

Vanadium-Catalyzed Oxidative Debenzylation of *O*-Benzyl Ethers at ppm Level

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Dedicated to Prof. Timothy C. Gallagher on the occasion of his 60th birthday.



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Abstract: An advantageous methodology for the oxidative debenzylation of ethers has been developed. Very low amounts of a catalyst system based on vanadyl acetylacetonate and a triazole type pincer ligand allow the selective oxidative cleavage of a number of *O*-benzyl ethers in the presence of oxygen as the sole oxidant. The methodology tolerates a number of functional groups such as halo-, alkoxy-, or trifluoromethylarenes, alkyne, alkene, ether, and acetal units. Large-scale deprotections can be also carried out by the optimized procedure, which is amenable to enantioenriched reactants as well.

Keywords: debenzylation; nitrogen ligands; oxidation; oxygen; vanadium

In the last years, process efficiency has become a priority for organic chemistry. Even so, many structurally complex organic products have to be prepared by multistep pathways and, therefore, protection/deprotection sequences of functional groups are often unavoidable.^[1] In these cases, the suitability, selectivity as well as the environmental and economical aspects of the protection process are crucial in order to optimize the synthetic route.

The benzyl group is commonly used to mask alcohol functionalities in numerous syntheses due to the easy preparation and high stability of benzyl ethers towards a number of reaction conditions.^[2] Cleavage is most often achieved reductively,^[3–5] by transition metal-catalyzed hydrogenolysis,^[3] or by use of Lewis^[6] or Brønsted acids.^[7] However, they are not compatible with several labile or reduction susceptible func-

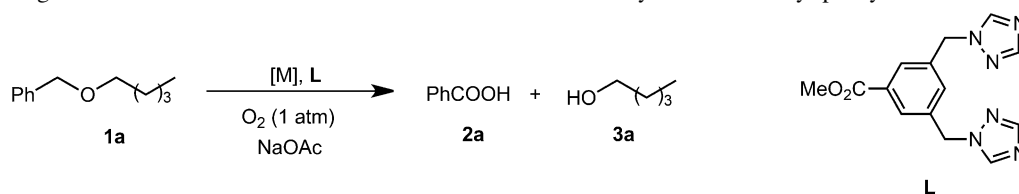
tional groups (alkenyl and alkynyl derivatives, carbonyls and halo compounds, some alkoxy groups, inter alia). Among the alternatives to the above procedures,^[8] oxidative cleavage is an advantageous strategy to carry out debenzylation in multifunctional substrates, although limitations regarding the type of substrates that can be deprotected have appeared even by this method.^[9]

Oxygen is clearly a sustainable and therefore advantageous option. However, in spite of the increasing number of metal-catalyzed aerobic oxidative processes reported in the last years,^[10] the molecular oxygen-mediated oxidative cleavage of ethers has been scarcely explored to date.^[9h]

Our research has shown that low amounts of palladium complexes and palladium- or nickel-ligand systems can promote the oxidation of arylcarbinols and arylmethylene compounds, arylacetylenes and styrene derivatives.^[11] Following this research line, we wish to present a general and selective method for the vanadium-catalyzed aerobic *O*-debenzylation of ethers.

To begin our investigation, benzyl pentyl ether **1a** was heated in an oxygen atmosphere for 24–96 h along with a transition metal source (0.01 mol%). A wide number of bases, ligands and solvents were assayed in a preliminary set of experiments, and cleavage products were observed in detectable yields only when NaOAc and the readily available bis-triazolyl ligand **L** were present in the mixture. These results led us to further explore the reaction conditions. As shown in Table 1, the reaction outcome was highly influenced by the metal species and reaction media (entries 1–11). Although no reaction happened when iron(II) bromide was employed (entries 2 and 7), cleavage of the substrate was observed when cobalt(II) chloride, nickel(II) bromide or vanadyl acetylacetonate were used in dioxane or PEG 400

Table 1. Screening of reaction conditions for the aerobic oxidative debenzylation of benzyl pentyl ether **1a**.^[a]



