www.wcprj.com 2025 Page: 63-74

World Current Pharmaceutical Research Journal

Review Article

Volume: 01
Issue: 04

SHORT REVIEW ON SYNTHETIC PROTOCOLS OF VARIOUS PHENOLIC COMPOUNDS

Soujanya Chaganti[1]*, Durga Kiranmai[1], Nandini Pathi[1] and Niharika Reddy Kotha[1]

[1]Department of Pharmaceutical Chemistry, Gokaraju Ranga Raju College of Pharmacy, Hyderabad - 500090, Telangana, India.

Article Received: 21 May 2025

Article Revised: 10 June 2025

Published on: 30 June 2025

***Corresponding Author: Soujanya Chaganti**

Department of Pharmaceutical Chemistry, Gokaraju Ranga Raju College of Pharmacy, Hyderabad - 500090, Telangana, India.

Email id: soujanya.chaganti18@gmail.com,

INTRODUCTION

Dihydric phenols like catechol, hydroquinone, and their methyl ethers are essential chemicals widely used in industries such as agrochemicals and pharmaceuticals. They serve as antioxidants, flavouring agents, and polymerization inhibitors. Catechol, a phenol derivative, is important for synthesizing industrial antioxidants such as 4-tert-butylcatechol and pharmaceutical compounds like adrenalone. Guaiacol acts as a precursor for vanillin, a major flavouring agent. Hydroquinone finds applications in photographic processes.

Traditional synthetic methods for these phenols include catalytic oxidation of aromatic hydrocarbons, hydroxylation of phenols, oxidative decarboxylation of aryl carboxylic acids, and hydrolysis of halo-benzenes. However, these methods often involve prolonged reaction times, harsh conditions, or expensive catalysts.

The Dakin reaction, which involves the conversion of aromatic aldehydes and ketones to phenols in the presence of alkaline hydrogen peroxide, is popular for its efficiency and simplicity. This reaction is especially effective for substrates containing hydroxyl groups at the ortho- or para-positions of aldehydes or ketones.

In contrast, the Dakin–West reaction converts amino acids into keto-amides using an acid anhydride and a base, typically pyridine, with applications in peptide and pharmaceutical chemistry. Both reactions are named after Henry Drysdale Dakin, a British chemist and surgeon renowned for his contributions to organic chemistry, particularly in oxidation processes and amino acid transformations. His work has had a lasting impact on the field, influencing numerous synthetic methodologies.[1] [2]

Although efficient, traditional Dakin reactions have certain limitations, such as slow reaction rates and the requirement for large quantities of reagents or extreme conditions. Recent developments have addressed these issues through the incorporation of hydrogen peroxide in combination with boric acid,[3] [4] selenium compounds, or sodium percarbonate.[5] [6] The innovation of new catalytic systems, such as Sn-Beta zeolites, has further enhanced the reaction, enabling high-yield transformations under milder conditions.[7] [8]

Innovative approaches based on green chemistry principles now allow the conversion of aryl aldehydes to phenols at room temperature in aqueous systems, without the use of transition metals, toxic ligands, or organic solvents. These advancements have made the Dakin reaction a more sustainable and economical route for industrial phenol production. Notably, enzymatic catalysis has recently emerged as a promising alternative that aligns well with environmentally friendly practices.

As a widely applicable tool for synthesizing valuable phenolic compounds such as catechol, hydroquinone, and their derivatives, the Dakin reaction continues to attract significant interest in both industrial and academic research. Other synthetically valuable products of Dakin oxidation include guaiacol (a precursor to flavourants), hydroquinone (used in photographic development), and antioxidants such as 2-tert-butyl-4-hydroxyanisole and 3-tert-butyl-4-hydroxyanisole, which are used to preserve packaged food. The Dakin reaction also plays a key role in the synthesis of indoquinones—naturally occurring compounds with notable antibiotic, antifungal, and antitumor activities.[1] [2]

Ongoing innovations in catalyst development and process optimization are driving further expansion of this reaction, reinforcing its role as a sustainable and efficient strategy for phenol synthesis.

