The Oxidation of Aromatic Aldehydes to Carboxylic Acids Using Hydrogen Peroxide in Formic Acid

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Received 19 August 1992

Aromatic aldehydes and particularly heteroaromatic aldehydes **1** are efficiently and conveniently oxidized to their corresponding carboxylic acids **2** by hydrogen peroxide in formic acid at 4°C.

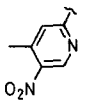
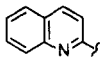
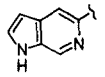
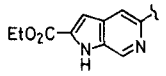
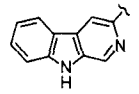
Numerous methods have been described for the transformation of aromatic aldehydes into their corresponding carboxylic acids.[1] Classic techniques make use of oxidants such as potassium permanganate (in aqueous, acidic or organic media), various chromium reagents (chromium (VI) oxide, pyridinium dichromate, pyridinium chlorochromate, Collin's reagent), and silver oxides [silver(I) or silver(II)]. The drawbacks inherent to the utilization of many of these reagents (toxicity, high cost, acidic or basic reaction conditions, formation of heterogeneous mixtures) has led to the development of new methodologies though not all are devoid of certain disadvantages. For example, hexafluoro-2-hydroperoxy-2-propanol (HPHI), effective for the transformation of aldehydes into acids under mildly basic conditions,[2] also produces *N*-oxidation of tertiary amines;[3] calcium hypochlorite treatment of benzaldehydes sometimes leads to nuclear chlorination instead of oxidation;[4] manganese(IV) oxide oxidation of aldehyde-derived cyanohydrins produces esters rather than acids;[5] the generality and practical limits of a recently published nickel-complex catalyzed oxidation of aldehydes to carboxylic acids by molecular oxygen remain to be shown.[6]

Another oxidant which has received recurrent interest over the years is hydrogen peroxide. Although capable by itself of oxidizing aromatic aldehydes to carboxylic acids under strongly basic conditions,[7] hydrogen peroxide is most useful for this purpose in conjunction with other reagents. For instance, the HPHI oxidant mentioned above is formed by reaction of hydrogen peroxide with hexafluoroacetone.[2] Combinations of hydrogen peroxide with sodium chlorite,[8] benzeneseleninic acid,[9] or ammonium molybdate[10] have been successfully used to synthesize a variety of aromatic and aliphatic carboxylic acids. In strongly acidic media and in the presence of methanol, benzaldehydes having electron-withdrawing substituents can also be transformed into their corresponding methyl esters by aqueous hydrogen peroxide.[11]

We have recently reported the preparation of 1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylic acids via treatment of the 5-carbaldehydes, **1p, 1q**, with hydrogen peroxide in formic acid at 0°C.[12,13] The use of this system was prompted by the necessity of obtaining a final product which could be isolated simply by filtration (i.e., the highly insoluble nature of these carboxylic acids in organic solvents makes their extraction from heterogeneous mixtures extremely difficult). Moreover, formation of an *N*-oxide or oxindole-type species had also to be avoided. While this method was quite successful in our case, a survey of the literature showed that, in fact, no reports concerning the practical use of performic acid (the reactive species produced by the addition of hydrogen peroxide to formic acid) for the oxidation of aromatic

$$Ar-CHO \xrightarrow[0-4°C,\ 12h]{H_2O_2/HCO_2H} Ar-CO_2H$$

1 → 2 (34–100%)

1, 2	Ar	1, 2	Ar	1, 2	Ar
a	Ph	g	3-$MeOC_6H_4$	m[18]	
b	2-$O_2NC_6H_4$	h	2-$MeOC_6H_4$	n	
c	4-$O_2NC_6H_4$	i	$PhCH_2$	o	
d	4-ClC_6H_4	j	2-pyridyl	p[12]	
e	2,6-$Cl_2C_6H_3$	k	3-pyridyl	q[13,18]	
f	4-$MeOC_6H_4$	l	4-pyridyl	r[19]	

aldehydes to carboxylic acids could be found[14] though the utilization of perbenzoic acid in methanol to effect this transformation has been documented,[15] as has the use of various peroxy acids other than performic acid.[16]

In the Table are shown the results of treatment of various aromatic and heteroaromatic aldehydes **1** with hydrogen peroxide in formic acid to give the corresponding carboxylic acids **2**.

