One-Step Oxidation of 2-Arylpropanols to 2-Arylpropionic Acids: Improving Sustainability in the Synthesis of Profens

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Abstract: Three oxidation procedures were evaluated for the synthesis of optically pure 2-arylpropionic acids. Efficient, mild, and eco-friendly conditions were obtained with the system comprising TEMPO, NaClO, and $NaClO_2$. Thus a series of profens were obtained in good to excellent yields.

Key words: oxidation, alcohols, carboxylic acids, anti-inflammatory agents, profens, TEMPO

Oxidation of alcohols is one of the most important and challenging transformation in the synthesis of fine chemicals and intermediates.[1] The oxidation of alcohols has been achieved with stoichiometric inorganic oxidants, notably Cr(VI)-based reagents.[2] Unfortunately, these oxidants are relatively expensive and produce large quantities of noxious heavy-metal waste, so that greener methods have attracted much attention for the development of sustainable chemistry in recent years.[3]

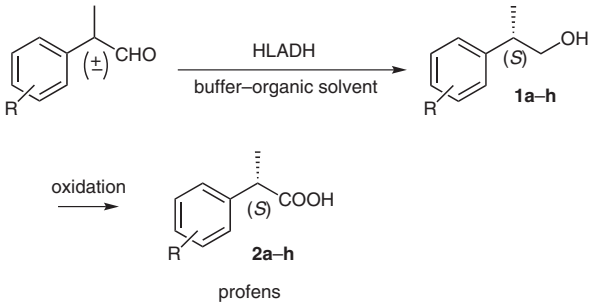
The oxidation of primary alcohols to the corresponding carboxylic acids can be considered a two-step oxidation and it was realized in a one-pot process with sustainable methods, such as Na_2WO_4 with H_2O_2,[4] and TEMPO with NaClO and $NaClO_2$.[5]

In the course of an ongoing project on the application of biocatalysis in the manufacturing of enantiomerically pure pharmaceutical ingredients,[6] we developed an efficient chemoenzymatic synthesis of a series of (*S*)-2-arylpropanols starting from racemic arylpropionic aldehydes with horse liver alcohol dehydrogenase (HLADH) in buffer–organic solvent medium. A one-pot oxidation of the (*S*)-2-arylpropanols (profenols) would give (*S*)-profens, an important class of nonsteroidal anti-inflammatory agents (Scheme 1). The important pharmaceutical properties of this class of drugs have been well illustrated by the introduction and extensive use of compounds such as ibuprofen, naproxen, flurbiprofen, and ketoprofen. The one-pot oxidation was already reported on some arylpropanols with $KMnO_4$,[7] or cromium(VI) reagents,[8] but those methods have serious drawbacks in the use of stoichiometric heavy-metal oxidants, unsatisfactory yields, and byproduct formation.

We thus sought for alternative procedures in the oxidation of enantiomerically pure 2-arylpropanols to 2-arylpropionic acids, and in this paper we report on the oxidation of a series of (*S*)-profenols to the corresponding (*S*)-profens under more efficient and environmentally benign procedures (Scheme 1 and Figure 1).

In particular we tested three oxidation procedures, the unfriendly $KMnO_4$ procedure in acidic conditions, the use of H_2O_2/tungstate system developed by Noyori,[4] and a TEMPO, NaClO, and $NaClO_2$ procedure,[5] to evaluate on comparison, conversion, byproduct formation, and maintenance of optical purity.

Compounds (*S*,*R*)-**1a**, (*S*)-**1a**, and (*R*)-**1a** are commercially available, racemic arylpropanols **1b–h** were obtained by reduction of racemic commercial acids,[9] and enantio-



Scheme 1 Chemoenzymatic route for the synthesis of (*S*)-profens starting from racemic 2-arylpropanals

