Letter

Sulfuric Acid-Promoted Oxidation of Benzylic Alcohols to Aromatic Aldehydes in Dimethyl Sulfoxide: An Efficient Metal-Free Oxidation Approach

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Abstract An efficient metal-free oxidation of benzylic alcohols to aromatic aldehydes is described. Heating a solution of the benzylic alcohol in DMSO in the presence of H_2SO_4 afforded the corresponding aldehyde in excellent yield. This oxidation reaction, which proceeds with a short reaction time and no side products, is akin to the Pfitzner–Moffatt oxidation, but without the need for *N*,*N*'-dicyclohexylcarbodiimide.

Key words benzylic alcohols, aromatic aldehydes, sulfuric acid, dimethyl sulfoxide, oxidation

Oxidation of primary alcohols to aldehydes is an important functional-group transformation in organic synthesis. Many protocols and a broad range of oxidizing reagents have been reported for this reaction, including chromium-based systems [CrO₃/H₂SO₄ (Jones oxidation),¹ CrO₃·py₂ (Collins oxidation),² pyridinium chlorochromate (Corey oxidation),³ or pyridinium dichromate];⁴ hypervalent iodine reagents [Dess–Martin periodinane⁵ or *o*-iodoxybenzoic ac-id⁶];⁷ TEMPO-based systems [TEMPO/polymer-bound haloate (I),^{8a} TEMPO/Br₂/NaNO₂,^{8b} TEMPO/[CuBr₂(bipy)],^{8c} TEMPO/1,3-dibromo-5,5-dimethylhydantoin/NaNO₂,^{8d}

TEMPO/HBr/*tert*-butyl nitrite,^{8e} TEMPO/HCl/NaNO₂,^{8f} or [imim-TEMPO]⁺X⁻/[imim-CO₂H]⁺X⁻/NaNO₂] (imim-CO₂ = 1carboxymethyl-3-methylimidazolium chloride);^{8g} the Corey–Kim reagent,⁹ the Oppenauer reagent,¹⁰ manganese dioxide;¹¹ or tetrapropylammonium perruthenate (Ley–Griffith reagent).^{8g,12} In recent years, several other strategies have been reported that use reagents such as O₂ and an amphiphilic resin-dispersion of palladium nanoparticles,^{13a} Au-Cu/SiO₂,^{13b} Ru(PPh₃)(OH)-salen complex,^{13c} Ru-CHNAP-MgO,^{8g} [Ru(bbp)(pydic)] (pydic = pyridine-2,6-dicarboxylic acid),^{13e} K₂[OSO₂(OH)₄]/chloramine-T,^{13d} an Ag–NHC complex,^{13f}



 $H_2O_2/Br/H^{+,13g}$ azobenzene/Na $^+/O_2,^{13h}$ NaIO_4/ γ -Fe_2O_3@HAp-Mn(salophen)OAc,^{13i} and 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine/visible light.^{13j}

Among the most important oxidation methods are DMSO-based systems, such as DMSO/DCC/H⁺ (Pfitzner-Moffatt oxidation),¹⁴ DMSO/SO₃·Py (Parikh–Doering oxidation),¹⁵ DMSO/oxalyl chloride (Swern oxidation))¹⁶, DM-SO/Ac₂O (Albright–Goldman oxidation),¹⁷ DMSO/P₂O₅ (Onodera oxidation),¹⁸ and DMSO/phenyl dichlorophosphate (Liu oxidation).¹⁹

However, some of these methods have significant disadvantages, such as the use of toxic and moisture-sensitive oxalyl chloride, the need for low temperatures to avoid Pummerer rearrangement, the requirement for anhydrous conditions for the Swern oxidation, the removal of urea in the Pfitzner–Moffatt oxidation, and the competitive formation of the methylthiomethyl ether byproducts for all of them. Consequently, it is still desirable to develop an efficient and simple method for the oxidation of primary alcohols.