Entry	M (mol%)	L (mol%)	Solvent	Temp. [°C]	Time [h]	2a [%] ^[b]	3a [%] ^[b]
1	FeBr ₂ (0.01 mol%)	0.01 mol%	dioxane	130°C	96 h	– ^[c]	–
2	CoCl ₂ (0.01 mol%)	0.01 mol%	dioxane	130°C	96 h	20	–
3	NiBr ₂ (0.01 mol%)	0.01 mol%	dioxane	120°C	96 h	53	40
4	VO(acac) ₂ (0.01 mol%)	0.01 mol%	dioxane	120°C	96 h	50	48
5	CoCl ₂ (0.01 mol%)	0.01 mol%	DMA	120°C	96 h	– ^[c]	–
6	FeBr ₂ (0.01 mol%)	0.01 mol%	PEG 400	120°C	96 h	– ^[c]	–
7	CoCl ₂ (0.01 mol%)	0.01 mol%	PEG 400	120°C	96 h	40	–
8	NiBr ₂ (0.01 mol%)	0.01 mol%	PEG 400	120°C	96 h	73	72
9	VO(acac) ₂ (0.01 mol%)	0.01 mol%	PEG 400	120°C	96 h	87	83
10	NiBr ₂ (0.01 mol%)	0.01 mol%	THF	120°C	96 h	< 5	< 5
11	VO(acac) ₂ (0.01 mol%)	0.01 mol%	H ₂ O	120°C	96 h	– ^[c]	–
12	NiBr ₂ (0.01 mol%)	–	PEG 400	120°C	96 h	– ^[c]	–
13	VO(acac) ₂ (0.01 mol%)	–	PEG 400	120°C	96 h	65	66
14	VO(acac) ₂ (0.01 mol%)	0.01 mol%	PEG 400	120°C	48 h	81	80
15	VO(acac) ₂ (0.01 mol%)	–	PEG 400	120°C	48 h	– ^[c]	–
16	VO(acac) ₂ (0.01 mol%)	0.01 mol%	PEG 1500	120°C	48 h	– ^[c]	–
17	VO(acac) ₂ (0.01 mol%)	0.01 mol%	glycerol	120°C	48 h	70	–
18	VO(acac) ₂ (0.01 mol%)	0.01 mol%	PEG 400	100°C	48 h	– ^[c]	–
19	VO(acac) ₂ (0.01 mol%)	0.01 mol%	PEG 400	120°C	24 h	67	62
20	VO(acac) ₂ (10 ^{–5} mol%)	10 ^{–5} mol%	PEG 400	120°C	48 h	81	80
21	VO(acac) ₂ (10 ^{–5} mol%)	10 ^{–5} mol%	PEG 400	120°C	24 h	53	49
22	–	10 ^{–5} mol%	PEG 400	120°C	48 h	– ^[c]	–
23	VO(acac) ₂ (10 ^{–5} mol%)	–	PEG 400	120°C	48 h	– ^[c]	–

^[a] Reaction conditions: [(pentyloxy)methyl]benzene (1 mmol), Na(OAc) (0.1 mmol), O₂ (1 atm), solvent (1 mL mmol^{–1} of substrate).

^[b] Isolated yield.

^[c] Starting material was recovered.

(entries 2–4 and 7–9). Whereas cobalt(II) chloride provided 1-pentanol only in moderate yields (entries 5 and 6) better results were achieved from nickel(II) bromide and vanadyl acetylacetonate in PEG-400 (entries 8 and 9).

Using the best catalyst system so far, that is, VO(acac)₂/L, we optimized the reaction time, temperature and catalyst loading. Reducing the reaction time by half only caused a slight decrease in reaction yield (entry 9 vs. 14). The drop in the yield was greater when shorter reaction times were used (entry 19). It was necessary to carry out the reaction at 120°C since only starting material was recovered when the reaction mixture was heated at 100°C (entry 18).

Cleavage to benzoic acid was also observed in glycerol, but we were unable to isolate *n*-pentanol probably due the high affinity between both aliphatic alcohols. With regard to the activity of the catalyst system, we were delighted to observe that comparable yields were obtained when only 10^{–5} mol% of VO(acac)₂/L were used (entry 14 vs. 20). 1-Pentanol

3a could be also obtained by using 0.01 mol% of VO(acac)₂ in the absence of bis-triazolyl derivative L, but with a lower yield (Table 1, entry 9 vs. 13). Interestingly, the use of ligand L proved to be crucial when shorter reactions times or lower catalytic loadings were used (entries 14 vs. 15 and 20 vs. 23). Likewise, blank experiments demonstrated that VO(acac)₂ was essential for the oxidative process (entry 22). Other vanadium sources (V₂O₅, VCl₃) were evaluated and found to be ineffective for the target transformation

