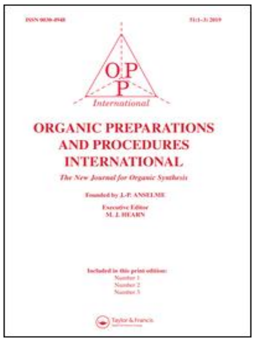

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EXPERIMENTAL PAPER

Oxidation of Benzylic Alcohols to Aromatic Aldehydes by DMSO/Water/I_2: A Chemoselective Oxidation

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One of the most important approaches to the preparation of aldehydes from benzylic alcohols is the use of DMSO-based systems, including DMSO/oxalyl chloride/Et_3N (Swern oxidation),[1,2] DMSO/DCC/H^+ (Pfitzner-Moffatt oxidation),[3] DMSO/P_2O_5 (Onodera oxidation),[4] DMSO/Ac_2O (Albright-Goldman oxidation),[5,6] and DMSO/SO_3·Py/Et_3N (Parikh-Doering oxidation)[7] (Figure 1). Although each of these protocols has its advantages and has been widely adopted, there are also disadvantages, among these the use of toxic and moisture sensitive reagents, the need for low temperatures to avoid Pummerer rearrangement, the requirement of anhydrous conditions, removal of by-products such as urea in the Pfitzner-Moffatt oxidation, and the competitive formation of methylthiomethyl ether.

DMSO/I_2 is of widening use as an oxidant.[8] Several selective methods for the oxidation of benzyl alcohols to aldehydes have been investigated.[9–11] Recently, Konwar and coworkers described molecular iodine as an inexpensive and low toxicity reagent, for the oxidation of alcohols. They used iodine in the presence of hydrazine, DMSO, water and MeCN,[12] and also in the presence of KI, K_2CO_3, and water.[13] They found that the first protocol led to selective oxidation of secondary alcohols. The use of KI and K_2CO_3 in the second protocol was necessary for the oxidation reaction. Benzyl alcohol was converted to benzaldehyde by the I_2/N_2H_4/DMSO/H_2O/MeCN system and the I_2/K_2CO_3/KI/H_2O system with 3.7% and 95% yields, respectively.

We now describe a novel DMSO-based approach for the chemoselective oxidation of benzylic alcohols to aromatic aldehydes by molecular iodine. Initially, the reaction conditions were optimized for the oxidation of benzyl alcohol **1a**. Different amounts of iodine and several solvents and temperatures were examined. The results are shown in Table 1. The oxidation of benzyl alcohol **1a** with DMSO provided only a trace amount of benzaldehyde **2a** under reflux conditions even after 7 h (Table 1, entry 1), whereas the production of benzaldehyde reached slightly better yield in the presence of 0.5 equiv. of I_2 after 7 h (Table 1, entry 2). The yield of desired product was increased to 35% through increasing of I_2 to 1.1 equiv. after 7 h (Table 1, entry 4). To our surprise, the yield was increased when water was added to the reaction mixture (Table 1, entry 5–9) and a better yield was achieved in the DMSO/H_2O mixture with a 1:2 ratio (Table 1, entry 8). Then, a diversity of solvents (DCM, acetone, toluene, MeCN, EtOAc, dioxane, ^{t}BuOH, THF, and DMF) in the optimum ratio (DMSO/solvent [1:2]) were

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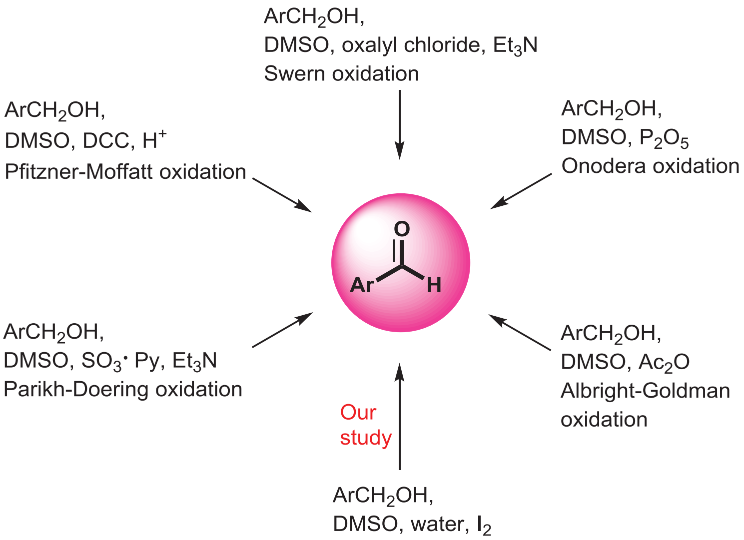
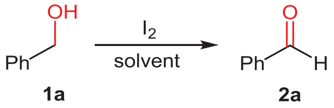


