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ELECTROCHEMICAL SYNTHESIS OF FLUORINATED HETEROCYCLIC COMPOUNDS (review).

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Fluorine-containing heterocycles play a crucial role in the pharmaceutical, agrochemical, and materials industries. The pursuit of effective and sustainable synthesis methods has driven the development of electrochemistry as a compelling alternative to conventional chemical transformations. Among these approaches, electrochemistry has emerged as a particularly promising technique for orchestrating multibond-forming processes under mild, environmentally benign conditions. This review highlights key advances over the past decade in the electrochemical synthesis of fluorinated heterocyclic compounds, encompassing bimolecular, trimolecular, and tetramolecular reactions. Emphasis is placed on multicomponent cascade strategies, radical-mediated couplings, and oxidant-free cyclizations that afford broad functional group tolerance and fluorine incorporation flexibility. Collectively, this work serves as a resource for researchers developing next-generation sustainable synthetic platforms tailored to fluorinated heterocycles with diverse structural and biological profiles.

Keywords: Electrochemistry, Heterocyclic Compounds, Fluorine, Fluorinated Pharmaceuticals, Green Chemistry, Sustainable Synthesis.

INTRODUCTION. Electrochemistry is a fascinating interdisciplinary branch of chemistry that studies the relationship between electrical energy and chemical reactions. At its core, it investigates processes where chemical energy is converted into electrical energy or where electrical energy is used to drive non-spontaneous chemical reactions. These transformations occur through redox reactions where electrons are transferred, typically at the interface between an electrode (an electrical conductor) and an electrolyte (an ion-conducting medium). The principles of electrochemistry underpin a vast array of modern technologies, from power sources like batteries and supercapacitors, to industrial processes such as the production of aluminum and chlorine, and analytical techniques like pH measurement and biosensors. [1–6].

Electrochemistry offers a powerful and increasingly vital approach to organic synthesis, enabling chemists to drive a wide range of transformations through the controlled transfer of electrons rather than relying solely on traditional chemical reagents. This method, often termed electrosynthesis, leverages the precise control of electrical potential to effect selective oxidations and reductions, allowing for the formation of C-C bonds, functional group interconversions, and the synthesis of complex molecules under remarkably mild conditions. Key advantages include enhanced selectivity (chemo-, regio-, and stereoselectivity), the elimination of hazardous or stoichiometric redox reagents, and the generation of cleaner reaction profiles with fewer byproducts. From sustainable anodic oxidations and cathodic reductions to electro-initiated radical reactions and the precise functionalization of sensitive substrates, electrosynthesis is revolutionizing synthetic routes, making complex organic transformations more efficient, environmentally friendly, and scalable. [7–16].

Electrochemistry offers compelling advantages over conventional organic synthesis methods, particularly in its alignment with green chemistry principles [17]. Foremost among these benefits is the replacement of stoichiometric chemical oxidants and reductants with electricity, which serves as a clean, tunable, and inexpensive reagent. This eliminates the need for often hazardous and costly reagents, significantly reducing waste generation and simplifying downstream purification processes. Furthermore, electrochemical reactions frequently proceed under milder conditions, such as ambient temperature and pressure, minimizing energy consumption and enabling the synthesis of sensitive compounds that might degrade under harsher thermal or chemical routes. The precise control over electron transfer at the electrode surface allows for unparalleled selectivity (chemo-, regio-, and stereoselectivity), leading to higher yields of desired products and fewer unwanted byproducts, thus contributing to greater efficiency and sustainability in modern organic synthesis. [18–21].

As part of our ongoing commitment to the design of modern pharmaceuticals [22–28]—particularly those incorporating residues of tailor-made amino acids [29–36] and fluorinated motifs [37–45]—we are strongly focused on developing innovative synthetic methodologies for their preparation [46–56]. Given that heterocyclic compounds and amino acids constitute the structural backbone of over 85% and 35% of contemporary drugs, respectively, these domains remain central to pharmaceutical research [57–65]. Notably, heterocyclic scaf-

folds serve as indispensable building blocks in medicinal chemistry, owing to their broad spectrum of biological activity and remarkable structural versatility, making them essential for rational drug design [66–71].

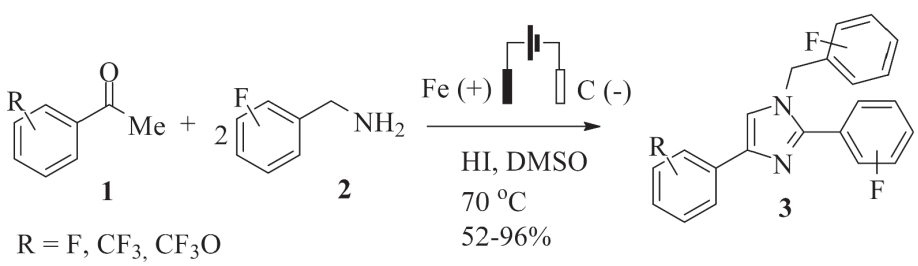
Recently, we presented a comprehensive overview of advancements in the synthesis of fluorinated heterocyclic compounds, highlighting innovative directions such as the use of carbon nanotubes as catalysts [72] and the application of mechanochemical principles [73]. In the present work, we extend this exploration by providing a detailed treatment of electrochemical methodologies for the synthesis of fluorinated heterocyclic compounds.

Electrochemistry is an emerging field with significant synthetic potential, offering sustainable and efficient alternatives to traditional chemical processes. Here, we summarize data published over the past decade on the electrochemical synthesis of fluorine-containing heterocycles. The material is organized according to the number of reacting species, focusing on reaction dynamics rather than mechanistic principles such as the molecularity of the rate-determining step. Accordingly, reactions involving three structural components—two of which are identical—are classified based on effective molecularity and treated as bimolecular in terms of structural diversity.

We believe this compilation will serve as a valuable resource for researchers and practitioners in synthetic and medicinal chemistry, as well as for those pursuing advances in green and sustainable methodologies.

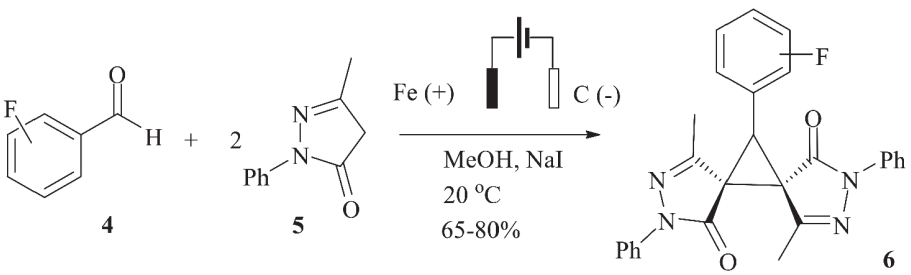
Bimolecular reactions.

In 2020, Yang *et al.* [74] introduced an efficient electrochemical strategy for synthesizing 1,2,4-trisubstituted (*1H*)-imidazoles **3** (Scheme 1), .utilizing readily available starting materials and carbon rod electrodes in an undivided cell under metal- and oxidant-free conditions The approach involves the electrooxidative tandem cyclization of acetophenones **1** and substituted benzylamines **2**, proceeding via in situ generation of 2-iodoacetophenone through anodic oxidation of molecular iodine, which subsequently engages with the ketone **1**. This protocol stands out for its broad functional group tolerance and consistent delivery of moderate to excellent yields. Notably, both starting materials—highly electrophilic ketones **1** [75, 76] and benzylamines **2**—can incorporate fluorinated substituents, enabling a high degree of fluorination and structural versatility in the resulting products **3**. Furthermore, this electrochemical protocol eliminates the need for external metal catalysts or chemical oxidants, making it a simple, cost-effective, and environmentally sustainable alternative. While the primary focus is on nitrogen-containing heterocycles, the methodology also holds promise for the synthesis of related scaffolds across diverse heterocyclic systems.



