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Pd/C-Catalyzed Deoxygenation of Phenol Derivatives Using Mg Metal and MeOH in the Presence of NH$_4$OAc

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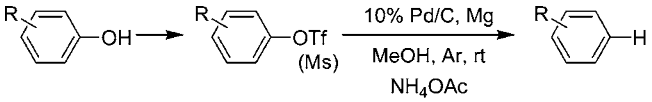
ABSTRACT



A Pd/C-catalyzed deoxygenation method of phenolic hydroxyl groups via aryl triflates or mesylates using Mg metal in MeOH at room temperature was developed. The addition of NH$_4$OAc dramatically affects the reactivity and reaction rate. This method is particularly attractive to provide an environmentally benign and widely applicable removal method of phenolic alcohols under quite mild reaction conditions.

Many phenolic moiety-containing organic compounds are well-known as biologically and functionally important compounds and phenolic hydroxyl groups frequently play an important role in expressing those activities.[1] Therefore, the development of a simple, efficient, and chemoselective method of deoxygenation of phenol derivatives is quite important to prepare the corresponding nonphenolic derivatives as reference compounds and/or biologically active natural or new synthetic molecules such as angelicin,[2] vancomycin,[3] and so on. Since a phenolic hydroxyl group is a quite poor leaving group, it should be activated prior to the deoxygenation. While a few direct deoxygenation methods of phenol derivatives have been reported,[4] such conventional procedures require, a vast amount (5−10 equiv) of the reagents,[4a−c] leading to low yields,[4a] and are limited to the phenolic hydroxyl group of fused aromatics.[4b,c] The conversion of the phenolic hydroxyl group to the corresponding sulfonate,[2,5,6,7] isourea,[5,8] dimethyl thiocarbamate,[5] aryl ether,[9] 5-phenyltetrazolyl ether,[10] and phosphate ester[11] is employed for activation as a substrate of reductive deoxygenation. Nevertheless, these conventional methods still include disadvantages such as lack of stability of the activated

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(1) (a) Okuda, T.; Yoshida, T.; Hatano, T. *Planta Med.* **1989**, *55*, 117. (b) Akiyama, H.; Sakushima, J.; Taniuchi, S.; Kanda, T.; Yanagida, A.; Kojima, T.; Teshima, R.; Kobayashi, Y.; Goda, Y.; Toyoda, M. *Biol. Pharm. Bull.* **2000**, *23*, 1370.

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(3) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700.

(4) (a) Severin, T.; Ipach, I. *Synthesis* **1973**, 796. (b) Konieczny, M.; Harvey, R. G. *J. Org. Chem.* **1979**, *44*, 4813. (c) Node, M.; Nishide, K.; Ohta, K.; Fujita, E. *Tetrahedron Lett.* **1982**, *23*, 689.

(5) Sebök, P.; Timar, T.; Eszenyi, T.; Patonay, T. *J. Org. Chem.* **1994**, *59*, 6318 and references therein.

(6) (a) Rottendorf, H.; Sternhell, S. *Aust. J. Chem.* **1963**, *16*, 647. (b) Clauss, K.; Jensen, H. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 918. (c) Lonsky, W.; Traitler, H.; Kratzl, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 169. (d) Subramanian, L. R. *Synthesis* **1984**, 481. (e) Cacchi, S.; Ciattini, P. G.; Morera, E.; Orter, G. *Tetrahedron Lett.* **1986**, *27*, 5541. (f) Chen, Q.-Y.; He, Y.-B.; Yang, Z.-Y, *J. Chem. Soc., Chem. Commun.* **1986**, 1452. (g) Cabri, W.; Bernardinis, S. D.; Francalanci, F.; Penco, S. *J. Org. Chem.* **1990**, *55*, 350. (h) Saa, J. M.; Dopico, M.; Martorell, G.; Garcia-Raso, A. *J. Org. Chem.* **1990**, *55*, 991. (i) Sasaki, K.; Sakai, M.; Sakakibara, Y.; Takagi, K. *Chem. Lett.* **1991**, 2017. (j) Kotsuki, H.; Datta, P. K.; Hayakawa, H.; Suenaga, H. *Synthesis* **1995**, 1348. (k) Lipshutz, B. H.; Buzard, D. J.; Vivian, R. W. *Tetrahedron Lett.* **1999**, *40*, 6871−6874.