Innovations in Dakin Reaction

Hydrogen Peroxide + Boric Acid	Enhances oxidation efficiency; greener alternative
Selenium Compounds	Acts as a catalyst; increases reaction speed
Sodium Percarbonate	Solid source of H_2O_2; safer, controlled release
Sn-Beta Zeolites	Microporous, reusable catalysts with high surface area
Room Temperature Aqueous Systems	Operates under mild conditions; eco-friendly
Enzymatic Catalysis	Uses biological enzymes; high

Literature review:

1. **H. D. Dakin (1923)** synthesized Catechol, also known as pyrocatechol, by the oxidation of salicylaldehyde and the demethylation of guaiacol. In the oxidation method, salicylaldehyde was treated with hydrogen peroxide in a basic medium, yielding catechol with 69-73% yield. Alternatively, guaiacol was demethylated using hydrobromic acid to produce catechol with 85-87%. These synthesis methods are conventional techniques since toluene and hydrobromic acid are used for extraction.[9] [10]

2. **Khemchand Surana et al**.**(2023)** have presented an environmentally friendly method for synthesizing catechol using the Dakin reaction. This technique employs hydrogen peroxide (H_2O_2) dissolved in tap water and reverse osmosis (RO) outlet water as solvents, utilizing aromatic aryl aldehydes as reagents. Conducted at room temperature, the reaction yields catechol ranging from 60% to 80%, depending on specific conditions and the concentrations of H_2O_2 used. Notably, this catalytic system does not require activation or any transition metal catalyst, toxic ligands, additives or promoters, bases, or organic solvents. Various substituted hydroxylated benzaldehydes were tested to explore the capabilities of this protocol. This approach aligns with green chemistry principles by replacing hazardous reagents and organic solvents with safer, more sustainable alternatives.[11] [12]

3. **Tomoya Nobuta et.(2024)** reported the synthesis of phenols and Catechol from salicylaldehyde and benzaldehyde substrates by Dakin reaction incorporating Oxone, which

contains potassium peroxymonosulfate as a mild oxidant instead of hydrogen peroxide, making it a green synthesis as this method does not require acidic additives or transition metal catalysts like hydrogen peroxide. It was concluded that Oxone when used in a mixed solvent of MeCN and MeOH is an efficient oxidant and was efficient in producing moderate to high yields of catechols and phenols from respective salicylaldehyde and benzaldehydes.[13] [14]

4. **Zhi Wang et.al. (2017)** have developed a green synthesis method by lipase, especially through Novozym 435 for Dakin reaction. This reaction uses substrates like salicylaldehyde, and hydroxylated benzaldehydes in the presence of urea hydrogen peroxide and ethyl acetate, which acts as solvent and source of peracid. This method produces phenols ranging from 90% to 97% yield. This reaction works under mild conditions, like at room temperature, and a reaction time of half an hour, which tells about its efficiency. Novozym 435, an immobilized lipase enzyme, can be reused for ten cycles without losing its activity.[15] [16]

5. **Shuai Chen et al.(2012)** have introduced an organocatalytic method for developing phenols through electron-rich aryl aldehydes by using catalysts such as hydro peroxyflavin for Dakin reaction. This method uses hydrogen peroxide as an oxidant under mild, basic conditions by using some solvents like DMSO, dichloromethane, and methanol. The phenols which were synthesized using this method including catechols are obtained with high efficiency. For example, oxidation of salicylaldehyde produced more than 95% by converting it to catechol using Hydroperoxy flavin 5a (R=Cl) as a catalyst with 1 equivalent H_2O_2 in 2 hours. Along with it, 2-hydroxy acetophenone is converted to catechol under similar conditions with a 90:10 DMSO/ MeOH solvent mixture. This method mainly focuses on green synthesis, especially in the aerobic environment by using O_2/Zn system which eliminates the use of H_2O_2 to make the process safer.[17] [18]

6. **Emerson Telxeira da Silva et al.(2008)** have introduced solvent-free Dakin oxidation, which converts aromatic aldehydes into phenols by using mCPBA in a solid-state reaction. These are formed by simple mixing of aldehyde and mCPBA in mortar and pestle that produces a paste-like mass that reacts within 10 minutes. Synthesised phenols like 3,4-methylenedioxyphenol,3,4-dimethoxyphenol,4-methoxyphenol, and 4-chlorophenol yield up to 95%. This reaction also includes hydrolysis of 10% aqueous Sodium hydroxide followed by extraction with diethyl ether and dichloromethane. This method represents a green synthesis approach due to solvent-free and solid-state properties.[19] [20]

