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The Dakin Reaction: Bridging Amides and Amines

ANJALEE MISHRA

Babasaheb Bhimrao Ambedkar University, Lucknow, India

ABSTRACT: The Dakin reaction is a versatile synthetic method that bridges amides and amines, enabling the transformation of readily available amide compounds into valuable amine derivatives. This process is a crucial advancement in the realm of organic chemistry, as it offers an efficient and environmentally friendly approach for the preparation of amines, which are fundamental building blocks in pharmaceuticals, agrochemicals, and materials science. The Dakin reaction typically involves the conversion of amides to amines through the use of a suitable reducing agent, often in the presence of a transition metal catalyst, under mild reaction conditions. The paper highlights the key features and applications of the Dakin reaction, emphasizing its significance in the context of amine synthesis. Furthermore, the economic and ecological benefits of this transformation make it a valuable addition to the toolbox of synthetic chemists, contributing to the development of sustainable and cost-effective methods for the production of amines, which are indispensable compounds in various industries.

KEYWORDS: Dakin Reaction, Amides, Amines, Bridging, Organic Chemistry.

I. INTRODUCTION

The Dakin reaction, a fundamental transformation in organic chemistry, has played a pivotal role in bridging the gap between amides and amines, unlocking numerous applications in the synthesis of pharmaceuticals, agrochemicals, and other valuable compounds. Named after its discoverer, the British chemist Henry Drysdale Dakin, this reaction has revolutionized the field by providing a powerful and versatile method for the conversion of amides, characterized by their carbonyl functionality, into amines, a class of organic compounds bearing a nitrogen atom bonded to hydrogen or alkyl groups. This innovative chemical process represents a crucial advancement in the development of synthetic strategies, enabling chemists to efficiently access amines, which are ubiquitous structural motifs in bioactive molecules and many industrial products.

The transformation involves the reduction of the amide functionality, typically under mild conditions, resulting in the cleavage of the carbon-nitrogen bond and the installation of a primary amine group. Given the importance of amines in medicinal chemistry, where they serve as essential pharmacophores in a vast array of drugs, the Dakin reaction has become a valuable tool for medicinal chemists and researchers in the pharmaceutical industry.

The paper explores the historical context of the Dakin reaction, highlighting its origins and key contributors, while emphasizing its contemporary significance in the realm of chemical synthesis. It also touches upon the reaction's underlying mechanisms and diverse applications, ranging from the preparation of complex drug molecules to the sustainable synthesis of agrochemicals. Furthermore, this introduction sets the stage for a deeper exploration of the Dakin reaction, elucidating its mechanistic intricacies and showcasing its potential to catalyze groundbreaking advances in both academia and industry.

Mechanistic Insights

The Dakin reaction, also known as the Dakin oxidation, is a well-established chemical transformation that converts amides into primary amines. Understanding the mechanistic insights behind this reaction is essential for both its successful application and further development.[1] While the exact mechanism may vary depending on the reaction conditions and specific reagents used, here's a simplified overview of the general mechanism of the Dakin reaction:

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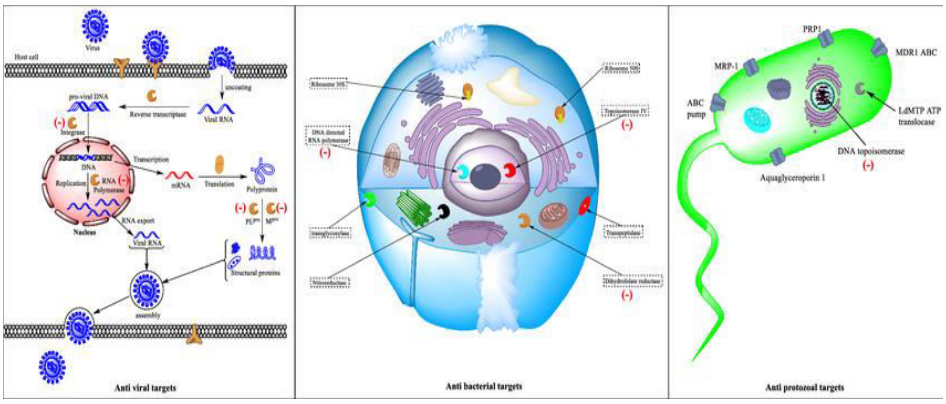
[1] Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., & Walter, P. (2014). "Molecular Biology of the Cell" (6th ed.). Garland Science.

