Oxidation and Deprotection of Primary Benzylamines by Visible Light Flavin Photocatalysis

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Abstract: We report a photocatalytic oxidation procedure that can be used to convert benzylamines into their corresponding aldehydes under mild conditions without over-oxidation, using riboflavin tetraacetate as photocatalyst and blue emitting LEDs (440 nm) as light source. Oxygen is the terminal oxidant and H_2O_2 and NH_3 appear as the only byproducts of the oxidation of primary benzylamines. Furthermore, we have developed a photocatalytic protocol for 4-methoxybenzyl (Mob) group deprotection of primary amines and alcohols. Double bonds, benzyl-protected esters and alcohols are tolerated under the applied conditions, whereas the deprotection of protected secondary amines is not applicable. Mob-protected carboxylic acids and carboxybenzoyl (Cbz) protected amines are inert under the photodeprotection conditions.

Key words: flavin, photooxidation, redox chemistry, electron transfer, benzyl protecting group

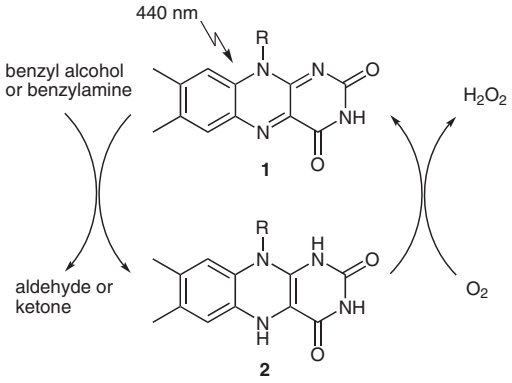
Flavins, acting as redox co-factors and photoreceptors, are ubiquitous in nature, and occur mostly in the form of flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN) co-factors.[1] Besides the application as flavoenzyme models for biochemical processes,[2] flavins have been used as organocatalysts in thermal[3] and photochemical[4] oxidation reactions.

Flavin-mediated photooxidation of benzyl alcohols[4] use the increased oxidation power of the isoalloxazine chromophore in its oxidized form **1** upon excitation by light.[5] Subsequent two-electron reduction and protonation gives dihydroflavin **2**, which is oxidized back to **1** by molecular air oxygen as the terminal oxidant, yielding hydrogen peroxide as sole stoichiometric byproduct (Scheme 1).[4]

Several methods for the oxidation of amines to their corresponding aldehydes have been reported in the literature. However, the reaction conditions are rather harsh, require the stoichiometric use of metallic reagents or suffer from over-oxidation or lack of selectivity towards other functional groups.[6] The use of air oxygen as stoichiometric oxidant is particularly desirable from an environmental and economical point of view. Some aerobic catalytic procedures for amine oxidation are available,[7] but examples of visible light photocatalysis accelerating or mediating the process are rare.[8]

The oxidation of amines by flavin in either its ground or excited state, has been studied extensively to elucidate the mechanism of monoamine oxygenase enzymes and their inhibition.[9] Thermal aerobic oxidation of amines to *N*-oxides using flavin catalysts has been accomplished,[3] but, to the best of our knowledge, no application of flavin-mediated photooxidation of amines to aldehydes has been described so far.

We report the scope and limitations of flavin-mediated aerobic photooxidation of benzylamines to aldehydes. The approach is used to cleave benzyl protecting groups selectively by blue light irradiation. Riboflavin tetraacetate (RFT, see Scheme 1)[10] is used as a readily available and nontoxic photocatalyst; blue-light-emitting high-power LEDs serve as a selective and efficient light source.



Scheme 1 Catalytic cycle of aerobic flavin-mediated photooxidation of benzyl alcohols or benzylamines [riboflavin: R = $C_5H_{11}O_4$; riboflavin tetraacetate (RFT): R = $C_{13}H_{19}O_8$].

Photooxidation of Benzylamines

4-Methoxybenzylamine (**3a**) was chosen as substrate to optimize the reaction conditions for the RFT-mediated photooxidation to **4a**. The course of the reactions were monitored by ^{1}H NMR analysis. Upon irradiation of a solution of benzylamine **3a** (c = $4 \cdot 10^{-3}$ mol/L) in 1 mL of D_2O (containing 4% of DMSO-d_6 and 10 mol% of RFT) with blue light (440 nm, 3 W LED), a decrease in intensity of the benzylamine resonance signals and the appearance of the aldehyde **4a** resonance signals was observed (Figure 1, top). Only traces (<5%) of a side product, presumable the imine **5**, could be detected. Without irradiation, only 6% of aldehyde **4a** was formed, whereas no reaction occurred when the solution was irradiated in the absence of RFT.

