Synthesis of 4,5-dihydro-1H-pyrazole derivatives based on 3-acetyl-5-nitropyridines

Alena Stalinskaya

Tyumen State University: Tumenskij gosudarstvennyj universitet

Daria Weber

Tyumen State University: Tumenskij gosudarstvennyj universitet

Tulegen Seilkhanov

Sh Ualikhanov Kokshetau State University

Ivan Kulakov (✉ i.v.kulakov@utmn.ru)

Tyumen State University <https://orcid.org/0000-0001-5772-2096>

Research Article

Keywords: 5-Nitropyridines, Pyridylchalcones, 4,5-Dihydro-1H-pyrazoles

Posted Date: February 25th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-217596/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Monatshefte für Chemie - Chemical Monthly on March 6th, 2021. See the published version at <https://doi.org/10.1007/s00706-021-02751-5>.

Abstract

Claisen-Schmidt-type aldol-crotonic condensation of 3-acetyl-5-nitropyridine derivatives with various aromatic aldehydes was used for the preparation of pyridylchalcones. Cyclization of the latter with hydrazine hydrate in acetic acid afforded the corresponding *N*-acetyl derivatives of 4,5-dihydro-1*H*-pyrazole.

Introduction

Chalcones are of important practical interest to chemists due to their availability and pronounced pharmacological activity of natural chalcones and their synthetic analogues. For example, it is worth noting their properties such as antibacterial and anti-inflammatory [1], antitumor [2, 3] antiparasitic [4], antimycobacterial [5], and others [6-10]. In addition, chalcone derivatives are valuable synthons in the formation of various heterocycles. For example, reactions of chalcones with binucleophiles are used in preparation of 4,5-dihydro-1*H*-pyrazoles [11, 12], as well as pyrimidines, pyridines, etc. [13-15]. 4,5-Dihydro-1*H*-pyrazole derivatives have luminescent properties [16] and also exhibit antibacterial [17], antioxidant [18], analgesic [19], anti-inflammatory [20], and antimycobacterial activity [21]. It should be noted that the pyridine-containing derivatives of 4,5-dihydro-1*H*-pyrazole have low toxicity, as well as their phenyl-substituted analogs. However, the presence of a pyridine core in the molecule increases bioavailability [22].

Previously, we have synthesized symmetric 3,5-bis-derivatives **2** and **3** containing α,β -unsaturated carbonyl moieties and 4,5-dihydro-1*H*-pyrazole rings starting from 3,5-diacetyl-2,6-dimethylpyridine **1** (Scheme 1) [23]. According to in vivo biological screening, the synthesized compounds exhibit moderately pronounced analgesic activity.

Polyfunctional pyridines, including 3-acetylpyridines, are of particular interest as versatile objects for chemical modification (for example, in 4,5-dihydro-1*H*-pyrazoles) and subsequent study of the structure-activity relationship of the obtained compounds.

The presence of a nitro group in the molecule can increase its antibacterial activity. Previously, we have studied the antimicrobial and analgesic activity of α,γ -diketoacid derivatives synthesized from 3-acetyl-5-nitropyridine **4** [24].

Herein, we reported the synthesis of a series of azachalcones based on available 3-acetyl-5-nitropyridines **4** and **5** (Fig. 1) and their cyclization to the corresponding 4,5-dihydro-1*H*-pyrazole derivatives.

The starting pyridines **4** and **5** were synthesized by the classical Hantzsch reaction, i.e., through the multicomponent synthesis of intermediate 1,4-dihydropyridines (1,4-DHPs) and their further aromatization into respective pyridines [25, 26].

Results And Discussion

In order to obtain pyridylchalcones **6a-6e** and **7a-7e** the Claisen-Schmidt condensation of 3-acetyl-5-nitropyridines **4**, **5** with various aromatic aldehydes in alkaline aqueous-alcoholic medium was carried out. Due to poor solubility in a water-alcohol medium, the starting 5-nitropyridines were pre-dissolved in a minimum amount of methylene chloride (Scheme 2). Pyridylchalcones **6a-6e** were obtained with excellent yields (92-99%) as fine-crystalline solids. Pyridylchalcones **7a-7e** were isolated with good yields (59-81%).