In 2002, Li and co-workers described the HBr-catalyzed oxidation of benzylic alcohols with DMSO. They claimed that among H₂SO₄, H₃PO₄, CeCl₃, TsOH, and aqueous HBr, only the reaction catalyzed by HBr gave a pure product in high yield.²⁰ They proposed a carbocation-based mechanism for this reaction, and they observed a decrease in the reaction rate with electron-withdrawing or bulky groups and an increase in the reaction rate with electron-donating groups. Although, the effects of electron-withdrawing and electron-donating groups were in agreement with the proposed mechanism, the notable effects observed with bulky groups were inconsistent with the formation of a planar carbocation. In addition, the reaction between HBr and DMSO forms bromodimethylsulfonium bromide as an activated sulfonium ion, whereas other acids cannot form this

reagent.²¹ It therefore seems likely that the reaction proceeds through activation of alcohol **1** by bromodimethyl-sulfonium bromide (**3**), followed by elimination of dimethyl sulfide (Scheme 1). In this mechanistic rationale, benzylic alcohols bearing bulky groups should show a decrease in reaction rate.



Scheme 1 More probable mechanism for the HBr-catalyzed oxidation of benzylic alcohols in DMSO

However, the question still remained as to whether other acids might react with benzylic alcohols under different reaction conditions to effect oxidation. Here, we describe an acid-catalyzed approach for the oxidation of benzylic alcohols to produce the corresponding aldehydes. Downloaded by: University of Leicester. Copyrighted material

To investigate the reaction conditions for acid-promoted oxidation of benzylic alcohols 1 to the corresponding aromatic aldehydes 2, we selected benzyl alcohol (1a) as a model substrate, and we examined the effects of several acids and various temperatures, times, solvents and amounts of the acid (Table 1). Initially, benzyl alcohol 1a was treated with H₂SO₄ (1 equiv) in DMSO at room temperature, but no reaction was observed after five hours (Table 1, entry 1). When this reaction was performed at 100 °C, benzaldehyde (2a) was obtained in 30 and 35% yields after one and two hours, respectively. The yield of 2a did not improve after five hours (entry 2). When the reaction was carried out at 150 °C, 2a was obtained in 43, 46, and 50% yields after one, two, and five hours, respectively (entry 3). However. by carrying out the reaction under reflux conditions. 2a was obtained in 94% yield after one hour, and the yield did not change after longer periods (entry 4). We also tested the reaction in the presence of two and three equivalents of H₂SO₄, but the yield of **2a** did not significantly improve (entries 5 and 6). On using 0.5 equivalents of H₂SO₄, the yield of **2a** after one hour decreased to 40%, but this increased to 90 and 91% after two and five hours, respectively (entry 7).

Table 1 Screening of Conditions for the Acid-Promoted Oxidation of Benzyl Alcohol (1a) to Benzaldehyde (2a)^a

OH acid, solvent						
			Ph´ 1a	Ph´ `H 2a		
Entry	Acid (equiv)	Solvent	Temp (°C)	Yield ^b (%) of 2a after 1	h Yield ^b (%) of 2a after 2 h	Yield [♭] (%) of 2a after 5 h
1	H ₂ SO ₄ (1.0)	DMSO	r.t.	NR ^c	NR	NR
2	H ₂ SO ₄ (1.0)	DMSO	100	30	35	35
3	H ₂ SO ₄ (1.0)	DMSO	150	43	46	50
4	H ₂ SO ₄ (1.0)	DMSO	reflux	94	94	94
5	H ₂ SO ₄ (2.0)	DMSO	reflux	94	95	95
6	H ₂ SO ₄ (3.0)	DMSO	reflux	93	93	95
7	H ₂ SO ₄ (0.5)	DMSO	reflux	40	90	91
8	H ₃ PO ₄ (1.0)	DMSO	reflux	51	63	63
9	H ₂ PO ₃ (1.0)	DMSO	reflux	22	57	59
10	TsOH (1.0)	DMSO	reflux	trace	13	17
11	MsOH (1.0)	DMSO	reflux	trace	15	23
12	H ₂ SO ₄ (1.0)	t-BuOH	reflux	NR	NR	NR
13	H ₂ SO ₄ (1.0)	DMF	reflux	NR	NR	NR
14	H ₂ SO ₄ (1.0)	THF	reflux	NR	NR	NR
15	H ₂ SO ₄ (1.0)	MeCN	reflux	NR	NR	NR
16	H ₂ SO ₄ (1.0)	CHCl ₃	reflux	NR	NR	NR
17	H ₂ SO ₄ (1.0)	toluene	reflux	NR	NR	NR
18	H ₂ SO ₄ (1.0)	H ₂ O	reflux	NR	NR	NR

^a Reaction conditions: BnOH (1a; 1 mmol), acid (1.0 or 0.5 equiv), solvent (3 mL).