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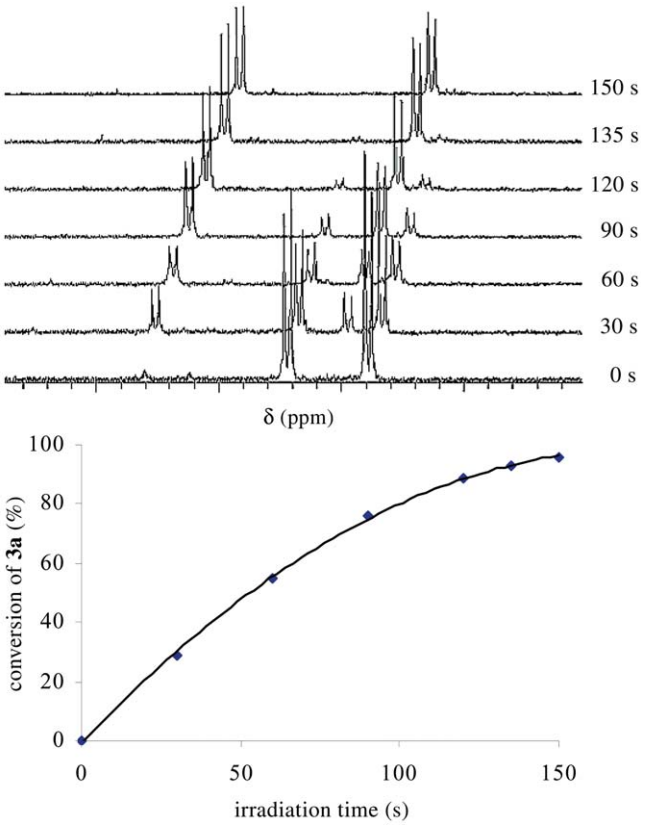


Figure 1 Photooxidation of **3a** ($4 \cdot 10^{-3}$ mmol) to **4a** with RFT (10 mol%) in D_2O (1 mL, 4% DMSO-d_6). Top: Stack plot of ^1H NMR spectra of the aromatic region (perspective view of spectra is used; no chemically induced shift of resonance signals was observed); bottom: reaction kinetic as monitored by NMR analysis.

No catalytic turnover was observed when the reaction was conducted in the absence of air oxygen. These findings confirm the proposed photocatalytic reaction mechanism. The quantum yield of the photocatalytic oxidation of **3a** was determined to be 0.023 [2.3%; c = 0.01 mol/L in 1 mL of H_2O and 1 mL of MeCN, 10 mol% of RFT, blue light (440 nm) irradiation]. At low catalyst concentrations (0.1 mol%) and prolonged reaction time (60 min), a minimal turnover number (TON) of 910 was determined. Imine **5** was formed exclusively when the reaction was performed in anhydrous acetonitrile. To demonstrate the use of the photocatalytic oxidation on a preparative scale, 1 mmol of **3a** was converted into **4a** using 1 mol% of RFT; under these conditions, aldehyde **4a** was isolated in 77% yield.

The optimized reaction conditions were then applied to the photocatalytic conversion of a variety of benzylamines; the results are summarised in Table 1.

The conversion rate of primary benzylamines depends on the electronic character of the arene: Benzene rings bearing electron-donating substituents lead to fast and complete conversion, while electron-poor arenes decelerate the photooxidation. This is in accordance with previous observations on flavin-mediated photooxidation of benzyl alcohols.[4]

Secondary amine **3e** was photooxidized to aldehyde **4c**, and branched benzylamine **3f** was likewise oxidized to the corresponding ketone, but benzylamine **3g**, having a *tert*-butyl group on the benzyl position, was converted into aldehyde **4a** through elimination of the substituent. This observation allows, in analogy to the photooxidation of 1-(4-methoxyphenyl)-2,2-dimethylpropan-1-ol,[11] the discrimination between electron-transfer and hydrogen-abstraction mechanisms for the photooxidation of benzylamines. Under the applied reaction conditions, we exclusively observe the electron-transfer pathway. Phenyl glycine methyl ester (**3h**) was not converted under the reaction conditions.

Compounds **3i** and **3k** were investigated for photooxidation as examples of aliphatic, rather than benzylic amines. Butylamine **3i** was not oxidized to butyraldehyde **4i** and rapid bleaching of RFT was observed after four minutes of irradiation. Butylamine was consumed when the irradiation time was prolonged to 60 minutes and the catalyst loading enhanced (100 mol% RFT), but no aldehyde formation could be detected by ^1H NMR analysis.