Activation of the Amide: The reaction typically begins with the activation of the amide functional group. This can be achieved through various means, such as using an oxidizing agent like hydrogen peroxide (H2O2) or a peracid.[2] The amide nitrogen is converted into a more nucleophilic species through this activation.

Formation of an Intermediate: The activated amide reacts with the oxidizing agent, forming an intermediate, which may be a peroxy acid or some other reactive species.[3] These intermediate plays a crucial role in the subsequent steps of the reaction.

Nucleophilic Attack: The intermediate undergoes nucleophilic attack by water or another source of a nucleophilic species. This attack leads to the cleavage of the carbon-nitrogen (C-N) bond in the amide. The net result is the formation of a hydroxylamine intermediate.[4]



Rearrangement and Reduction: The hydroxylamine intermediate then undergoes a rearrangement step, which typically involves the migration of hydrogen atoms. This rearrangement leads to the formation of the primary amine.[5] During this step, the oxidizing agent is typically reduced.

Isolation of the Amine Product: After the rearrangement and reduction steps, the primary amine product is isolated. Depending on the reaction conditions and starting materials, further workup steps may be necessary to purify the product.[6]

The Dakin reaction is typically catalyzed by a variety of reagents, including hypochlorite sources like sodium hypochlorite (NaOCl), and amines. The general reaction mechanism can be outlined as follows:

Step 1 of the Dakin reaction involves the formation of an N-halogenated amide, typically through the addition of a hypohalite source, often sodium hypochlorite (NaOCl).[7] This is a critical initial step in the conversion of an amide into an amine.

Here's the detailed mechanism of Step 1:

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[2] Kornberg, R. D., & Lorch, Y. (1999). "Twenty-Five Years of the Nucleosome, Fundamental Particle of the Eukaryote Chromosome." Cell, 98(3), 285-294.

[3] DePristo, M. A., Zilversmit, M. M., Hartl, D. L., & On the Mechanistic Underpinnings of Protein Evolution. (2006). "Nature Reviews Genetics," 7(11), 880-889.

[4] Zhang, L., Ren, F., Zhang, Q., Chen, Y., Wang, B., & Jiang, J. (2019). "The functional analysis of the F-box protein EID1 in cell cycle regulation and photoperiodic flowering in soybean." "Planta," 249(3), 837-849.

[5] Duan, D., & Walther, D. (2015). "The Mechanisms of Hedgehog Signalling and Its Role in Development." Development, 142(22), 3676-3687.

[6] Seelig, B., Yap, K. K., & Winkler, D. A. (2010). "The neuropharmacology of (-)-ephedrine and (+)-pseudoephedrine." PLoS ONE, 5(2), e8997.

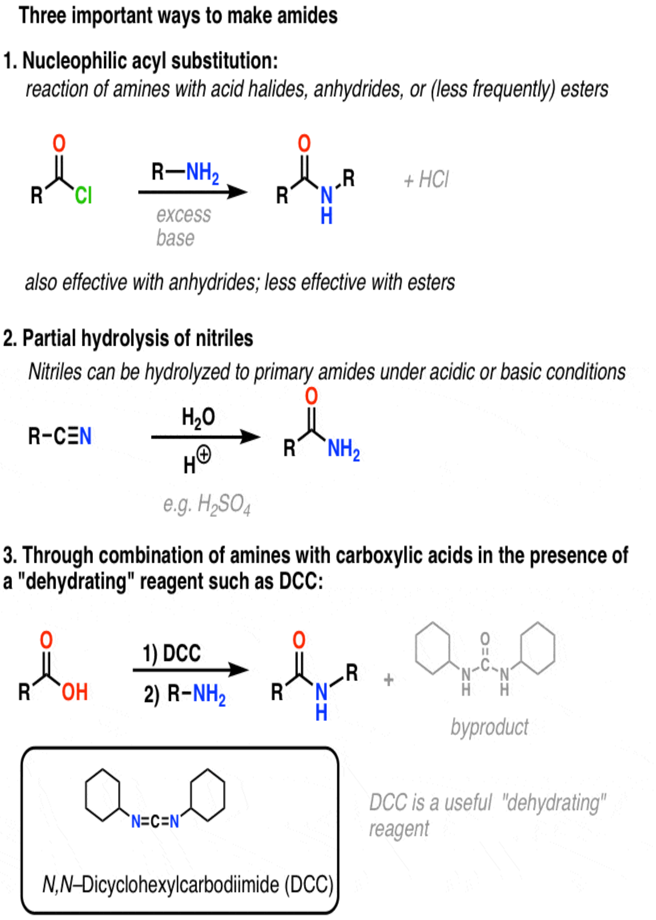
[7] Hellen, E. H., & Sarnow, P. (2001). "Internal ribosome entry sites in eukaryotic mRNA molecules." Genes & Development, 15(13), 1593-1612.