^b Isolated yield.

^c NR = no reaction.

Other acids such as H_3PO_4 , H_2PO_3 , TsOH, or MsOH were studied. Although, H_3PO_4 and H_2PO_3 led to 63 and 57% yields after two hours (entries 8 and 9), only very low amounts of product were detected when using TsOH or MsOH (entries 10 and 11). These results can be explained by the difference in the acidity of these acids. For an additional control test, we examined the reaction in various solvents such as *t*-BuOH, DMF, THF, MeCN, CHCl₃, toluene, and water. However, all these solvents were inappropriate for this transformation (entries 12–18). Thus, optimal conditions for the oxidation of benzyl alcohol (**1a**) to benzaldehyde (**2a**) were determined to be 1.0 or 0.5 equivalents of H_2SO_4 in boiling DMSO for one or two hours, respectively (Table 1, entries 4 and 7).

This oxidation approach is similar to the Pfitzner–Moffatt oxidation, but without the need for dicyclohexylcarbodiimide (DCC); consequently, the difficulty of removing the dicyclohexylurea (DCU) byproduct is avoided (Scheme 2).



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Scheme 2 Comparison of Pfitzner–Moffat oxidation with our method

To demonstrate the generality and scope of this protocol, we examined the reactions of various benzylic alcohols **1** in the presence of H_2SO_4 in DMSO. These reactions proceeded cleanly under reflux conditions to afford the corresponding aromatic aldehydes **2**, and no side reactions were observed (Table 2). All the reactions went to completion after convenient reaction times. ¹H NMR analyses of the reaction mixtures clearly indicated the formation of the corresponding aldehydes **2** in excellent yields. All the products were characterized on the basis of their ¹H and ¹³C NMR spectroscopic data.²²

Table 2Oxidation of Benzylic Alcohols to Aromatic Aldehydes by the H2SO4/DMSO System								
		OH H ₂ SO ₄ , (prot. A: 1 equiv; prot. B: 0.5 equiv), DMSO						
		Ar 1	reflux	Ar	2 2			
Entry	Alcohol	Aldehyde	Product	Protocol A ^a		Protocol B ^t	Protocol B ^b	
				Time	Yield ^c (%)	Time	Yield ^c (%)	
1	BnOH	РһСНО	2a	60	94	120	90	
2	ОН	СНО	2Ь	60	93	120	92	
3	ОН	CHO	2c	60	93	120	90	
4	ОН	СНО	2d	60	91	125	92	
5	СІ	СІСНО	2e	60	94	125	91	
6	СІ	СНО	2f	60	92	130	88	
7	Вг	Br	2g	60	95	120	91	
8	MeO	MeO	2h	55	90	110	89	

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Table 2 (continued)

Entry	Alcohol	Aldehyde	Product	Protocol A ^a	Protocol A ^a		Protocol B ^b	
				Time	Yield ^c (%)	Time	Yield ^c (%)	
9	МеО ОН	MeO CHO MeO	2i	40	93	85	90	
10	МеО ОН	MeOCHO OMe	2j	50	89	110	88	
11	ОН	CHO	2k	35	90	70	87	
12	OH	CHO	21	65	93	120	90	
13	O ₂ N OH	O ₂ N CHO	2m	90	80	165	78	
14	O ₂ N OH	O ₂ N CHO	2n	85	84	145	84	

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^a Reaction conditions: alcohol (1 mmol), H₂SO₄ (1 mmol), DMSO (3 mL), reflux.

^b Reaction conditions: alcohol (1 mmol), H₂SO₄ (0.5 mmol), DMSO (3 mL), reflux.

^c Isolated yield.

A proposed mechanism for this reaction is provided in Scheme 3. At first, treatment of benzylic alcohol **1** with H_2SO_4 yields a carbocation intermediate **5** through removal of H_2O . This intermediate is readily converted into the alkoxysulfonium ion intermediate **6** through a nucleophilic addition reaction of DMSO. Next, in the presence of HSO_4^- , intermediate **6** is deprotonated to give the sulfur ylide **7**. Finally, in a five-membered-ring transition state, the sulfur ylide **7** undergoes elimination of dimethyl sulfide (DMS) to form the corresponding aldehyde **2** through deprotonation of the benzylic hydrogen.