Heteroaromatic aldehydes, **1j–r**, gave particularly satisfactory results. In only one case, **1j**, was a small amount of *N*-oxide formed concomitantly. Although the presence of electron-withdrawing groups on the aromatic ring was compatible with the reaction conditions (e.g., **1b–d, 1m, 1q**), electron-donating substituents (e.g. **1f–h**) sometimes gave less satisfactory results. Thus, the *p*-anisic acid formed by oxidation of *p*-anisaldehyde **1f** could only be isolated by chromatography of a dichloromethane extract of the reaction mixture. Oxidation of *o*-anisaldehyde **1h** under the same conditions gave a reaction mixture too complex to be preparatively useful. In contrast, *m*-anisaldehyde **1g** gave the corresponding carboxylic acid in good yield. Competing phenol[14,15] and quinone[14] formation

Table. Carboxylic Acids **2a–r** Prepared

Product	Yield (%)[a]	mp (°C)[b]	Molecular Formula[c] or Lit. mp (°C)[d]	^1H NMR (solvent/TMS)[e] δ, J (Hz)
2a	93	118–120	122–123	$CDCl_3$: 7.42 (t, 2H, J = 2.0, 8.0, H-3, H-5), 7.65 (m, 1H, H-4), 8.15 (t, 2H, H-2, H-6)
2b	50	143–145	146–148	$CDCl_3$: 7.73 (m, 2H, H-3, H-6), 7.95 (m, 2H, H-4, H-5)
2c	51	234–235	239–241	DMSO-d_6: 8.16 (d, 2H, J = 9, H-3, H-5), 8.34 (d, 2H, H-2, H-6)
2d	50	235–236	239–241	Acetone-d_6: 7.40 (d, 2H, J = 7, H-3, H-5), 8.10 (d, 2H, H-2, H-6)
2e	trace[f]			
2f	34	180–182	182–185	$CDCl_3$: 3.80 (s, 3H, CH_3), 6.80 (d, 2H, J = 7.3, H-3, H-5), 8.20 (d, 2H, H-2, H-6)
2g	62	102–103	106–108	$CDCl_3$: 3.86 (s, 3H, CH_3), 7.15 (d, 1H, J = 8.1, H-4), 7.38 (t, 1H, H-5), 7.62 (s, 1H, H-2), 7.72 (d, 1H, J = 7.4, H-6)
2h	[g]			
2i	48	77–78	77–78.5	$CDCl_3$: 2.90 (s, 2H, CH_2), 7.30 (m, 5H, H_{arom})
2j	70[h]	134–135	139–142	Acetone-d_6: 7.60 (dt, 1H, J = 6.0, 8.0, H-5), 7.90 (dt, 1H, J = 8.0, 2.0, H-4), 8.05 (dd, 1H, H-3), 8.63 (dd, 1H, H-6)
2k	86	229–230	236–239	DMSO-d_6: 7.60 (t, 1H, J = 4.9, 8.0, H-5), 8.86 (d, J = 8.0, H-6), 8.95 (d, 1H, H-4), 9.17 (s, 1H, H-2)
2l	100	307–309 (subl.)	310–315 (subl.)	DMSO-d_6: 7.84 (d, 2H, J = 4.8, H-3, H-5), 8.81 (d, 2H, H-2, H-6)
2m	95	181–182	$C_7H_6N_2O_4$ (182.1)	DMSO-d_6: 2.62 (s, 3H, CH_3), 8.25 (s, 1H, H-3), 9.25 (s, 1H, H-6)
2n	78	157–159	157–159	CD_3OD: 7.20 (t, 1H, J = 7.0, H-6), 7.90 (t, 1H, J = 7.0, H-7), 8.05 (d, 1H, J = 10.0, H-4), 8.23 (dd, 2H, H-5, H-8), 8.55 (d, 1H, H-3)
2o	100	252–253	254–255	Acetone-d_6: 7.75 (t, 1H, J = 7.5, H-6), 7.90 (t, 1H, H-7), 8.20 (d, 1H, J = 4.4, H-3), 8.60 (dd, 2H, J = 7.5, H-5, H-8), 9.10 (d, 1H, H-2)
2p	92	325–328 (dec)	$C_8H_6N_2O_2$ (162.1)	DMSO-d_6: 6.86 (d, 1H, J = 3.0, H-3), 7.96 (d, 1H, H-2), 8.52 (s, 1H, H-4), 8.96 (s, 1H, H-7), 12.22 (br s, 1H, NH)
2q	89	310–311	$C_{11}H_{10}N_2O_4$ (234.2)	DMSO-d_6: 1.37 (t, 3H, J = 7.0, CH_3), 4.41 (q, 2H, CH_2), 7.37 (s, 1H, H-3), 8.48 (s, 1H, H-4), 8.89 (s, 1H, H-7), 9.83 (bs, 1H, H-3)
2r	98	310–311	309–310[19]	DMSO-d_6: 7.33 (t, 1H, J = 7.2, H-6), 7.58–7.71 (m, 2H, H-5, H-7), 8.42 (d, 1H, J = 7.8, H-8), 8.95 (s, 1H, H-4), 8.99 (s, 1H, H-1), 12.07 (s, 1H, NH)