(7) Recently Pd(OAc)$_2$-catalyzed reductive deoxygenation methods of polymer supported aromatic sulfonates are reported as a quite useful tool for combinatorial chemistry, while a perfluorated linker, phosphine ligand, and heating conditions are required; see: (a) Pan, Y.; Holmes, C. P. *Org. Lett.* **2001**, *3*, 2769. (b) Cammidge, A. N.; Ngaini, Z. *Chem. Commun.* **2004**, 1914. (c) Revell, J. D.; Ganesan, A. *Chem. Commun*, **2004**, 1916.

(8) Vowinkel, E.; Wolff, C. *Chem. Ber.* **1974**, *107*, 907.

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(10) (a) Musliner, W. J.; Gates, J. W., Jr. *J. Am. Chem. Soc.* **1966**, *88*, 4271. (b) Hussey, J.; Johnstone, R. A. Q. *Tetrahedron* **1982**, *38*, 3775.

(11) (a) Pelletier, S. W.; Locke, D. M. *J. Org. Chem.* **1958**, *23*, 131. (b) Kenner, G. W.; Williams, N. R. *J. Chem. Soc.* **1955**, 522. (c) Goldkamo, A. H.; Hoehn, W. M.; Mikulec, R. A.; Nutting, E. F.; Cook, D. L. *J. Med. Chem.* **1965**, *8*, 409. (d) Rossi, R. A.; Bunnett, J. F. *J. Org. Chem.* **1973**, *38*, 2314. (e) Shafer, S. J.; Closson, W. D.; van Dijk, J. M. F.; Piepers, O.;

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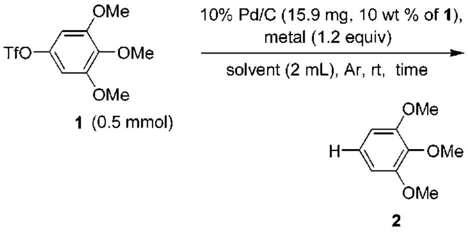
starting materials,[6g] requirement of an environmentally harmful phosphine ligand, and/or a vast amount of a metal-reducing catalyst or reagent, and so on.

In the course of our investigations to develop new Pd/C-catalyzed synthetic reactions, we have found that Mg metal is a particularly effective and mild reagent for the heterogeneous Pd/C-catalyzed traceless deoxygenation of aryltriflates[12] to arenes in MeOH.[13]

Initially, we examined 10% Pd/C-catalyzed deoxygenation of 3,4,5-trimethoxyphenyl triflate (**1**) with 1.2 equiv of Mg metal[14] in MeOH under Ar atmosphere. Amazingly, the corresponding 1,2,3-trimethoxybenzene (**2**) was obtained in 100% conversion yield (by ^{1}H NMR) at room temperature while the use of 0.5 equiv of Mg metal reduced the conversion yield to ca. 50% (Table 1, entry 2), and the reaction did not proceed without Mg metal (entry 1) or 10% Pd/C as a catalyst (entry 4). In contrast, the addition of Zn[15] or Fe powder, Al or Ni turnings, was not effective for the reaction (entries 5−8). It should be noted that the reaction is entirely solvent-specific and the use of MeOH as a solvent is quite essential for the progress of this reaction (compare entry 3 with entries 9−12).

Table 1. Pd/C-Catalyzed Reductive Cleavage of 3,4,5-Trimethoxyphenyl Triflate (**1**) Using Various Metals and Solvents

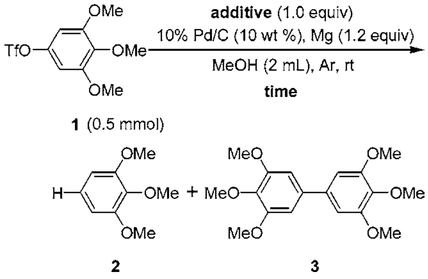


entry	metal	solvent	time (h)	**1/2**[a]
1	none	MeOH	24	100:0
2	Mg (0.5 equiv)	MeOH	24	55:45
3	Mg	MeOH	12	0:100
4[b]	Mg	MeOH	24	100:0
5	Zn	MeOH	24	100:0
6	Al	MeOH	24	100:0
7	Fe	MeOH	24	100:0
8	Ni	MeOH	24	100:0
9	Mg	H_2O	24	100:0
10	Mg	EtOH	24	100:0
11	Mg	^{i}PrOH	24	100:0
12	Mg	THF	24	100:0

[a] Determined by ^{1}H NMR. [b] Without 10% Pd/C.