Figure 1. Comparison with our study of named DMSO-based oxidations of benzylic alcohols to aromatic aldehydes.

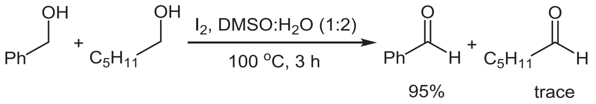
Table 1. Optimization for the oxidation of benzyl alcohol **1a** in the presence of I_2.[a]



Entry	I_2 (equiv.)	Solvent	Conditions	Yield after 1 h (%)[b]	Yield after 3 h (%)[b]	Yield after 7 h (%)[b]
1	–	DMSO	Reflux	Trace	Trace	Trace
2	0.5	DMSO	Reflux	Trace	Trace	18
3	1.0	DMSO	Reflux	Trace	Trace	23
4	1.1	DMSO	Reflux	Trace	Trace	35
5	1.1	DMSO/H_2O (3:1)	Reflux	30	33	47
6	1.1	DMSO/H_2O (2:1)	Reflux	50	53	59
7	1.1	DMSO/H_2O (1:1)	Reflux	56	56	62
8	1.1	DMSO/H_2O (1:2)	Reflux	60	67	75
9	1.1	DMSO/H_2O (1:3)	Reflux	54	57	58
10	1.1	DMSO/DCM (1:2)	Reflux	Trace	Trace	Trace
11	1.1	DMSO/Acetone (1:2)	Reflux	Trace	Trace	26
12	1.1	DMSO/Toluene (1:2)	Reflux	Trace	17	22
13	1.1	DMSO/MeCN (1:2)	Reflux	Trace	Trace	19
14	1.1	DMSO/EtOAc (1:2)	Reflux	30	33	35
15	1.1	DMSO/Dioxane (1:2)	Reflux	28	31	38
16	1.1	DMSO/^{t}BuOH (1:2)	Reflux	45	52	57
17	1.1	DMSO/THF (1:2)	Reflux	15	18	20
18	1.1	DMSO/DMF (1:2)	Reflux	24	27	32
19	**1.1**	**DMSO/H_2O (1:2)**	**100 °C**	73	**92**	**92**
20	1.1	DMSO/H_2O (1:2)	80 °C	Trace	17	29
21	1.1	DMSO/H_2O (1:2)	50 °C	No reaction	Trace	23
22	1.1	DMSO/H_2O (1:2)	r.t.	No reaction	No reaction	No reaction

[a] Benzyl alcohol (1 mmol), I_2 (related amount), solvent (3 mL).
[b] Isolated yield.

investigated for this reaction. However, it was found that the reaction did not give better yields in these solvents (Table 1, entries 10–18). Serendipitously, we found that



Scheme 1. The chemoselectivity screening for benzyl alcohol against 1-hexanol. Reaction conditions: benzyl alcohol (0.5 mmol), 1-hexanol (0.5 mmol), I_2 (1.1 mmol), DMSO (1 mL), H_2O (2 mL), at 100 °C, for 3 h.

heating of benzyl alcohol **1a** in the presence of I_2 (1.1 equiv.) in DMSO/H_2O (1:2) at 100 °C for 3 h, led to benzaldehyde **2a** in 92% yield (Table 1, entry 19).

Then, the oxidation of an equimolar ratio of benzyl alcohol and 1-hexanol was examined in the presence of iodine in DMSO-water (1:2) at 100 °C to test the chemoselectivity of benzylic alcohol against non-activated alcohol. This oxidation strongly favored the formation of benzaldehyde and led to benzaldehyde in 95% yield and only a trace amount of 1-hexanone (Scheme 1).