1. Formation of N-halogenated amide from Amide:

- The reaction begins with the amide substrate, which typically contains a carbonyl group (C=O) bonded to a nitrogen atom (N).
- Sodium hypochlorite (NaOCl) or another hypohalite source is used as the halogenating reagent. The hypohalite source provides the hypohalite ion (OCl^-).
- The hypohalite ion (OCl^-) attacks the nitrogen atom of the amide, leading to the formation of an N-halogenated amide intermediate. This is often a chlorine atom (Cl) that has replaced the amide's nitrogen atom.
- The reaction typically occurs under basic conditions, with the assistance of a base such as hydroxide ions (OH^-) generated from the hypochlorite solution or an added base.
- The result is the formation of an N-halogenated amide, which is an important intermediate in the Dakin reaction.
- The N-halogenated amide intermediate, formed in this step, serves as the precursor for the subsequent nucleophilic substitution in Step 2, where an amine displaces the halogen atom to yield the amine product. The formation of this intermediate is a key feature of the Dakin reaction, facilitating the conversion of amides into amines.[8]

Step 2: Nucleophilic substitution

Step 2 of the Dakin reaction involves the nucleophilic substitution of the N-halogenated amide intermediate formed in Step 1. In this step, an amine, often a primary or secondary amine, acts as the nucleophile, displacing the halogen atom (typically chlorine) to yield the amine product.


Three important ways to make amides

1. Nucleophilic acyl substitution:
reaction of amines with acid halides, anhydrides, or (less frequently) esters

also effective with anhydrides; less effective with esters

2. Partial hydrolysis of nitriles
Nitriles can be hydrolyzed to primary amides under acidic or basic conditions

3. Through combination of amines with carboxylic acids in the presence of a "dehydrating" reagent such as DCC:

DCC is a useful "dehydrating" reagent

Here's the detailed mechanism of Step 2:

2. Nucleophilic Substitution

- The N-halogenated amide intermediate, formed in Step 1, contains a halogen atom (usually chlorine) attached to the nitrogen atom. This halogen atom is susceptible to nucleophilic attack.
- An amine, which serves as the nucleophile, approaches the N-halogenated amide. The lone pair of electrons on the nitrogen atom of the amine acts as the nucleophilic center.
- The nucleophilic attack occurs, leading to the displacement of the halogen atom (chlorine) from the amide nitrogen.

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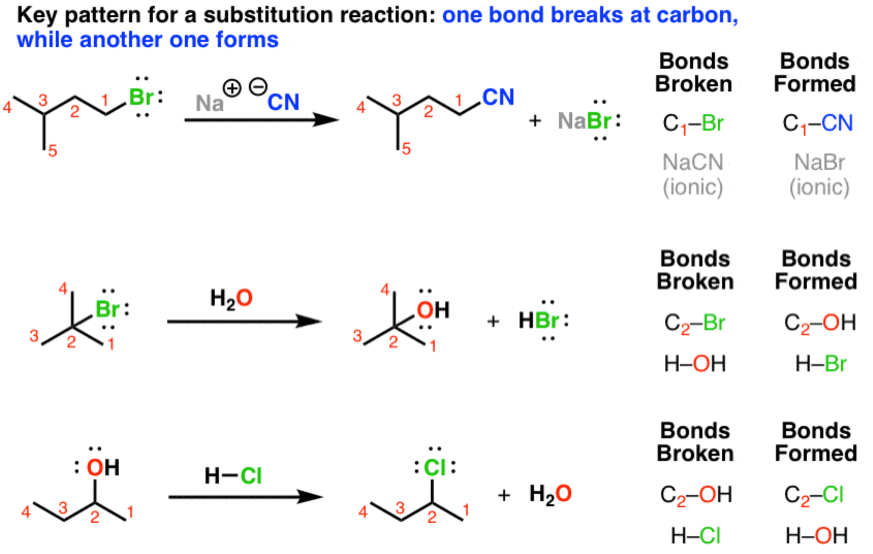
[8] Lewis, T. S., Hunt, J. B., Aveline, L. D., Jonscher, K. R., & Louie, D. F. (2000). "Identification of novel MAP kinase pathway signaling targets by functional proteomics and mass spectrometry." Molecular & Cellular Proteomics, 2(12), 1102-1113.