7. **Seong-Ryu Joo et al. (2022)** have synthesized phenols by using green synthesis. Phenols are formed by reacting with various hydroxy aryl aldehydes and ketones by using the combination of hydrogen peroxide and aqueous choline hydroxide. The whole procedure was performed at ambient temperature in an aerobic environment. The reactivity of ChOH/ $H_2O_2$was dependent upon the position of the hydroxyl group of the aromatic ring. The yield of the synthesized phenols was found up to 95% based on eleven examples.[21] [22]

8. **Roberta Bernini et al. (2005)** have synthesized an efficient method for the preparation of phenols. These are formed by the oxidation of hydroxylated and methoxylated benzaldehydes and acetophenones by using hydrogen peroxide/ methyltrioxorhenium in ionic liquids like BF_4 and PF_6. Good yields of products within short reaction times are produced. Example: Conversion of 4-methoxybenzaldehyde to 4-methoxy phenol in the presence of H_2O_2/ CH_3ReO_3 and ionic liquids BF_4/PF_6 at 50 degrees for 4 hours yields up to 85-87%.[23] [24]

9. **Bishwajit Saikia et al. (2015)** discussed a green synthesis method for the Dakin reaction, in which hydroxylated benzaldehydes are converted into phenols by using hydrogen peroxide and Water Extract of Banana (WEB) as the catalysts. Water Extract of Banana is derived from banana ash, this acts as the catalyst, ligand, solvent, and base, eliminating the need for hazardous reagents, transition metal catalysts, or organic solvents. The synthesis was performed at room temperature under aerobic conditions, showcasing an eco-friendly approach. Phenols, including hydroxylated phenols and catechols, were synthesized with a 90%-98% yield. This protocol is not only efficient but also aligns with principles of green chemistry making it an alternative sustainable method to conventional methods. This study highlights the wide range of applications of phenols in pharmaceuticals, agrochemicals, and antioxidants. The approach emphasizes operational simplicity, cost-effectiveness, and minimal environmental impact.[25] [26]

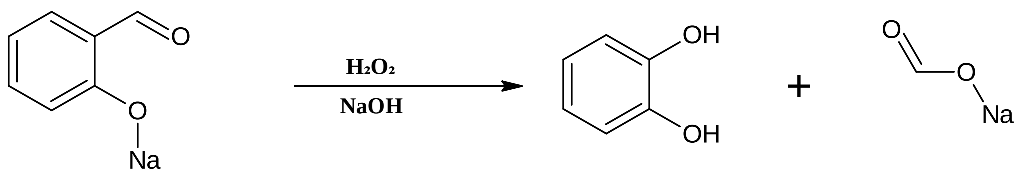
10. **Ishwari A. Kale et al. (2019)** focused on the green synthesis of phenols by the Dakin oxidation method using the natural catalysts extracted from agricultural waste. In this reaction, aldehydes act as the starting materials, and natural extracts like potato peel extract (PPE), mango peel extract (MPE), grape pomace extract (GPE), pomegranate pomace extract (PE), all rich in gallic acid and Water extract of banana (WEB) is used as both catalyst and base. This method synthesizes various phenolic compounds, such as 4-hydroxyphenol, 2,4-dichlorophenol, and 2-bromophenol with high yields. For example, 2-bromophenol achieved 95% with mango peel extract and 4-hydroxyphenol achieved 93% yield with mango peel

extract. This reaction is carried out at room temperature under aerobic conditions with low reaction times, emphasizing principles of green chemistry, and environmentally friendly. While the pharmacological actions of derived phenols are not detailed the process highlights their potential, as phenols have anti-inflammatory, antimicrobial, and antioxidant properties. This method is a sustainable approach to chemical synthesis using agricultural waste, presenting an economical and eco-friendly method to conventional methods.[27] [28]