The optimized reaction conditions (Table 1, entry 20) were then successfully applied to a number of benzyl ethers. As shown in Table 2, the oxidative rupture of alkyl benzyl ethers provided selectively benzoic acid and the corresponding alcohol regardless of the electronic nature of the alkyl radical and the steric hindrance present in the substrate. Moreover, the cleavage occurred with total retention of configuration at stereogenic centers, even when bearing the benzyloxy moiety. This fact was confirmed by comparison of the optical rotation of (1*R*,2*S*,5*R*)-(–)-menthol

Table 2. Substrate scope for the oxidative cleavage of benzyl alkyl ethers.^[a]

$$\text{Ph-CH}_2\text{-O-R} \xrightarrow[\text{NaOAc (10 mol\%)}]{\text{O}_2 \text{ (1 atm), VO(acac)}_2 \text{ } 10^{-5} \text{ mol\%, L } 10^{-5} \text{ mol\%}} \text{PhCOOH} + \text{R-OH}$$

$$\text{1a-i} \quad \quad \quad \text{2a} \quad \quad \quad \text{3a-i}$$
 PEG-400, 120 °C, 48 h

Entry	1	2a (%) ^[b]	3a (%) ^[b]
1		PhCOOH 2a (81%)	HO-CH ₂ -C(CH ₃) ₃ 3a (80%)
2		PhCOOH 2a (86%)	HO-CH ₂ -C(CH ₃) ₂ -CH ₂ -CH ₂ -CH ₃ 3b (79%)
3		PhCOOH 2a (76%)	HO-CH ₂ -CH(CH ₃)-CH ₂ -CH ₃ 3c (70%)
4		PhCOOH 2a (81%)	HO-CH ₂ -CH(CH ₃)-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₃ 3d (78%)
5		PhCOOH 2a (81%)	HO-CH ₂ -C ₆ H ₁₁ 3e (63%)
6		PhCOOH 2a (68%)	HO-CH ₂ -C(CH ₃) ₂ -CH ₂ -C(CH ₃) ₃ 3f (61%)
7		PhCOOH 2a (93%)	HO-CH ₂ -C ₆ H ₁₀ (CH ₃) ₂ 3g (90%)
8		PhCOOH 2a (80%)	HO-CH ₂ -C ₁₀ H ₁₅ 3h (70%)
9		PhCOOH 2a (78%)	HO-CH ₂ -CH ₂ -O-CH ₃ 3i (76%)

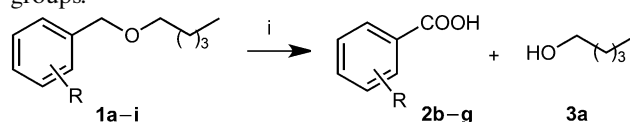
^[a] Reaction conditions: **1** (1 mmol), VO(acac)₂ (10⁻⁵ mol%), **L** (10⁻⁵ mol%), Na(OAc) (0.1 mmol), O₂ (1 atm), PEG (1 mL mmol⁻¹), 120 °C, 48 h.

^[b] Isolated yield.

3g and (1*S*,2*R*,4*S*)-(-)-borneol **3h** performed before the etherification and after the clean debenzoylation step.^[12] On account of the excellent results so far, we attempted to broaden the scope of the procedure to other benzyl-based protecting groups.

As displayed in Table 3, the *p*-methylbenzyl, *p*-fluorobenzyl (PFB), *p*-trifluoromethylbenzyl, *p*-methoxy-

Table 3. Oxidation of other benzyl-based protecting groups.^[a]



i: O₂ (1 atm), VO(acac)₂ 10⁻⁵ mol%, **L** 10⁻⁵ mol%, NaOAc (10 mol%), PEG-400, 120 °C, 48 h

Entry	1	2 (%) ^[b]	3a (%) ^[b]
1		PhCOOH 2b (82%)	HO-CH ₂ -C(CH ₃) ₃ 3a (76%)
2		PhCOOH 2c (71%)	HO-CH ₂ -C(CH ₃) ₃ 3a (68%)
3		PhCOOH 2d (83%)	HO-CH ₂ -C(CH ₃) ₃ 3a (79%)
4		PhCOOH 2e (70%)	HO-CH ₂ -C(CH ₃) ₃ 3a (68%)
5		PhCOOH 2f (83%)	HO-CH ₂ -C(CH ₃) ₃ 3a (81%)
6		PhCOOH 2g (55%)	HO-CH ₂ -C(CH ₃) ₃ 3a (74%)

^[a] Reaction conditions: **1** (1 mmol), VO(acac)₂ (10⁻⁵ mol%), **L** (10⁻⁵ mol%), Na(OAc) (0.1 mmol), O₂ (1 atm), PEG (1 mL mmol⁻¹), 120 °C, 48 h.

