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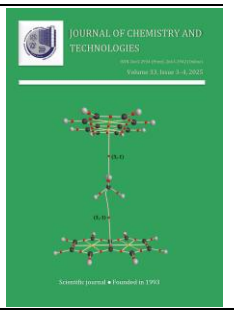

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HARNESSING FERROCENECARBOXALDEHYDE IN MULTICOMPONENT REACTIONS FOR THE SYNTHESIS OF BIOACTIVE HETEROCYCLIC FERROCENES

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Abstract

Multicomponent reactions (MCRs) offer a sustainable and efficient approach to synthesizing complex molecular scaffolds, aligning with green chemistry principles. This study explores the underexploited synthetic potential of ferrocenecarboxaldehyde in MCRs to construct heterocyclic ferrocene derivatives, motivated by their promising bioactivity in medicinal chemistry, potential in materials science, organic synthesis and environmental testing. Through reactions such as the Biginelli condensation, photocatalyzed synthesis, and tandem processes involving malononitrile, ketosulfone, and hydrazines, a diverse array of heterocyclic compounds was synthesized. Structural confirmation was achieved using ^{1}H and ^{13}C NMR, GCMS, and LCMS, despite challenges with solubility and side reactions like decarboxylation and Cannizzaro processes. Successful syntheses included pyrimidine, pyridine and benzimidazole derivatives, with yields ranging from 5 % to 69 %. Several procedures were employed that avoided the need for column chromatography in target product isolation. These findings highlight ferrocenecarboxaldehyde versatility in generating bioactive heterocycles, paving the way for further exploration in drug discovery and materials science.

Keywords: condensation; heterocycles; ferrocenecarboxaldehyde; multicomponent reactions (MCR).

ВИКОРИСТАННЯ ФЕРОЦЕНКАРБОКСАЛЬДЕГІДУ В БАГАТОКОМПОНЕНТНИХ РЕАКЦІЯХ ДЛЯ СИНТЕЗУ БІОАКТИВНИХ ГЕТЕРОЦИКЛІЧНИХ ФЕРОЦЕНІВ

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Анотація

Багатокомпонентні реакції (МКР) пропонують сталий та ефективний підхід до синтезу складних молекулярних каркасів, що відповідає принципам зеленої хімії. Дана робота досліджує недостатньо використаний синтетичний потенціал фероценкарбоксальдегіду в МКР для побудови гетероциклічних похідних фероцену, що мотивовано їхньою багатообіцяючою біоактивністю в медичній хімії. За допомогою таких реакцій, як конденсація Біджинеллі, фотокаталітичний синтез та тандемні процеси, що включають малононітрил, кетосульфон та гідразини, було синтезовано різноманітний спектр гетероциклічних сполук. Підтвердження будови було досягнуто за допомогою ^{1}H та ^{13}C ЯМР, ГХМС та РХМС, незважаючи на проблеми з розчинністю та побічні реакції, такі як декарбоксилювання та реакція Канніццаро. Успішні синтези включали похідні піримідину та бензімідазолу з виходами від 5 % до 69 %. Ці результати підкреслюють універсальність фероценкарбоксальдегіду у створенні біоактивних гетероциклів, прокладаючи шлях для подальших досліджень у галузі розробки ліків та матеріалознавства.

Ключові слова: конденсація; фероценкарбоксальдегід; гетероцикли; багатокомпонентні реакції.

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Introduction

Multicomponent reactions (MCRs), also known as one-pot reactions, involve the combination of at least three or four reactants to produce a single, structurally complex product that incorporates atoms from each starting material. MCRs are highly efficient, enabling the rapid generation of diverse molecular frameworks while minimizing purification steps and overall reaction time. This approach offers considerable versatility, making it particularly valuable in drug discovery and the development of functional molecules. By enabling the synthesis of a broad range of compounds from common starting materials, MCRs align well with the principles of green chemistry, aiming to reduce waste and reaction steps.

MCRs are regarded as practical and sustainable strategies in synthetic chemistry, offering several advantages over traditional reactions. These include fewer sequential steps, improved overall yields, and a reduction in intermediate purification. The products of MCRs frequently include heterocyclic compounds [1].

Concurrently, ferrocene derivatives containing heterocyclic fragments are of growing interest due to their bioactivity [2]. Notable examples of bioactive ferrocenes include the antimalarial agent Ferroquine [3], antimicrobial compounds [4; 5], and anticancer agents [6–12] (Fig. 1).