In order to introduce a new pharmacophore 1*H*-pyrazole ring into the molecules of compounds **6a-6e** and **7a-7e**, a heterocyclization reaction with hydrazine hydrate in the presence of acetic acid was performed (Scheme 2).

In the case of 4,5-dihydro-1*H*-pyrazole **8b**, which contains two acidophobic furan rings, the reaction is accompanied by much tarring. Nevertheless, it was possible to isolate the target product with a yield of 30%. It was purified by silica gel column chromatography. 4,5-Dihydro-1*H*-pyrazole **9b** was also obtained in a low yield (30%), probably for the same reason: low stability of the furan ring when heated in acidic media. 4,5-Dihydro-1*H*-pyrazole derivatives **8a**, **9a** and **8c-8e**, **9c-9e** bearing aromatic substituents were isolated by treating the reaction mixtures with ice water and subsequent recrystallization from an appropriate solvent. Yields of the target compounds varied from 47 to 83% (Table 1).

Conclusion

In summary, a series of new potentially biologically active pyridylchalcone and 4,5-dihydro-1*H*-pyrazole derivatives was synthesized based on poorly studied 3-acetyl-5-nitropyridines **4** and **5**. Moreover, it was shown that the presence of an acceptor nitro group in the pyridine nucleus greatly facilitates their chemical modification at the acetyl group. The presence of a furyl ring in the 4-position of 5-nitropyridine **4** leads to an increase in the yields of pyridylchalcones to almost quantitative, but significantly reduces the yields and complicates the subsequent isolation of the corresponding derivatives of 4,5-dihydro-1*H*-pyrazole. The obtained azachalcones and 4,5-dihydro-1*H*-pyrazole derivatives can be promising objects for search antibacterial agents. After reduction of the nitro group, the resulting amino derivatives of pyrazoles can exhibit excellent luminescent properties.

Experimental

IR spectra were recorded on an Infracum FT-801 spectrometer in KBr pellets. ¹H and ¹³C NMR spectra were acquired on a Bruker DRX400 instrument (400 and 100 MHz, respectively) using CDCl₃ or DMSO-*d*₆ the internal standard was TMS or residual solvent signals (7.25 and 77.0 ppm in the case of CDCl₃ for ¹H and ¹³C nuclei, respectively; 2.49 and 39.9 ppm ¹H and for ¹³C nuclei in DMSO-*d*₆). Elemental analysis was performed on a Carlo Erba EA 1106 automatic CHN-analyzer. The reaction progress and purity of the obtained compounds were controlled by TLC on Sorbfil AF-A-UV plates, visualization in iodine vapor and under UV light. Melting points were determined using a Kofler hot bench.

1-[4-(Furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]ethan-1-one (**4**) and 1-(2-methyl-5-nitro-6-phenylpyridin-3-yl)-3-phenylprop-2-en-1-one (**5**) were synthesized according to published procedures [20, 21].

General procedure for the synthesis of pyridylchalcones **6a-6e, 7a-7e**

A solution of 0.2 g KOH (4 mmol) in 3 cm³ H₂O and 15 cm³ EtOH was cooled in an ice bath (0-5 °C). Then 3-acetyl-5-nitro-6-phenylpyridine **4** or **5** (4 mmol) in 1 cm³ CH₂Cl₂ was added, and the constantly stirred mixture was treated by dropwise addition of the appropriate aromatic aldehyde (4 mmol). A precipitate of pyridylchalcone **6a-6e, 7a-7e** formed after 10 min. The mixture was stirred at room temperature for additional 3 h. Then the precipitate is filtered, washed with a water-alcohol solution and dried in air. The crude product was purified by recrystallization from an appropriate solvent.