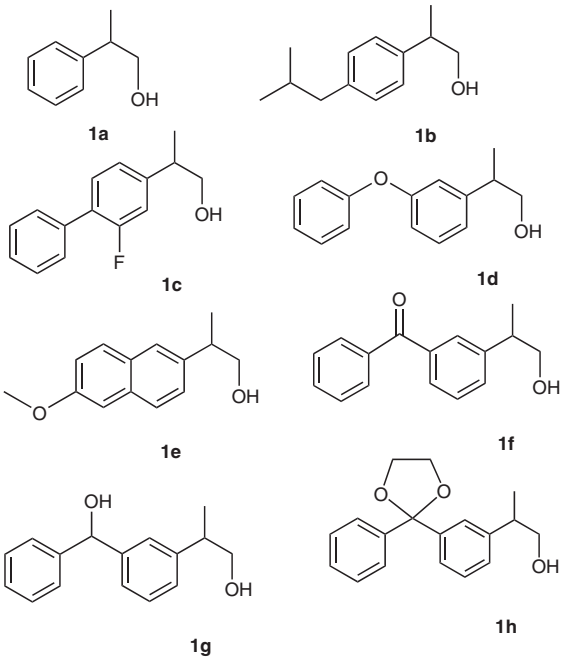


Figure 1 2-Arylpropanols used as starting materials for the oxidation to 2-arylpropionic acids

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merically pure (*S*)-**1b–f** were obtained by enantioselective biocatalysis starting from the corresponding racemic aldehydes.[6c]

Oxidation of (*S*)-ibuprofenol, (*S*)-**1b**, with $KMnO_4$ in acetone and H_2SO_4, was already reported in the literature[7] (Table 1, entry 1), but on application of the same procedure on (*S*)-**1a**, (S)-**1c**, and (*S*)-**1d** we obtained unsatisfactory results (Table 1, entries 3 and 4). The yields of the isolated carboxylic acids were low with a significant amount of arylmethylketone byproducts **4a**,**c**,**d**. Starting from pure (*S*)-**1a**, the enantiomeric ratio was maintained in the product (*S*)-**2a**.

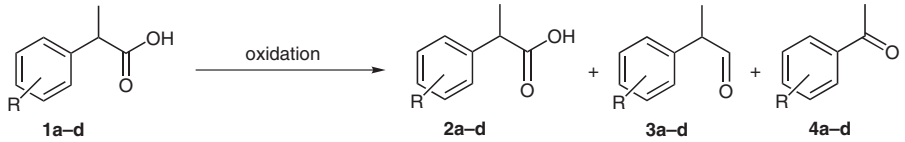
Application of the Noyori's oxidation protocol, H_2O_2 with tungstate catalyst (2 mol%), gave poor yields, even on increasing the amount (10 mol%) of catalysts (Table 1, entries 9 and 11). Substitution of the quaternary ammonium salt Aliquat with Bu_4NHSO_4 or of H_2O_2 with peracetic acid was uneffective (Table 1, entries 10–13). In order to rule out the possibility that any racemization of the stereogenic center was occurring during this oxidation protocol we tested (*S*)-**1a** or (*R*)-**1a**, and the enantiomeric purity was maintained in products (*S*)-**2a** and (*R*)-**2a**, respectively (Table 1, entries 7 and 8).

In a number of oxidation experiments (Table 1) significant amounts of arylmethylketones **4a–d** were obtained, in particular with $KMnO_4$ and with H_2O_2 and Na_2WO_4, a certain amount of aldehydes **3a**,**b** was also recovered.

The formation of acetophenone from 2-phenylpropanol derives from an oxidative C–C bond cleavage. The scission of a C–C bond leading to loss of one carbon atom was already observed in the PCC oxidation of homobenzylic alcohols[10] and in oxidation of cumenes with hydrogen peroxide catalyzed by manganese(III) porphyrins.[11] It derives from a competition between a C–H or C–C bond cleavage as discussed by Baciocchi et al. in the oxidation of benzylic alcohols catalyzed by iron(III) porphyrin.[12] Moreover, even the conversion of 2-phenylpropanal into acetophenone was reported in the literature through a metal catalysis.[13] Therefore two side reactions converge towards arylmethylketones: one from the starting alcohol and one from the intermediate aldehyde, both hampering the formation of aryl propionic acids whenever metal oxidants were used.