Aliphatic amine **3k**, which bears an electron-rich aromatic system, was photooxidized under the standard conditions to give aldehyde **4a** and a small amount of an unidentified side-product. The RFT photocatalyst bleached rapidly during the conversion of this substrate and addition of more RFT (two times 10 mol%) was necessary to complete the reaction.

As an example of a cyclic secondary benzylamine, tetrahydroisoquinoline **6** was submitted to the standard photooxidation conditions. Compound **6** was oxidized to the corresponding isoquinoline **7** in nearly quantitative yield; oxidative ring opening was not observed.

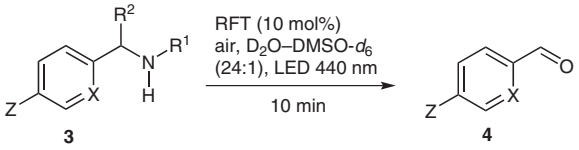
Photocatalytic Cleavage of Benzyl Protecting Groups

Benzyl protecting groups are widely used in organic synthesis for the protection of amines, carboxylic acids and alcohols. For their cleavage, various conditions are used, e.g., reduction, acetylation or oxidation, depending on the electron density on the benzyl protecting group.[12] However, benzyl deprotection in the presence of other functional groups that are easy to oxidize or reduce, can be difficult. One option to circumvent these problems is the use of photochemical methods for removing benzyl protecting groups.[12]

We investigated the use of the flavin-mediated photooxidation of benzylamines described above, to remove benzyl protecting groups under mild conditions to extend the scope of photocleavage methods.

Several benzyl-protected compounds were submitted to flavin-mediated photodeprotection on an analytical scale [c = 0.01 mol/L; 10 mol% of RFT in MeCN (0.5 mL) and H_2O (0.5 mL); LED irradiation]. Each sample was irradiated by two LEDs (440 nm, 3 W) under stirring in capped sample vials for the time given in Table 2.

Table 1 Photocatalytic Oxidation of Benzylamines[a]



3 4

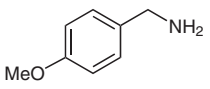
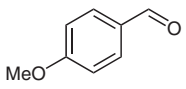
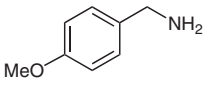
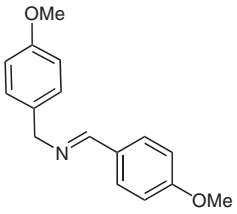
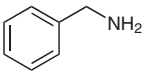
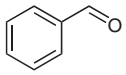
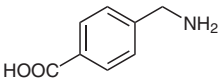
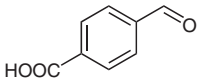
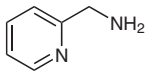
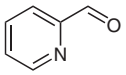
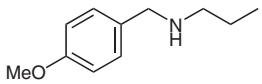
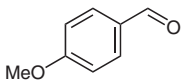
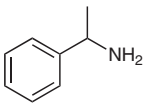
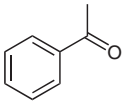
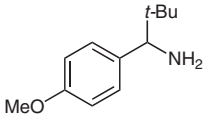
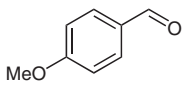
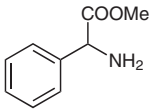
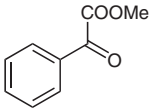
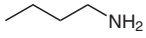
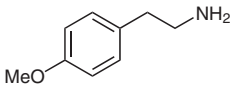
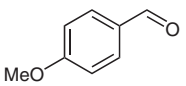
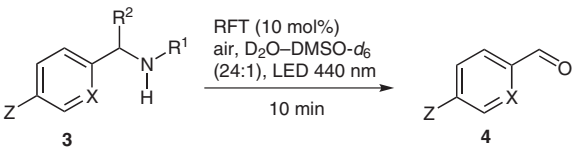
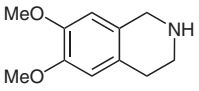
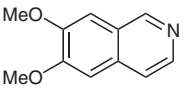
Amine	Product	Conversion (%)[b]
 **3a**	 **4a**	96 6[c] 0[d] 31[e] 91[f] 77[g]
 **3a**	 **5**	95[h]
 **3b**	 **4b**	79
 **3c**	 **4c**	16
 **3d**	 **4d**	50
 **3e**	 **4e**	90
 **3f**	 **4f**	44
 **3g**	 **4a**	95
 **3h**	 **4h**	0
 **3i**	 **4i**	0[i]
 **3k**	 **4a**	89[j]