1-[4-(Furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-3-phenylprop-2-en-1-one (6a, C₂₅H₁₈N₂O₄) White crystals; m.p.: 138-140 °C (2-PrOH); yield: 1.13 g (92%); IR (KBr): = 1668 (C=O), 1530, 1334 (NO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 2.63 (s, 3H, CH₃), 6.43 (dd, *J* = 3.7 Hz, 1.9 Hz, 1H, H-4 furan), 6.73 (d, *J* = 3.7 Hz, 1H, H-3 furan), 6.82 (d, *J* = 16.0 Hz, 1H, 2-CH=), 7.30 (d, *J* = 16.0 Hz, 1H, -CH=), 7.36-7.43 (m, 3H, H-3',4',5' Ph), 7.45-7.52 (m, 6H, H-5 furan, H-3,4,5 Ph, H-2',6' Ph), 7.63-7.66 (m, 2H, H-2,6 Ph) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 23.3 (CH₃), 112.5, 114.8, 126.4, 128.0 (2C Ar), 128.6 (2C Ar), 128.87 (2C Ph), 128.97, 129.0 (2C Ph), 130.1, 131.3, 131.6, 133.7, 135.3, 142.2, 143.3, 145.5, 146.8, 150.7, 157.1, 194.8 (C=O) ppm.

1-(2-Methyl-5-nitro-6-phenylpyridin-3-yl)-3-phenylprop-2-en-1-one (7a, C₂₁H₁₆N₂O₃) White crystals; m.p.: 155-156 °C (2-PrOH); yield: 992 mg (96%); IR (KBr): = 1665 (C=O), 1505, 1331 (NO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 2.80 (s, 3H, CH₃), 7.18 (d, *J* = 15.3, 1H, 2-CH=), 7.45-7.51 (m, 6H, 3-CH=, H-2',3',4',5',6' Ph), 7.59-7.64 (m, 5H, H-2,3,4,5,6 Ph), 8.29 (s, 1H, H-4 pyridine) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 24.0 (CH₃), 124.8, 128.3 (2C Ph), 128.8 (4C Ph), 129.2 (2C Ph), 130.2, 131.6, 132.1, 132.7, 133.7, 135.9, 143.5, 147.9, 153.3, 160.7, 192.0 (C=O) ppm.

3-(Furan-2-yl)-1-[4-(furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]prop-2-en-1-one (6b, C₂₃H₁₆N₂O₅) Bright-beige crystals; m.p.: 150-152 °C (2-PrOH); yield: 1.10 g (94%); IR (KBr): = 1623 (C=O), 1543, 1375 (NO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 2.62 (s, 3H, CH₃), 6.44 (dd, *J* = 3.7 Hz, 1.8 Hz, 1H, H-4' furan), 6.50 (dd, *J* = 3.7 Hz, 1.8 Hz, 1H, H-4 furan), 6.66-6.75 (m, 3H, 2-CH=, H-3 furan, H-3' furan), 7.06 (d, *J* = 16.0 Hz, 1H, 3-CH=), 7.46-7.50 (m, 4H, H-3,4,5 Ph, H-5' furan), 7.52 (d, *J* = 1.3 Hz, 1H, H-5 furan), 7.60-7.64 (m, 2H, H-2,6 Ph) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 23.2 (CH₃), 112.4, 113.0, 114.9, 117.7, 123.7, 128.0 (3C Ph), 128.9 (3C Ph), 130.0, 131.6, 132.4, 135.4, 143.3, 145.5, 146.0, 150.3, 150.7, 157.0, 194.3 (C=O) ppm.

