 MHz, $CDCl_3$) 4.62 (2H, s, OCH_2), 4.63 (2H, s, OCH_2), 7.29 – 7.38 (5H, m), 7.52 (1H, dd, ^3J = 8.0 Hz, ^3J = 8.0 Hz), 7.68 – 7.71 (1H, m), 8.13 – 8.16 (1H, m), 8.23 – 8.24 (1H, m); δ_C (100.5 MHz, $CDCl_3$) 70.8 (OCH_2), 72.8 (OCH_2), 122.3 (CH), 122.6 (CH), 127.8 (2C, CH), 128.0 (CH), 128.6 (2C, CH), 129.3 (CH), 133.4 (CH), 137.5 (C_{quat}), 140.5 (C_{quat}), 148.3 (C_{quat}).

2-Aminophenol (34). – colorless solid; mp. 173 °C (Lit. 174 °C[15]); ν_{max} (KBr/cm^{-1}) 3377 (NH), 3306 (NH), 1608, 1515, 1475, 1406, 1285, 1271, 900, 751, 745; δ_H (400 MHz, DMSO-d^6) 4.70 (2H, bs), 6.40 (1H, d, ^3J = 7.6 Hz), 6.54 – 6.59 (2H, m), 6.65 (1H, d, ^3J = 6.8 Hz), 8.70 (1H, bs, OH); δ_C (100.5 MHz, DMSO-d^6) 114.5 (2C, CH), 116.5 (CH), 119.5 (CH), 136.4 (C_{quat}), 144.0 (C_{quat}); MS (EI, 70 eV) *m/z* (%) 109 (M^+,100), 80 (32).

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