As shown in Table 2, alcohols with electron-donating groups were oxidized faster, and the presence of *ortho*-substituents on the alcohol did not affect the reaction rate. These results are in agreement with a carbocation-based mechanism. In addition, the catalytic behavior of the sulfuric acid can be explained by our proposed mechanism.

In conclusion, we have developed an efficient and metal-free approach for the oxidation of benzylic alcohols to the corresponding aromatic aldehydes by a H₂SO₄/DMSO system under reflux conditions. This oxidation procedure extends the Pfitzner–Moffatt oxidation, doing away with the need to add DCC and, consequently, eliminating the need to remove DCU. In addition, this protocol has notable advantages such as readily available and inexpensive chemicals, short reaction times, a simple procedure and workup, high yields of products, and lack of byproduct formation.

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References and Notes

- (a) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. J. Chem. Soc. **1946**, 39. (b) Heilbron, S. I.; Jones, E. R. H.; Sondheimer, F. J. Chem. Soc. **1949**, 604.
- (2) (a) Collins, J. C.; Hess, W. W.; Frank, F. J. Tetrahedron Lett. 1968,
 9, 3363. (b) Collins, J. C.; Hess, W. W. Org. Synth. Coll. Vol. VI;
 Wiley: London, 1988, 644.
- (3) Corey, E. J.; Suggs, J. W. Tetrahedron Lett. 1975, 16, 2647.
- (4) Corey, E. J.; Schmidt, G. Tetrahedron Lett. 1979, 20, 399.
- (5) (a) Dess, D. B.; Martin, J. C. J. Org. Chem. 1983, 48, 4155. (b) Dess,
 D. B.; Martin, J. C. J. Am. Chem. Soc. 1991, 113, 7277.
- (6) (a) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, 36, 7945.
 (b) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. J. Org. Chem. **1995**, 60, 7272.
- (7) (a) Zhdankin, V. V.; Stang, P. J. Chem. Rev. 2002, 102, 2523.
 (b) Stang, P. J. J. Org. Chem. 2003, 68, 2997. (c) Wirth, T. Angew. Chem. Int. Ed. 2005, 44, 3656.
- (8) (a) Brünjes, M.; Sourkouni-Argirusi, G.; Kirschning, A. Adv. Synth. Catal. 2003, 345, 635. (b) Liu, R.; Liang, X.; Dong, C.; Hu, X. J. Am. Chem. Soc. 2004, 126, 4112. (c) Gamez, P.; Arends, I. W. C. E.; Sheldon, R. A.; Reedijk, J. Adv. Synth. Catal. 2004, 346, 805. (d) Liu, R.; Dong, C.; Liang, X.; Wang, X.; Hu, X. J. Org. Chem. 2005, 70, 729. (e) Xie, Y.; Mo, W.; Xu, D.; Shen, Z.; Sun, N.; Hu, B.; Hu, X. J. Org. Chem. 2007, 72, 4288. (f) Wang, X.; Liu, R.; Jin, Y.; Liang, X. Chem. Eur. J. 2008, 14, 2679. (g) Kantam, M. L.; Pal, U.; Sreedhar, B.; Bhargava, S.; Iwasawa, Y.; Tada, M.; Choudary, B. E. Adv. Synth. Catal. 2008, 350, 1225.
- (9) Corey, E. J.; Kim, C. U. J. Am. Chem. Soc. 1972, 94, 7586.
- (10) (a) Oppenauer, R. V. *Recl. Trav. Chim. Pays-Bas* **1937**, 56, 137.
 (b) Graves, C. R.; Zeng, B.-S.; Nguyen, S. T. *J. Am. Chem. Soc.* **2006**, 128, 12596.
- (11) (a) Fatiadi, A. J. Synthesis 1976, 65. (b) Fatiadi, A. J. Synthesis 1976, 133. (c) Lou, J.-D.; Xu, Z.-N. Tetrahedron Lett. 2002, 43, 6149. (d) Alhumaimess, M.; Lin, Z.; He, Q.; Lu, L.; Dimitratos, N.; Dummer, N. F.; Conte, M.; Taylor, S. H.; Bartley, J. K.; Kiely, C. J.; Hutchings, G. J. Chem. Eur. J. 2014, 20, 1701.
- (12) (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. J. Chem. Soc., Chem. Commun. 1987, 1625. (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. Synthesis 1994, 639.