3-(Furan-2-yl)-1-(2-methyl-5-nitro-6-phenylpyridin-3-yl)prop-2-en-1-one (7b, C₁₉H₁₄N₂O₄) Yellow crystals; m.p.: 160-161 °C (2-PrOH); yield: 712 mg (71%); IR (KBr): = 1657 (C=O), 1504, 1326 (NO₂) cm⁻¹; ¹H NMR

(400 MHz, CDCl_3): δ = 2.80 (s, 3H, CH_3), 6.55 (br. s, 1H, H-4 furan), 6.80 (d, J = 3.0 Hz, 1H, H-3 furan), 7.07 (d, J = 15.2 Hz, 1H, 2-CH=), 7.41 (d, J = 15.2 Hz, 1H, 3-CH=), 7.46-7.50 (m, 3H, H-3,4,5 Ph), 7.58 (m, 3H, H-5 furan, H-2,6 Ph), 8.30 (s, 1H, H-4 pyridine) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ = 24.1 (CH_3), 113.1, 118.2, 121.7, 128.3 (2C Ph), 128.8 (2C Ph), 130.1, 132.1, 132.8, 132.9, 135.9, 143.5, 146.1, 150.7, 153.3, 160.8, 191.0 (C=O) ppm.

1-[4-(Furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-3-(thiophen-2-yl)prop-2-en-1-one (6c, $\text{C}_{23}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$)

Beige crystals; m.p.: 148-149 °C (2-PrOH); yield: 1.20 g (95%); IR (KBr): = 1643 (C=O), 1530, 1375 (NO_2) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 2.64 (s, 3H, CH_3), 6.45 (br. s, 1H, H-4 furan), 6.62 (d, J = 16.8 Hz, 1H, 2-CH=), 6.75 (d, J = 3.1 Hz, 1H, H-3 furan), 7.08 (t, J = 4.6 Hz, 1H, H-4 thiophene), 7.30 (d, J = 3.1 Hz, 1H, H-3 thiophene), 7.43 (d, J = 16.8 Hz, 1H, 3-CH=), 7.41-7.52 (m, 6H, H-3,4,5 Ph, H-5 furan, H-5 thiophene), 7.62-7.68 (m, 2H, H-2,6 Ph) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ = 23.3 (CH_3), 112.4, 114.9, 125.0, 128.0 (2C Ph), 128.6, 128.9 (2C Ph), 128.9, 130.1, 130.4, 131.5, 132.9, 135.3, 139.0, 139.1, 142.2, 143.3, 145.5, 150.7, 157.1, 194.1 (C=O) ppm.

1-(2-Methyl-5-nitro-6-phenylpyridin-3-yl)-3-(thiophen-2-yl)prop-2-en-1-one (7c, $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$)

Bright-yellow crystals; m.p.: 166-168 °C (2-PrOH); yield: 746 mg (71%); IR (KBr): = 1656 (C=O), 1503, 1323 (NO_2) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 2.79 (s, 3H, CH_3), 6.95 (d, J = 16.8 Hz, 1H, 2-CH=), 7.14 (d, J = 4.6 Hz, 1H, H-4 thiophene), 7.40 (d, J = 3.0 Hz, 1H, H-3 thiophene), 7.47-7.55 (m, 4H, H-5 thiophene, H-3,4,5 Ph), 7.61 (d, J = 4.5 Hz, 2H, H-2,6 Ph), 7.75 (d, J = 15.3, 1H, 3-CH=), 8.28 (s, 1H, H-4 pyridine) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ = 24.0 (CH_3), 123.3, 128.2 (2C Ph), 128.7, 128.8 (2C Ph), 130.2, 130.7, 132.0, 132.7, 133.4, 135.8, 139.2, 140.0, 143.4, 153.2, 160.6, 191.2 (C=O) ppm.