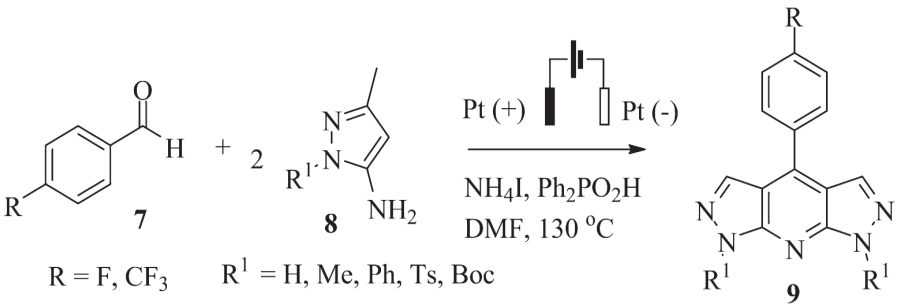
Scheme 1. Electrochemical strategy for synthesizing 1,2,4-trisubstituted (1*H*)-imidazoles.

Elinson and co-workers developed highly stereoselective electrocatalytic approach for synthesizing substituted (*R**,*R**)-*bis*-(spiro-2,4-dihydro-3*H*-pyrazol-3-one)cyclopropanes **6** (Scheme 2) [77] via an electrochemical multi-step cyclization reaction. This one-pot strategy employs fluoro-aldehydes **4** and pyrazolin-5-ones **5** as starting materials, proceeding through a direct electrochemical transformation to access functionally rich cyclopropane scaffolds. The process utilizes sodium iodide or bromide as a redox mediator in an undivided cell, with methanol as the solvent, and is conducted at ambient temperature. By circumventing conventional halogenation reagents and leveraging mild electrolysis conditions, the method delivers good yields (65–80%) with high current efficiency and virtually complete diastereoselectivity of relative (*R**,*R**) configuration. The underlying mechanism follows a typical mediator system: iodine is generated anodically, while methanol is deprotonated cathodically to produce methoxide anions and evolve hydrogen gas.



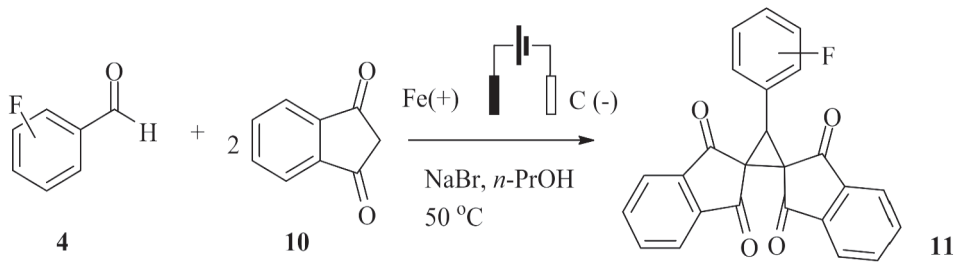
Scheme 2. Synthesis of (*R**,*R**)-*bis*-(spiro-2,4-dihydro-3*H*-pyrazol-3-one)cyclopropanes.

Qian *et al*. have recently introduced a novel electrochemical cascade cyclization strategy for the synthesis of *bis*-pyrazolo[3,4-*b*:4',3'-*e*] pyridines **9** (Scheme 3) [78]. Leveraging the enhanced electrophilicity of fluorinated aldehydes **7** [74, 79, 80], this method exploits their high reactivity in nucleophilic addition reactions. The transformation between fluoroaldehydes **7** and pyrazol-5-amines **8** proceeds smoothly under metal- and oxidant-free conditions. This electrochemical approach affords a diverse array of mono- and trifluoromethyl-substituted *bis*-pyrazolo[3,4-*b*:4',3'-*e*]pyridines **9** in moderate yields (50–70%). Key advantages of the protocol include its operational simplicity, broad substrate scope, and environmentally benign character, making it a promising alternative to conventional multistep syntheses.



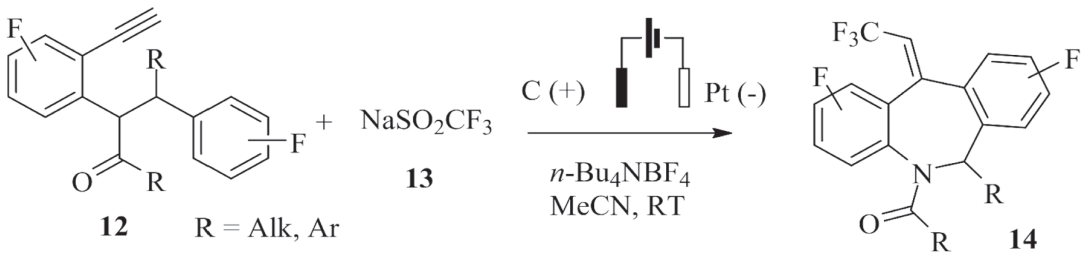
Scheme 3. Electrochemical approach for preparation of *bis*-pyrazolo[3,4-b:4',3'-e]pyridines.

A highly effective and operationally convenient electrochemical method has been developed for the synthesis of fluoro-spirocyclopropanes **11** (Scheme 4) [81], achieved by reacting indan-1,3-dione **10** with aromatic fluoro-aldehydes **4**. The reaction is conducted at 50 °C in a mixture of propanol and sodium bromide under constant current electrolysis. This method offers several significant advantages, including mild halogen production, the use of low-concentration currents, a neutral reaction solution pH, no need for by-product isolation, synthetically attractive yields (>75%), inexpensive reagents, environmental sustainability, and easy product isolation.



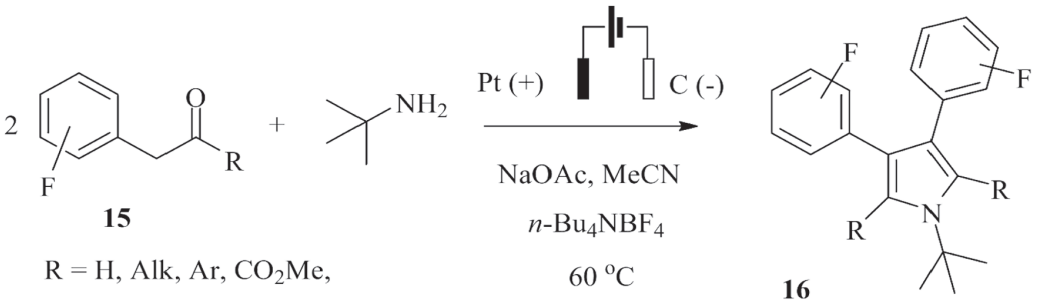
Scheme 4. Electrochemically aided synthesis of fluoro-spirocyclopropanes.

