



# Direct Azo Coupling in Imidazoheterocycles through C–Heteroatom Bond Functionalization

Jitendra Kumar<sup>1</sup> and Rajesh Ranjan Pandey<sup>1</sup>

<sup>1</sup>Department of Chemistry, A. M. College, Gaya, Magadh University, Bodh-Gaya 824234, Bihar, India.

## Abstract:

A practical and efficient method has been developed for the synthesis of azo-functionalized imidazo[1,2-a]pyridines under mild, neutral conditions. This protocol enables the preparation of diverse (E)-3-(aryldiazenyl)imidazo[1,2-a]pyridines with broad functional group tolerance and high yields, requiring minimal purification. Notably, the method extends to other heterocycles such as imidazo[2,1-b]thiazoles, benzo[d]imidazo[2,1-b]thiazoles, and indolizines, demonstrating wide substrate scope and versatility. The use of non-toxic reagents, eco-friendly solvents, and simple operations enhances its practicality for pharmaceutical, materials, and heterocyclic synthesis applications.

## Introduction:

C–H functionalization has emerged as a powerful tool in modern organic synthesis, offering a direct and atom-economical approach to forming carbon–carbon (C–C) and carbon–heteroatom (C–X) bonds.[1-7] By selectively activating inert C–H bonds, this strategy eliminates the need for pre-functionalized substrates and streamlines the synthesis of complex molecules.[8-12] Among these transformations, C–heteroatom bond formation is especially significant, playing a crucial role in the synthesis of pharmaceuticals, agrochemicals, and functional materials. The development of efficient, sustainable protocols for such transformations remains an active area of research.[13]

Aromatic azo compounds, defined by the presence of an –N=N– linkage, are highly valued across various industries for their vivid coloration, photophysical properties, and broad applications in dyes, pigments, indicators, food additives, and advanced materials.[14-16] Their light-responsive behavior has also led to applications in molecular switches, photoresponsive materials, and sensor technologies. In pharmaceuticals, many azo derivatives exhibit promising biological activity, further driving the need for diverse and efficient synthetic methods.[17, 18]

Traditionally, azo compounds are synthesized via the oxidation of anilines or reduction of nitrobenzenes. However, these methods often rely on toxic heavy metals or costly catalysts, raising environmental and

economic concerns.[17-19] Asymmetric azo compounds—particularly azoheterocycles that incorporate heteroaromatic moieties—are even more challenging to access but are of high interest due to their unique photochemical, electronic, and biological properties. Their ability to undergo reversible cis–trans isomerization upon light exposure has enabled applications in nonlinear optics, liquid crystals, photodynamic therapy, and smart materials.[2, 3, 20, 21]

In parallel, imidazo[1,2-a]pyridines have garnered attention for their wide-ranging bioactivity, including anticancer, antiviral, antibacterial, and anti-inflammatory effects.[2, 21] Their electron-rich fused structure also makes them attractive for applications in organic electronics and photoluminescent materials. As such, C–H functionalization strategies have been increasingly employed for their selective modification.[4-6, 22]

Recognizing the complementary features of azo compounds and imidazoheterocycles, our research has focused on integrating these two structural motifs to create multifunctional scaffolds with both chromophoric and bioactive potential. While symmetric azo compounds are well-documented, methods for synthesizing asymmetric azoheterocycles remain underdeveloped. Our group has aimed to address this gap by developing practical and sustainable protocols for the direct C–H functionalization of imidazo[1,2-a]pyridines.[23]

### Experimental Section:

All chemicals and solvents used in this study were obtained from reputable commercial suppliers and used without further purification unless otherwise noted. The general synthetic procedure for the preparation of target compounds (as depicted in Schemes, compounds 3, 5, and 7) involved a diazotization step followed by azo coupling with a heterocyclic partner. In a typical reaction, an aniline derivative (0.22 mmol) was dissolved in ethanol (1.5 mL), and tert-butyl nitrite (tBuONO, 0.24 mmol; 25 mg or 29  $\mu$ L) was added. The mixture was stirred at room temperature for approximately 3 minutes to generate the diazonium salt in situ. Subsequently, the appropriate heterocycle—imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazole, or indolizine (0.20 mmol; compounds 1, 4, or 6)—was introduced into the reaction mixture.

The reaction was stirred at ambient temperature for 8 hours with TLC monitoring. Upon completion, the appearance of an orange precipitate typically indicated successful coupling. The solid product was isolated by vacuum filtration and washed with ethanol (5 mL) and a 10% ethyl acetate/petroleum ether solution (3 mL) to remove impurities. The final product was dried under reduced pressure, affording analytically pure material. All reactions were performed under ambient conditions without the use of an inert atmosphere or specialized equipment, unless otherwise stated.