1-[4-(Furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-3-(3-nitrophenyl)prop-2-en-1-one (6d, $\text{C}_{25}\text{H}_{17}\text{N}_3\text{O}_6$)

Bright-beige crystals; m.p.: 146-148 °C (2-PrOH- CHCl_3); yield: 1.30 g (98%); IR (KBr): = 1656 (C=O), 1530, 1353 (NO_2) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 2.64 (s, 3H, CH_3), 6.45 (br. s, 1H, H-4 furan), 6.75 (d, J = 3.1 Hz, 1H, H-3 furan), 6.86 (d, J = 16.8 Hz, 1H, 2-CH=), 7.34 (d, J = 16.8 Hz, 1H, 3-CH=), 7.45-7.52 (m, 4H, H-3,4,5 Ph, H-5 furan), 7.58 (t, J = 8.4 Hz, 1H, H-5 Ar), 7.63-7.65 (m, 2H, H-2,6 Ph), 7.76 (d, J = 7.6 Hz, 1H, H-6 Ar), 8.24 (d, J = 9.1 Hz, 1H, H-4 Ar), 8.30 (s, 1H, H-2 Ar) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ = 23.4 (CH_3), 112.7, 115.0, 122.8, 125.3, 128.0 (2C Ph), 128.6, 128.9 (2C Ph), 129.0, 130.2, 130.3, 131.0, 133.9, 135.2, 135.5, 142.1, 142.9, 143.2, 145.7, 148.6, 151.1, 157.2, 193.9 (C=O) ppm.

1-(2-Methyl-5-nitro-6-phenylpyridin-3-yl)-3-(3-nitrophenyl)prop-2-en-1-one (7d, $\text{C}_{21}\text{H}_{15}\text{N}_3\text{O}_5$)

White crystals; m.p.: 183-185 °C (2-PrOH- CHCl_3); yield: 689 mg (59%); IR (KBr): = 1669 (C=O), 1605, 1366 (NO_2) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 2.85 (s, 3H, CH_3), 7.33 (d, J = 15.2 Hz, 1H, 2-CH=), 7.50-7.54 (m, 3H, H-3,4,5 Ph), 7.62-7.65 (m, 2H, H-2,6 Ph), 7.67-7.73 (m, 2H, 3-CH=, H-5 Ar), 7.95 (d, J = 7.6 Hz, 1H, H-6 Ar), 8.33 (d, J = 7.6 Hz, 1H, H-4 Ar), 8.36 (s, 1H, H-2 Ar), 8.50 (s, 1H, H-4 pyridine) ppm; ^{13}C (100 MHz, CDCl_3): δ = 24.3 (CH_3), 123.0, 125.6, 126.9, 128.3 (2C Ph), 128.9 (2C Ph), 130.3, 130.4, 131.9, 132.3, 134.2, 135.5, 135.7, 143.4, 144.3, 148.7, 153.8, 161.0, 190.8 (C=O) ppm.

3-(4-Fluorophenyl)-1-[4-(furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]prop-2-en-1-one (6e, C₂₅H₁₇FN₂O₄)

Bright-beige crystals; m.p.: 136-138 °C (2-PrOH); yield: 1.30 g (99%); IR (KBr): = 1670 (C=O), 1532, 1319 (NO₂) cm⁻¹; ¹H (400 MHz, CDCl₃): δ = 2.63 (s, 3H, CH₃), 6.44 (br. s, 1H, H-4 furan), 6.72-6.76 (m, 2H, 2-CH=, H-3 furan), 7.08 (t, *J* = 8.4 Hz, 2H, H-3,5 Ar), 7.26 (d, *J* = 15.2 Hz, 1H, 3-CH=), 7.46-7.55 (m, 6H, H-5 furan, H-3,4,5 Ph, H-2,6 Ar), 7.62-7.68 (m, 2H, H-2,6 Ph) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 23.3 (CH₃), 112.5, 114.8, 116.3 (d, ²*J*_{C-F} = 22.1 Hz, 2C Ar), 126.0, 128.0 (2C Ph), 128.9 (2C Ph), 128.95, 130.0, 130.1, 130.6 (d, ³*J*_{C-F} = 8.6 Hz, 2C Ar), 131.5, 135.3, 142.1, 143.3, 145.4, 145.5, 150.8, 157.1, 164.4 (d, ¹*J*_{C-F} = 253.1 Hz), 194.6 (C=O) ppm.

