Acceleration of the Dakin reaction by trifluoroacetic acid

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An acceleration of the Dakin reaction caused by addition of trifluoroacetic acid is described. The modified protocol converts aromatic aldehydes to the corresponding phenols within 4 hours at room temperature by means of hydrogen peroxide in acidic medium. This acceleration is attributed to the stability of hydrogen peroxide in an acidic medium. This modified protocol provides alternative and easy access to important phenolic precursors that have been used in the synthesis of various natural products.

Keywords: Dakin reaction, trifluoroacetic acid

Phenols are key precursors in the synthesis of numerous oxygen heterocyclic natural products of pharmacological importance.[1] There are many synthetic methods available for their preparation; however, the Dakin reaction[2] is one of the privileged protocols used for preparation of differently substituted phenols from their corresponding aldehydes. Several modifications and improvements to the Dakin reaction have been made.[3–17] However, all the evolved methods are sluggish and require anything between 12 hours and a few days for their completion. These reactions are also accompanied by some oxidised side products. In order to assist our work on the synthesis of oxygen heterocycles, which requires phenolic intermediates, we tried to develop an improved protocol for the Dakin reaction in terms of time and yield. We thought that the sluggishness of the reaction could be due to the possible decomposition of hydrogen peroxide. It has been reported that hydrogen peroxide is stored under slightly acidic conditions to avoid its decomposition. We therefore applied this logic and considered whether the Dakin reaction can be accelerated using an acidic medium.

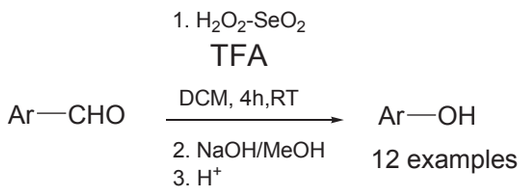
Table 1 Results of screening of acid additive (10% v/v) in the Dakin reaction

Entry	Acid	Time/h	Yield/% Phenol	Yield/% Benzoic acid
1	MSA	8	60	32
2	Cl-SA	6	26	62
3	TFA	4	80	12

We screened methanesulfonic acid (MSA), chloromethylsulfonic acid (Cl-SA) and trifluoroacetic acid (TFA). A solution of benzaldehyde in dichloromethane, 30% H_2O_2, a pinch of SeO_2 and an acid additive was stirred at room temperature. The reaction was monitored by TLC (Merck 60 F254 silica gel plates) and we found that there was considerable decrease in reaction time with almost all the acid additives (Table 1).

However, addition of TFA notably reduced the reaction time to 4 hours. It was also observed that formation of side products was minimal in the presence of TFA. Furthermore, we varied the percentage of TFA added to the reaction mass and optimised it for the best results in terms of reaction time and fewer side products (1.2 equiv. with respect to aldehydes; Scheme 1).

These reaction conditions were generalised to 11 differently substituted aromatic aldehydes (Table 2). The formation of phenol was confirmed by comparison of TLC and physical constants[18] with the standard phenols. Compounds **11** and



Scheme 1 TFA accelerated Dakin protocol.

Table 2 Differently substituted phenols obtained by TFA accelerated Dakin reaction

Entry	Ar–CHO	Ar–OH	Yield/%[a]	M.p./°C	B.p./°C	Lit.[18,19] m.p./ b.p./°C
1	C_6H_5CHO	C_6H_5OH	80		182	182
2	4-OMe–C_6H_4CHO	4-OMe–C_6H_4OH	78	56		56
3	3-OMe–C_6H_4CHO	3-OMe–C_6H_4OH	76		Oil	Oil
4	3,4-Di-OMe–C_6H_3CHO	3,4-Di-OMe–C_6H_3OH	78	80		79–82
5	3,5-Di-OMe–C_6H_3CHO	3,5-Di-OMe–C_6H_3OH	80	44		44–46
6	4-Br–C_6H_4CHO	4-Br–C_6H_4OH	82	62		61–64
7	4-Cl–C_6H_4CHO	4-Cl–C_6H_4OH	80		220	220
8	3,4-Di-Cl–C_6H_3CHO	3,4-Di-Cl–C_6H_3OH	84	66		67–68
9	3-NO_2–C_6H_4CHO	3-NO_2–C_6H_4CHO	88	96		96–98
10	2-OMe–$C_{10}H_6$–CHO	2-OMe–$C_{10}H_6$–OH	80		oil	326
11	4-OMe–$C_{10}H_6$–CHO	4-OMe–$C_{10}H_6$–OH	82	124		126
12	3-Br-4-OMe–$C_{10}H_5$–CHO	3-Br-4-OMe–$C_{10}H_5$–OH	81	118		118

[a]The yields mentioned are isolated yields.