### Results and Discussion:

The development of a sustainable and efficient synthetic protocol for the construction of (E)-3-(aryldiazenyl)imidazo[1,2-a]pyridines was guided by dual objectives: the synthesis of novel bioactive heteroaromatic systems and the design of chromophoric materials with tunable photoresponsive behavior. The incorporation of the azo ( $-N=N-$ ) functionality not only introduces intense coloration but also imparts notable biological activities, including antimicrobial, anticancer, and enzyme-inhibitory properties. Motivated by the

potential of these hybrid frameworks, we initiated a comprehensive investigation using commercially available anilines and imidazo[1,2-a]pyridines in the presence of *tert*-butyl nitrite (tBuONO)—a mild and eco-friendly diazotizing agent. A particular focus was placed on the use of benign solvents and mild thermal conditions to enhance environmental compatibility and synthetic simplicity.

Initial optimization studies employed a model reaction between *p*-toluidine and 8-methyl-2-phenylimidazo[1,2-a]pyridine. Using DMSO as the solvent, the reaction yielded the target azo compound in 68% yield. Encouraged by this result, a solvent screening was conducted to evaluate the influence of solvent properties on reaction efficiency. Solvents such as DMF, acetonitrile, 1,4-dioxane, and THF supported the transformation but gave lower yields (43–63%), likely due to their varied dielectric constants and inability to adequately stabilize the reactive intermediates. In contrast, the reaction failed entirely in DCM, a non-polar aprotic solvent, underscoring the necessity of solvent polarity and hydrogen-bonding capacity for efficient diazotization and coupling.

A marked improvement was observed when reactions were conducted in protic solvents like methanol and ethanol. Ethanol, in particular, emerged as the optimal medium, affording the azo product in an excellent 88% yield after 8 hours at ambient temperature. The superior performance in ethanol is attributed to its ability to stabilize diazonium ions through hydrogen bonding, thereby promoting a more efficient electrophilic substitution at the imidazopyridine ring. Further reaction time extension did not increase the yield, confirming the rapid and complete nature of the transformation under these conditions. However, performing the reaction at 0 °C resulted in negligible conversion, suggesting that thermal activation is crucial for both diazotization and subsequent azo coupling.

With optimized parameters established—namely ethanol as the solvent, room temperature, 8-hour reaction time, and a 1.1:1.2 molar ratio of aniline to tBuONO—the method's generality was thoroughly investigated. A wide range of anilines was tested to assess functional group tolerance and electronic effects. Anilines bearing electron-withdrawing substituents (e.g., cyano, nitro, ester, ketone, and acyl groups) consistently yielded higher product amounts compared to electron-donating analogs. This behavior is attributed to the enhanced stability and reactivity of diazonium salts derived from electron-deficient anilines, which facilitate smoother coupling at the electron-rich C-3 position of imidazopyridines. Halogenated anilines (Cl, F, I) also gave good yields and offer sites for further functionalization via cross-coupling or nucleophilic substitution.

The reaction also demonstrated excellent reactivity with heteroaryl amines. Substrates such as aminopyridines and aminopyrazoles participated efficiently, yielding heteroaryl azo derivatives with good efficiency. This compatibility greatly expands the method's scope toward the synthesis of more structurally diverse, drug-like molecules. Moreover, 2-aminobenzenesulfonamide underwent coupling smoothly, introducing pharmaceutically relevant sulfonamide functionalities into the azoimidazopyridine scaffold.

In addition to varying the aniline component, modifications to the imidazopyridine ring were explored. Substituents at the pyridine moiety—particularly halogens and electron-withdrawing nitrile groups—were well tolerated. Substitution at the C-2 position with aryl or heteroaryl units led to successful product formation, indicating that steric hindrance at this position is not a limiting factor. Conversely, imidazopyridines lacking

substitution at C-2 or containing bulky non-conjugating groups (e.g., isobutyl or trifluoromethyl) failed to deliver the desired products. This observation highlights the critical role of electronic stabilization at C-2 for the carbocationic intermediate formed during azo coupling.

To evaluate the broader applicability of the strategy, we extended the methodology to structurally related imidazo-fused heterocycles. Benzo[d]imidazo[2,1-b]thiazoles and imidazo[2,1-b]thiazoles were effectively transformed into their azo derivatives using various anilines, often yielding the products within just one hour. This rapidity underscores the high reactivity and general efficiency of the process. Likewise, indolizine derivatives, particularly those with ester or cyano substituents, underwent smooth and regioselective azo coupling, further emphasizing the method's versatility.