3-(4-Fluorophenyl)-1-(2-methyl-5-nitro-6-phenylpyridin-3-yl)prop-2-en-1-one (7e, C₂₁H₁₅FN₂O₃)

White crystals; m.p.: 173-174 °C (2-PrOH); yield: 869 mg (80%); IR (KBr): = 1666 (C=O), 1510, 1345 (NO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 2.79 (s, 3H, CH₃), 7.07-7.15 (m, 3H, 2-CH=, H-3,5 Ar), 7.46-7.51 (m, 3H, 3-CH=, H-2,6 Ar), 7.54-7.63 (m, 5H, H-2,3,4,5,6 Ph), 8.28 (s, 1H, H-4 pyridine) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 24.0 (CH₃), 116.5 (d, ²*J*_{C-F} = 22.1 Hz, 2C Ar), 124.4, 128.3 (2C Ph), 128.8 (2C Ph), 130.1, 130.2, 130.8 (d, ³*J*_{C-F} = 8.6 Hz, 2C Ar), 132.1, 132.6, 135.8, 143.5, 146.4, 153.3, 160.7, 164.6 (d, ¹*J*_{C-F} = 254.0 Hz), 191.6 (C=O) ppm.

General procedure for the synthesis of 4,5-dihydro-1*H*-pyrazoles 8a-8e, 9a-9e

A solution of 0.3 cm³ N₂H₄·H₂O (5 mmol) in 4 cm³ *i*-PrOH was constantly stirred and treated by dropwise addition of a solution of the appropriate pyridylchalcone **6a-6e** or **7a-7e** (0.5 mmol) in 10 cm³ AcOH. The mixture was refluxed for 20 h, then it was cooled and poured into 50 cm³ ice-water mixture. The formed precipitate of 4,5-dihydro-1*H*-pyrazole **8a-8e**, **9a-9e** was filtered off, washed with H₂O, and air-dried. The crude product was purified by recrystallization or by silica gel column chromatography (compound **8b**).

1-[3-[4-(Furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]ethan-1-one

(8a, C₂₇H₂₂N₄O₄) Beige crystals; m.p.: 198-200 °C (2-PrOH); yield: 137 mg (59%); IR (KBr): = 1670 (C=O), 1536, 1350 (NO₂) cm⁻¹; ¹H (400 MHz, CDCl₃): δ = 2.40 (s, 3H, COCH₃), 2.55 (dd, ²*J* = 16.8 Hz, ³*J* = 4.6 Hz, 1H, 4-CH₂ pyrazole), 2.74 (s, 3H, CH₃), 3.29 (dd, ²*J* = 18.4 Hz, ³*J* = 12.3 Hz, 1H, 4-CH₂ pyrazole), 5.62 (dd, ³*J* = 10.7 Hz, ³*J* = 4.6 Hz, 1H, 5-CH pyrazole), 6.36 (br. s, 1H, H-4 furan), 6.64 (d, *J* = 3.1 Hz, 1H, H-3 furan), 7.17 (br. s, 3H, H-3',4',5' Ph), 7.27-7.32 (m, 1H, H-4 Ph), 7.33-7.39 (m, 2H, H-2',6' Ph), 7.48 (s, 3H, H-3,5 Ph, H-5 furan), 7.60 (d, *J* = 7.6 Hz, 2H, H-2',6' Ph) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 21.9 (CH₃), 24.2 (COCH₃), 45.5 (4-CH₂ pyrazole), 59.6 (5-CH pyrazole), 112.1, 114.4, 124.7, 125.3 (2C Ph), 127.7, 127.9 (3C Ph), 128.9 (4C Ph), 130.1, 131.0, 135.2, 140.9, 143.3, 145.3, 150.4, 152.1, 159.2, 169.0 (COCH₃) ppm.