Optimization studies produced remarkable enhancement in the reactivity, primarily as a result of the acceleration effect of the addition of NH_4OAc as an additive.[16] The use of ammonium salts generally gave the essential effect (Table 2, entries 2, 3, and 5) while NaOAc rather decreased the conversion ratios (entry 4).[17] Thus, the reaction in the presence of 1.0 equiv of NH_4OAc could be completed within only *0.5 h* at room temperature (entry 3) although the completion of the reaction required 12 h without NH_4OAc (entry 1).

Table 2. Effect of Additive on the Pd/C-Catalyzed Reductive Cleavage of 3,4,5-Trimethoxyphenyl Triflate (**1**)



entry	additive	time (h)	**1/2/3**[a]
1	none	12	0:100:0
2	NH_4OAc (0.01 equiv)	6	0:100:0
3	**NH_4OAc**	**0.5**	**0:100:0**
4	NaOAc	24	73:22:6
5	NH_4Cl	1	0:100:0

[a] Determined by ^{1}H NMR.

These optimized reaction conditions[18] are generally applicable toward diverse aryl triflates with both electron-donating and -withdrawing groups in 83−99% isolated yields of the corresponding arene products (Table 3).

Buck, H. M. *J. Am. Chem. Soc.* **1977**, *99*, 5118. (f) Dominianni, S. J.; Ryan, C. W.; DeArmitt, C. W. *J. Org. Chem.* **1977**, *42*, 344. (g) Welch, S. C.; Walters, M. E. *J. Org. Chem.* **1978**, *43*, 4797. (h) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y. *J. Org. Chem.* **1979**, *44*, 4508.

(12) Recently, a practical and convenient synthetic method of preparing aryl triflates under aqueous conditions was reported by Merck's research group; see: Frantz, D. E.; Weaver, D. G.; Carey, J. P.; Kress, M. H.; Dolling, U. H. *Org. Lett.* **2002**, *4*, 4717.

(13) (a) A selective reduction method of conjugated multiple bonds by excess amount of Mg metal−MeOH has been well-known, see: Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999; p 13. (b) Olah et al. reported a Pd/C-catalyzed reduction of nonconjugated multiple bonds with 5 equiv of Mg metal−MeOH; see: Olah, G. A.; Prakash, G. K. S.; Arranaghi, M.; Bruce, M. R. *Angew. Chem., Int. Ed.* **1981**, *20*, 92.

(14) Mg turnings for a Grignard reaction can be used without any pretreatment.

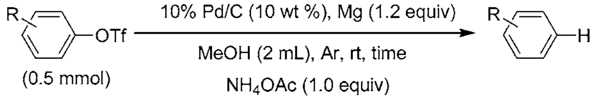
(15) Sakai et al. reported[6i] a homogeneous Ni(0)−dppp/PPh_3-catalyzed reduction of aryl triflates with Zn powder although such pioneering method required phosphine ligands and unstable in situ generated Ni(0) complex as a catalyst.

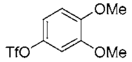
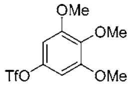
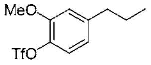
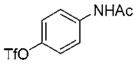
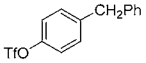
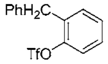
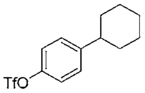
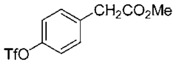
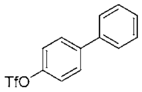
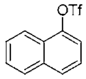
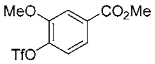
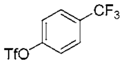
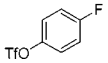
(16) Recently, we have reported the acceleration effect of NH_4OAc toward the monoalkylation method of amines using nitriles as an alkylating agent; see: Sajiki, H.; Ikawa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 4977.