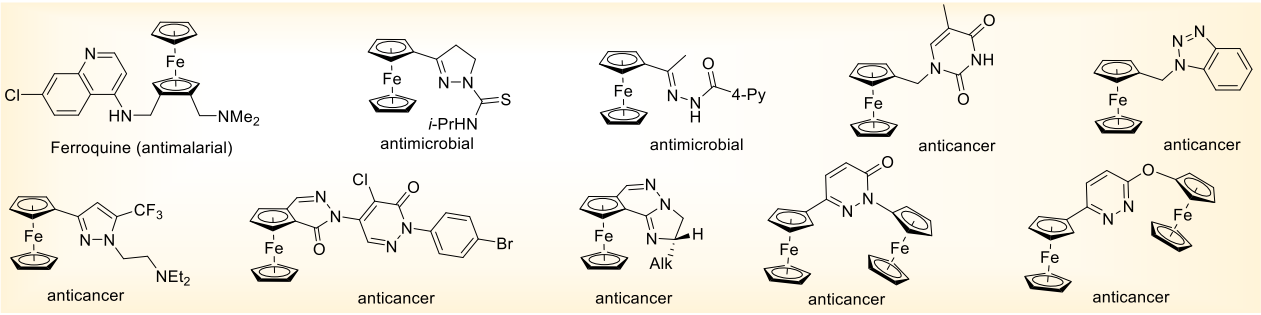


Fig. 1. Representative bioactive ferrocenes

Aromatic aldehydes are well-established starting materials in the synthesis of heterocyclic compounds. Ferrocenecarboxaldehyde represents the ferrocene analogue of such aldehydes. Our literature survey indicates that, in contrast to aryl aldehydes, the application of ferrocenecarboxaldehyde in heterocycle synthesis remains underexplored (**Fig. 2**).

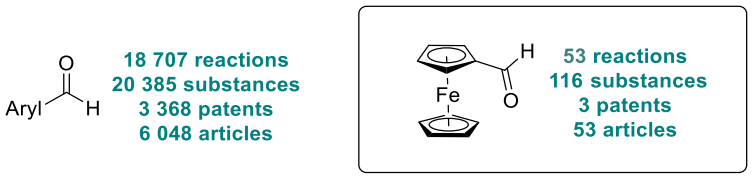
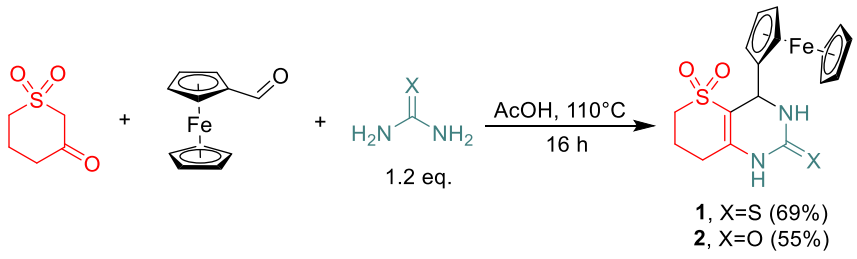


Fig. 2. Literature survey of N-, O-, and S-containing heterocycle synthesis from aryl aldehydes and ferrocenecarbaldehyde (data from Reaxys® database)

These findings motivated us to investigate the synthetic potential of ferrocenecarboxaldehyde in the construction of heterocyclic scaffolds, particularly through multicomponent reactions. This study also extends our group's ongoing research on heterocycles, nitrogen-containing compounds, and ferrocene derivatives [13–17].

Results and Discussion

The initial target heterocycles were synthesized via the Biginelli reaction, yielding compounds **1** and **2** through the reaction of ferrocenecarboxaldehyde, ketosulfone, and urea or thiourea in acetic acid (16 h) [18]. The yields were 69 % and 55 % for compounds **1** and **2**, respectively (Scheme 1). Structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy.