1-[3-(2-Methyl-5-nitro-6-phenylpyridin-3-yl)-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl]ethan-1-one

(9a, C₂₃H₂₀N₄O₃) Yellow crystals; m.p.: 191-193 °C (2-PrOH); yield: 96 mg (48%); IR (KBr): = 1670 (C=O), 1536, 1350 (NO₂) cm⁻¹; ¹H (400 MHz, CDCl₃): δ = 2.45 (s, 3H, COCH₃), 3.05 (s, 3H, CH₃), 3.26 (dd, ²*J* = 16.8 Hz,

$^3J = 4.6$ Hz, 1H, 4-CH₂ pyrazole), 3.87 (dd, $^2J = 16.8$ Hz, $^3J = 12.2$ Hz, 1H, 4-CH₂ pyrazole), 5.64 (dd, $^3J = 12.2$ Hz, $^3J = 4.6$ Hz, 1H, 5-CH pyrazole), 7.22-7.36 (m, 5H, H-2',3',4',5',6' Ph), 7.49 (m, 3H, H-3,4,5 Ph), 7.59 (d, $J = 7.63$ Hz, 2H, H-2,6 Ph), 8.10 (s, 1H, H-4 pyridine) ppm; ^{13}C NMR (100 MHz, CDCl₃): $\delta = 22.1$ (CH₃), 27.2 (COCH₃), 43.9 (4-CH₂ pyrazole), 59.6 (5-CH pyrazole), 125.1, 125.4 (2C Ph), 128.0, 128.3 (2C Ph), 128.8 (2C Ph), 129.1 (2C Ph), 130.1, 131.9, 135.8, 141.0, 143.7, 150.2, 151.4, 161.1, 169.0 (COCH₃) ppm.

1-[5-(Furan-2-yl)-3-[4-(furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-4,5-dihydro-1H-pyrazol-1-yl]ethan-1-one (8b, C₂₅H₂₀N₄O₅) Beige crystals; m.p.: 176-178 °C (SiO₂, EtOAc-hexane (1:3)); yield: 68 mg (30%); IR (KBr): = 1665 (C=O), 1542, 1358 (NO₂) cm⁻¹; ^1H NMR (400 MHz, CDCl₃): $\delta = 2.32$ (s, 3H, COCH₃), 2.77 (s, 3H, CH₃), 2.97 (dd, $^2J = 18.3$ Hz, $^3J = 6.1$ Hz, 1H, 4-CH₂ pyrazole), 3.11 (dd, $^2J = 18.3$ Hz, $^3J = 12.2$ Hz, 1H, 4-CH₂ pyrazole), 5.66 (dd, $^3J = 12.2$ Hz, $^3J = 4.6$ Hz, 1H, 5-CH pyrazole), 6.33 (d, $^3J = 4.6$ Hz, 1H, H-4' furan), 6.36 (d, $^3J = 3.1$ Hz, 1H, H-3' furan), 6.50 (br. s, 1H, H-4 furan), 6.71 (d, $J = 3.1$ Hz, 1H, H-3 furan), 7.34 (br. s, 1H, H-5' furan), 7.45-7.54 (m, 4H, H-3,4,5 Ph, H-5 furan), 7.60-7.62 (m, 2H, H-2,6 Ph) ppm; ^{13}C NMR (100 MHz, CDCl₃): $\delta = 22.0$ (CH₃), 24.0 (COCH₃), 41.2 (4-CH₂ pyrazole), 53.3 (5-CH pyrazole), 107.9, 110.7, 112.3, 114.7, 124.5, 128.0 (2C Ph), 128.9 (2C Ph), 130.2, 130.9, 135.3, 142.0, 143.0, 143.5, 145.5, 150.7, 151.3, 152.4, 159.4, 169.2 (COCH₃) ppm.