The use of stable nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as catalyst for mild oxidation of alcohols is well established,[5] and we then tested it on 2-arylpropanols. We used the system TEMPO and NaClO as catalysts, $NaClO_2$ as oxidant and MeCN–buffer as reaction solvent.[14] The results reported in Table 2 demonstrated the high efficiency of the procedure. The 2-arylpropionic acids were directly isolated by basic–acid

Table 1 Oxidation of Arylpropanols with H_2O_2 and Tungstate or $KMnO_4$



1a–d **2a–d** **3a–d** **4a–d**

Entry	Alcohol	Conditions	Yield of **2** (%)[a]	*S*/*R* ratio of **2**	Yield of **3** (%)[b]	Yield of **4** (%)[15]
1	(*S*)-**1b**	$KMnO_4$, acetone–H_2SO_4 3 N, 0 °C	77[c]	–	–	–
2	(*S*)-**1a**	$KMnO_4$, acetone–H_2SO_4 3 N, 0 °C	36	–	–	55
3	(*S*)-**1c**	$KMnO_4$, acetone–H_2SO_4 3 N, 0 °C	47	>99:1	–	50
4	(*S*)-**1d**	$KMnO_4$, acetone–H_2SO_4 3 N, 0 °C	51	>99:1	–	12
5	(*S*,*R*)-**1a**	H_2O_2, Na_2WO_4 (2 mol%), Aliquat 138 (2 mol%), $KHSO_4$ (2 mol%), 90 °C	27	–	10	30
6	(*S*,*R*)-**1a**	H_2O_2, Na_2WO_4 (2 mol%), Aliquat 138 (2 mol%), $KHSO_4$ (2 mol%), r.t.	12	–	–	40
7	(*S*)-**1a**	H_2O_2, Na_2WO_4 (2 mol%), Aliquat 138 (2 mol%), $KHSO_4$ (2 mol%), 90 °C	20	>99:1	5	17
8	(*R*)-**1a**	H_2O_2, Na_2WO_4 (2 mol%), Aliquat 138 (2 mol%), $KHSO_4$ (2 mol%), 90 °C	25	<1:99	2	16
9	(*S*,*R*)-**1a**	H_2O_2, Na_2WO_4 (10 mol%), Aliquat 138 (10 mol%), $KHSO_4$ (10 mol%), 90 °C	40	–	4	28
10	(*S*,*R*)-**1a**	H_2O_2, Na_2WO_4 (2 mol%), Bu_4NHSO_4 (2 mol%), 90 °C	20	–	2	18
11	(*S*,*R*)-**1a**	H_2O_2, Na_2WO_4 (10 mol%), Bu_4NHSO_4 (10 mol%), 90 °C	36	–	9	40
12	(*S*,*R*)-**1a**	AcOOH, Na_2WO_4 (10 mol%), Bu_4NHSO_4 (10 mol%), 70 °C	5	–	5	30
13	(*S*,*R*)-**1b**	H_2O_2, Na_2WO_4 (20 mol%), Bu_4NHSO_4 (20 mol%), 90 °C	15	–	15	44

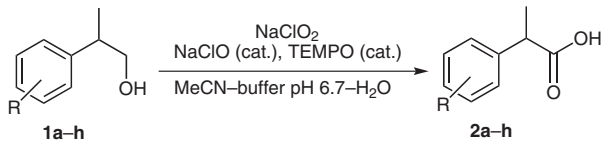
[a] Yields refer to isolated compounds.
[b] Yields estimated on GC or NMR analysis of the crude.

workup with a purity >99% by HPLC. 2-Phenyl-propanoic acid (**2a**), ibuprofen (**2b**), flurbiprofen (**2c**), and fenoprofen (**2d**) were isolated in excellent yields. In some cases the reaction was quite slow and needed a further addition of catalysts/oxidant (Table 2, compare, for instance, entries 1, 5, 7, or 12).

