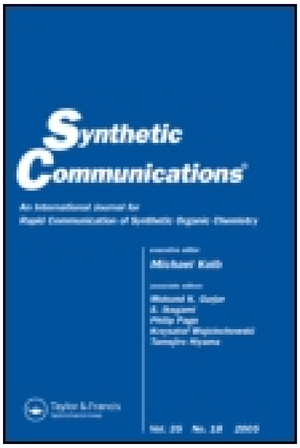

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Improved Solvent-Free Dakin Oxidation Protocol

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Improved Solvent-Free Dakin Oxidation Protocol

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Abstract: A solvent-free Dakin reaction with *m*CPBA was accomplished with various aromatic aldehydes, resulting in an easy and improved methodology for the preparation of corresponding phenols. 3,4-Methylenedioxyphenol, 3,4-dimethoxyphenol, 4-methoxyphenol, 4-chlorophenol, and other functionalized phenols were obtained in high yields from the corresponding aromatic aldehydes in a few minutes. This new methodology represents an efficient alternative for this important synthetic conversion.

Keywords: Dakin reaction, *m*CPBA, solvent-free, synthesis of phenols

The Dakin reaction formally consists of the conversion of hydroxybenzaldehydes into phenols, by using alkaline hydrogen peroxide (Scheme 1).[1] Phenols are suitable intermediates for many purposes and have proved to be useful in the synthesis of several biologically active compounds.[2]

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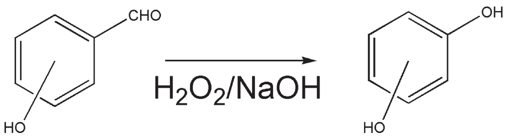


Scheme 1. Original Dakin reaction.

Although there are several different methodologies focusing on the preparation of phenols from benzaldehydes,[3] we exploited the Dakin reaction during our research program for the synthesis and evaluation of new bioactive compounds.[4] In the course of these studies, we discovered that the reaction mentioned previously could be optimized by mixing net *m*CPBA and the corresponding benzaldehydes, resulting in shorter reaction times and easier workup.

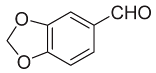
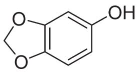
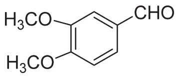
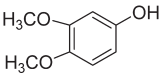
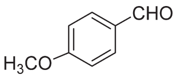
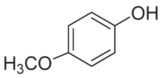
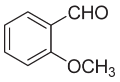
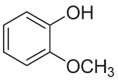
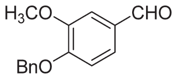
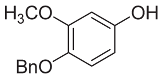
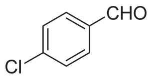
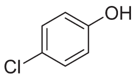
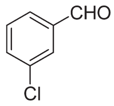
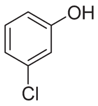
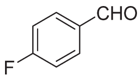
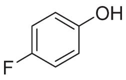
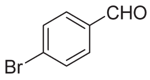
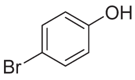
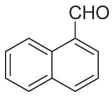
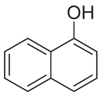
It is now well established that some organic reactions can occur efficiently in the solid state,[5] resulting in environmentally friendly synthetic products. In this context, we herein report an efficient and unprecedented solid-state oxidation of activated and nonactivated aromatic aldehydes using *m*CPBA.

Previous studies carried out by Varma and Naicker[3f] described a solid-state procedure using an urea–hydrogen peroxide adduct useful only for activated hydroxylated benzaldehydes in glass tubes at high temperature. Using our protocol (Table 1), various nonactivated benzaldehydes could be converted to the corresponding phenols with remarkable reduction of reaction time and high yield, in comparison with other previously reported procedures in solution.[3] Simply mixing together the aromatic aldehyde and *m*CPBA by using a pestle in a mortar results in a pasty mass and after few minutes yields the desired phenol derivative, which was easily isolated after a sequence of alkaline hydrolysis with a 10% aqueous sodium hydroxide. The results obtained are displayed in Table 1. Remarkably this procedure does not show a preference for an electron-rich substrate (entries 1–5), so other substrates could be oxidized as well (entries 6–10).