A straightforward and green electrochemical method for synthesizing CF_3-containing benzazepines has been developed by Zhang et al. via the radical cascade cyclization of alkynes. Starting compounds **12** (Scheme 5) [82], bearing an acetylenic residue properly positioned relative to the aromatic ring, were subjected to electrochemical conditions in an undivided cell with sodium trifluoromethanesulfinate **13** in acetonitrile at ambient temperature, yielding cyclized products **14** with a trifluoromethyl group bonded to the olefinic moiety. This transformation provides a novel approach to synthesizing seven-membered heterocycles without requiring any external catalyst or oxidant, operating under mild reaction conditions. A gram-scale experiment further demonstrated the practicality of this method. Benzazepines are an important class of seven-membered nitrogen-containing heterocyclic compounds, widely present in natural products and pharmaceuticals. They exhibit diverse biological activities, making them valuable in medicinal chemistry [83].



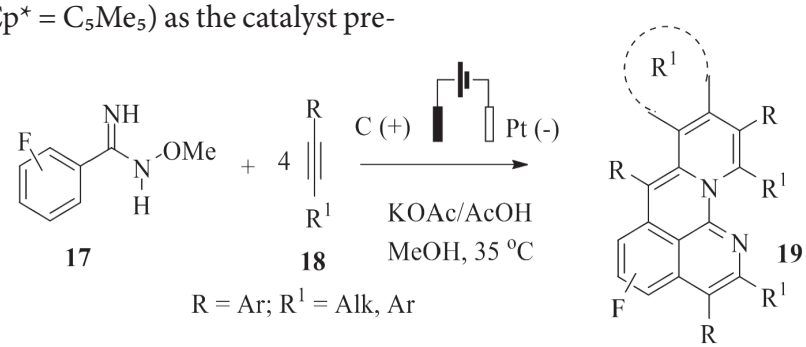
Scheme 5. Electrochemical synthesis of fluorinated benzazepines.

Lei *et al*. described a one-pot electrochemical oxidation-induced intermolecular annulation reaction for the synthesis of tetrasubstituted pyrroles **16** (Scheme 6) [84]. The reaction was conducted in an undivided cell at a constant current of 10 mA, using simple and readily available fluorinated ketones **15** and tert-butyl amine in the presence of tetrabutylammonium tetrafluoroborate (n-Bu_4NBF_4) as an electrolyte. Tetrasubstituted pyrroles **16** were obtained with yields ranging from 42% to 79%. Substituting *tert*-butyl amine with other amines led to complications due to the instability of intermediate imines, thereby limiting the synthetic utility of this method.



Scheme 6. Electrochemical preparation of tetrasubstituted pyrroles.

Ackermann *et al*. describe a rhodium-catalyzed cascade C–H activation and alkyne annulation for the novel synthesis of nitrogen-doped polycyclic aromatic hydrocarbons (aza- nanographenes) **19** (Scheme 7) [85], demonstrating high chemo- and regioselectivity. The method employs a specially designed multifunctional O-methylamidoxime directing group, using amidoxime **17** and various disubstituted **18** for the envisioned rhoda-electrocatalyzed cascade C–H annulation. The reaction is conducted with KOAc as the base, $[Cp^*RhCl_2]_2$ ($Cp^* = C_5Me_5$) as the catalyst precursor, MeOH as the solvent, and a constant current of 4.0 mA, yielding the desired products **19** in 42–94% yield. Through the identification of two key rhodacyclic intermediates, the authors determined the precise sequence in which the three steps of C–H activation occur. The metalla-electrocatalyzed multiple C–H transformations exhibit a unique functional group tolerance, accommodating even highly reactive iodo and azido groups. This innovative approach holds promising applications in materials science.

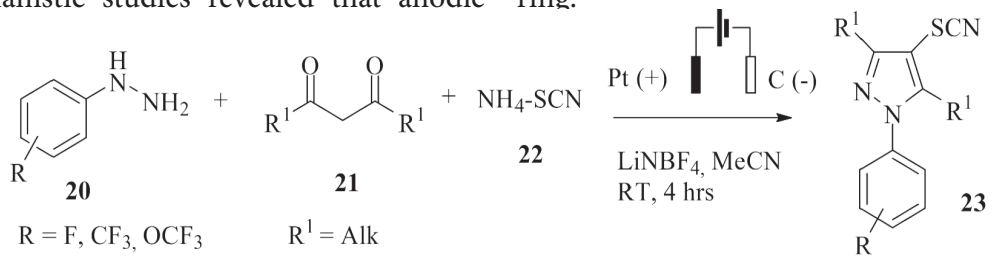


Scheme 7. Electrochemical synthesis of fluorine-containing aza-nanographene derivatives.

Trimolecular reactions.

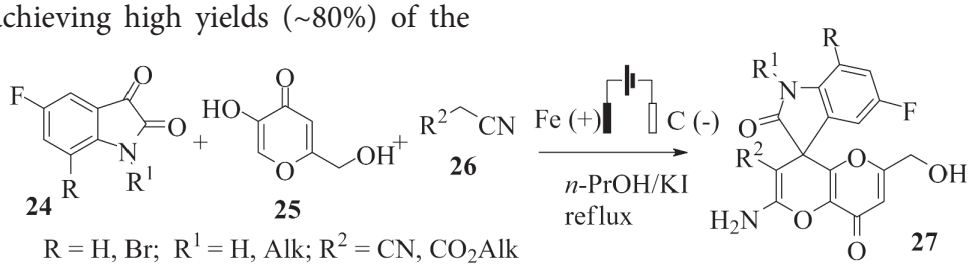
Yao *et al.* demonstrated the synthesis of fluorine-containing 4-thiocyanato-1*H*-pyrazoles **23** (Scheme 8) [86] under mild, metal- and oxidant-free conditions, using fluorinated arylhydrazines **20**, 1,3-diketones **21**, and ammonium thiocyanate **22** in an undivided electrochemical cell. The reaction was performed at room temperature for 4 hours in an undivided cell equipped with graphite felt (GF) as the anode, a platinum plate (Pt) as the cathode, and $LiBF_4$ as the electrolyte, maintaining a constant current of 10 mA. This process afforded fluorinated phenyl-4-thiocyanato-1*H*-pyrazole **23** in moderate to excellent yields (41–94%).

Mechanistic studies revealed that anodic oxidation generates SCN• radicals, which subsequently undergo electrophilic substitution with the pyrazole intermediate adduct. The practicality and scalability of this thiocyanation protocol make it both cost-effective and environmentally friendly. Given its simplicity, mild reaction conditions, and neutral medium, this electrochemical multicomponent tandem approach is highly appealing for applications in the pharmaceutical and fine chemical industries, offering high scalability and functional group tolerance. Notably, fluorination in products **23** can manifest as a single fluorine atom, two fluorine atoms, or trifluoromethyl and trifluoromethoxy groups on the aromatic ring.



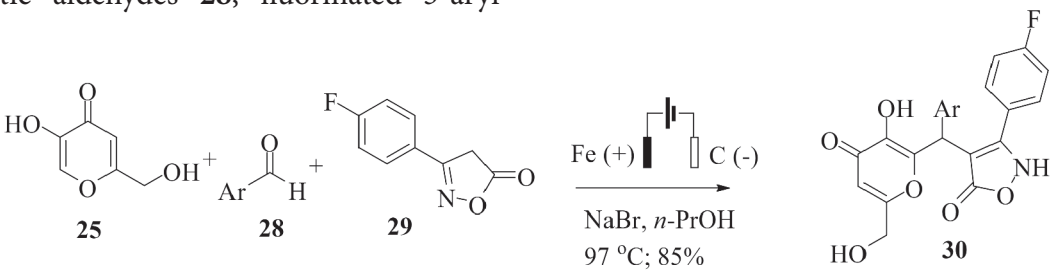
Scheme 8. Electrochemical approach to fluorinated 1-phenyl-4-thiocyanato-1*H*-pyrazoles.