Naproxen (**2e**) was obtained in lower yield, probably due to its poor solubility, being the starting alcohol (**1e**) in H_2O–MeCN the less soluble of the series, or because of the deactivating 4-methoxynaphthyl substituent (Table 2, entries 9–11). Yields were low for ketoprofen (**2f**) and zero for the diol **2g** (Table 2, entries 12–17), probably due to the possibility to form a stable benzophenone-type radical intermediate which stops the catalytic cycle of oxidation. As a matter of fact the 2-arylpropanol protected at the ketone group **1h** gave the corresponding acid **2h** in satisfactory yields (Table 2, entry 17). In all cases, even when yields were low, the formation of byproduct arylmethylketones **4** were inhibited, as well as the aldehydes **3** as intermediates in the oxidation. The presence of aldehydes could represent a serious drawback because of an easy racemization of 2-arylpropanals in the aqueous medium.[6c] In the case of oxidation with TEMPO this event was probably limited because the labile aldehyde intermediate was rapidly oxidized to the carboxylic acid by sodium chlorite. As a proof of the absence of any racemization, the enantiomeric purity of the starting arylpropanols were always maintained.

In conclusion, we reported here on the oxidation of 2-arylpropanols to 2-arylpropionic acids. The reaction with TEMPO, NaClO and $NaClO_2$ in comparison to H_2O_2 with Na_2WO_4 or $KMnO_4$ gave excellent results in terms of yields and high selectivity without remarkable presence of byproducts. The enantiomeric purity of the starting arylpropanols is totally retained in the final acids. The chemoenzymatic DKR reduction of arylpropanals[6] coupled with the oxidation reported here looks promising as a more environmental friendly alternative route to the synthesis of enantiomerically pure profens[16] and contributes to improve the sustainability of the synthesis of important drugs. Further investigations on the use of immobilized

Table 2 Oxidation of Arylpropanols **1a–h** with TEMPO



1a–h **2a–h**

Entry	Alcohol	Temp (°C)	$NaClO_2$ (equiv)	NaClO (%)	TEMPO (%)	Time (h)	Yield of **2** (%)[a]	*S*/*R* ratio of **2**
1	(*S*,*R*)-**1a**	35	2	2	2	6	93	–
2	(*S*)-**1a**	35	2	2	2	4	88	>99:1
3	(*R*)-**1a**	35	2	2	2	4	92	>1:99
4	(*S*)-**1b**	35	4	4	4	21	99	>99:1
5	(*S*,*R*)-**1c**	r.t.	3	4	4	24	88	–
6	(*S*)-**1c**	r.t.	3	4	4	24	85	98:2[b]
7	(*S*,*R*)-**1d**	35	3	4	4	24	97	–
8	(*S*)-**1d**	35	3	4	4	26	96	98:2[b]
9	(*S*,*R*)-**1e**	r.t.	4	6	6	21	65	–
10	(*S*,*R*)-**1e**	35	3	4	4	20	32	–
11	(*S*)-**1e**	r.t.	4	6	6	26	59	>99:1
12	(*S*,*R*)-**1f**	r.t.	4	6	6	24	25	–
13	(*S*,*R*)-**1f**	35	3	4	4	24	40	–
14	(*S*)-**1f**	35	3	4	4	24	42	97:3[b]
15	(*S*,*R*)-**1g**	r.t.	8	12	12	24	–	–
16	(*S*,*R*)-**1g**	35	6	8	8	20	–	–
17	(*S*,*R*)-**1h**	r.t.	3	4	4	20	62	–

[a] Yields of isolated products.
[b] Enantiomeric ratio of the 2-arylpropionic acids was congruent with the enantiomeric ratio of the starting alcohols.

TEMPO,[17] aerobic oxidation with TEMPO,[18] or other oxidants in the synthesis of profens are under way.