The generality of this oxidation protocol was examined using a number of alcohols, in the presence of 1.1 equiv. of I_2 in DMSO/H_2O (1:2) mixture. The oxidation of benzylic alcohols proceeded very cleanly at 100 °C to afford aromatic aldehydes **2** without any side products (Table 2, entries 1–12). It is worth noting that substituent methyl groups were not also oxidized (entries 2 and 3). The non-activated aliphatic alcohols (ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol and 1-decanol) did not cleanly oxidize under these reaction conditions (Table 2, entries 13–18).

All the reactions involving benzylic alcohols went to completion cleanly after 3 h. ^{1}H NMR analysis of the reaction mixtures clearly indicated the formation of the corresponding aromatic aldehydes **2** in excellent yields. The known products were characterized from ^{1}H and ^{13}C NMR spectral data and by melting point data for solids.

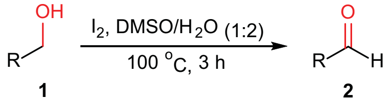
This oxidation approach introduces the simple, low-cost and chemoselective DMSO-based system without the use of expensive and complex reagents. There are no problems with removing byproducts (Figure 1). In comparison with the Konwar protocols, the need for N_2H_4 and MeCN, or K_2CO_3 and KI is avoided and yields are uniformly high. The products did not require further purification.

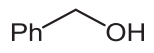
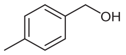
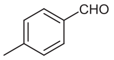
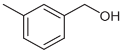
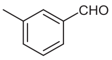
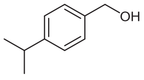
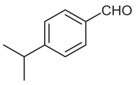
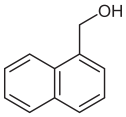
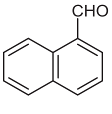
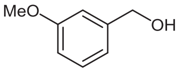
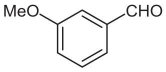
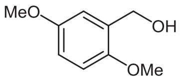
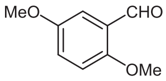
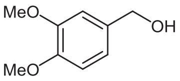
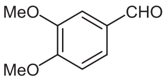
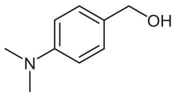
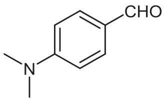
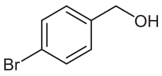
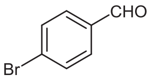
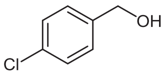
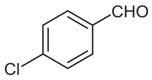
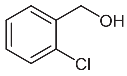
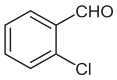
In conclusion, we have developed an efficient metal-, acid-, and base-free approach for the oxidation of benzylic alcohols using the DMSO/H_2O/I_2 system. This protocol leads to the corresponding aromatic aldehydes with excellent yields and without any side products such as methylthiomethyl ethers and carboxylic acids. The chemoselectivity of the protocol, ready availability of the reagents and simple procedures are major advantages of this method. Future work may focus on the selectivity of the method for substrates having more than one site potentially subject to oxidation.

Experimental section

Alcohols, iodine, and dimethyl sulfoxide were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Solvents were analytical reagent grade, 99% pure. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.2 mm Huanghai silica gel plates (HSGF-254) using UV light as visualizing agent. The TLC solvent was ^{n}hexane-ethyl acetate (4:1). Melting points were

Table 2. The oxidation of benzylic alcohols to aromatic aldehydes by DMSO/H_2O/I_2 system.[a]



Entry	Alcohols **1**	Aldehydes **2**	Yields of **2** (%)[b]	Entry	Alcohols **1**	Aldehydes **2**	Yields of **2** (%)[b]
1		PhCHO	**2a**, 92	2			**2b**, 91
3			**2c**, 92	4			**2d**, 93
5			**2e**, 92	6			**2f**, 90
7			**2g**, 88	8			**2h**, 89
9			**2i**, 87	10			**2j**, 96
11			**2k**, 95	12			**2l**, 93
13	C_2H_5OH	CH_3CHO	NR[c]	14	C_3H_7OH	C_2H_5CHO	Trace
15	C_4H_9OH	C_3H_7CHO	NR[c]	16	$C_5H_{11}OH$	C_4H_9CHO	NR[c]
17	$C_6H_{13}OH$	$C_5H_{11}CHO$	Trace	18	$C_{10}H_{21}OH$	$C_9H_{19}CHO$	Trace