Table 1 Photocatalytic Oxidation of Benzylamines[a] (continued)



3 4

Amine	Product	Conversion (%)[b]
 **6**	 **7**	97[k]

[a] Reaction conditions: amine ($4 \cdot 10^{-3}$ mmol) in D_2O (1 mL, 4% DMSO-d_6), RFT (10 mol%), Irradiation for 10 min at 440 nm (LED).
[b] Determined by ^1H NMR analysis.
[c] Without irradiation.
[d] Without catalyst.
[e] RFT 0.1 mol%, reaction time 60 min.
[f] RFT 30 mol%, 20% DMSO-d_6, deoxygenated solution.
[g] Isolated yield, amine (1 mmol), RFT (1 mol%), reaction time 2 h.
[h] Amine (0.1 mmol), anhydrous MeCN (1 mL).
[i] Reaction time 4 min.
[j] RFT 30 mol%, reaction time 15 min.
[k] 24% DMSO-d_6.

As expected from the results for the benzylamine oxidations, the unsubstituted benzyl protecting group (Bzl) was cleaved slower from primary amines than the 4-methoxybenzyl (Mob) group: The Mob protecting group was cleaved within 15 minutes giving only amines **10** and **13**, aldehyde **4a** and RFT, as indicated by HPLC (entries 1–3). Protected prolines **14** and **16** (entries 4 and 5) gave complex product mixtures upon photocatalytic flavin oxidation. In these cases, the deprotected secondary amine may act as an electron donor for the flavin, yielding unwanted amine oxidation side-products. The allylic double bond was not affected by flavin-mediated photodeprotection of allyl-amine **17** (entry 6), which was deprotected without any detectable side-products within 15 minutes. At pH 3 (adjusted by 0.1 N HCl), Mob-protected nitroaniline **19** (entry 7) was deprotected in a clean reaction, whereas a complex product mixture was obtained in a H_2O–MeCN mixture. This might be the result of overoxidation of the product of the deprotection reaction, aniline (**20**), as in the case of secondary amines.

The Mob-protected carboxylic acid **21** (entry 8) was partly deprotected under the applied conditions, whereas no conversion was obtained for the Bzl-protected acid **23** (entry 9).

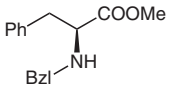
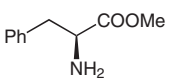
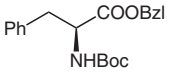
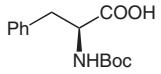
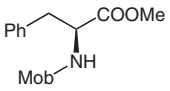
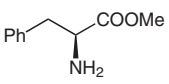
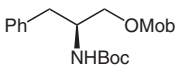
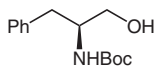
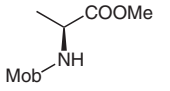
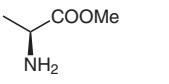
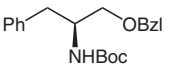
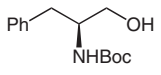
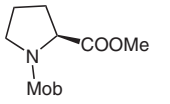
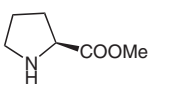
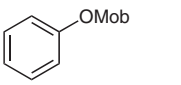
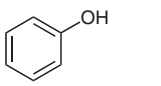
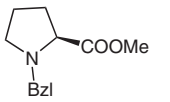
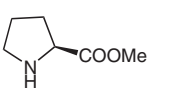
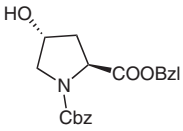
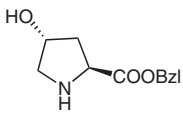
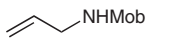
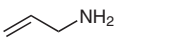
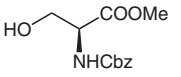
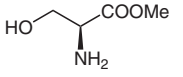
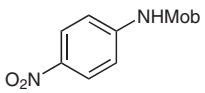
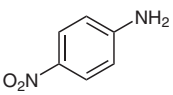
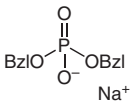
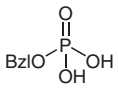
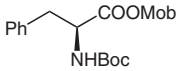
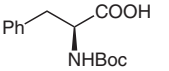
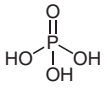
The protected alcohols **25** and **27** behaved similarly: Only the Mob group was partly cleaved under photocatalytic oxidation conditions (entry 10) within 15 minutes, whereas the Bzl-protecting group showed no reactivity at all. Mob-protected phenol **29** was deprotected (aldehyde **4a** was detected), but phenol **30** was immediately further oxidized to unidentified products under the photooxidative conditions.