11. **Natu et al. (2014)** developed a modified and efficient protocol for the Dakin reaction using trifluoroacetic acid (TFA) as an acid additive to accelerate the conversion of aromatic aldehydes to their corresponding phenols. Traditional Dakin reactions are often time-consuming and require harsh conditions or additional reagents such as selenium dioxide (SeO_2). In this work, the authors demonstrated that the use of TFA in dichloromethane (DCM) with hydrogen peroxide at room temperature significantly improved reaction rates and yields, achieving up to 92% product yield within 4 hours without the need for SeO_2. The study also showed that TFA stabilized hydrogen peroxide under acidic conditions, which prevented its decomposition and enhanced the efficiency of the reaction. A variety of substituted benzaldehydes were successfully converted to phenols, highlighting the method's versatility and potential application in the synthesis of natural product precursors like flavonoids and coumarins. This improved protocol offers a cleaner, faster, and more environmentally benign approach to the classic Dakin reaction.[29] [30]

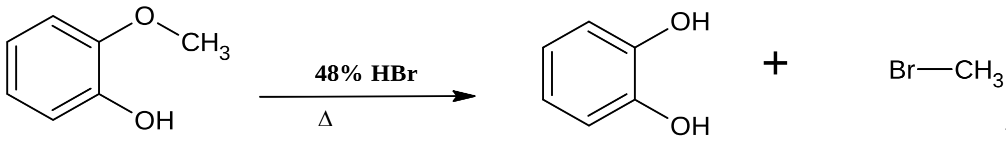
12. **Banerjee et al. (2022)** demonstrated that Dakin oxidation reaction can occur spontaneously in aqueous microdroplets containing only ketones or aldehydes, without any added oxidants, acids, bases, or catalysts. These reactions are driven by hydrogen peroxide (H_2O_2) generated in situ at the air–water interface of microdroplets under ambient conditions. Factors such as droplet size, high surface-to-volume ratio, and short reaction times significantly influence the reaction efficiency. Mass spectrometry confirmed the formation of oxidation products and intermediates. Dakin reactions benefited from surface OH^- and H^+ ions. This work highlighted the potential of aqueous microdroplets as green microreactors for promoting environmentally friendly oxidation chemistry.[31] [32]

1.a)



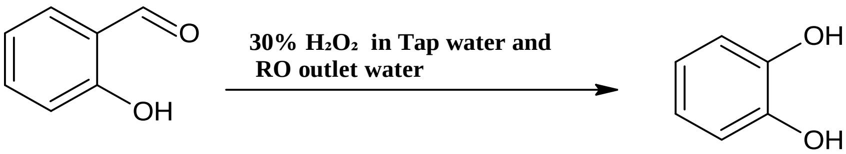
[9] [10]

1.b)



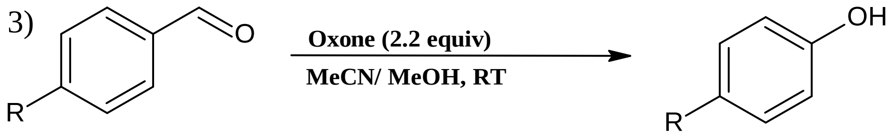
[9] [10]

2)



[11] [12]

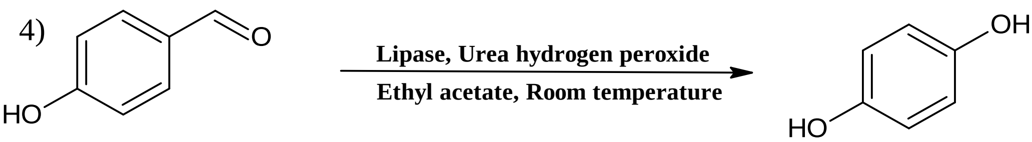
3)



R= OH, OMe, Alkyl, Ph, NHAc

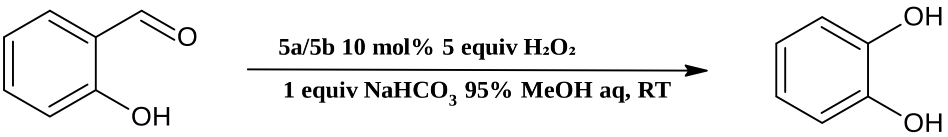
[13] [14]

4)



[15] [16]

5)

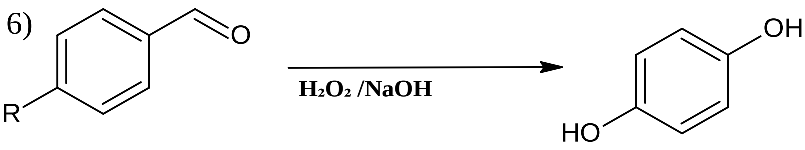


5a- > 95%, 20 min
63% (5 mol%)
32% (1 mol%)
5% (0 mol%)