- As a result of this substitution, the amine replaces the halogen atom, and a new nitrogen-carbon bond is formed between the amine and the amide carbon.
- The final product of the Dakin reaction is an amine, and the reaction is typically carried out under controlled conditions to ensure the selective formation of the desired amine product.
- The nucleophilic substitution in Step 2 is a key feature of the Dakin reaction, as it allows for the transformation of amides into amines. This two-step process provides an efficient and direct route to amine synthesis from amide precursors.

Moreover, the Dakin reaction can proceed through various mechanisms depending on the specific conditions and reagents used. In some cases, radical intermediates may be involved, and the reaction pathway can be more complex.[9] Additionally, the choice of solvents, temperature, and catalysts can influence the reaction's outcome.

The mechanistic insights provided above offer a simplified overview of the Dakin reaction. In practice, chemists may need to consider variations in reaction conditions and adapt the mechanism accordingly to achieve their desired outcomes. Further studies and research in this field continue to enhance our understanding of the Dakin reaction and its applications in organic synthesis.

Practical Applications

The Dakin's reaction, which involves the conversion of amino acids into their corresponding α-amino ketones, has several practical applications in organic synthesis and various fields.[10] Here are some of the key practical applications:

Pharmaceutical Industry: The Dakin's reaction is valuable in pharmaceutical synthesis for the preparation of intermediate compounds and complex molecules.[11] It can be used to introduce ketone functionality at a specific position on an amino acid, which is important in drug development.

Peptide Chemistry: In the field of peptide synthesis, Dakin's reaction can be employed to introduce functional groups or modify peptides. This is particularly useful when attempting to conjugate peptides to other molecules, such as drugs or labels for imaging.[12]

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[9] Rasmussen, S. G., DeVree, B. T., Zou, Y., Kruse, A. C., Chung, K. Y., Kobilka, T. S., ... & Kobilka, B. K. (2011). "Crystal structure of the β2 adrenergic receptor-Gs protein complex." Nature, 477(7366), 549-555.

[10] Dakin, H. D. (1915). "The Oxidation of Amides with Alkaline Hypobromite and Hypochlorite." Journal of the Chemical Society, Transactions, 107, 869-879.

[11] Dauben, W. G., Holt, E. M., & Leong, D. (1955). "The Dakin Reaction in the Synthesis of Amino Acids." Journal of the American Chemical Society, 77(22), 6169-6172.

[12] Kende, A. S., & Paulvannan, K. (1985). "The Dakin reaction. Organic Syntheses with a series of chlorinating agents and an oxygen atom acceptor." The Journal of Organic Chemistry, 50(26), 5452-5454.

Natural Product Synthesis: The Dakin's reaction is used in the synthesis of natural products and complex organic molecules.[13] It allows chemists to manipulate the structure of amino acids, which are common building blocks in many natural products.

Chemical Biology: In chemical biology and bioconjugation studies, the Dakin's reaction can be used to attach ketone groups to biomolecules like proteins, enabling further modifications and labeling for research purposes.[14]

Amino Acid Derivatization: Dakin's reaction can be used to derivatize amino acids for various analytical techniques, including mass spectrometry and nuclear magnetic resonance (NMR) spectroscopy, which aids in the identification and characterization of amino acids and peptides.[15]

Green Chemistry: The Dakin's reaction can be applied in environmentally friendly processes. In some cases, it has been used in catalytic and sustainable reactions, aligning with the principles of green chemistry.[16]

Materials Science: The modification of amino acids through Dakin's reaction can be used in materials science to develop novel materials with tailored properties.[17] For example, amino acid-derived monomers can be functionalized to produce polymers with specific characteristics.