Elinson *et al.* reported the synthesis of spiro-indole-3,4'-pyrano-pyranones **27** via electrochemical cascade trimolecular cyclization, using fluoro-isatins **24**, pyran-4-one **25**, and malonic acid derivatives **26** (Scheme 9) [87]. The reaction is conducted under reflux conditions in undivided cells, with potassium iodide as the electrolyte and *n*-propanol as the solvent, achieving high yields (~80%) of the spiro-heterocyclic system **27**. This catalytically efficient procedure requires no complex equipment, is easily executable, and allows straightforward product isolation. As a result, this novel approach provides significant advantages for large-scale processes, supporting environmentally friendly synthesis while enabling high molecular diversity.



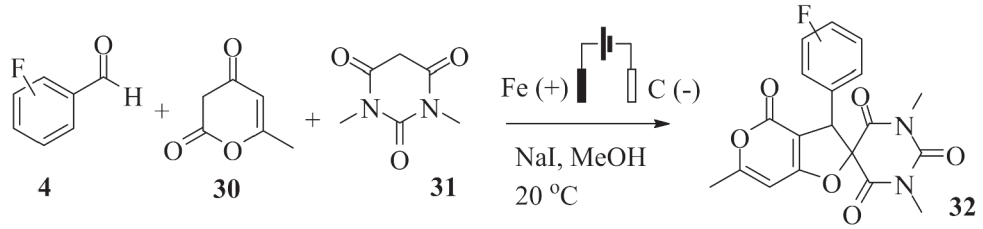
Scheme 9. Electrochemical approach to fluorinated spiro-indole-3,4'-pyrano- pyranones.

Fluorinated derivatives of 4*H*-pyran-2yl-(aryl)methyl-isoxazol-5(2*H*)-one **30** (Scheme 10) [88] can be synthesized electrochemically in propanol, heating at 97 °C, via a one-pot, three-component reaction involving aromatic aldehydes **28**, fluorinated 3-aryl-substituted isoxazol-5(4*H*)-one **29**, and pyran-4-one **25**. This method represents a significant achievement, performed in an undivided electrochemical cell using graphite as the anode and iron as the cathode.



Scheme 10. Electrocatalytic trimolecular reaction affording fluorinated isoxazol-5(2*H*)-ones.

Fluorine-containing carbonyl compounds are highly effective reagents in various addition reactions performed under conventional conditions [89, 90]. A similar reactivity is observed for aldehydes **4** (Scheme 11) [91] in an electrochemical assembly with 6-methyl-3*H*-pyran-2,4-dione **30** and barbituric acid **31**. The reaction is carried out in an undivided electrochemical cell using sodium iodide as a mediator in methanol. The process yields fluorine-containing spiro[furo[3,2-*b*]-pyran-2,5'-pyrimidines **32** with high efficiency, achieving 73–82% yields.

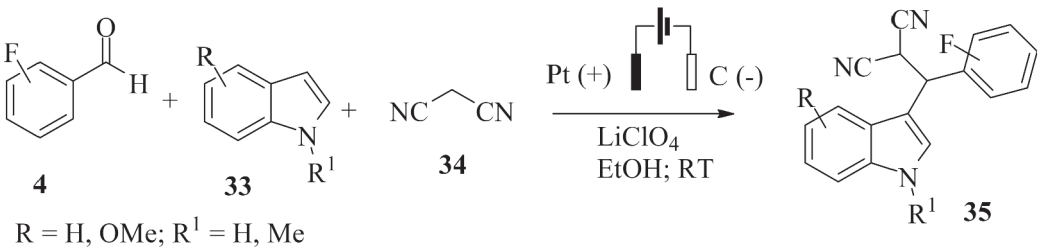


Scheme 11. Electrochemical synthesis of fluorine-containing spiro[furo[3,2-*b*]-pyran-2,5'-pyrimidines.

Indoles serve as a fundamental scaffold in drug design, valued for their versatile biological activity and capacity to interact with diverse molecular targets. They are widely present in both natural and synthetic pharmaceuticals, playing critical roles in anticancer, antimicrobial, anti-inflammatory, and neuroprotective therapies. Their structural adaptability enables medicinal chemists to optimize potency, selectivity, and bioavailability, making them indispensable in modern drug discovery [92–95]. Various strategies have been developed for synthesizing indole derivatives [96–99], including fluorine-containing variants [100–103].

Singh *et al.* developed an electrocatalytic tandem condensation method for synthesizing tri-substituted indoles **35** (Scheme 12) [104]. The process involves an electrocatalytic

conversion of fluorinated aldehydes **4**, indole **33**, and malononitrile **34**, conducted in EtOH at a current density of 10–15 mA/cm², using $LiClO_4$ as the electrolyte. Fluorinated benzaldehydes exhibit high reactivity and distinct reactivity patterns, which vary depending on the number and position of fluorine atoms on the aromatic ring [105, 106].



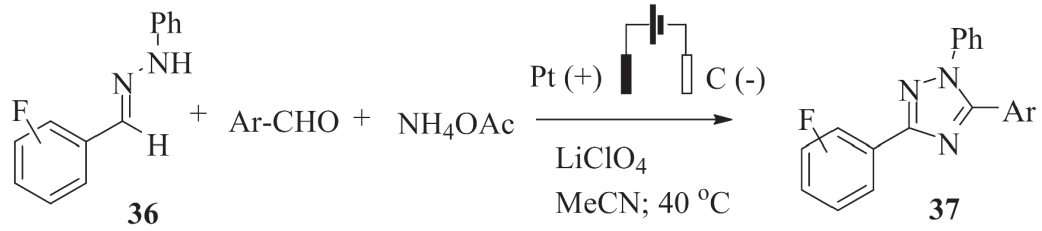
4 **33** **34** **35**

R = H, OMe; R^1 = H, Me

Scheme 12. Electrochemical synthesis of fluorine-containing indoles.

Triazoles and their derivatives exhibit a wide range of biological activities, making them valuable in medicinal chemistry. They are known for their antimicrobial, antiviral, antitubercular, anticancer, anticonvulsant, analgesic, antioxidant, anti-inflammatory, and antidepressant properties [107, 108].

Zhao *et al.* developed an electrochemical multicomponent [3+1+1] annulation reaction for the synthesis of fluoro-substituted 1,2,4-triazoles **37** (Scheme 13) [109], without the use of transition metals, acids, bases, or external oxidants. The electrolysis was conducted in an undivided cell, equipped with a graphite carbon anode, a platinum cathode, and 20 mol% $LiClO_4$ as the electrolyte, under constant current conditions. Substituted 1,2,4-triazoles **37** were obtained through the reaction of 1-benzylidene-2-phenylhydrazine **36** (derived from fluorinated benzaldehydes), aromatic aldehydes, and ammonium acetate. Given the ready availability of raw materials, reasonable yields (~75%), feasible scalability, and experimental convenience, this protocol offers a practical and efficient approach to triazole synthesis.