Scheme 1. Biginelli reaction of ferrocenecarboxaldehyde with ketosulfone and urea/thiourea

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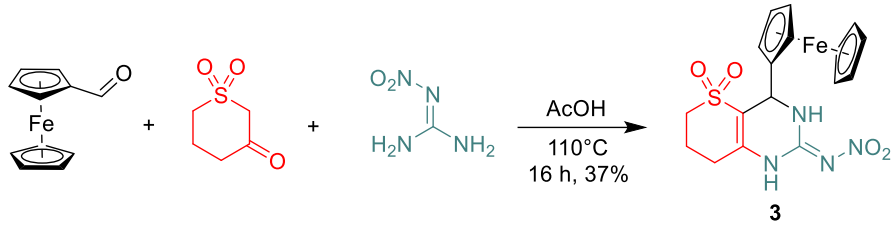
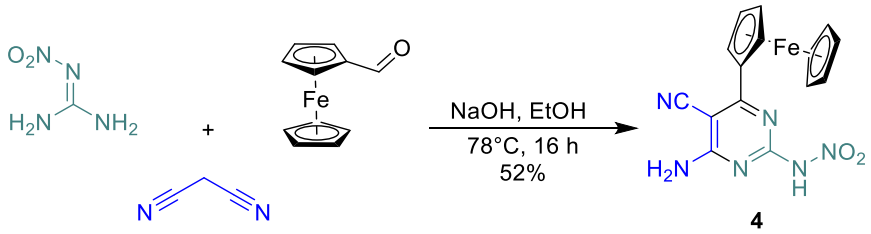
The ^{1}H NMR spectra exhibited characteristic CH_2 signals from the sulfone moiety (2.14, 2.42, 3.23 ppm), ferrocenyl resonances (4.12, 4.19, 4.27 ppm), the proton adjacent to the ferrocenyl fragment (Fc–CH, 5.04 ppm), and NH signals of the pyrimidine ring (9.50, 10.49 ppm), exemplified by compound **1**.

Next, the Biginelli reaction was extended to include nitroguanidine (Scheme 2). The product **3** structure was confirmed via LCMS, although poor solubility precluded NMR analysis.



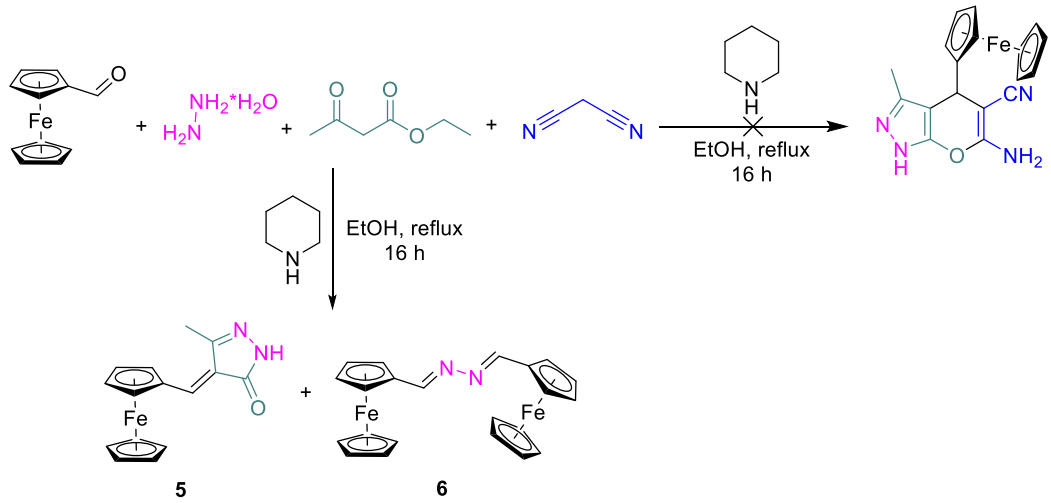
Scheme 2. Biginelli reaction with nitroguanidine

Ferrocenecarboxaldehyde was also condensed with malononitrile and nitroguanidine in ethanol under NaOH catalysis [19], affording pyrimidine derivative **4** (Scheme 3). The structure was confirmed via GCMS and LCMS; however, NMR analysis was again impeded by solubility issues.



Scheme 3. Reaction with malononitrile and nitroguanidine

A four-component reaction involving ferrocenecarboxaldehyde, malononitrile, ethyl acetoacetate, and hydrazine hydrate in ethanol with piperidine catalysis [20] gave a mixture of compounds **5** and **6**, confirmed by GCMS (Scheme 4).



Scheme 4. Four-component reaction leading to compound mixture

An attempt to synthesize compound **7** via room-temperature ultrasonication of ferrocenecarboxaldehyde with 1-tetralone and malononitrile (2 eq.) in ethanol failed. However, heating the mixture [21] afforded pyridine derivative **8** (30 % yield, Scheme 5), confirmed by NMR.