The carboxybenzoyl (Cbz) protected amines in compounds **31** and **33** were not affected under the reaction conditions (entries 13 and 14), which should allow the selective deprotection of benzyl-protected amines in the presence of a Cbz-protected amine.

Sodium dibenzyl phosphonate **35** (entry 16) did not react under the applied reaction conditions. The solvent mixture of water and acetonitrile used for the deprotection reaction is of importance because no deprotection of the compounds shown in entries 2, 8 and 10 was observed using acetonitrile without addition of water. No reactions were observed when solutions of compounds **11** and **25** were irradiated in the absence of RFT or when the samples were stirred in the dark in the presence of 10 mol% RFT at pH 3. The presence of RFT and blue light irradiation is therefore essential for the benzyl photodeprotection.

Compounds **11** and **25** were photodeprotected on a 1 mmol scale (entries 2 and 10). For ease of purification, only 1 mol% of RFT was used as photocatalyst and the reactions were performed under acidic conditions (pH 3 adjusted with 0.1 N HCl)[13] in 250 mL Erlenmeyer flasks under irradiation with 12 LEDs (3 W each).[14] The hydrochloride salt of phenylalanine methyl ester was isolated by extraction and crystallization in 90% yield after 60 minutes irradiation of compound **11**. The deprotected alcohol **26** was isolated in 65% yield via column chromatography after 60 minutes of irradiation. All analytical data, including optical rotation of phenylalanine methyl ester hydro-

Table 2 Photocatalytic Deprotection of Benzyl Compounds[a]

Entry	Benzyl-protected compound	Product	Conversion (%)[b]	Time (min)	Entry	Starting material	Product	Conversion (%)[b]	Time (min)
1	 **9**	 **10**	81	60	9	 **23**	 **24**	0	30
2	 **11**	 **10**	91 90[c]	15	10	 **25**	 **26**	45 65[c]	30
3	 **12**	 **13**	99	15	11	 **27**	 **28**	0	30
4	 **14**	 **15**	product mixture[d]	15	12	 **29**	 **30**	0[d]	30
5	 **16**	 **15**	product mixture[d]	15	13	 **31**	 **32**	0	60
6	 **17**	 **18**	99	15	14	 **33**	 **34**	0	60
7	 **19**	 **20**	98[e]	30	15	 **35**	 **36a**	0	240
8	 **21**	 **22**	9	30			 **36b**		

[a] Reaction conditions: substrate (0.01 mmol) in H_2O (0.5 mL) and MeCN (0.5 mL), RFT (10 mol%), irradiation at 440 nm with two LEDs (3 W each) for the time indicated.
[b] Calculated from crude HPLC data of reaction mixtures.
[c] Isolated yield. Substrate (1.0 mmol), RFT (1 mol%), pH 3 adjusted with 0.1 N HCl, reaction time 60 min.
[d] Starting material was consumed.
[e] pH 3 adjusted with 0.1 N HCl.

chloride and alcohol **26**, were consistent with the analytical data of authentic samples.

In conclusion, photocatalytic oxidation of benzylamines to their corresponding aldehydes under mild conditions without over-oxidation has been accomplished using RFT as photocatalyst. The use of LEDs emitting in the visible region at 440 nm as light source for RFT excitation avoids undesired non-sensitized photo processes. Oxygen is employed as the terminal oxidant and H_2O_2 and NH_3 appear as sole side-products of the oxidation of primary benzylamines. The protocol is limited to benzylic amines bearing an electron-rich arene group.

Furthermore, we have developed a photocatalytic protocol for Mob group deprotection of primary amines and alcohols. Double bonds, benzyl-protected esters and alcohols are tolerated under the applied conditions. Mob esters react much slower and Cbz-protected amines and benzyl phosphate esters are inert under the photodeprotection conditions. The deprotection of protected secondary amines is not applicable, presumable due to the oxidation of the electron-rich secondary amines by excited RFT.

The reported procedures are easy to perform and robust on a laboratory scale. The photocatalyst and the light sources are readily available and the application limits of the process are well defined, which facilitate their use in organic synthesis.