An intriguing extension of the strategy involved an intramolecular azo coupling that generated a fused benzo[e]pyrrolo[2,1-c][1,2,4]triazine skeleton—an analogue of pharmacologically significant antifungal agents. This transformation represents a valuable approach for accessing polycyclic scaffolds with potential biological relevance.

To demonstrate the practicality and scalability of the protocol, a gram-scale synthesis of the model compound was performed under the optimized reaction conditions. The target azoimidazopyridine was isolated in 84% yield, closely mirroring the yield from the small-scale reaction, thereby validating the method's reproducibility and industrial viability.

Mechanistically, the transformation proceeds via in situ formation of a diazonium salt from aniline and tBuONO, followed by electrophilic substitution at the C-3 position of the imidazo[1,2-a]pyridine ring. Subsequent deprotonation yields the final azo compound. Notably, the requirement for an aryl substituent at the C-2 position is mechanistically rationalized by its role in stabilizing the carbocationic intermediate through resonance, thereby facilitating the overall transformation.

## Conclusion:

We report a mild, efficient, and environmentally benign approach for the synthesis of (E)-3-(aryldiazenyl)imidazo[1,2-a]pyridines using tert-butyl nitrite under neutral conditions. The method shows broad substrate scope, excellent functional group tolerance, and consistently high yields, requiring no elaborate purification. Its general applicability is demonstrated by successful extension to various heterocycles, including imidazo[2,1-b]thiazoles, benzo[d]imidazo[2,1-b]thiazoles, and indolizines. This scalable and straightforward protocol, relying on non-toxic reagents and simple filtration, provides a valuable synthetic tool for generating azo-functionalized heterocycles relevant to pharmaceuticals, advanced materials, and heterocyclic chemistry.

## Acknowledgment

The authors are grateful to the Department of Chemistry, A. M. College, Gaya and Magadh University, Bodh Gaya for providing the necessary laboratory facilities and academic support to carry out this research work. We sincerely thank the faculty members and staff of the department for their valuable assistance and encouragement throughout the course of this study.



## References:

- [1] P. Gandeepan, C.H. Cheng, Transition-Metal-Catalyzed  $\pi$ -Bond-Assisted C–H Bond Functionalization: An Emerging Trend in Organic Synthesis, *Chemistry - An Asian Journal* 10 (2015) 824. <https://doi.org/10.1002/asia.201403224>
- [2] Y. Kuninobu, Transition Metal-Catalyzed Highly Efficient and Novel Transformations, *Journal of Synthetic Organic Chemistry Japan* 71 (2013) 425. <https://doi.org/10.5059/yukigoseikyokaishi.71.425>
- [3] C. Jacob, B. Maes, G. Evano, Transient Directing Groups in Metal–Organic Cooperative Catalysis, *Chemistry - A European Journal* 27 (2021) 13899. <https://doi.org/10.1002/chem.202101598>
- [4] Y. Wang, A.A. Liu, D. Ma, S. Li, C. Lu, T. Li, C. Chen, TiO<sub>2</sub> Photocatalyzed C–H Bond Transformation for C–C Coupling Reactions, *Catalysts* 8 (2018) 355. <https://doi.org/10.3390/catal8090355>
- [5] J. Li, P. Shen, Z. Zhao, B. Tang, Through-Space Conjugation: A Thriving Alternative for Optoelectronic Materials, *CCS Chemistry* 1 (2019) 181. <https://doi.org/10.31635/ccschem.019.20180020>
- [6] Z. Li, M. Xia, R. Boyd, Theoretical study on the mechanism of iridium-catalyzed  $\gamma$ -functionalization of primary alkyl C–H bonds, *Canadian Journal of Chemistry* 94 (2016) 1028. <https://doi.org/10.1139/cjc-2016-0287>
- [7] N. Fernández, G. Gaube, K. Woelk, M. Burns, D. Leitch, Tandem C–O and C–H Activation at Palladium Enables Catalytic Direct C–H Alkenylation with Enol Pivalates, (2021). <https://doi.org/10.26434/chemrxiv-2021-s62r6>
- [8] H.R. Bjørsvik, V. Elumalai, Synthesis of the Carbazole Scaffold Directly from 2-Aminobiphenyl by Means of Tandem C–H Activation and C–N Bond Formation, *European Journal of Organic Chemistry* 2016 (2016) 5474. <https://doi.org/10.1002/ejoc.201601191>
- [9] J. Belani, N. Ayyagari, Synthesis of Tetracyclic Flavonoids via Palladium-Catalyzed Intramolecular Oxidative Cyclization, *Synlett* 25 (2014) 2350. <https://doi.org/10.1055/s-0034-1378615>
- [10] C. Brown, M. Reed, Synthesis of Seven-Membered N,O-Heterocycles by Using a Palladium(sulfoxide) White-Type Catalyst, *Synfacts* 18 (2021) 0021. <https://doi.org/10.1055/s-0041-1737213>
- [11] D.S. Kim, Y.-S. Seo, C.H. Jun, Synthesis of Pyrroles through Rhodium(III)-Catalyzed Reactions of Allylamines and Alkenes, *Organic Letters* 17 (2015) 3842. <https://doi.org/10.1021/acs.orglett.5b01811>
- [12] S. Kawamorita, R. Murakami, T. Iwai, M. Sawamura, Synthesis of Primary and Secondary Alkylboronates through Site-Selective C(sp<sup>3</sup>)–H Activation with Silica-Supported Monophosphine–Ir Catalysts, *Journal of the American Chemical Society* 135 (2013) 2947. <https://doi.org/10.1021/ja3126239>
- [13] J. Yeston, A trio helps activate C–H bonds in alcohols, *Science* 349 (2015) 1500. <https://doi.org/10.1126/science.349.6255.1500-m>
- [14] Y.X. Tan *et al.*, An Unconventional *trans* - *exo* -Selective Cyclization of Alkyne-Tethered Cyclohexadienones Initiated by Rhodium(III)-Catalyzed C–H Activation via Insertion Relay, *CCS Chemistry* 3 (2020) 1582. <https://doi.org/10.31635/ccschem.020.202000339>