[a] Reaction conditions: alcohols (1 mmol), I_2 (1.1 mmol), DMSO/H_2O ([1:2], 3 mL), at 100 °C, for 3 h.
[b] Isolated yield.
[c] No reaction.

measured on an Electrothermal 9100 apparatus. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DPX-250 (at 250.1 and 62.5 MHz, resp.) instrument with TMS as an internal standard. All of the products were known compounds and were identified by matching their proton and carbon NMR spectra with values in the literature cited; in the case of solids, melting points matched those of the literature cited.

Procedure

A mixture of benzyl alcohol (0.108 g, 1 mmol), I_2 (0.279 g, 1.1 mmol) in DMSO (1 mL) and water (2 mL) was stirred at 100 °C for 3 h. Then, the reaction mixture was cooled to room temperature. To the reaction mixture was added 2 mL of aqueous sodium thiosulfate solution and the organic phase was extracted with 5 mL of dichloromethane. Finally, the organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. In all cases, the reaction products were obtained in high purity, and did not require further purification by distillation or column chromatography.

Benzaldehyde (2a)[14]

Colorless liquid, yield = 0.098 g, 92%. ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta = 9.96$ (s, 1H, CHO), 7.82 (d, $J = 7.5$ Hz, 2H, 2 × CH), 7.57 (t, $J = 7.5$ Hz, 1H, CH), 7.47 (t, $J = 7.5$ Hz, 2H, 2 × CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 192.4$ (C=O), 136.2 (C), 134.3, 130.0 and 128.9 (3 × CH).

4-Methylbenzaldehyde (2b)[14]

Colorless liquid, yield = 0.110 g, 91%. ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta = 9.90$ (s, 1 H, CHO), 7.73 (d, $J = 7.6$ Hz, 2 H, 2 × CH), 7.27 (d, $J = 7.6$ Hz, 2 H, 2 × CH), 2.38 (s, 3 H, CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 191.9$ (C=O), 145.4 and 134.0 (2 × C), 129.7 and 129.6 (2 × CH), 21.7 (CH_3).

3-Methylbenzaldehyde (2c)[15]

Pale yellow liquid, yield = 0.111 g, 92%. ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta = 9.90$ (s, 1 H, CHO), 7.60–7.53 (m, 2H, 2 × CH), 7.35–7.26 (m, 2H, 2 × CH), 2.34 (s, 3 H, CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 192.3$ (C=O), 138.7 and 136.3 (2 × C), 135.1, 129.8, 128.7 and 127.0 (4 × CH), 20.9 (CH_3).

4-Isopropylbenzaldehyde (2d)[16]

Colorless liquid, yield = 0.138 g, 93%. ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta = 9.90$ (s, 1H, CHO), 7.75 (d, $J = 7.4$ Hz, 2H, 2 × CH), 7.31 (d, $J = 7.4$ Hz, 2H, 2 × CH), 2.96–2.85 (m, 1H, $(CH_3)_2CH$), 1.21 (d, $J = 6.2$ Hz, 6H, 2 × CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 191.8$ (C=O), 156 and 134.4 (2 × C), 129.9 and 127.0 (2 × CH), 34.3 $(CH_3)_2CH$), 23.4 $(CH_3)_2CH$).

1-Naphthaldehyde (2e)[17]

Yellow liquid, yield = 0.144 g, 92%. ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta = 10.33$ (s, 1H, CHO), 9.25 (d, $J = 8.5$ Hz, 1H, CH), 8.01 (d, $J = 8.2$ Hz, 1H, CH), 7.90-7.84 (m, 2H, 2 × CH), 7.65 (t, $J = 7.6$ Hz, 1H, CH), 7.57-7.51 (m, 2H, 2 × CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 193.5$ (C=O), 136.7 and 135.2 (2 × CH), 133.6, 131.2 and 130.4 (3 × C), 128.9, 128.4, 126.9, 124.8 and 127.7 (5 × CH).