General Procedure for the Oxidation of 2-Arylpropanols 1a–h to 2-Arylpropionic Acids 2a–h

Method A

Solid $KMnO_4$ (0.88 mmol, 139 mg) was added to a solution of (2*S*)-phenyl-propanol **1a** in acetone (2 mL) and H_2SO_4 3 N (2 mL) at 0 °C under stirring. The solution was kept at 0 °C for 4 more hours and at r.t. for 30 min. Conversion was followed by TLC. The reaction was diluted by adding 5 mL of HCl (1 N) and solid Na_2SO_3 until the discoloring of the solution. The aqueous phase was extracted twice with EtOAc (2 × 10 mL), the organic phase was then extracted with a 2% NaOH solution (2 × 10 mL). The collected aqueous phase was acidified to pH 1 with HCl (2 N) and extracted twice with CH_2Cl_2 (2 × 10 mL). The final organic phase was dried over Na_2SO_4 and concentrated in vacuum obtaining acid **2a** in 36% yield.

Method B

Representative Procedure for Entry 5, Table 1

In a round-bottom flask fitted with a water condenser the following reagents were added: 2-phenylpropanol **1a** (3.65 mmol, 0.5 mL), Aliquat 138 (2%, 0.07 mmol, 29 mg), $KHSO_4$ (2%, 0.07 mmol, 20 mg), $Na_2WO_4{\cdot}2\ H_2O$ (2%, 0.07 mmol, 24 mg), and H_2O_2 (2 mL, 30% soln). The solution was kept at 90 °C, and the reaction progress was followed by GC. The solution was then cooled to r.t. and 10 mL of a 10% Na_2CO_3 aq solution were added followed by extraction with EtOAc (2 × 10 mL). After concentration in this organic phase unreacted alcohol **1a** and byproducts **3a** and **4a** could be isolated. The aqueous phase were then acidified with diluted HCl until pH 2 and re-extracted with EtOAc (2 × 10 mL). After evaporation pure acid **2a** (150 mg, 27%) could be obtained.

Method C

To a stirred solution of alcohol **1a**–**h** (0.4 mmol) in MeCN (2 mL) the following reagents were added: a solution of $NaClO_2$ (0.8 mmol, 85 mg) in H_2O (0.4 mL), TEMPO (0.008 mmol), 0.67 M phosphate buffer pH 6.7 (1.5 mL), and a solution of commercial household bleach (5.25% in NaClO, 10.6 μL) in H_2O (0.2 mL). The temperature was maintained at the values reported in Table 2 with a silicon oil bath. The conversion was monitored by TLC and further portions of TEMPO/NaClO/$NaClO_2$ (0.008:0.4:0.008 mmol ratios) were eventually added as reported in the Tables. When the reaction was complete (TLC monitoring) it was quenched at 0 °C by adding H_2O (3 mL), aq sat. solution of $NaHCO_3$ till pH 8 and Na_2SO_3 (1.4 mmol, 183 mg). After a 30 min stirring, EtOAc (2 mL) was added, and the solution was stirred for further 15 min. The organic layer was separated and discharged. HCl (1 N) was then slowly added at 0 °C till pH 2 to the aq solution which was then extracted with EtOAc (2 × 5 mL). The collected organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 2-arylpropionic acids pure by HPLC or NMR analysis.

Enantiomeric ratios of acids **2a**–**h** were determined by HPLC analysis on chiral columns, configuration of the major isomer was established by direct comparison with commercial products or by comparing the optical rotation with reported data.

Compound 2a

t_R = 5.5 min (*R*), 6.0 min (*S*), Daicel AD, hexane–*i*-PrOH (92:8), TFA 0.1%, 1 mL/min.

Compound 2b

t_R = 7.9 min (*R*), 8.9 min (*S*), Daicel OD, hexane–*i*-PrOH (98:2), TFA 0.1%, 1 mL/min.

Compound 2c

t_R = 6.2 min (*R*), 8.0 min (*S*), Daicel AD, hexane–*i*-PrOH (90:10), TFA 0.1%, 1 mL/min.

Compound 2d

t_R = 6.8 min (*R*), 8.0 min (*S*), Daicel AD, hexane–*i*-PrOH (90:10), TFA 0.1%, 1 mL/min.