- (13) (a) Uozumi, Y.; Nakao, R. Angew. Chem. Int. Ed. 2003, 42, 194.
 (b) Della Pina, C.; Falletta, E.; Rossi, M. J. Catal. 2008, 260, 384.
 (c) Mizoguchi, H.; Uchida, T.; Ishida, K.; Katsuki, T. Tetrahedron Lett. 2009, 50, 3432. (d) Zhou, X.-T.; Ji, H.-B.; Liu, S.-G. Tetrahedron Lett. 2013, 54, 3882. (e) Devari, S.; Deshidi, R.; Kumar, M.; Kumar, A.; Sharma, S.; Rizvi, M.; Kushwaha, M.; Gupta, A. P.; Shah, B. A. Tetrahedron Lett. 2013, 54, 6407. (f) Han, L.; Xing, P.; Jiang, B. Org. Lett. 2014, 16, 3428. (g) Liu, C.; Fang, Z.; Yang, Z.; Li, Q.; Guo, S.; Zhang, K.; Ouyang, P.; Guo, K. Tetrahedron Lett. 2015, 56, 5973. (h) Liu, C.; Fang, Z.; Yang, Z.; Li, Q.; Guo, S.; Guo, K. RSC Adv. 2015, 5, 79699. (i) Saffar-Teluri, A. RSC Adv. 2015, 5, 70577. (j) Samanta, S.; Biswas, P. RSC Adv. 2015, 5, 84328.
- (14) Pfitzner, K. E.; Moffatt, J. G. J. Am. Chem. Soc. **1963**, 85, 3027.
- (15) Parikh, J. R.; Doering, W. von. E. J. Am. Chem. Soc. **1967**, 89, 5505. (16) (a) Omura, K.; Swern, D. Tetrahedron **1978**, 34, 1651.
- (b) Mancuso, A. J.; Brownfain, D. S.; Swern, D. J. Org. Chem. 1979, 44, 4148.
 (17) (a) Albainty J. D.; Caldman, J. J. Am. Chem. 552, 1965, 97, 4214.
- (17) (a) Albright, J. D.; Goldman, L. J. Am. Chem. Soc. 1965, 87, 4214.
 (b) Albright, J. D.; Goldman, L. J. Am. Chem. Soc. 1967, 89, 2416.
- (18) Onodera, K.; Hirano, S.; Kashimura, N. J. Am. Chem. Soc. **1965**, 87, 4651.
- (19) Liu, H.-J.; Nyangulu, J. M. Tetrahedron Lett. 1988, 29, 3167.
- (20) Li, C.; Xu, Y.; Lu, M.; Zhao, Z.; Liu, L.; Zhao, Z.; Cui, Y.; Zheng, P.; Ji, X.; Gao, G. Synlett 2002, 2041.
- (21) (a) Choudhury, L. H.; Parvin, T.; Khan, A. T. *Tetrahedron* 2009, 65, 9513. (b) Inagaki, M.; Matsumoto, S.; Tsuri, T. J. Org. Chem. 2003, 68, 1128. (c) Majetich, G.; Hicks, R.; Reister, S. J. Org. Chem. 1997, 62, 4321.

(22) Aldehydes 2a-n; General Procedures

Protocol A: A mixture of the benzylic alcohol **1** (1 mmol) and 98% H_2SO_4 (1 mmol) in DMSO (3 mL) was stirred for the appropriate time under reflux conditions. The mixture was then cooled to r.t., and brine (4 mL) was added. The organic phase was extracted with CH_2Cl_2 (6 mL), and the organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. In all cases, the reaction products were obtained with high purity, and did not require further purification by distillation or column chromatography.

Protocol B: A mixture of benzylic alcohol (1 mmol) and 98% H_2SO_4 (0.5 mmol) in DMSO (3 mL) was stirred for the appropriate reaction time under reflux conditions. The reaction mixture was then worked up as described in Protocol A.