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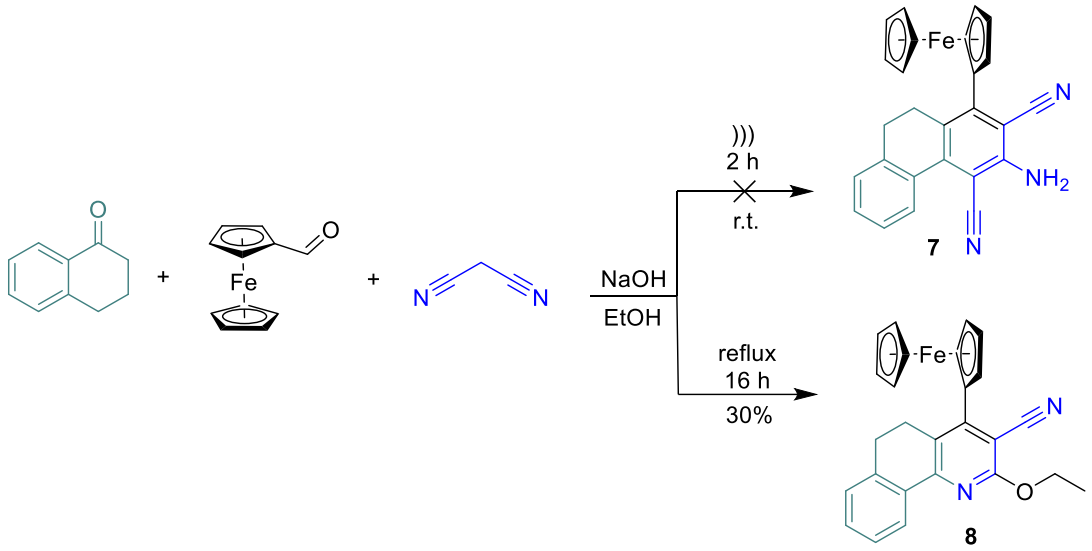
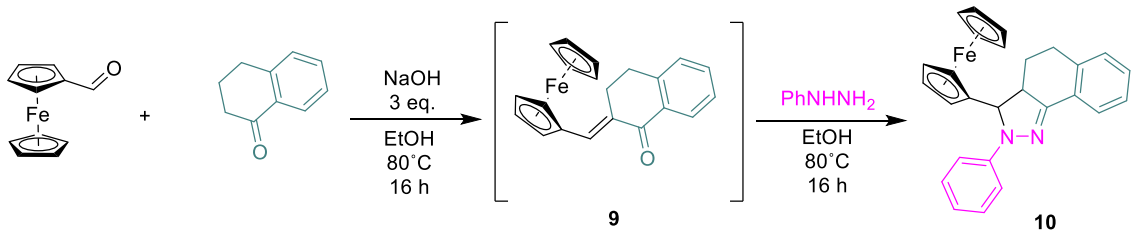

 ))) 2 h r.t. NaOH EtOH reflux 16 h 30% 7 8

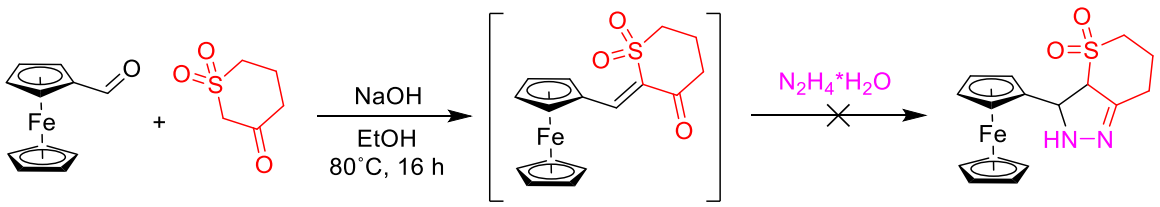
Scheme 5. Reaction of ferrocenecarboxaldehyde with malonodinitrile and 1-tetralone

Compound **10** was formed by first reacting ferrocenecarboxaldehyde with 1-tetralone under basic conditions to obtain intermediate **9**, followed by *in situ* reaction with phenylhydrazine [22; 23] (Scheme 6). GCMS confirmed the structure, though low yield (5 %) prevented isolation for NMR analysis.


 NaOH 3 eq. EtOH 80°C 16 h PhNHNH2 EtOH 80°C 16 h 9 10

Scheme 6. Tandem reaction via hydrazone intermediate

A related reaction using ketosulfone and hydrazine hydrate also failed (Scheme 7).