(17) Formation of a small amount (6% in each case) of the homocoupling product (**3**) was also observed.

(18) **General Procedure for Reductive Cleavage of Various Aryl Triflates.** After two vacuum/Ar cycles to remove air from the reaction tube, the mixture of the aryl triflate (0.5 mmol), 10% Pd/C (10 wt % of the aryl triflate), magnesium metal (14.6 mg, 0.6 mmol), and ammonium acetate (38.6 mg, 0.5 mmol) in MeOH (1 mL) was stirred at ordinary pressure (balloon) and at temperature (ca. 20 °C) for the appropriate time (see Table 3). The reaction mixture was filtrated using a membrane filter (Millipore, Millex-LH, 0.45 μm), and the filtrate was partitioned between ether (10 mL) and water (10 mL). The aqueous layer was extracted with ether (10 mL × 3), and then combined organic layers were washed with brine (10 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure.

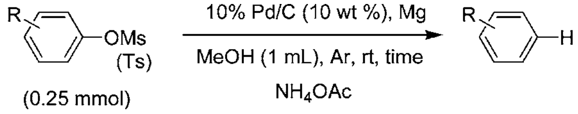
Table 3. Pd/C-Catalyzed Reductive Cleavage of Various Aryl Triflates

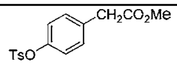
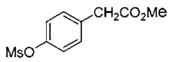
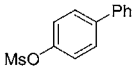
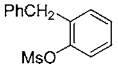
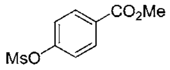
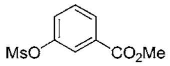
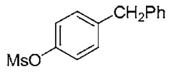
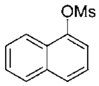


entry	substrate	time (h)	yield (%)[a]
1		1	99
2		1	89
3		0.5	95
4		1	97
5		0.5	95
6		0.5	98
7		1	94
8		0.5	83
9		1	92
10		0.5	84
11		2.5	92[b]
12		24	100[c]
13		24	100[c]

[a] Isolated yield. [b] 3.0 equiv of NH$_4$OAc was used, and the reaction completed within 2.5 h. [c] Reaction was performed without NH$_4$OAc and determined by GC/MS because of the low boiling point of the products.

Table 4. Pd/C-Catalyzed Reductive Cleavage of Aryl Mesylates or Tosylates



entry	substrate	Mg (equiv)	NH$_4$OAc (equiv)	time (h)	yield (%)[a]
1		1.2	none	24	-[b]
2		1.2	1.0	24	recovery
3		1.2	none	24	14[c]
4		1.2	1.0	12	98[d]
5		2.4	3.0	3	92
6		2.4	30	5	89
7		1.2	5.0	24	78
8		2.4	30	2	80
9		2.4	30	6	57
10		2.4	3.0	24	85
11		2.4	30	24	32[e]

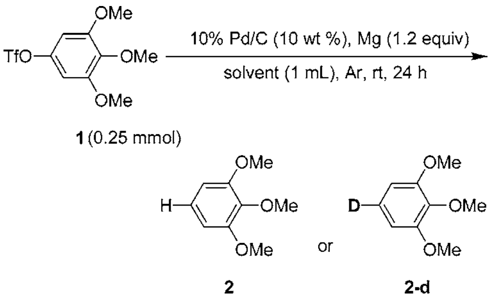
[a] Isolated yield. [b] 65% of the starting substrate was remained intact, and 35% of the hydrogenolysis product, 4-hydroxyphenyl acetic acid methyl ester, was produced. Determined by ^{1}H NMR. [c] 86% of the starting substrate was remained unchanged. Determined by ^{1}H NMR. [d] 2% of the starting substrate was remained unchanged. Determined by ^{1}H NMR. [e] The low isolated yield of the product is due to the volatile nature.