Tetraacetyl riboflavin,[10] *N*-propyl-4-methoxybenzylamine (**3e**),[15] 2-(4-methoxyphenyl)ethanamine (**3k**),[16] Bzl-Phe-OMe (**9**), Mob-Phe-OMe (**11**), Mob-Ala-OMe (**12**),[17] Mob-Pro-OMe (**14**),[18] Bzl-Pro-OMe (**16**),[19] Boc-Phe-OMob (**21**),[20] Boc-Phe-OBzl (**23**),[21] *tert*-butyl 1-(benzyloxy)-3-phenylpropan-2-ylcarbamate (**27**),[22] and Cbz-(OH)-Pro-OBzl (**31**),[23] were prepared as previously reported. All other chemicals were purchased from commercial suppliers and used as received. Anhydrous DMF was purchased from Fluka. TLC was performed on silica gel 60 F254 aluminium sheets (Merck), with detection under 254 nm or 333 nm UV light. Flash column chromatography was carried out on silica gel (0.035–0.070 mm, 60 Å), obtained from Acros. NMR spectra were recorded with a Bruker spectrometer operating at 300 MHz (^{1}H NMR) or 75 MHz (^{13}C NMR) with TMS as the external standard. Electron-impact (EI) and chemical ionization (CI) mass spectra were recorded with a Finnigan TSQ 710 spectrometer. Electrospray ionization (ES) mass spectra were recorded with a ThermoQuest Finnigan MAT 9595 spectrometer. IR spectra were recorded with a Biorad Spectrometer Excalibur FTS 3000. Optical rotation was recorded with a Perkin–Elmer 241 Polarimeter. Melting points were determined with a Lambda Photometrics OptiMelt MPA 100. Luxeon high power royal blue LEDs [3 W, irradiation maximum 440 nm (+/– 10 nm)] were used as light sources. Petroleum ether (PE), where used, had a boiling range of 60–80 °C.

Photooxidation of Benzyl Amines on an Analytical Scale; General Procedure

Reaction mixtures of the amine ($4 \cdot 10^{-3}$ mmol) and RFT (10 mol%) in D_2O (1 mL) containing 4% DMSO-d_6 were irradiated by one LED (3 W; 440 nm) in capped sample vials. The course of the reaction was monitored by ^{1}H NMR analysis.

Benzylamine Photooxidation on 1 mmol Scale; Typical Procedure

4-Methoxybenzylamine (**3a**; 1.0 mmol) and RFT (0.01 mmol) were dissolved in MeCN–H_2O (4 mL/96 mL). The mixture was irradiated at 440 nm with 12 LEDs (3 W each) in a 250-mL Erlenmeyer flask, open to air, for 2 h. The pH was adjusted to 1 by addition of 1 N HCl and the product was extracted into Et_2O. The organic layer was dried over $MgSO_4$, concentrated and the residue was taken up in PE and filtered. Concentration of the filtrate gave aldehyde **4a** as a colourless oil (105 mg, 0.77 mmol, 77%).

Benzylamine Photodeprotection Reaction on an Analytical Scale; General Procedure

A reaction mixture containing the benzyl-protected compound (0.01 mmol) and RFT (10 mol%) in MeCN (0.5 mL) and H_2O (0.5 mL) was irradiated at 440 nm with two LEDs (3 W each) in a capped sample vial under air. When anaerobic or anhydrous conditions were used for comparison, the reaction mixtures were irradiated under inert atmosphere in sample vials capped with septa or vials mounted with $CaCl_2$-filled syringes. Degassing of solutions was achieved by three freeze-pump-thaw cycles.

Photodeprotection Reaction on 1 mmol Scale; General Procedure

A reaction mixture containing the benzyl-protected amine (1.0 mmol) and RFT (1 mol%) in MeCN (50 mL) and H_2O (50 mL) at pH 3 (adjusted by 0.1 N HCl), was irradiated at 440 nm with 12 LEDs (3 W each) in a 250 mL Erlenmeyer flask open to air. The conversion was monitored by TLC until completion of the reaction. MeCN was removed in vaccuo and the residue was washed with Et_2O. Concentration of the aqueous layer by lyophilization gave the crude product, which was crystallized from acetone–Et_2O in the case of the hydrochloride salt of phenylalanine methyl ester, or purified over silica (PE–EtOAc) in the case of compound **26**.

1-(4-Methoxyphenyl)-2,2-dimethylpropan-1-one[24]

Anisole (2.16 g, 20 mmol) and pivaloyl chloride (1.21 g, 10 mmol) were dissolved in toluene (6 mL) and $AlCl_3$ (1.33 g, 20 mmol) was added. The mixture was stirred at 70 °C for 20 min, cooled and 1 N HCl was added. The product was extracted into PE (3 × 10 mL), the organic layer was washed with sat. $NaHCO_3$ (30 mL) and dried over $MgSO_4$. Removal of the solvent and Kugelrohr distillation (160 °C/0.99 mbar) gave the title compound.