 NaOH EtOH 80°C, 16 h N2H4*H2O

Scheme 7. Reaction of ferrocenealdehyde with phenylhydrazine and ketosulfone

The reaction with phenyl- and fluorethylhydrazine leads to the formation of multicomponent hard-to-separate mixtures. In reactions aiming to synthesize compounds **11–13**, the condensation stopped at the formation of dinitrile intermediate **14** (Scheme 8), as supported by GCMS. Additionally, decarboxylation and Cannizzaro side reactions were observed, producing ferrocene and ferrocenylmethanol (Scheme 9).

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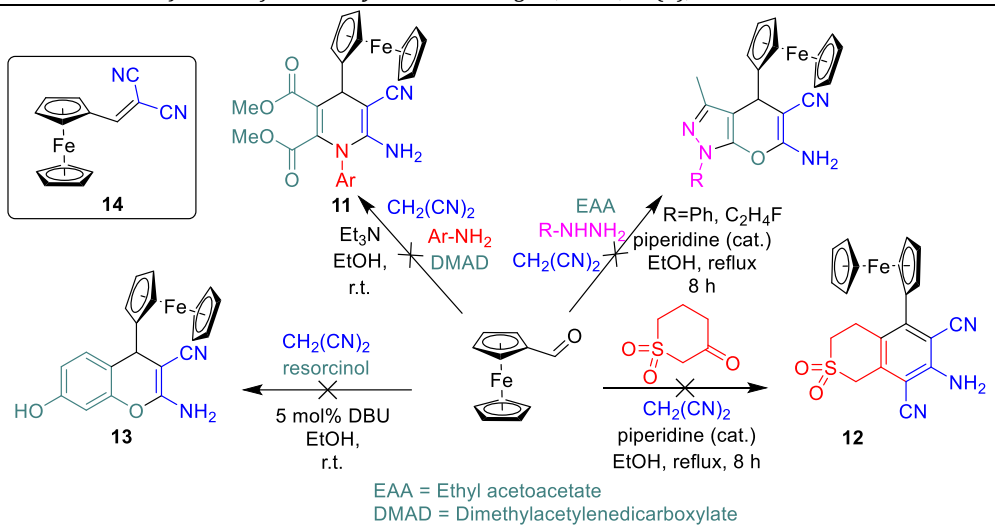
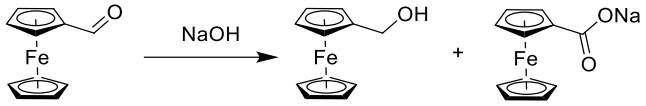
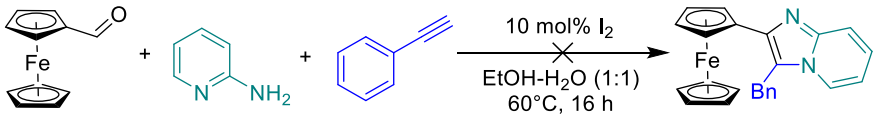


Scheme 8. Condensations of ferrocenecarboxaldehyde with malonodinitrile

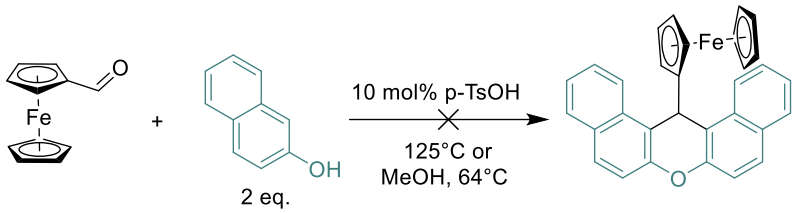


Scheme 9. Cannizzaro-type side reaction of ferrocenecarboxaldehyde

The three-component reaction of ferrocenecarboxaldehyde, 2-aminopyridine, and phenylacetylene under iodine catalysis in aqueous ethanol [24] failed to proceed (Scheme 10). Similarly, reactions with 2-naphthol in methanol with p-TsOH or under solvent-free conditions [25] yielded no target products (Scheme 11).