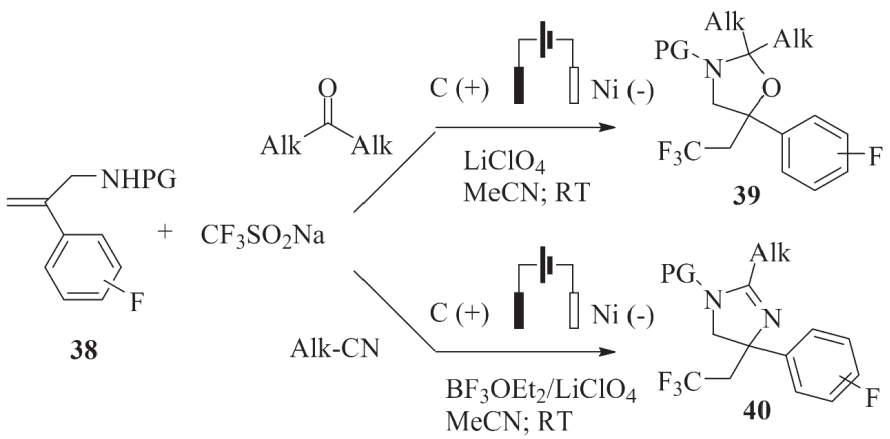


36 **37**

Scheme 13. Electrochemical preparation of fluorinated 1,2,4-triazole derivatives.

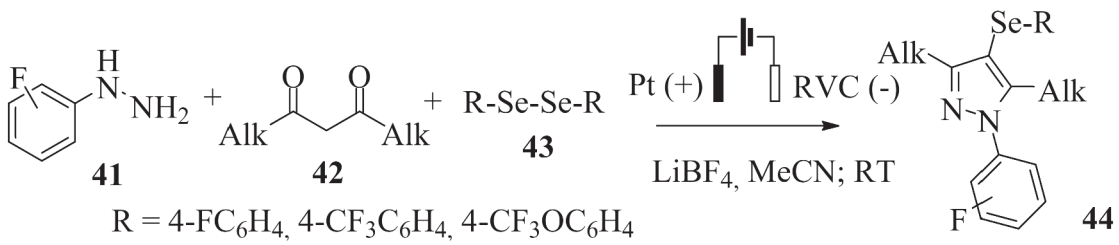
Imidazolines and oxazolidines exhibit diverse biological activities, making them valuable in medicinal chemistry [110–113]. Claraz *et al.* reported a one-pot, eco-friendly electrochemical method for synthesizing oxazolidine **39** (Scheme 13) [114] and imidazoline derivatives **40**, incorporating trifluoromethyl groups and aromatic fluorine substitutions under mild, environmentally benign conditions. The method involves electrochemical tandem

radical trifluoromethylation of allylamines **38**, followed by a formal (3+2)-cycloaddition with Alk-CN or aliphatic ketones. The starting allylamines are typically tosyl-protected, facilitating the reaction. The electrochemical reaction of tosyl-amines **38** with Langlois reagent (CF_3SO_2Na) is carried out in acetonitrile and dichloromethane using $LiClO_4$ as the supporting electrolyte, enabling the one-pot electrosynthesis of fluorinated 1,3-oxazolidines **39** and 2-imidazolines **40**.



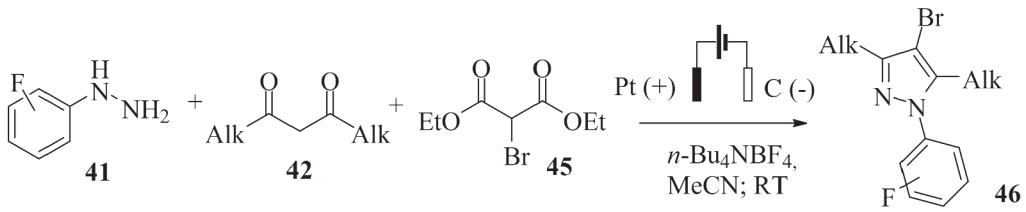
Scheme 14. Three-component synthesis of fluorinated imidazolines and oxazolidines.

Selenium-containing heterocyclic compounds exhibit a range of biological activities, making them valuable in medicinal chemistry and materials science [115, 116]. The reaction reported by He *et al*. involves the electrochemical transformation of fluoro-phenylhydrazine **41** (Scheme 15) [117], diketone **42**, and diphenyl diselenide **43**. Using readily available starting materials, the approach outlined in Scheme 15 provides a versatile method for synthesizing a broad range of fluorinated 4-selanylpyrazole derivatives **44**, achieving high yields (71–96%). Notably, fluorine atoms are both on the phenyl ring of the starting hydrazine **41** and on the selenide **43**. The reaction is conducted in an undivided electrochemical cell with reticulated vitreous carbon (RVC) as the anode, a platinum plate as the cathode, and $LiBF_4$ (20 mol%) as the electrolyte. Under mild conditions, at ambient temperature for 9 hours with a constant current of 6 mA, the desired fluorinated 4-phenylselanyl-pyrazoles **44** are obtained in MeCN, without the need for catalysts or chemical oxidants.



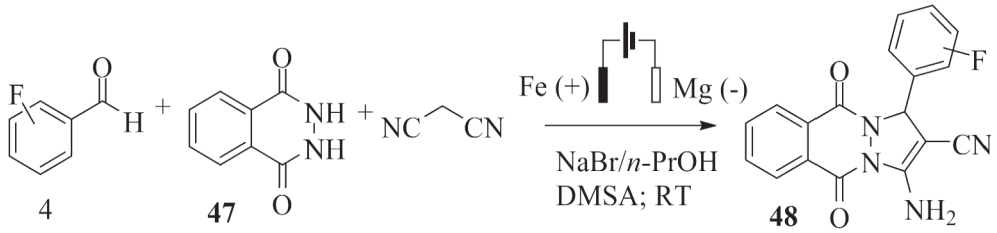
Scheme 15. Electrochemical approach to fluorinated 4-selanylpyrazoles.

Weimin *et al.* reported a mechanistically similar method to Scheme 15 for the synthesis of various 4-bromopyrazoles **46** (Scheme 16) [118], employing a three-component reaction involving fluorinated aryl-hydrazine **41**, diketone **42**, and bromomalonate **45** in an environmentally friendly approach. The reaction was conducted in an undivided electrochemical cell for 10 hours, using *n*-Bu_4NBF_4 (20 mol%) as the electrolyte in MeCN at ambient temperature. Mechanistically, hydrazine **41** undergoes condensation with diketone **42**, forming the pyrazole ring, which is subsequently brominated to yield 4-bromopyrazole **46**. This method can be generalized for the bromination of heterocyclic compounds, offering a sustainable and efficient synthetic strategy.



Scheme 16. Electrochemical approach to fluorinated 4-bromopyrazoles.

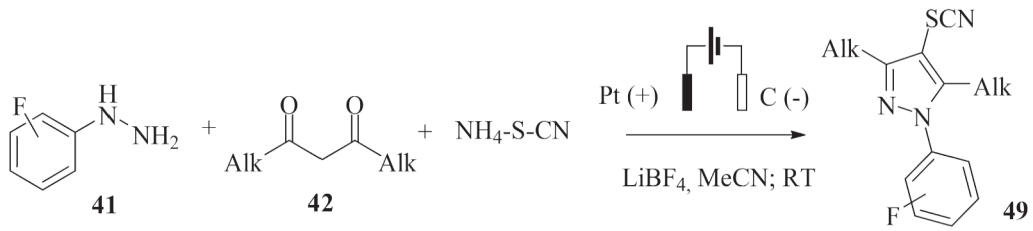
As emphasized throughout this review, fluorine-containing carbonyl compounds are highly valuable synthetic building blocks exhibiting significantly enhanced reactivity compared to their non-fluorinated counterparts [119–122]. Mohammadi *et al.* employed an electrochemical approach for the successful synthesis of fluorinated phthalazine derivatives **48** (Scheme 17) [123]. The reaction was conducted in an undivided electrochemical cell at a current density of 12 mA/cm^2, using NaBr as the electrolyte. This one-pot, three-component reaction involved fluorinated benzaldehydes 4, phthalhydrazide **47**, and malononitrile, carried out in propanol. The method efficiently yielded fluorine-containing pyrazolo[1,2-*b*]phthalazines **48** in good to excellent yields (75–92%).