Yield: 1.56 g (81%); colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 9.06 Hz, 2 H, ArH), 6.90 (d, *J* = 9.06 Hz, 2 H, ArH), 3.85 (s, 3 H, CH_3), 1.37 (s, 9 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.3 (q, 1 × C), 162.0 (q, 1 × C), 131.0 (+, 2 × C), 130.1 (q, 1 × C), 113.2 (+, 2 × C), 55.4 (+, 1 × C), 43.9 (q, 1 × C), 28.4 (+, 3 × C).

MS (EI): *m*/*z* (%) = 192.1 (4) $[M]^+$, 135.0 (100).

1-(4-Methoxyphenyl)-2,2-dimethylpropan-1-amine (3g)

1-(4-Methoxyphenyl)-2,2-dimethylpropan-1-one (580 mg, 3.0 mmol) was dissolved in formamide (6 mL) and formic acid (3 mL) and the mixture was heated at reflux for 2 h. H_2O (20 mL) and Et_2O (20 mL) were added, and the organic layer was separated and washed with brine (30 mL), dried over $MgSO_4$ and the solvent was removed. The residue was dissolved in 1 N HCl (15 mL) and the mixture was heated at reflux for 1 h. The mixture was diluted with H_2O (50 mL) and a pH >10 was set by the addition of solid NaOH. The product was extracted into Et_2O (3 × 15 mL), the organic layer was dried over $MgSO_4$ and the solvent was removed to yield the title compound that solidified upon cooling.

Yield: 480 mg (83%); pale-yellow oil; mp 44–45 °C; R_f = 0.2 ($CHCl_3$–MeOH, 9:1).

IR (ATR): 3374, 3011, 2957, 2867, 1612, 1584, 1515, 1247, 1192, 1032, 818 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, J = 8.78 Hz, 2 H, ArH), 6.83 (d, J = 8.78 Hz, 2 H, ArH), 3.80 (s, 3 H, CH_3), 3.67 (s, 1 H, CH), 1.74 (br s, 2 H, NH_2), 0.89 (s, 9 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.4 (q, 1 × C), 135.7 (q, 1 × C), 129.2 (+, 2 × C), 112.9 (+, 2 × C), 64.7 (+, 1 × C), 55.2 (+, 1 × C), 35.1 (q, 1 × C), 26.8 (+, 1 × C), 26.5 (+, 1 × C), 26.4 (+, 1 × C).

MS (CI, NH_3): m/z (%) = 194.2 (17) $[M + H]^+$, 177.1 (100).

N-(4-Methoxybenzyl)prop-2-en-1-amine (17)[25]

Allylamine (428 mg, 7.5 mmol) and 4-methoxybenzaldehyde (**4a**; 1.36 g, 10 mmol) were dissolved in EtOH (15 mL) and the solution was stirred at r.t. for 18 h. $NaBH_4$ (709 mg, 18.7 mmol) was added and the mixture was stirred until gas evolution had ceased. H_3PO_4 (0.5 N, 10 mL) was added and the mixture was further stirred until gas evolution had ceased. The product was extracted into CH_2Cl_2 (3 × 10 mL), dried over $MgSO_4$ and the solvent was removed. The residue was purified by Kugelrohr distillation (125 °C/0.12 mbar) to yield the title compound.

Colourless oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.76 Hz, 2 H, ArH), 6.88 (d, J = 8.76 Hz, 2 H, ArH), 5.98–5.86 (m, 1 H, CH), 5.22–5.15 (m, 1 H, CH_2), 5.13–5.08 (m, 1 H, CH_2), 3.79 (s, 3 H, CH_3), 3.73 (s, 2 H, CH_2), 3.27 (d, J = 6.03 Hz, 2 H, CH_2), 1.44 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6 (q, 1 × C), 136.9 (+, 1 × C), 132.4 (q, 1 × C), 129.4 (+, 2 × C), 116 (–, 1 × C), 113.8 (+, 2 × C), 55.3 (+, 1 × C), 52.7 (–, 1 × C), 51.7 (–, 1 × C).

MS (CI, NH_3): m/z (%) = 178.1 (100) $[M + H]^+$.

N-(4-Methoxybenzyl)-4-nitrobenzenamine (19)[26]

4-Nitroaniline (1.04 g, 7.5 mmol) and 4-methoxybenzaldehyde (**4a**; 1.02 g, 7.5 mmol) were dissolved in MeOH (15 mL) and the solution was stirred at r.t. for 18 h. $NaBH_4$ (709 mg, 18.75 mmol) was added and the mixture was stirred until gas evolution had ceased. H_2O (30 mL) was added to the mixture and the product was extracted into EtOAc (3 × 10 mL). The organic layer was washed with 1 N HCl (20 mL), sat. $NaHCO_3$ (20 mL), dried over $MgSO_4$ and the solvent was removed. Purification over silica ($CHCl_3$) gave the title compound.