3-Methoxybenzaldehyde (2f)[18]

Pale yellow liquid, yield = 0.122 g, 90%. ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta = 9.92$ (s, 1H, CHO), 7.40-7.11 (m, 4H, 4 × CH), 3.80 (s, 3H, OCH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$) $\delta = 192.1$ (C=O), 160.0 and 137.6 (2 × C), 129.9, 123.4, 121.3 and 111.9 (4 × CH), 55.3 (2 × OCH_3).

2,5-Dimethoxybenzaldehyde (2g)[19]

Yellow crystal, yield = 0.146 g, 88%; m.p. 49 °C. ^{1}H NMR (250.1 MHz, $CDCl_3$): $\delta = 10.43$ (s, 1H, CHO), 7.31 (d, $J = 1.6$ Hz, 1H, CH), 7.12 (dd, $J = 9.0$, 1.6 Hz, 1H, CH), 6.93 (d, $J = 9.0$, Hz, 1H, CH), 3.88 and 3.79 (2s, 6H, 2 × OCH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 189.5$ (C = O), 156.6, 153.5 and 124.8 (3 × C), 123.4, 113.2 and 110.2 (3 × CH), 56.0 and 55.7 (2 × OCH_3).

3,4-Dimethoxybenzaldehyde (2h)[18]

White solid, yield = 0.148 g, 89%; m.p. 41–43 °C. ^1H NMR (250.1 MHz, $CDCl_3$): $\delta = 9.80$ (s, 1 H, CHO), 7.41 (d, $J = 8.1$ Hz, 1 H, CH), 7.35 (s, 1 H, CH), 6.92 (d, $J = 8.1$ Hz, 1 H, CH), 3.91 and 3.89 (2s, 3 H, 2 × OCH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 190.8$ (C = O), 154.3, 149.4 and 129.9 (3 × C), 126.8, 110.2 and 108.7 (3 × CH), 56.1 and 55.8 (2 × OCH_3).

4-(Dimethylamino)benzaldehyde (2i)[16]

Pale yellow solid, yield = 0.130 g, 87%; m.p. 73–75 °C. ^1H NMR (250.1 MHz, $CDCl_3$): $\delta = 9.73$ (s, 1H, CHO), 7.72 (d, $J = 8.0$ Hz, 2H, 2 × CH), 6.73 (d, $J = 8.0$ Hz, 2H, 2 × CH), 3.06 (s, 6H, 2 × CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$) $\delta = 190.2$ (C = O), 153.9 (C), 131.8 (CH), 125.5 (C), 111.4 (CH), 40.2 (2 × CH_3).

4-Bromobenzaldehyde (2j)[14]

White solid, yield = 0.178 g, 96%; m.p. 57–58 °C. ^1H NMR (250.1 MHz, $CDCl_3$): δ = 9.94 (s, 1H, CHO), 7.72 (d, $J = 7.9$ Hz, 2H, 2 × CH), 7.65 (d, $J = 7.9$ Hz, 2H, 2 × CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 191.0 (C = O), 134.9 (C), 132.3 and 130.9 (2 × CH), 129.6 (C).

4-Chlorobenzaldehyde (2k)[20]

Pale yellow crystal, yield = 0.133 g, 95%; m.p. 46–47 °C. ^1H NMR (250.1 MHz, $CDCl_3$): $\delta = 9.96$ (s, 1H, CHO), 7.80 (d, $J = 8.2$ Hz, 2H, 2 × CH), 7.49 (d, $J = 8.2$ Hz, 2H, 2 × CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 190.8$ (C = O), 140.8 and 134.6 (2 × C), 130.8 and 129.3 (2 × CH).

2-Chlorobenzaldehyde (2l)[14]

Colorless liquid, yield = 0.130 g, 93%. ^1H NMR (250.1 MHz, $CDCl_3$): $\delta = 10.30$ (s, 1H, CHO), 7.74 (d, $J = 7.6$ Hz, 1H, CH), 7.37 (t, $J = 7.6$ Hz, 1H, CH), 7.28 (d, $J = 7.6$ Hz, 1H, CH), 7.22 (t, $J = 7.6$ Hz, 1H, CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 189.3$ (C = O), 137.6 (C), 134.9 (CH), 132.2 (C), 130.4 (CH), 129.1 and 127.1 (2 × CH).

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