^[b] Isolated yield.

benzyl (PMB), *m*-methoxybenzyl (MMB), and 2-naphthylmethyl (NAP) ethers of 1-pentanol were effectively cleaved to provide the latter carbinol and the corresponding arenecarboxylic acids. Slightly better yields were obtained for the cleavage from substrates bearing non-substituted (Bn) or electron-donating groups (PFB, PMB, NAP) (Table 1, entry 1 and Table 3, entries 1, 3, 5, 6 vs. Table 3, entries 2 and 4).

A clear effect of electronic or steric factors on the reaction rates was not found, although the presence of alkoxy groups provoked a decrease in the rate of the reaction (e.g., full conversion was achieved for ethers **1a** or **1l** after 36 h under the optimized reaction conditions, but 48 h were required for substrates **1m** or **1n**).

Interestingly, only the cleavage product resulting from the selective oxidation of the *O*-benzylic position was observed when other unsaturated C–C

bonds were present in the starting material (Table 4, entries 7–9). No other type of oxidation products were detected, and the high selectivity for the *O*-benzylic position was evidenced by the cleavage of benzyl phenethyl ether **1s** (Table 4, entry 4).

Benzoic acid derivatives were exclusively obtained from symmetrical dibenzyl ethers **1p** and **1q** (Table 4, entries 1 and 2). However, the aerobic debenzoylation of non-symmetric 5-[(phenylmethoxy)methyl]-1,3-

benzodioxole **1r** provided both carboxylic acid **2a** and piperonyl alcohol **3j** (entry 3).

It can therefore be proposed that the presence of the methylenedioxy group, following the aforementioned trend of alkoxyated substrates, slows down the oxidation of the benzylic position next to the benzodioxolane. This fact opens new possibilities for the debenzoylation of benzyl alcohol derivatives.

Phenol **3i** was also obtained from (benzyloxy)benzene (entry 5), and other alkoxyated or phenoxyated substrates underwent reaction most effectively under the optimized conditions (**1i** and **1u**, Table 2, entry 9 and Table 4, entry 6 respectively).

It should be pointed out the simple catalyst–product separation was achieved by extraction from the polyethylene glycol solution. As expected, both cleavage products could be easily separated by acid–base extraction strategies. This aqueous protocol for the separation of oxidation products prevented recovery of the PEG reaction medium. Alternatively, the latter solvent could be recovered by extraction of the crude with ethyl acetate and then reused.

Moreover, *O*-debzoylation could be performed at a larger scale. Treatment of 1.5 g of ether **1a** provided benzoic acid **2a** and alcohol **3a** in 80% and 77% yield, respectively.^[12]

Finally, there are no conclusive results regarding the reaction pathway. The conversion rate vs. time kinetic plot for the debenzoylation of ether **1a** clearly shows an induction time which could suggest the participation of heterogeneous catalysts.^[12] However, the results for poisoning assays support the hypothesis of active homogeneous catalytic species, since the addition of substoichiometric or overstoichiometric amounts of Hg, CS₂, PPh₃, Py and PVPy had no influence in the outcome of the reaction.^[12] A partial degradation of polyethylene glycol under thermal aerobic conditions is expected to occur,^[13] thus forming small amounts of formate groups at the end of the polymer chains that would account for hydride transfer processes and hydroperoxide formation by oxygen insertion.^[11d,14]

In conclusion, a general, efficient procedure for the oxidative debenzoylation of ethers has been developed. The methodology is clearly advantageous since infinitesimal amounts of the vanadium-based catalyst system and molecular oxygen as the only oxidant at atmospheric pressure are needed. A number of functionalities usually affected by other debenzoylation procedures are tolerated by our method, thus featuring an excellent selectivity for the oxidation at the *O*-benzylic carbon over other labile positions. Chirality is preserved under the reaction conditions, which are also suitable for the aerobic deprotection of other benzyl-based protecting groups (PMB, MMB, PFB, and NAP *inter alia*). Gram-scale reactions can be easily performed, and the use of the polyethylene