Yellow solid.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, J = 9.33 Hz, 2 H, ArH), 7.26 (d, J = 8.78 Hz, 2 H, ArH), 6.90 (d, J = 8.78 Hz, 2 H, ArH), 6.56 (d, J = 9.33 Hz, 2 H, ArH), 4.83 (br s, 1 H, NH), 4.35 (d, J = 5.49 Hz, 2 H, CH_2), 3.81 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (q, 1 × C), 153.1 (q, 1 × C), 138.2 (q, 1 × C), 129.3 (q, 1 × C), 128.8 (+, 2 × C), 126.4 (+, 2 × C), 114.3 (+, 2 × C), 11.3 (+, 2 × C), 55.4 (+, 1 × C), 47.2 (–, 1 × C).

MS (CI, NH_3): m/z (%) = 276.2 (100) $[M + NH_4]^+$, 259.2 (14) $[M + H]^+$.

***tert*-Butyl 1-(4-Methoxybenzyloxy)-3-phenylpropan-2-ylcarbamate (25)[27]**

Boc-phenylalaninol (1.5 g, 6.0 mmol) was dissolved in anhydrous DMF (12 mL) under a nitrogen atmosphere. The solution was cooled to 0 °C and NaH (60%, 552 mg, 13.8 mmol) was added portion-wise. The mixture was stirred for 60 min at 0 °C and 4-methoxybenzyl bromide (1.33 g, 6.6 mmol) was added. The mixture was allowed to warm to r.t. and stirred for an additional 18 h. The reaction was quenched with sat. NH_4Cl (20 mL) and H_2O (20 mL) was added. The product was extracted into Et_2O (3 × 15 mL), and the organic layer was washed with brine (20 mL), dried over $MgSO_4$ and concentrated. Purification over silica (PE–EtOAc) gave the title compound.

Yield: 1.44 g (3.86 mmol, 64%); colourless solid.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, J = 8.51 Hz, 2 H, ArH), 7.25–7.15 (m, 5 H, ArH), 6.90 (d, J = 8.51 Hz, 2 H, ArH), 4.93–4.87 (m, 1 H), 4.48 (d, J = 11.52 Hz, 1 H, CH_2), 4.39 (d, J = 11.52 Hz, 1 H, CH_2), 3.93 (br s, 1 H), 3.82 (s, 3 H, CH_3), 3.40–3.31 (m, 2 H, CH_2), 2.94–2.80 (m, 2 H, CH_2), 1.42 (s, 9 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (q, 1 × C), 155.4 (q, 1 × C), 138.3 (q, 1 × C), 130.2 (q, 1 × C), 129.5 (+, 2 × C), 129.5 (+, 2 × C), 128.4 (+, 2 × C), 126.3 (+, 2 × C), 79.3 (q, 1 × C), 72.9 (–, 1 × C), 69.7 (–, 1 × C), 55.3 (+, 1 × C), 51.7 (+, 1 × C), 37.9 (–, 1 × C), 28.4 (+, 3 × C).

MS (ESI): m/z (%) = 372.0 (100) $[M + H]^+$.

1-Methoxy-4-(phenoxymethyl)benzene (29)[28]

4-Methoxybenzyl chloride (320 mg, 2.05 mmol) was added to a mixture of phenol (565 mg, 6.0 mmol) and K_2CO_3 (1000 mg) in anhydrous acetone (10 mL) under nitrogen. The mixture was heated at reflux for 18 h, cooled and filtered. After removing the solvent, the crude product was purified over silica to yield the title compound.

Yield: 360 mg (1.98 mmol, 82%); colourless solid.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38 (d, J = 8.78 Hz, 2 H, ArH), 7.33–7.27 (m, 2 H, ArH), 7.00–6.97 (m, 3 H, ArH), 6.93 (d, J = 8.78 Hz, 2 H, ArH), 5.00 (s, 2 H, CH_2), 3.83 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5 (q, 1 × C), 158.9 (q, 1 × C), 129.5 (+, 2 × C), 129.3 (+, 2 × C), 129.1 (q, 1 × C), 120.9 (+, 1 × C), 114.9 (+, 2 × C), 114.0 (+, 2 × C), 69.7 (–, 1 × C), 55.3 (+, 1 × C).

MS (EI): m/z (%) = 214.1 (2) $[M]^+$, 121.1 (100).

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