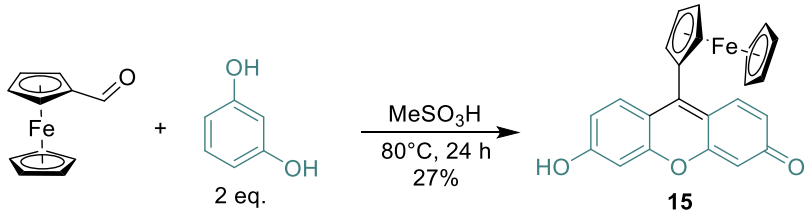


Scheme 10. Unsuccessful reaction with 2-aminopyridine and phenylacetylene



Scheme 11. Unsuccessful reactions with 2-naphthol

Condensation with resorcinol in methanesulfonic acid [26] afforded compound **15**, which was confirmed by LCMS but not NMR (Scheme 12).



Scheme 12. Reaction with resorcinol

The reaction of ferrocenecarboxaldehyde and 2-aminopyridine in nitromethane–DMF with $FeCl_3$ [27] led to tar formation, likely due to oxidative degradation of the ferrocene unit (Scheme 13).

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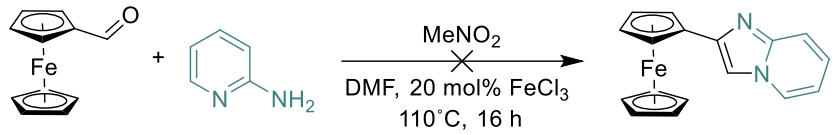
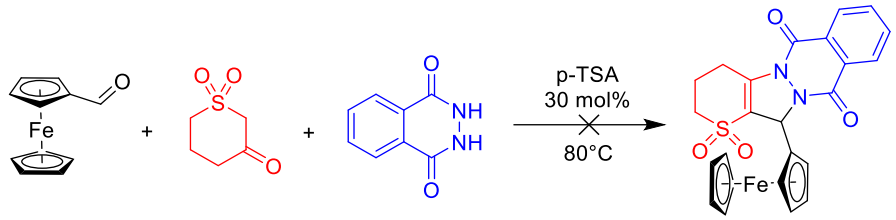


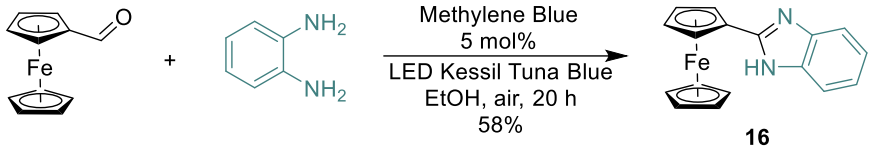
Scheme 13. Reaction of ferrocenecarboxaldehyde with 2-aminopyridine in nitromethane-DMF

Attempts at solvent-free reaction with ketosulfone and phthalohydrazide in the presence of PTSA [28] were unsuccessful (Scheme 14).



Scheme 14. Failed condensation with phthalohydrazide

Photocatalyzed condensation of ferrocene-carboxaldehyde and o-phenylenediamine in ethanol with blue light (450 nm) and Methylene Blue as photocatalyst gave compound **16** (Scheme 15). Among various tested photocatalysts (eosyn Y, Rose Bengale, etc.), Methylene Blue afforded the best yield. NMR spectra for compound **16** matched literature data [29].



Scheme 15. Visible light-mediated synthesis of ferrocenylbenzimidazole 16

Experimental

All reagents were purchased from Enamine Ltd. (www.enamine.net). Solvents were purified according to standard procedures. Thin-layer chromatography (TLC) was performed on Merck aluminum-backed DC 60 F254 plates (0.2 mm). Spots were visualized under UV light (λ_{max} = 254 nm), followed by staining and heating with potassium permanganate solution. ^{1}H NMR spectra were recorded at 500 or 400 MHz, and ^{13}C NMR spectra at 126, or 101 MHz using Bruker spectrometers. Chemical shifts were calibrated against residual undeuterated $CHCl_3$ (δ = 7.26 ppm for ^{1}H, 77.16 ppm for ^{13}C) and DMSO-d_6 (δ = 2.50 ppm for ^{1}H, 39.52 ppm for ^{13}C). Coupling constants (J) are reported in Hz; multiplicities are denoted as s (singlet), d (doublet), and m (multiplet). Reactions were conducted in 5 mL Wheaton V-vials (Thermo Fisher Scientific) sealed with PTFE screw caps and heated in a preheated oil bath. Product purity was assessed by GC-MS using a Shimadzu GCMS-QP2020 equipped with a Restek Rxi-5ms column (30 m × 0.25 mm, 0.25 µm film). Helium served as the carrier gas (flow rate 2.08 mL/min), with a split injection at 250°C. The temperature program ranged from 100°C to 300°C at 30 °C/min, followed by an 8-minute isothermal hold at 300°C. Mass spectra were recorded in electron impact (EI) mode (70 eV) over the *m/z* range 50–800. High-resolution mass spectra (HRMS) were recorded on an Agilent 6224 TOF LC/MS mass spectrometer by electrospray ionization time-of-flight reflectron experiments.