Compound 2e

t_R = 10.8 min (*R*), 11.8 min (*S*), Daicel AD, hexane–*i*-PrOH (90:10), TFA 0.1%, 1 mL/min.

Compound 2f

t_R = 12.9 min (*R*), 15.3 min (*S*), Daicel AD, hexane–*i*-PrOH (90:10), TFA 0.1%, 1 mL/min.

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References and Notes

(1) Ley, S. V.; Madfin, A. In *Comprehensive Organic Synthesis*, Vol. 7; Trost, B. M.; Fleming, I.; Ley, S. V., Eds.; Pergamon: Oxford, **1991**, 251.
(2) Cainelli, G.; Cardillo, G. *Chromium Oxidations in Organic Chemistry*; Springer: Berlin, **1984**.
(3) (a) Arends, W. C. E.; Sheldon, R. A. In *Modern Oxidation of Alchols using Environmentally Benign Oxidants,* In *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, **2004**, 83. (b) ten Brink, G. J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636.
(4) Noyori, R.; Aoki, M.; Sato, K. *Chem. Commun.* **2003**, 1977.
(5) For reviews of TEMPO-catalyzed alcohol oxidations, see: (a) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153. (b) Adam, W.; Saha-Möller, C. R.; Ganeshpur, P. A. *Chem. Rev.* **2001**, *101*, 3499. (c) Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774. (d) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051. (e) Vogler, T.; Studer, A. *Synthesis* **2008**, 1979.
(6) (a) Giacomini, D.; Galletti, P.; Quintavalla, A.; Gucciardo, G.; Paradisi, F. *Chem. Commun.* **2007**, 4038. (b) Giacomini, D.; Cainelli, G.; Galletti, P.; Gucciardo, G.; Quintavalla, A. WO 2008074717, **2008**. (c) Galletti, P.; Emer, E.; Gucciardo, G.; Quintavalla, A.; Pori, M.; Giacomini, D. *Org. Biomol. Chem.* **2010**, *8*, 4117.
(7) (a) Li, X.; List, B. *Chem. Commun.* **2007**, 1739. (b) Cleij, M.; Archelas, A.; Furstoss, R. *J. Org. Chem.* **1999**, *64*, 5029.
(8) Basak, A.; Nag, A.; Bhattacharya, G.; MandalS, ; Nag, S. *Tetrahedron: Asymmetry* **2000**, *11*, 2403; and references cited therein.
(9) Compounds **1b**–**g** were obtained by $BH_3{\cdot}SMe_2$ reduction from commercially available racemic acids. Compound **1h** was easily obtained in a three steps synthesis starting from ketoprofen (EtOH, $BF_3{\cdot}OEt_2$ cat.; ethylene glycol, TsOH cat. in toluene; $LiAlH_4$ in THF).
(10) Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1275.
(11) RebeloS, L. H.; Simões, M. M. Q.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S. *J. Mol. Catal. A: Chem.* **2003**, *201*, 9.
(12) Baciocchi, E.; Belvedere, S.; Bietti, M. *Tetrahedron Lett.* **1998**, *39*, 4711.

(13) Tokunaga, M.; Aoyama, H.; Shirogane, Y.; Obora, Y.; Tsuji, Y. *Catal. Today* **2006**, *117*, 138.
(14) (a) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564. (b) Zhao, M.; Li, J.; Mano, E.; Song, Z. J.; Tschaen, D. M. *Org. Synth.* **2005**, *81*, 195.
(15) Referred to reported data, see ref. 7.
(16) Cann, M. C.; Connelly, M. E. *The BHC Company Synthesis of Ibuprofen,* In *Real-World Cases in Green Chemistry*; American Chemical Society: Washington DC, **2000**.
(17) Röben, C.; Studer, A.; Hemme, W. L.; Eckert, H. *Synlett* **2010**, 1110; and references cited therein.
(18) Figiel, P. J.; Sibaouih, A.; Ahmad, J. U.; Nieger, M.; Räisänen, M. T.; Leskelä, M.; Repo, T. *Adv. Synth. Catal.* **2009**, *351*, 2625.