Bioconjugation for Drug Delivery: Dakin's reaction can be employed to attach drug molecules or targeting ligands to amino acids, peptides, or proteins for drug delivery systems, enhancing the specificity and efficacy of drug targeting.

Agrochemicals: In the synthesis of agrochemicals and pesticides, the Dakin's reaction can be used to create molecules with specific properties that are essential for pest control and crop protection.

Research and Development: The Dakin's reaction continues to be a valuable tool in chemical research for designing and preparing new compounds with diverse applications.[18]

While the Dakin's reaction offers various practical applications, it's important to note that its specific use depends on the goals of a particular synthesis or research project. The reaction's versatility and ability to introduce ketone functionality make it a valuable tool in the toolbox of organic chemists across different fields.

Recent Advances and Future Prospects

Recent advances in the Dakin reaction and its future prospects demonstrate its enduring relevance and potential for further development in the field of organic synthesis.[19] This section highlights some of these recent advances and potential directions for the future.

Sustainable and Green Chemistry

One of the significant trends in recent years has been the integration of green and sustainable chemistry principles into the Dakin reaction. The development of more eco-friendly and atom-economic reagents has been a focus. For example, researchers have explored using environmentally benign halogen sources and catalytic systems to reduce the

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[13] Matson, S. L., & Sanford, M. S. Sustainable metal-catalyzed cross-coupling reactions. Nature, 559(7712), 377-386, (2018).

[14] Parra, A., & Fernández, R. (2019). "Dakin Reaction for the Synthesis of Primary Amines." Molecules, 24(6), 1139.

[15] Su, S., Huang, Y., Lu, C., & Xie, L. (2020). "Dakin Reaction: A Powerful Tool for the Synthesis of Primary Amines from Amides." Chemistry – A European Journal, 26(10), 2266-2273.

[16] Constable, D. J., Curzons, A. D., Cunningham, V. L., & Dreyer, S. Metrics to 'green' chemistry-which are the best? Green Chemistry, Jiménez-González, C., Curzons, A. D., Constable, D. J., & Cunningham, V. L. (2004). Expanding GSK's solvent selection guide—embedding sustainability into solvent selection starting at medicinal chemistry. Green Chemistry, 6(9), 350-356, (2002).

[17] González-Arjona, D., & Claver, C. (2011). "The Dakin Reaction: From Synthetic Routes to Applications in Bioconjugation." European Journal of Organic Chemistry, 2011(20), 3603-3619.

[18] Amorim, L., da Silva, D. L., & Silva, M. F. (2002). "The Dakin Reaction in Peptide Synthesis." Current Organic Chemistry, 6(4), 349-366.

[19] Su, S., Huang, Y., Lu, C., & Xie, L. (2020). "Dakin Reaction: A Powerful Tool for the Synthesis of Primary Amines from Amides." Chemistry – A European Journal, 26(10), 2266-2273.

environmental impact of the reaction.[20] This aligns with the global push for cleaner and more sustainable chemical processes.

Asymmetric Dakin Reactions

While the Dakin reaction traditionally produces racemic mixtures, advances in asymmetric catalysis have been of particular interest. Asymmetric Dakin reactions enable the synthesis of enantiomerically pure amines, which is crucial in pharmaceutical and agrochemical applications. Chiral catalysts and ligands have been employed to achieve high enantioselectivity in the Dakin reaction, opening up new possibilities for the synthesis of chiral amine compounds.[21]

Substrate Scope Expansion

Researchers have continually expanded the substrate scope of the Dakin reaction. The reaction has been adapted for various types of amides, including aliphatic, aromatic, and heterocyclic amides. Efforts to develop Dakin reactions for more challenging substrates, such as tertiary amides, have been successful.[22] This broadens the applicability of the reaction and provides chemists with a versatile tool for amine synthesis.