Table 4. Oxidative rupture of symmetric and labile groups-containing benzyl ethers.^[a]

Entry	1	2 (%) ^[b]	3 (%) ^[b]
1		PhCOOH 2a (90%)	---
2		MeO-C6H4-COOH 2h (83%)	---
3		PhCOOH 2a (82%)	HO-CH2-C6H3(OCH2)2 3j (82%)
4		PhCOOH 2a (77%)	HO-CH2-CH2-Ph 3k (73%)
5		PhCOOH 2a (60%)	HO-C6H5 3i (53%)
6		PhCOOH 2a (87%)	HO-CH2-CH2-O-Ph 3m (85%)
7		PhCOOH 2a (69%)	HO-(CH2-CH=CH-CH2)2 3n (63%)
8		PhCOOH 2a (66%)	HO-CH2-CH2-C≡CH 3o (54%)
9		PhCOOH 2a (62%)	HO-CH2-CH2-CH2-C≡CH 3p (60%)

^[a] Reaction conditions: **1** (1 mmol), VO(acac)₂ (10⁻⁵ mol%), **L** (10⁻⁵ mol%), Na(OAc) (0.1 mmol), O₂ (1 atm), PEG (1 mL mmol⁻¹), 120 °C, 48 h.

^[b] Isolated yield.

^[c] Reaction time: 96 h.

glycol 400 as solvent facilitates catalyst–product separation.

Experimental Section

General Information

Commercially available reagents were used throughout without purification unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz for ^1H and 75.4 MHz for ^{13}C) at 20 °C. Chemical shifts (δ) are given in ppm downfield from Me_4Si and are referenced as internal standard to the residual solvent (unless indicated) CDCl_3 ($\delta=7.26$ for ^1H and $\delta=77.00$ for ^{13}C). Coupling constants, J , are reported in hertz (Hz). Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F254, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 230–400 mesh ASTM). IR spectra were recorded on Perkin–Elmer 1600 FT and JASCO FTIR-4100 infrared spectrophotometers as thin films, and only noteworthy absorptions are reported in cm^{-1} . Drying of organic extracts during work-up of reactions was performed over anhydrous Na_2SO_4 . Evaporation of solvents was accomplished with a Büchi rotatory evaporator. MS and HR-MS were measured using a Waters GCT mass spectrometer. Optical rotations were measured at 20 °C on a Jasco P-2000 polarimeter with sodium lamp at 589 nm and a path length of 1 dm. Solvent and concentration are specified in each case.

General Procedure for the Aerobic Cleavage of Benzyl Ethers in the Presence of $\text{VO}(\text{acac})_2$ and Methyl 3,5-Bis[(1*H*-1,2,4-triazol-1-yl)methyl]benzoate **L**

A round-bottom flask equipped with a magnetic stirrer bar was charged with ether **1** (1 mmol), NaOAc (8.0 mg, 0.1 mmol), $\text{VO}(\text{acac})_2$ (20 μL of a 5×10^{-6} M solution in PEG-400, 10^{-7} mmol), **L** (20 μL of a 5×10^{-6} M solution in PEG-400, 10^{-7} mmol) and PEG 400 (1 mL) at room temperature. The system was purged with molecular oxygen, and an oxygen-filled balloon (1–1.2 atm) was connected. The mixture was heated at 120 °C under stirring for 48 h. The reaction outcome was monitored by ^1H NMR. Upon completion, the mixture was cooled to room temperature and HCl 0.5 M (10 mL) was added. The acidified mixture was refluxed for 5 h, and after cooling, water was added (30 mL approx.). The resulting solution was extracted with Et_2O (4 \times 6 mL) and the combined organic layers were washed with brine (1 \times 5 mL), dried over anhydrous Na_2SO_4 and evaporated under vacuum to give a residue which was purified by flash column chromatography using hexane:ethyl acetate as eluent (see the Supporting Information).

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Vanadium-Catalyzed Oxidative Debenzylation of *O*-Benzyl Ethers at ppm Level

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