5b- > 95%, 60 mins

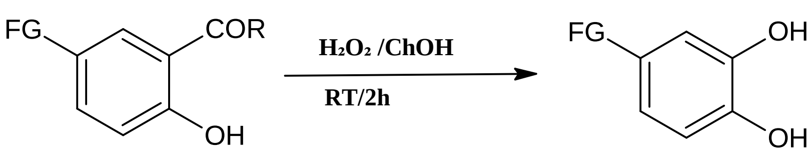
[17] [18]

6)



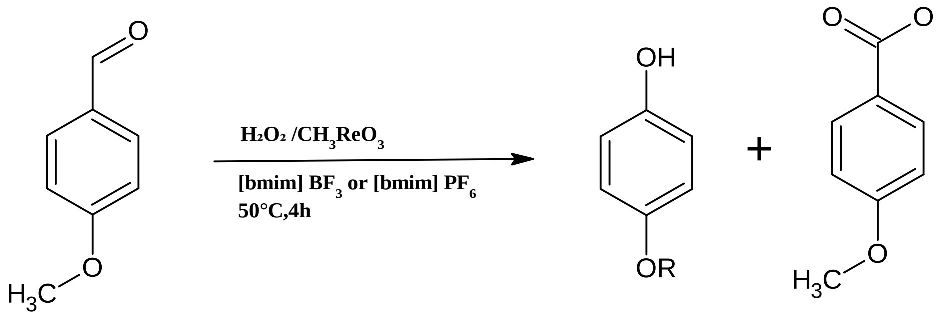
[19] [20]

7)



R:H,CH_3, Ph
FG:H,alkyl,alkoxy,Halogen

[21] [22]

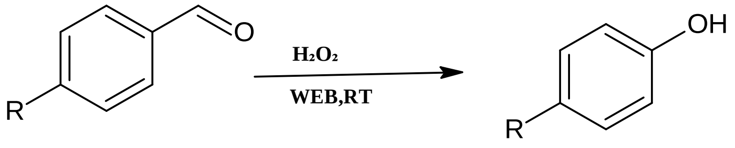
8) 

1

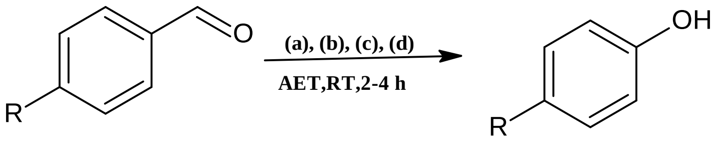
2 (R:CH_3)
3 (R:H)

4

[23] [24]

9) 

[25] [26]

10) 

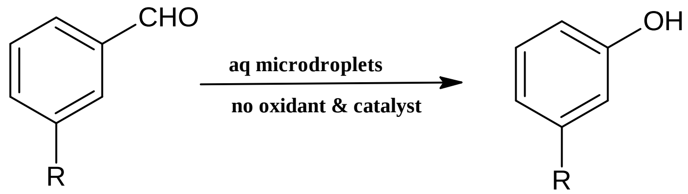
1

2(a-m)

(a) mango peel extract
(b) grape peel extract
(c) pomagranate peel extract
(d) potato peel extract

[27] [28]

11) Ar-CHO $\xrightarrow[\text{TFA, DCM, 4h, RT}]{\text{1. } H_2O_2\text{- } SeO_2}$ Ar-OH [29] [30]

12) 

[31] [32]

CONCLUSION

The Dakin reaction has become an important method for producing hydroxylated compounds such as catechols, phenols, and their derivatives, which are highly useful in the pharmaceutical, agrochemical, and other sectors. Although existing alternative methods are competent, they often pose challenges due to harsh reaction conditions, long reaction times, and the use of toxic reagents. The Dakin reaction has seen notable improvements in terms of green chemistry and catalytic systems, making it more economical and convenient.

Recent studies suggest that the reaction has been significantly enhanced by the use of eco-friendly reagents such as hydrogen peroxide, novel catalysts like enzymes (e.g., Novozyme 435) and organocatalysts, and innovative oxidation systems such as peroxodicarbonate and Oxone. Some methods even utilize agricultural residues such as banana ash or fruit peel extracts as natural catalysts, thereby promoting sustainability.