*General method for the synthesis of compounds **1–3***. A stirred reaction mixture of dihydro-2H-thiopyran-3(4H)-one **1** (74 mg, 0.5 mmol, 1 equiv), an urea/thiourea/nitroguanidine (0.6 mmol, 1.2 equiv), and ferrocene-carboxaldehyde (107 mg, 0.5 mmol, 1 equiv.) in acetic acid (2 mL) was heated at 110 °C for 16 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the precipitate formed was filtered, washed with hot ethanol and dried.

*4-Ferrocenyl-4,6,7,8-tetrahydro-1H-thiopyrano[3,2-d]pyrimidine-2(3H)-thione 5,5-dioxide **(1).*** Yield: 133 mg (69 %). Brown solid, m.p. >300 °C. ^{1}H NMR (500 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 2.14 (m, 2H), 2.42 (m, 2H), 3.23 (m, 2H), 4.12 (m, 2H), 4.19 (m, 2H), 4.27 (m, 5H), 5.04 (s, 1H), 9.50 (s, 1H), 10.49 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6), ppm: 17.97, 25.04, 45.53, 50.03, 65.27, 66.85, 67.11, 67.31, 68.61, 91.22, 110.84, 139.68,

174.88. HRMS (ESI-TOF), m/z: found 387.0458, calculated for $C_{17}H_{19}FeN_2O_3S$ $[M+H]^+$ 387.0460.

4-Ferrocenyl-4,6,7,8-tetrahydro-1H-thiopyrano[3,2-d]pyrimidin-2(3H)-one 5,5-dioxide ***(2).*** Yield: 111 mg (55 %). Brown solid, m.p. decomposes ≈270˚C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.16 (m, 2H), 2.34 (m, 2H), 3.19 (m, 2H), 4.10 (m, 3H), 4.22 (m, 6H), 5.06 (s, 1H), 7.66 (s, 1H), 9.19 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6), ppm: 18.12, 25.42, 45.54, 50.18, 65.34, 66.87, 66.98, 68.52, 92.17, 109.12, 142.69, 152.58. HRMS (ESI-TOF), m/z: found 403.0235, calculated for $C_{17}H_{19}FeN_2O_2S_2$ $[M+H]^+$ 403.0232.

(E)-N-(5,5-dioxido-4-ferrocenyl-4,6,7,8-tetrahydro-1H-thiopyrano[3,2-d]pyrimidin-2(3H)-ylidene)nitramide ***(3).*** Yield: 80 mg (37 %). Brown solid, m.p. >300˚C. MS-ES-API (m/z): 429.0 (M-H). HRMS (ESI-TOF), m/z: found 431.0474, calculated for $C_{17}H_{19}FeN_4O_4S$ $[M+H]^+$ 431.0471.

N-(4-Amino-5-cyano-6-ferrocenylpyrimidin-2-yl)nitramide ***(4).*** A mixture of ferrocenecarboxaldehyde (107 mg, 0.5 mmol), 1-nitroguanidine (52 mg, 0.5 mmol, 1 equiv.), malononitrile (33 mg, 0.5 mmol, 1 equiv.), NaOH (0.25 mmol, 0.5 equiv.), and 2.5 mL EtOH (95 %) was stirred at 78 ˚C for 16 h. After completion of the reaction (monitored by TLC), the solvent was removed and the product was purified by column chromatography on silica gel with EtOAc-hexane (1:3) – EtOAc – EtOAc-*i*PrOH (1:1) as an eluent. Fractions containing the product were combined and evaporated to give **4**. Yield: 94 mg (52 %). Pink solid. R_f (EtOAc) 0.725, m.p. decomposes ≈190˚C. Mass spectrum (EI), m/z (I_{rel}, %): 318.9 [M-NO_2] (100), 253.9 (59), 211.9 (25), 146.0 (20), 121.0 (12), 56.0 (23). HRMS (ESI-TOF), m/z: found 365.0442, calculated for $C_{15}H_{13}FeN_6O_2$ $[M+H]^+$ 365.0444.