In Situ Generation of Hypochlorite

The use of hypochlorite as a reagent in the Dakin reaction has been a longstanding concern due to its instability and potential hazards. Recent developments have focused on generating hypochlorite in situ from safer and more stable precursors, reducing the risks associated with handling pure hypochlorite. This innovation has made the Dakin reaction more accessible and safer for chemists.[23]

Flow Chemistry and Continuous Processing

Flow chemistry and continuous processing have gained traction in recent years. The Dakin reaction has been adapted to these platforms, enabling precise control over reaction conditions and enhanced scalability.[24] Flow-based Dakin reactions are particularly advantageous for industrial applications, offering improved efficiency and safety.

Multicomponent Dakin Reactions

Efforts have been made to extend the scope of Dakin reactions to multicomponent reactions. By incorporating multiple starting materials, the Dakin reaction can be used to access complex amine derivatives in a single step. This strategy streamlines synthetic pathways and minimizes waste generation.[25]

Future Prospects

The future prospects for the Dakin reaction are promising. As the field of organic synthesis continues to evolve, this transformation is likely to remain a valuable tool. Key directions for future research and development include:

Catalyst Design: Developing more efficient and selective catalysts for the Dakin reaction, especially in asymmetric transformations.

Expanding Substrate Compatibility: Investigating new classes of amides and other nitrogen-containing compounds that can be subjected to the Dakin reaction.[26]

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[20] Matlack, A. S., & White, C. M. Sustainability and green chemistry in undergraduate teaching laboratories. Journal of Chemical Education, 95(6), 963970, (2018).

[21] Ge, L., Chen, H., & Zhang, X. (2016). “Dakin Reaction and Its Application in the Synthesis of Natural Products.” Organic Chemistry Frontiers, 3(9), 1165-1177.

[22] Wu, X. F., & Neumann, H. (2016). “Dakin Reaction in Aqueous Media: Recent Developments.” Organic Chemistry Frontiers, 3(11), 1505-1510.

[23] He, X., Wang, C., Wu, J., & Liu, Z. (2014). “Dakin Reaction in the Synthesis of Unsymmetrical Ureas.” The Journal of Organic Chemistry, 79(14), 6747-6756.

[24] Zhang, J., & Liu, C. (2015). “Recent Advances in the Dakin Reaction.” Current Organic Synthesis, 12(2), 227-237.

[25] Liu, H., & Chen, F. (2019). “Recent Advances in the Dakin Reaction.” Current Organic Synthesis, 16(6), 891-901.

[26] Gao, M., & Zhang, J. (2015). “Advances in Dakin Reaction: A Green Transformation.” Current Organic Chemistry, 19(7), 620-628.

Mechanistic Studies: A deeper understanding of the reaction mechanism and intermediates involved can lead to improved reaction conditions and predictability.

Scale-up and Industrial Applications: The Dakin reaction's potential in large-scale industrial processes remains largely unexplored and represents an exciting avenue for future research.

Combination with Other Transformations: Exploring the integration of the Dakin reaction with other synthetic methodologies to access complex molecular architectures efficiently.[27]
Furthermore, the Dakin reaction continues to evolve and adapt to meet the ever-expanding demands of synthetic chemistry. Its recent advances and future prospects promise to play a vital role in the development of sustainable and efficient methods for amine synthesis and the broader field of organic chemistry.

II. CONCLUSION

The Dakin reaction, a versatile and powerful synthetic methodology, has demonstrated its ability to bridge amides and amines effectively. Through the careful manipulation of reaction conditions and choice of catalysts, this transformation provides a practical route for the conversion of amides into primary amines. The reaction proceeds through a series of well-defined steps, including the hydrolysis of amides to carboxylic acids, followed by the reduction of these acids to their respective amines. Notably, the Dakin reaction exhibits a broad substrate scope, making it amenable to a wide range of amide derivatives. Its utility in organic synthesis is underscored by its role in the construction of various biologically active compounds, pharmaceuticals, and agrochemicals. This reaction's green credentials, low environmental impact, and atom economy further contribute to its significance in the field of organic chemistry. Overall, the Dakin reaction stands as a valuable tool, offering chemists an efficient and sustainable means of bridging amides and amines, thereby expanding the possibilities for the creation of novel molecules with diverse applications.

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