The reviewed literature highlights the Dakin reaction's ability to achieve high yields under mild conditions while adhering to green chemistry principles. These methods eliminate the need for transition metal catalysts, toxic ligands, and organic solvents, making them safer and more sustainable. Furthermore, the scalability and versatility of these approaches underscore their significance in industrial applications.

Overall, advancements in the Dakin reaction not only enhance the synthesis of valuable phenolic compounds but also contribute to the broader goal of sustainable industrial practices. Continued focus on green innovations and catalyst development is expected to further improve the reaction’s efficiency, solidifying its role as a cornerstone of environmentally conscious chemical synthesis.

Abbreviations:

RT = Room Temperature

DMSO = Dimethyl sulfoxide

MeOH = Methanol

mCPBA = meta-chloroperoxybenzoic acid

BF_4 = Tetrafluoroborate anion

PF_6 = Hexaflurophosphate

Equiv = Equivalent

CH_3ReO_3 = Methylrhenium trioxide

AET = Aqueous Ethanolic Treatment

ChOH = Hydroxy-substituted Carbon

HBr = Hydro bromic acid

NaOH = Sodium hydroxide

MeCN = Methyl Cynide

$NaHCO_3$ = Sodium bicarbonate

REFERENCES

1. C. organic redox reaction in which an ortho- or para-hydroxylated phenyl aldehyde or ketone reacts with hydrogen peroxide in base to form a benzenediol and a carboxylate [Internet]. Wikipedia.org. Wikimedia Foundation, Inc.; 2006 [cited 2025 Apr 4]. Available from: https://en.m.wikipedia.org/wiki/Dakin_oxidation
2. Varma S, Naicker KP. The Urea−Hydrogen Peroxide Complex: Solid-State Oxidative Protocols for Hydroxylated Aldehydes and Ketones (Dakin Reaction), Nitriles, Sulfides, and Nitrogen Heterocycles. Organic Letters, 1999 May 29; 1(2): 189–92.
3. Roy, A.; Reddy, KR.; Mohanta, PK.; Ila, H.; Junjappat, H. Hydrogen Peroxide/Boric Acid: An Efficient System for Oxidation of Aromatic Aldehydes and Ketones to Phenols. Synthetic Communications, 1999 Nov; 29(21): 3781–91.
4. Kurz ME, Johnson GJ. Aromatic hydroxylation with hydrogen peroxide-aluminum chloride. The Journal of Organic Chemistry, 1971 Oct 1; 36(21): 3184–7
5. G.W. Kabalka, Reddy, NK.; Narayana, C. Sodium percarbonate: A convenient reagent for the dakin reaction. Tetrahedron Letters, 1992 Feb; 33(7): 865–6.
6. Hassall, C.H. Org reactions; Wiley, New York, 1957; 9: 73-116.
7. Otomo, R.; Kosugi, R.; Kamiya, Y.; Tatsumi, T.; Yokoi, T. Modification of Sn-Beta zeolite: characterization of acidic/basic properties and catalytic performance in Baeyer–Villiger oxidation. Catalysis Science & Technology., 2016; 6(8): 2787–95.
8. Ten Brink GJ., Arends IWCE, Sheldon RA. The Baeyer−Villiger Reaction: New Developments toward Greener Procedures. Chemical Reviews., 2004 Sep; 104(9): 4105–24.
9. Dakin, H, D.; Clarke, H, T.; Taylor, E. R. Catechol. Org. Synth. Coll., 1941; 1: 149-152.
10. Magidson.; Porozovska.; Seligsohn.; Trans. Sci. Chem. Pharm. Inst., 1923; 6: 23.
11. Surana, K.; Bhawar, S.; Sonawane, V.; Patil, D.; Sonawane, D.; Mahajan, S. Tap Water and RO Outlet Water a Novel Greener Route to Catechol Synthesis in H2O2. Asian J Green Chem., 2023; 7(3): 189-98.
12. Dakin, H.D. Am. Chem. J., 1909; 62: 477.
13. Tomoya, N.; Kiriko, F.; Mineno, T. Oxone-mediated dakin reaction of benzaldehydes to phenols. J. Indian Chem. Soc., 2024; 101(8): 101186–6.
14. Webb, KS, Ruszkay, SJ. Oxidation of aldehydes with Oxone® in aqueous acetone. Tetrahedron, 1998 Jan; 54(3-4): 401–10.
15. Wang, Z.; Chen, X.; Wang, C.; Zhang, L.; Li, F.; Zhang, W. A mild and efficient Dakin reaction mediated by lipase. Green Chem Lett Rev., 2017; 10(4): 269–73.