[a] Yield of pure crystalline product.
[b] Uncorrected, measured on a Buchi apparatus.
[c] Satisfactory microanalyses obtained: C ± 0.30, H ± 0.30, N ± 0.30.
[d] Taken from the Aldrich Chemical Co. catalogue unless otherwise stated.
[e] Determined on Bruker 200- or 250-MHz instruments. All carboxylic acids showed a very broad, D_2O-exchangeable singlet.
[f] After 48 h at 24°C; as determined by comparison with an authentic sample by TLC.
[g] Present in a complex mixture but not isolated.
[h] Approximately 5% of the carboxylic acid *N*-oxide was also isolated.

may explain the difficulties observed with the oxidations of **1f** and **1h**. The poor reactivity of 2,6-dichlorobenzaldehyde (**1e**) towards oxidation, previously observed by others,[9] may be attributed to steric hindrance. Alkyl carbaldehydes, **1i**, also appear to be efficiently oxidized under these reaction conditions, but this has not yet been studied in detail.

Finally, the use of co-solvents (dimethylformamide, tetrahydrofuran, hexane) in this procedure consistently gave less satisfactory results, as did the use of acetic acid instead of formic acid.

In conclusion, the oxidation of aryl aldehydes to their corresponding benzoic acids using hydrogen peroxide in formic acid, a Baeyer–Villiger-type reaction, represents an inexpensive, efficient procedure, particularly in the case of heteroaromatic aldehydes. This technique may prove to be especially useful in cases where the insolubility of the product carboxylic acid precludes use of heterogeneous oxidation systems.

Starting aldehydes **1a–l**, **1n** and **1o** were obtained from Aldrich Chemical Co. Formic acid and H_2O_2 (30% aqueous solution) were from Prolabo, Paris, France and were used without further purification. Thin layer chromatography and preparative chromatography were performed using Merck silica gel 60 plates with fluorescent indicator and CH_2Cl_2/EtOH (95:5) as developer. Elemental analyses were obtained at the ICSN, CNRS, Gif-sur-Yvette, France.