Scheme 17. Electrochemical synthesis of fluorinated pyrazolo[1,2-*b*]phthalazines.

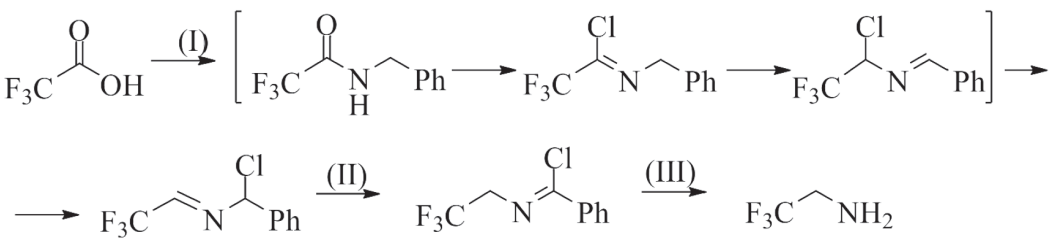
Mechanistically and strategically similar to the electrochemical transformations described in Schemes 15 and 16, the method reported by He *et al.* enables the synthesis of 4-thiocyanato-1*H*-pyrazoles **49** (Scheme 18) [124]. Under mild, metal- and oxidant-free conditions, fluorinated arylhydrazines **41**, 1,3-diketones **42**, and ammonium thiocyanate undergo electrochemical coupling in an undivided cell, affording fluorine-containing products

49 in moderate to excellent yields (41–94%). Optimal results were obtained using graphite felt (GF) as the anode, a platinum plate as the cathode, and $LiBF_4$ as the electrolyte, at room temperature for 4 hours under a constant current of 10 mA. This setup efficiently produced fluorinated phenyl-4-thiocyanato-1*H*-pyrazole scaffolds **49**. Mechanistic investigations suggest that anodic oxidation generates an SCN• radical, which subsequently reacts with a pyrazole intermediate via electrophilic substitution. Owing to its cost-effectiveness, practicality, and scalability, this electrochemical thiocyanation protocol is not only environmentally benign but also highly appealing for applications in the pharmaceutical and fine chemical industries, thanks to its operational simplicity, mild reaction conditions, and broad functional group tolerance.



Scheme 18. Electrochemical synthesis of fluorinated phenyl-4-thiocyanato-1*H*-pyrazoles.

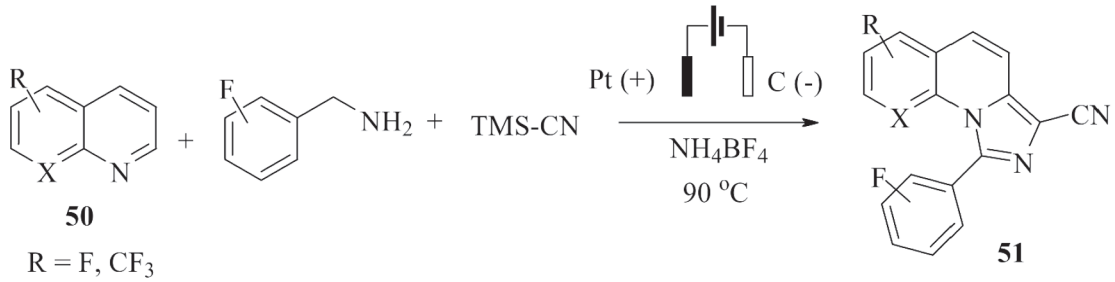
Benzylamines and their derivatives, such as pyridoxamine, play a significant role in biological enzymatic transamination, facilitating the interconversion of α-keto and α-amino acids [125–127]. Inspired by this natural process, biomimetic synthetic approaches have largely focused on the reductive amination of carbonyl compounds, employing benzylamines both as a nitrogen source and as a self-oxidizing agent through oxidative deamination [128–133]. Remarkably, both α-hydrogens of the CH_2–NH_2 moiety in benzylamine can participate in the reductive amination of carboxylic acids, yielding the corresponding amine products, while the benzylamine itself is oxidized to the corresponding carboxylic acid (Scheme 19) [134].



Key: (I) $BnNH_2$ (1 eq), Ph_3P (4 eq)/CCl_4 (4 eq), TEA (1.5 eq), $CHCl_3$ reflux, 40 min.; (II) TEA (3 eq)/H_2O; (III) MeOH/HCl (conc), reflux, 24 hr

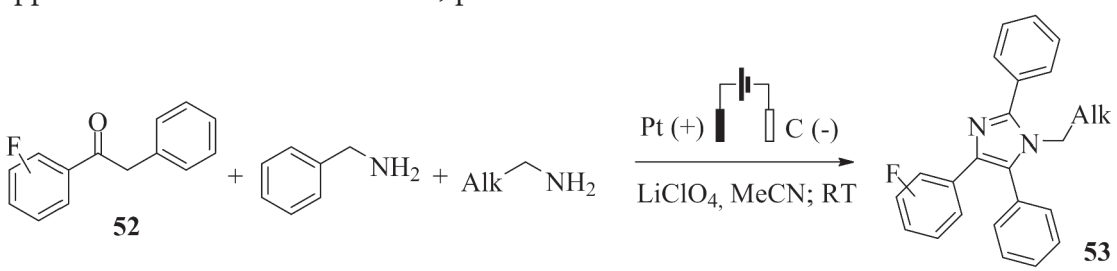
Scheme 19. Reductive amination of trifluoroacetic acid to 2,2,2-trifluoroethylamine via 'double' biomimetic transamination.

A comparable transformation—oxidation of benzylamine to a formal benzoic acid residue—was reported by Wang *et al*. via an electrochemical three-component reaction involving quinoline derivatives **50**, benzylamines, and trimethylsilyl cyanide, yielding imidazo-fused *N*-heterocycles **51** with good to excellent efficiency (Scheme 20) [135]. Fluorine substituents, either as a single fluorine atom or a trifluoromethyl group, can be introduced on both the quinoline derivatives **50** and the benzylamine substrates, expanding the scope of this methodology. This anodic oxidation–driven cyclization proceeds under metal- and chemical oxidant-free conditions in an undivided cell, employing readily available starting materials. The method is notable for its substrate generality, environmental friendliness, mild reaction conditions, and excellent scalability, making it particularly appealing for applications in complex heterocycle synthesis.



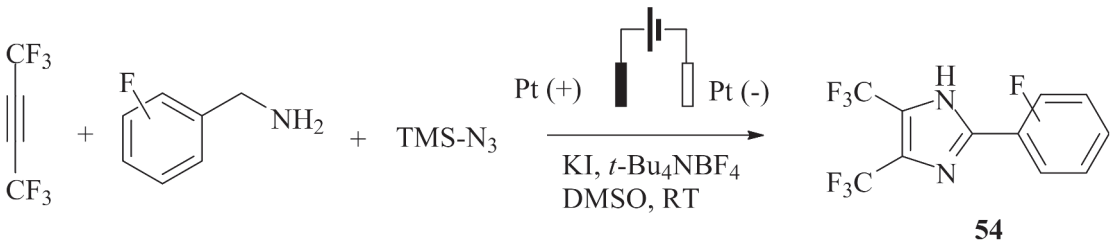
Scheme 20. Electrochemical synthesis of fluorinated imidazo-fused *N*-heterocycles.