Methyl 3-methoxybenzoate derived from the corresponding triflate was accessed in excellent yield (92%) while the reaction required slightly longer reaction time (2.5 h) and 3.0 equiv of NH$_4$OAc as an additive (entry 11). In the case of 4-trifluoromethylphenyl triflate (entry 12) and 4-fluorophenyl triflate (entry 13), the reactions were performed without NH$_4$OAc and the formation of deoxygenated products was determined by GC/MS (100% conversion, respectively) because of the volatile nature of the corresponding products.

Moreover, it is noted that the present Pd/C-catalyzed reduction reaction using a Mg−MeOH combination of aryl triflates can be applicable to aryl mesylates (Table 4).

Although the reduction of a methane sulfonyloxy (MsO) group from the corresponding aryl mesylate is quite difficult in the absence of NH$_4$OAc (entry 3), the addition of 1.0 equiv of NH$_4$OAc should lead reduction of mesylates and a similar protocol allows for triflates to be compatible with the method (entry 4). Slow and poor conversions were frequently observed with aryl mesylates, which can be overcome by using greater amounts of Mg metal (2.4 equiv for entries 5,

Table 5. Determination of the Hydrogen Source



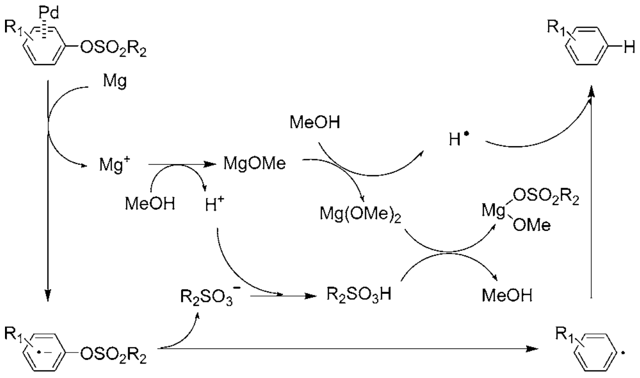
entry	solvent	H or **D**
1	CH$_3$OH	H (89)
2	$\mathbf{CD}_3$OH	H (80)
3	CH$_3$O$\mathbf{D}$	**D** (86)
4	$\mathbf{CD}_3$O$\mathbf{D}$	**D** (76)

6, and 8−11) and NH_4OAc (3.0−30 equiv). On the other hand, the present method was not applicable to aryl tosylate, regardless of the addition of NH_4OAc (entries 1 and 2).

Since the present method did not require the use of hydrogen gas, the hydrogen incorporated to the substrate should result from MeOH. To clarify the hydrogen source, the reductive elimination of the MsO group was carried out using three types of deuterated methanols as a solvent. According to a comparison between entries 2 and 3 in Table 5, it is apparent that the deuterium (hydrogen) source of these reactions is the acidic deuterium of deuterated methanols.

We believe that the present reductive deoxygenation proceeds through the pathway outlined in Scheme 1. Initial single electron transfer (SET) to the palladium (0)-activated benzene ring from Mg metal as a single electron donor should afford an anion radical, which may convert to the traceless benzene ring by the subsequent elimination of the (trifluoro)-methane sulfonic anion to give the reduced arene product via an aryl radical intermediate. Since the initial SET may proceed toward the electron-poor aromatic ring of the tosyl group rather than the phenolic ring in the case of aryl tosylates, the reduction is entirely blocked (Table 4, entries 1 and 2).

Scheme 1. Plausible Reaction Mechanism



In conclusion, we have developed a Pd/C-catalyzed deoxygenation method of phenolic hydroxyl groups via aryl triflates or mesylates using Mg metal in MeOH at room temperature. The addition of NH_4OAc dramatically affects the reactivity and reaction rate. Current efforts are aimed at further elucidating the mechanism and the effect of NH_4OAc. The present method may be characterized by its environmentally benign nature (ligandless and heterogeneous catalyst), wide applicability, simple procedure (simple filtration to remove Pd/C and general extraction of the filtrate without requiring further purification), easy availability of reagents (stable and commercially available 10% Pd/C, Mg turning for Grignard reaction can be used without any pretreatment), and mild reaction conditions (room temperature). Therefore, the method is promising as a general, practical, and traceless deoxygenation process in the field of synthetic organic chemistry and industry.

Supporting Information Available: Spectroscopic data and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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