Oxidation of Aromatic Aldehydes 1 to Carboxylic Acids 2; General Procedure:

The starting aldehyde **1** was dissolved in 3–5 eq. of HCO_2H (or more if the aldehyde was poorly soluble), the solution was cooled to 0°C and a minimum of 3 eq of cold 30% aq H_2O_2 was slowly added. In most cases, the product carboxylic acid **2** precipitated from the mixture after standing at 4°C overnight. In cases where the resulting carboxylic acid did not precipitate even after addition of H_2O, the mixture was repeatedly diluted with EtOH and concentrated under reduced pressure (**caution!**)[17] until crystallization occurred spontaneously or could be induced by addition of hexane. The precipitate was collected by filtration, washed with cold H_2O and dried to give pure carboxylic acid.

In the particular case of **1f**, the mixture was diluted with H_2O, extracted with CH_2Cl_2 (3×) and the combined organic extracts were dried (Na_2SO_4). After evaporation of solvents, the crude residue was purified by preparative chromatography, yielding **2f**.

We thank DRET for financial support (contract 89/157) and Dr. Pierre Potier for fruitful discussions.

(1) Ogliaruso, M.A.; Wolfe, J.F. In *Synthesis of Carboxylic Acids, Esters and Their Derivatives*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1991; pp 40–51 and 357–360.
(2) Ganem, B.; Heggs, R.P.; Biloski, A.J.; Schwartz, D.R. *Tetrahedron Lett.* **1980**, *21*, 685.
(3) Ganem, B.; Biloski, A.J.; Heggs, R.P. *Tetrahedron Lett.* **1980**, *21*, 689.
(4) Nwauka, S.O.; Keehn, P.M. *Tetrahedron Lett.* **1982**, *23*, 3131.
(5) Corey, E.J.; Gilman, N.W.; Ganem, B.E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.
(6) Yamada, T.; Rhode, O.; Takai, T.; Mukaiyama, T. *Chem. Lett.* **1991**, 5.
(7) Birkinshaw, J.H.; Raistrick, H.; Ross, D.J.; Stickings, C.E. *Biochem. J. (London)* **1952**, *5*, 610.
(8) Delcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.
(9) Choi, J.-K.; Chang, Y.-K.; Hong, S.Y. *Tetrahedron Lett.* **1988**, *29*, 1967.
(10) Trost, B.M.; Masuyama, Y. *Tetrahedron Lett.* **1980**, *21*, 685.
(11) Matsumoto, M.; Kobayashi, H.; Hotta, Y. *J. Org. Chem.* **1984**, *49*, 4740.
(12) Dellouve-Courillon, C.; Dorey, G.; Poissonnet, G.; Doisy, X.; Potier, P.; Dodd, R.H. *Tetrahedron* **1990**, *46*, 3245.
(13) Dodd, R.H.; Doisy, X.; Potier, P.; Potier, M.-C.; Rossier, J. *Heterocycles* **1989**, *28*, 1101.
(14) The mixture H_2O_2/HCO_2H has been recently used to transform methoxybenzenes into quinones and phenols:
Orita, H.; Shimizu, M.; Hayakawa, T.; Takehira, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1652.
(15) Ogata, Y.; Sawaki, Y. *J. Org. Chem.* **1969**, *34*, 3985.
(16) Pikh, Z.G.; Pirig, Y.N.; Yatchishin, I.I.; Horvath, I. *Kinet. Katal.* **1978**, *19*, 1329; *Chem. Abstr.* **1979**, *90*, 3834.
Pikh, Z.G.; Pirig, Y.N.; Yatchishin, I.I.; Horvath, I. *Zh. Org. Khim.* **1979**, *15*, 2459; *Chem. Abstr.* **1980**, *92*, 146219.
(17) Although no problems were encountered when using this technique on gram quantities of aldehyde, all due precautions should be utilized, particularly if the reactions are scaled-up.
(18) Dodd, R.H.; Ouannès, C.; Robert-Géro, M.; Potier, P. *J. Med. Chem.* **1989**, *32*, 1272.
(19) Cain, M.; Weber, R.W.; Guzman, F.; Cook, J.M.; Barker, S.A.; Rice, K.C.; Crawley, J.N.; Paul, S.M.; Skolnick, P. *J. Med. Chem.* **1982**, *25*, 1081.