To show the benefits of our protocol, we followed the oxidative procedure described by Nam and co-workers,[2] employing H_2O_2 in MeOH and catalytic H_2SO_4 at room temperature to obtain 3,4-methylenedioxyphenol (entry 1), 3,4-dimethoxyphenol (entry 2), 4-methoxyphenol (entry 3), and 4-chlorophenol (entry 6) in comparable yields after 48 h. By applying our procedure, we can prepare them in approximately, 10 min. When exploiting another procedure,[3g] sesamol, 4-methoxyphenol and 4-chlorophenol were obtained from the corresponding benzaldehydes, after 2 h and in lower yield, by treatment with 1-butyl-3-methylimidazoliumhexafluorophosphate in the presence of H_3BO_3/H_2SO_4 as a catalyst.

In summary, the present article discloses an efficient solid-state procedure for the preparation of various functionalized phenols, which in comparison

Table 1. Oxidation of aromatic aldehydes using *m*CPBA solvent-free procedure

Entry	Starting material	Product	Yield[a] (%)	Microanalysis data[b]
1			95	Anal. calcd. for $C_7H_6O_3$: C, 60.87; H, 4.38; found: C, 60.67; H, 4.35.
2			90	Anal. calcd. for $C_8H_{10}O_3$: C, 62.33; H, 6.54; found: C, 62.08; H, 6.49.
3			87	Anal. calcd. for $C_7H_8O_2$: C, 67.73; H, 6.50; found: C, 67.59; H, 6.43.
4			85	Anal. calcd. for $C_7H_8O_2$: C, 67.73; H, 6.50; found: C, 67.66; H, 6.39.
5			85	Anal. calcd. for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13; found: C, 72.75; H, 6.12.
6			81	Anal. calcd. for C_6H_5ClO: C, 56.06; H, 3.92; found: C, 55.88; H, 3.87.
7			80	Anal. calcd. for C_6H_5ClO: C, 56.06; H, 3.92; found: C, 55.93; H, 3.83.
8			84	Anal. calcd. for C_6H_5FO: C, 64.28; H, 4.50; found: C, 63.99; H, 4.47.
9			65	Anal. calcd. for C_6H_5BrO: C, 41.65; H, 2.91; found: C, 41.57; H, 2.90.
10			78	Anal. calcd. for $C_{10}H_8O$: C, 83.31; H, 5.59; found: C, 83.20; H, 5.48.

[a] The yield refers to isolated product, after 10 min of reaction, including oxidation and hydrolysis.

[b] Microanalyses were obtained with a Perkin-Elmer 240 analyzer, using a Perkin-Elmer AD-4 balance.

with previous reports appears to be a superior alternative in terms of shorter reaction time, cleaner product formation, and easier workup.

GENERAL PROCEDURE

A combination of 0.5 mmol of the appropriate aromatic aldehyde and 1.5 eq. of solid *m*CPBA (~55%) were mixed with a pestle in a fume cupboard. The solids immediately melt and in some cases moderate evolution of heat was observed. After 5 min, thin-layer chromatographic (TLC) inspection indicated the end of the reaction. At this point, 5 mL of a 10% aqueous sodium hydroxide solution was added and mixed until complete dissolution. After an additional 5 min of stirring and washing with diethyl ether (2 × 10 mL), the pH of the aqueous phase was adjusted to 6–7 and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to furnish the corresponding pure phenols, which were analyzed by ^1H NMR and gas chromatography coupled to mass spectrometry (GC-MS) and compared with authentic samples, showing a high degree of purity.

Example (entry 1): mp 60–62°C (lit. 64–65°C); ^1H NMR (200 MHz, $CDCl_3$) 6.65 (d, $J = 8.33$ Hz, 1H); 6.43 (d, $J = 2.47$, 1H); 6.25 (dd, $J = 8.33$ and 2.56 Hz, 1H); 5.9 (s, 2H); 5.46 (br, 1H, OH).

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