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12 were characterised using IR (PerkinElmer Spectrum BX FT-IR), NMR (Varian mercury spectrometer on 300 MHz using $CDCl_3$ as the solvent) spectra and confirmed by comparison with literature data.[19] The utility of this methodology was proved by our being able to synthesise some of the important phenolic precursors. For example, veratraldehyde was converted to the corresponding phenol **4**, which was utilised as a precursor for synthesis of natural products.[14] Similarly compounds **11** and **12** are key intermediates in the synthesis of pyranonaphthoquinones whereas some of these phenols are key precursors in the synthesis of coumarins, flavones and chromans.

We further carried out the TFA accelerated Dakin reaction in the absence of SeO_2.

A solution of benzaldehyde in dichloromethane, 30% H_2O_2, and TFA was stirred at room temperature and the reaction was monitored by TLC. It was observed that even after 24 h stirring, there was no reaction. This observation indicates that the use of SeO_2 is mandatory as it plays important role as either carbonyl activator or a participator in the reaction by forming peroxyseleninic acid which has been reported as the actual oxidising species in Dakin reaction.[10,11]

In conclusion we have standardised the protocol to achieve the Dakin reaction in just 4 hours by acceleration through addition of TFA and generalised the reaction to a group of substituted aldehydes to provide easy access to phenols.

Experimental

All solvents were purified and dried by standard procedures prior to use. All melting points were uncorrected. TLC was performed on Merck 60 F254 silica gel plates and visualisation was accomplished by irradiation in UV or iodine. Crude products were purified by column chromatography on 100–200 mesh silica gel. IR spectra were recorded on a PerkinElmer Spectrum BX FT-IR as a thin film or KBr pellet and were expressed in cm^{-1}. ^1H NMR spectra were recorded on a Varian mercury spectrometer on 300 MHz. using $CDCl_3$ as solvent. Chemical shifts were reported in δ ppm with reference to TMS as an internal standard.

Accelerated Dakin reaction; general procedure

Hydrogen peroxide (30%, 10 mL), selenium dioxide (0.1 g) and TFA (1 mL, 12 mmol) were added to a solution of aromatic aldehyde (1 g, 9 mmol) in dichloromethane (10 mL). The biphasic reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was then poured into water and the organic layer separated, washed with water, 10% Na_2CO_3, again with water, dried over anhydrous Na_2SO_4 and concentrated to obtain a formyl ester intermediate, which was dissolved as such in methanol (5 mL). This solution was added to 20% methanolic KOH (5 mL) and the resulting dark red solution was refluxed for 1 hour. Excess methyl alcohol was removed under reduced pressure and the residue was acidified using conc. HCl to a light brown solid, which was filtered, dried and recrystallised from alcohol–water to obtain the desired phenols in excellent yields (Table 2).

1-Methoxy-4-hydroxynaphthalene (**11**): M.p. 124 °C, (lit.[3] m.p. 124–126 °C); IR (KBr) 3300, 1564, 1080, 766; ν_{max}: ^1H NMR ($CDCl_3$, 300 MHz) δ ppm., 8.12–8.2 (m, 2H), 7.56 (m, 2H), 6.72 (d, J=8 Hz) 1H), 6.62 (d, J=8 Hz) 1H), 5.24 (bs, 1H), 3.92 (s, 3H) (spectral data is in accordance with ref. 19).

2-Bromo-1-methoxy-4-hydroxy naphthalene **(12)**: M.p. 118 °C, (Lit.[19] m.p. 118 °C); IR (KBr) 3300, 1560, 1090, 763; ν_{max}; ^1H NMR ($CDCl_3$, 300 MHz) δ ppm, 8.12 (m, 2H), 7.48 (m, 2H), 6.96 (s, 1H), 5.34 (bs, 1H), 3.96 (s, 3H) (spectral data is in accordance with ref. 19).

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