Analogous to biomimetic transamination involving reduction of carbonyl compounds and the oxidation of benzylamine [136–138], the electrochemical reaction reported by Yang *et al*. describes the synthesis of 1,2,4-trisubstituted imidazoles **53** via a three-component coupling of fluorine-containing ketones **52**, benzylamine, and alkyl amines (Scheme 21) [139]. The reaction employs readily available starting materials in an undivided electrochemical cell equipped with carbon rod electrodes, proceeding under metal- and oxidant-free conditions. This electrochemical strategy offers a practical and scalable approach to the synthesis of fluorinated heterocycles **53**, with moderate to excellent yields across a broad substrate scope. Owing to its functional group tolerance, simplicity, and environmental compatibility, the method holds significant promise for large-scale applications in heterocyclic and medicinal chemistry.



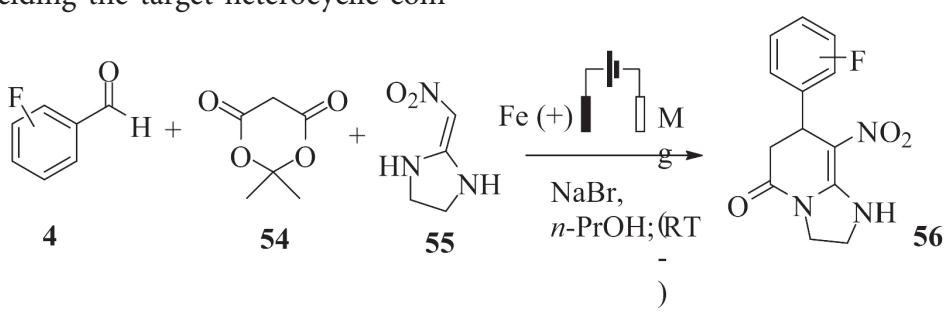
Scheme 21. Electrochemical synthesis of fluorinated 1,2,4-trisubstituted-(1*H*)imidazoles.

Another compelling example of electrochemical oxidation of benzylamine derivatives, analogous to biomimetic transamination processes [140–142], was developed by Chen *et al.* (Scheme 22) [143]. Their strategy enables the efficient synthesis of imidazole derivatives **54** under undivided electrolytic conditions, demonstrating the effectiveness of electrochemical-oxidation-induced three-component condensation. The methodology is notably metal- and peroxide-free, rendering it environmentally benign and sustainable. It also exhibits broad substrate compatibility, allowing for the introduction of fluorine substituents into the imidazole ring with consistently high yields. A particularly noteworthy application involves the reaction of di-trifluoromethylacetylene (perfluorobut-2-yne) with fluorinated benzylamine and trimethylsilyl azide (TMS-N_3), affording imidazole products **54** bearing two trifluoromethyl groups and a fluorinated phenyl ring—a valuable structural motif for pharmaceutical and agrochemical development.



Scheme 22. Electrochemical synthesis of fluorinated imidazoles.

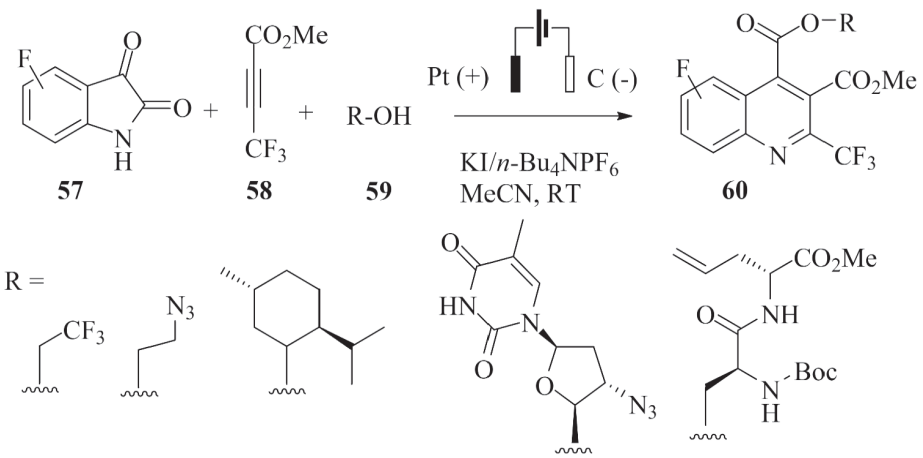
Mohammedi *et al.* reported the synthesis of a novel tetrahydroimidazo[1,2-*a*]pyridine-5(1*H*)-one derivative **56** (Scheme 23) [144] via a one-pot electrochemical strategy, combining fluoro-aldehydes **4**, Meldrum's acid **54**, and 2-(nitromethylene)imidazolidine **55**. The reaction proceeds in propanol using sodium bromide as the electrolyte within an undivided cell, maintained under a constant current of 50 mA, yielding the target heterocyclic compounds in good to excellent yields (70–96%). This green protocol demonstrates significant potential for the construction of fused polycyclic frameworks relevant to bioactive heterocycles. It offers several advantages, including high product yields, simple experimental setup, and environmentally benign conditions, making it an attractive approach for sustainable synthetic chemistry.



Scheme 23. Electrochemical preparation of fluorine-containing imidazo-pyridines.

Gao *et al*. demonstrated that an electrochemical strategy can be effectively employed to construct complex biologically relevant molecules bearing trifluoromethyl-substituted quinoline scaffolds **60** (Scheme 24) [145]. The method relies on a paired electrolysis–driven cascade annulation, designed to achieve two key objectives simultaneously: the direct synthesis of quinolines and their convergent incorporation into bioactive molecular frameworks. The transformation involves the electro-reduction–induced reaction of fluoro-substituted isatin **57**, methyl 4,4,4-trifluorobut-2-ynoate **58**, and alcohol-containing substrates **59**. Conducted in CH_3CN within an undivided cell equipped with a graphite rod anode and platinum cathode, and using KI (20 mol%) as the electrolyte, the reaction proceeds under a constant current of 5 mA, affording the desired quinoline derivatives **60** in moderate to excellent yields (40–99%). The reaction exhibits broad substrate tolerance—the R group in alcohol **59** can encompass virtually any organic residue: from simple aliphatic alcohols to heterocycles, fluorinated side chains, natural and tailor-made amino acids [146–148], as well as peptides, peptidomimetics, steroids, and small-molecule drugs. Of over sixty examples explored, only a few representative cases are shown in Scheme 24.

Importantly, the stereochemical integrity of chiral centers is preserved under the mild electrochemical conditions. Fluorine incorporation is also highly tunable, occurring as monofluoroaryl, aryl–CF_3, or aliphatic–CF_3 functionalities, providing access to a structurally diverse library of fluorinated quinolines with pharmaceutical potential.

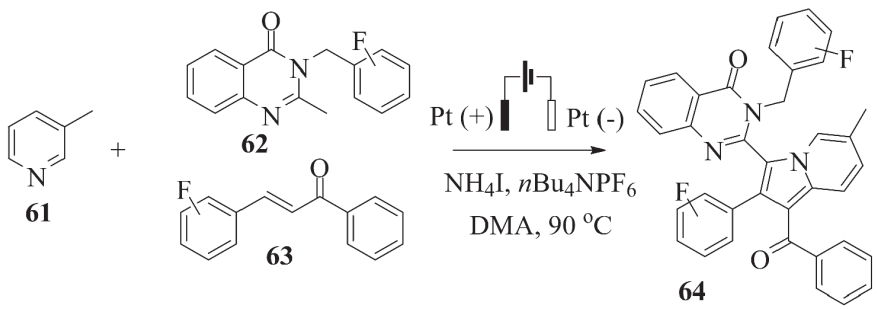


Scheme 24. Application of electrochemical approach for preparation of various quinoline-substituted bioactive molecules.