16. Fredrik, Björkling.; Frykman, H.; Sven, Erik, Godtfredsen.; Kirk, O. Lipase catalyzed synthesis of peroxycarboxylic acids and lipase mediated oxidations. Tetrahedron., 1992 Jan 1; 48(22): 4587–92.
17. Chen, S.; Hossain, MS.; Foss, FW Jr. Organocatalytic Dakin Oxidation by Nucleophilic Flavin Catalysts. Org Lett., 2012; 14(11): 2806-9.
18. Silverman, R, B. The Organic Chemistry of Enzyme-Catalyzed Reactions, revised edition; Academic Press: San Diego, 2002; 717.
19. Teixeira, E.; Celso, AC.; Antunes, C.; Barreiro, EJ.; Carlos, AMF. Improved Solvent-Free Dakin Oxidation Protocol. Synthetic Communications., 2008; 38(5): 784–8.
20. Matsumoto, M.; Kobayashi, H.; Hotta, Y. Acid-catalyzed oxidation of benzaldehydes to phenols by hydrogen peroxide. J. Org. Chem., 1984; 49: 4740 – 4741.
21. Joo, SR.; Kim, SH. Dual Functionality of Choline Hydroxide for the Dakin Reaction. Lett Org Chem., 2022; 19(5): 341–6.
22. Abe, T.; Itoh, T.; Tominari Choshi.; Satoshi Hibino.; Minoru Ishikura. One-pot synthesis of tryptanthrin by the Dakin oxidation of indole-3-carbaldehyde. Tetrahedron Letters, 2014 Aug 1; 55(38): 5268–70.
23. Bernini, R.; Coratti, A.; Provenzano, G.; Fabrizi, G.; Tofani, D. Oxidation of aromatic aldehydes and ketones by H2O2/CH3ReO3 in ionic liquids: a catalytic efficient reaction to achieve dihydric phenols. Tetrahedron., 2005; 61(7): 1821–5.
24. Kanogi, T.; Atoguchi, T.; Yao, S.; JP Patent 2003246761, 2003.
25. Saikia, B.; Borah, P.; Barua, NC. H2O2 in WEB: a highly efficient catalyst system for the Dakin reaction. Green Chem., 2015; 17(9): 4533–6.
26. Anastas, P,T, ; Farris, CA. Benign by Design. ACS symposium series. American Chemical Society, 1994.
27. Kale, IA.; Gore, NS.; Sarkate, AP.; Sakhale, BK.; Khandare, AL.; Sinha, SN. Peel extract associated oxidative green dakin synthesis of some phenols using aqueous banana extract catalyst. Eur.Chem. Bull., 2019; 8(5): 160.
28. Jimena Scoccia,; Perretti, MD.; Monzón, DM.; Pinacho, FR.; Carrillo, R. Sustainable oxidations with air mediated by gallic acid: Potential applicability in the reutilization of grape pomace. Green Chemistry, 2016 Mar 11; 18(9).
29. Natu, AD.; Burde, AS.; Limaye, RA.; Paradkar, MV. Acceleration of the Dakin reaction by trifluoroacetic acid. J Chem Res., 2014; 38(6): 381–2.
30. Hong, S.; Lee, J.; Jeong, W.; Kim, N.; Jin, H.; Hwang, B.; Lee, H.; Lee, S.; Jang, D.; Lee, D. Bioorg. Med. Chem. Lett., 2002; 12: 2345.

31. Banerjee, S.; Ghosh, A.; Zare, R N. Spontaneous Dakin and Baeyer–Villiger oxidation in aqueous microdroplets. Chemical Science, 2022; 13(5): 1353–1360.
32. X, Yan.; R, M, Bain.; R, G, Cooks, Angew. Chem., Int. Ed., 2016; 55: 12960.