- [15] Z. Huang, C. Feng, J. Sun, B. Xu, T. Huang, X. Wang, F. Dai, D. Sun, Ultrathin Metal–Organic Framework Nanosheets-Derived Yolk–Shell Ni <sub>0.85</sub> Se@NC with Rich Se-Vacancies for Enhanced Water Electrolysis, *CCS Chemistry* 3 (2020) 2696. <https://doi.org/10.31635/ccschem.020.202000537>
- [16] W.J. Guo, Y.Z. Chen, C.H. Tung, L.Z. Wu, Ultralong Room-Temperature Phosphorescence of Silicon-Based Pure Organic Crystal for Oxygen Sensing, *CCS Chemistry* 4 (2021) 1007. <https://doi.org/10.31635/ccschem.021.202100932>
- [17] C. Sivaraj, A. Ramkumar, N. Sankaran, T. Gandhi, Transition-metal-catalyzed C–H bond activation/functionalization and annulation of phthalazinones, *Organic & Biomolecular Chemistry* 19 (2021) 8165. <https://doi.org/10.1039/d1ob01616d>
- [18] J. Docherty, T. Lister, G. McArthur, M. Findlay, P. Domingo-Legarda, J. Kenyon, S. Choudhary, I. Larrosa, Transition-Metal-Catalyzed C–H Bond Activation for the Formation of C–C Bonds in Complex Molecules, *Chemical Reviews* 123 (2023) 7692. <https://doi.org/10.1021/acs.chemrev.2c00888>
- [19] S.I. Murahashi, Transition-Metal-based Lewis Acid, Base, and Ambiphilic Catalysts: Development of Non-Salt Alternative Processes, *Journal of Synthetic Organic Chemistry Japan* 61 (2003) 425. <https://doi.org/10.5059/yukigoseikyokaishi.61.425>
- [20] J. Yan, 2018.
- [21] Y. Nai-he, H. Luo, Transition metal mediated activation of C(sp<sup>3</sup>)–C(sp<sup>2</sup>) bond in aromatic hydrocarbons, *Synthetic Communications* 52 (2021) 157. <https://doi.org/10.1080/00397911.2021.2003817>
- [22] S. Hernández, I. Moreno, R. SanMartín, G. Gómez, M. Herrero, E. Domínguez, Toward Safer Processes for C–C Biaryl Bond Construction: Catalytic Direct C–H Arylation and Tin-Free Radical Coupling in the Synthesis of Pyrazolophenanthridines, *The Journal of Organic Chemistry* 75 (2009) 434. <https://doi.org/10.1021/jo902257j>
- [23] L. Wang, H. Sun, X. Li, Synthesis of Iron Hydrides by Selective C–F/C–H Bond Activation in Fluoroarylimines and Their Applications in Catalytic Reduction Reactions, *European Journal of Inorganic Chemistry* 2015 (2015) 2732. <https://doi.org/10.1002/ejic.201500313>