Sharma *et al*. developed a novel electrochemically induced oxidative cascade cyclization for the synthesis of fluorinated quinazolinone- and quinoline-decorated indolizine derivatives **64** (Scheme 25) [149]. This transformation proceeds in an undivided cell under metal- and oxidant-free conditions, showcasing an environmentally friendly approach. The reaction involves a three-component coupling of substituted pyridines **61**, fluorobenzyl-containing quinazolinone **62**, and fluoro-chalcones **63**. Conducted at 90 °C using two platinum plate electrodes,

with $NH_4I/n\text{-}Bu_4NPF_6$ as the electrolyte and dimethylacetamide (DMA) as the solvent, the method enables efficient construction of heterocycle-rich molecular frameworks.

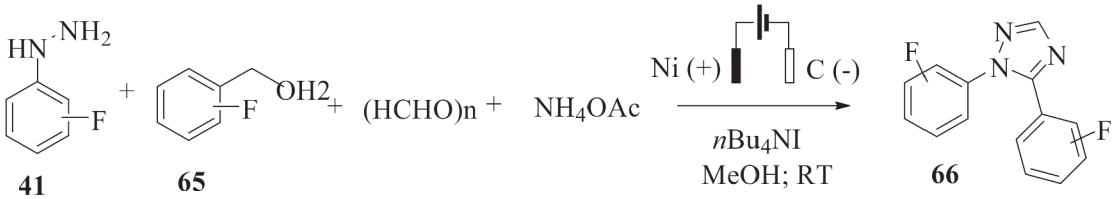
A gram-scale synthesis was performed to demonstrate the scalability and practical applicability of the protocol. The study highlights the potential to expand this strategy toward the synthesis of more complex polycyclic architectures, offering broad utility in medicinal chemistry and materials science.



Scheme 25. Electrochemical synthesis of complex fluorinated quinazolin-indolizines.

Tetramolecular reactions.

Yang *et al.* developed a tetramolecular electrochemical strategy for the synthesis of fluorine-substituted 1,2,4-triazoles **66** (Scheme 26) [150]. The reaction combines fluorinated aryl hydrazines **41**, benzyl alcohols **65**, paraformaldehyde $(HCHO)_n$, and ammonium acetate (NH_4OAc) in a single pot. Electrolysis was performed under constant current conditions in an undivided cell equipped with a graphite rod anode and a nickel plate cathode. Notably, benzyl alcohol serves both as solvent and reactant, while $n\text{-}Bu_4NI$ (TBNI) acts as a redox mediator and *t*-BuOK as the base. The reaction proceeds under mild, metal- and oxidant-free conditions at room temperature, reflecting its practicality and environmental appeal. In the resulting triazole derivatives **66**, fluorine atoms are introduced on both aromatic rings, allowing for structural diversification and the potential to fine-tune biological properties of the synthesized compounds.



Scheme 26. Electrochemical synthesis of fluoro-substituted substituted 1,2,4-triazoles.

CONCLUSIONS. This review has showcased the breadth and sophistication of electrochemical strategies for synthesizing fluorine-containing heterocycles, highlighting their relevance to modern pharmaceutical, agrochemical, and materials-oriented research. Across a wide array of reaction classes, the recurring theme is the ability of electrochemical methods to drive

complex, multibond-forming transformations under sustainable, operationally simple, and transition-metal-free conditions.

Electrooxidative multicomponent reactions—including two-, three-, and four-component assemblies—have proven highly effective for constructing structurally rich heterocycles such as pyrazoles, imidazoles, triazoles, quinolines, and fused polycyclic systems. Many of these transformations rely on fluorinated building blocks (e.g., fluorinated aryl hydrazines, benzylamines, or fluoroalkynes) to deliver final products that possess both high synthetic value and tunable biological properties.

These methodologies also provide remarkable flexibility in fluorine incorporation, enabling the installation of fluorine in diverse chemical environments. Substituents may include single or multiple fluoroaromatic rings, aromatic CF_3 groups, aliphatic trifluoromethyl moieties, or combinations thereof, offering wide-ranging opportunities for structural design and biological fine-tuning. This versatility significantly enhances the utility of electrochemical platforms in the discovery and development of functional fluorinated heterocycles.

Several reactions capitalize on the oxidative transformations of benzylamine moieties, drawing biomimetic parallels to enzymatic transamination processes. These processes enable carbon–nitrogen bond construction via *in situ* formation of reactive imine intermediates, thus opening pathways to reductive amination and tandem heterocycle formation from simple precursors such as carboxylic acids, aldehydes, and ketones.

Noteworthy contributions include anodic SCN• radical generation for thiocyanation of fluorinated pyrazoles under mild, scalable conditions; electrosynthesis of imidazoles and triazoles from benzyl alcohols, fluorinated ketones, and amines in metal- and oxidant-free systems; cascade annulations involving complex bio-derived alcohols and trifluoromethyl alkynes, preserving stereochemical integrity during quinoline ring construction; and electrochemically induced ring-forming condensation of fluoroaryl fragments with isatins, azides, and heteroaromatic substrates, giving rise to heterocycle-rich molecular frameworks with structural and functional diversity.

The methodologies described herein employ commonly available electrodes (e.g., graphite felt, platinum, nickel), green solvents, and electrochemical mediators (such as tetrabutylammonium iodide), supporting both environmental and synthetic economy. Mild temperatures, functional group tolerance, and gram-scale validations further underscore the practical potential of these approaches.

In conclusion, the reviewed strategies demonstrate that electrochemistry is not merely a replacement for traditional oxidants and catalysts, but a powerful platform capable of orchestrating molecular complexity with precision—particularly in the realm of fluorinated heterocyclic synthesis. Future research is expected to further integrate paired redox processes, flow electrolysis, and computationally guided design, expanding the boundaries of what is synthetically and environmentally possible in this field.

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ЕЛЕКТРОХІМІЧНИЙ СИНТЕЗ ФТОРОВАНИХ ГЕТЕРОЦИКЛІЧНИХ СПОЛУК (огляд)

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Фторвмісні гетероцикли відіграють ключову роль у фармацевтичній, агрохімічній та матеріалознавчій промисловості. Прагнення до ефективних та сталих методів синтезу сприяло розвитку електрохімії як привабливої альтернативи традиційним хімічним перетворенням. Серед цих підходів електрохімія виявилася особливо перспективною технікою для здійснення багатозв'язкових процесів у м'яких, екологічно чистих умовах.

Цей огляд висвітлює ключові досягнення за останнє десятиліття в електрохімічному синтезі фторованих гетероциклічних сполук, що охоплюють бімолекулярні, тримолекулярні та чотиримолекулярні реакції. Особливу увагу приділено багатокомпонентним каскадним стратегіям, радикально-опосередкованим сполученням та безокиснювальним циклізаціям, які забезпечують широку толерантність до функціональних груп та гнучкість введення фтору. Сукупно ця робота слугує ресурсом для дослідників, які розробляють стійкі синтетичні платформи нового покоління, адаптовані до фторованих гетероциклів із різноманітними структурними та біологічними профілями.

Ключові слова: електрохімія, гетероциклічні сполуки, фтор, фторовані фармацевтичні препарати, зелена хімія, сталий синтез.

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