2-Ethoxy-4-ferrocenyl-5,6-dihydrobenzo[h]quinoline-3-carbonitrile ***(8).*** A mixture of ferrocenecarboxaldehyde (107 mg, 0.5 mmol), malononitrile (33 mg, 0.5 mmol), tetralone (66 µL, 0.5 mmol), and NaOH (20 mg, 0.5 mmol) in EtOH (1.5 ml, 96% aqueous) was refluxed for 14 h. The progress of the reaction was monitored by TLC using silica gel coated plates and EtOAc/hexanes (1 : 4) as the eluent. At the end of the reaction, product precipitated in the mixture and was filtered after cooling to room temperature. The product was washed with EtOH and dried. Yield: 65 mg (30%). Brown solid. R_f (EtOAc-Hexane 1:3) 0.7, m.p. decomposes ≈235 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.19-1.32 (m, 3H), 2.02-2.26 (m, 2H), 2.56-2.73 (m, 2H), 2.84-3.07 (m, 2H), 4.18 (s, 5H), 4.38-4.50 (m, 2H), 4.52–4.63 (m, 2H), 7.21-7.26 (m, 1H), 7.28–7.35 (m, 1H), 7.40-7.53 (m, 1H), 8.03 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$), ppm: 23.43, 29.82, 29.85, 39.31, 70.01, 71.26, 126.75, 127.05, 127.30, 128.88, 132.78, 133.49, 144.60, 198.45. Mass spectrum (EI), m/z (I_{rel}, %): 434.9 [M+H] (32), 433.9 [M] (100), 368.9 (32), 340.9 (26), 338.9 (21), 121.0 (19), 56.0 (13). HRMS (ESI-TOF), m/z: found 435.1156, calculated for $C_{26}H_{23}FeN_2O$ $[M+H]^+$ 435.1154.

6-Hydroxy-9-ferrocenyl-3H-xanthen-3-one ***(15).*** Ferrocenecarboxaldehyde (214 mg, 1 mmol), and m-dihydroxybenzene (220 mg, 2 mmol) was dissolved in methanesulfonic acid (2.5 mL). The solution was stirred at 80 ˚C for 24 h. After being cooled to r.t., the reaction mixture was poured into 20 mL NaOAc solution (3 M). Brown precipitate was collected and washed with water (3x5 mL). After drying, the precipitate was twice purified by column chromatography (silica gel, CH_2Cl_2/MeOH 10:1). Yield: 107 mg (27%). Brown solid. R_f (CH_2Cl_2-MeOH 10:1) 0.25, m.p. >300˚C. MS-ES-API (m/z): 398.0 (M+2H). HRMS (ESI-TOF), m/z: found 397.0520, calculated for $C_{23}H_{17}FeO_3$ $[M+H]^+$ 397.0522.

2-Ferrocenyl-1H-benzo[d]imidazole ***(16).*** To the 10 ml of EtOH (96 % aqueous) in 50 ml round-bottom flask ferrocenealdehyde (107 mg, 0.5 mmol), o-phenylenediamine (54 mg, 0.5 mmol) and Methylene Blue (8 mg, 5 mol%) were added. The reaction mixture was stirred until dissolution and then irradiated with 450 nm blue LED for 20 hours at room temperature while open to air. After 20 hours solvent was removed *in vacuo* and the mixture was subjected to column chromatography on silica gel with EtOAc-hexane (1 : 2–1 : 1) as an eluent. After evaporation of the corresponding fractions the product was obtained as a brown-orange oil. Yield: 87 mg (58 %). R_f (EtOAc-Hexane 1:1) 0.425. Mass spectrum (EI), m/z (I_{rel}, %): 303.1 [M+H] (21), 302.1 [M] (100), 237.1 (33), 154.1 (11), 121.1 (13), 56.0 (23). NMR spectra for compound **16** matched literature data [29].

Conclusions

This study demonstrates the synthetic potential of ferrocenecarboxaldehyde in the formation of diverse heterocyclic compounds via multicomponent and related reactions. Reactions under Biginelli conditions, as well as with tetralone, malononitrile, and phenylhydrazine, were successful. Additionally, the photochemical synthesis of ferrocenylbenzimidazole was achieved. The structures of the synthesized

compounds were confirmed through ^{1}H and ^{13}C NMR, GCMS, and LCMS. Considering the potential applications of heterocycle-functionalized ferrocenes in medicinal chemistry and materials science. Continued investigation in this field is strongly justified and holds significant promise.

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