1-[5-(Furan-2-yl)-3-(2-methyl-5-nitro-6-phenylpyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl]ethan-1-one (9b, C₂₁H₁₈N₄O₄) Bright-yellow crystals; m.p.: 141-142 °C (CHCl₃-hexane); yield: 59 mg (30%); IR (KBr): = 1667 (C=O), 1545, 1347 (NO₂) cm⁻¹; ^1H NMR (400 MHz, CDCl₃): $\delta = 2.42$ (s, 3H, -COCH₃), 3.04 (s, 3H, CH₃), 3.56 (dd, $^2J = 16.7$ Hz, $^3J = 4.6$ Hz, 1H, 4-CH₂ pyrazole), 3.70 (dd, $^2J = 18.4$ Hz, $^3J = 10.6$ Hz, 1H, 4-CH₂ pyrazole), 5.74 (dd, $^3J = 10.6$ Hz, $^3J = 4.6$ Hz, 1H, 5-CH pyrazole), 6.36 (br. s, 1H, H-4 furan), 6.40 (br. s, 1H, H-3 furan), 7.33 (br. s, 1H, H-5 furan), 7.47-7.52 (m, 3H, H-3,4,5 Ph), 7.59-7.64 (m, 2H, H-2,6 Ph), 8.17 (s, 1H, H-4 pyridine) ppm; ^{13}C NMR (100 MHz, CDCl₃): $\delta = 22.1$ (CH₃), 27.1 (COCH₃), 39.6 (4-CH₂ pyrazole), 53.0 (5-CH pyrazole), 108.3, 110.7, 125.0, 128.3 (2C Ph), 128.8 (2C Ph), 130.1, 132.0, 135.9, 142.2, 143.7, 150.4, 151.1, 151.4, 161.2, 169.1 (COCH₃) ppm.

1-[3-[4-(Furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl]ethan-1-one (8c, C₂₅H₂₀N₄O₄S) Beige crystals; m.p.: 189-190 °C (2-PrOH); yield: 111 mg (47%); IR (KBr): = 1676 (C=O), 1534, 1349 (NO₂) cm⁻¹; ^1H NMR (400 MHz, CDCl₃): $\delta = 2.35$ (s, 3H, -COCH₃), 2.75 (s, 3H, CH₃), 2.81 (dd, $^2J = 18.4$ Hz, $^3J = 4.6$ Hz, 1H, 4-CH₂ pyrazole), 3.23 (dd, $^2J = 18.4$ Hz, $^3J = 12.2$ Hz, 1H, 4-CH₂ pyrazole), 5.87 (dd, $^3J = 10.6$ Hz, $^3J = 4.6$ Hz, 1H, 5-CH pyrazole), 6.44 (br. s, 1H, H-4 furan), 6.66 (d, $J = 4.6$ Hz, 1H, H-3 furan), 6.94-6.96 (m, 2H, H-3,4 thiophene), 7.23 (d, $J = 4.5$ Hz, 1H, H-5 thiophene), 7.33 (br. s, 1H, H-5 furan), 7.42-7.51 (m, 3H, H-3,4,5 Ph), 7.57-7.65 (m, 2H, H-2,6 Ph) ppm; ^{13}C NMR (100 MHz, CDCl₃): $\delta = 22.0$ (CH₃), 24.2 (COCH₃), 45.3 (4-CH₂ pyrazole), 55.3 (5-CH pyrazole), 112.3, 114.6, 124.5, 124.66, 124.69, 126.9, 127.9 (2C Ph), 128.9 (2C Ph), 130.2, 131.0, 135.2, 143.1, 143.4, 143.9, 145.4, 150.6, 152.0, 159.2, 169.2 (COCH₃) ppm.

1-[3-(2-Methyl-5-nitro-6-phenylpyridin-3-yl)-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl]ethan-1-one (9c, C₂₁H₁₈N₄O₃S) Beige crystals; m.p.: 174-175 °C (2-PrOH); yield: 169 mg (83%); IR (KBr): = 1676 (C=O), 1534, 1349 (NO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 2.43 (s, 3H, COCH₃), 3.04 (s, 3H, CH₃), 3.43 (dd, ²J = 16.7 Hz, ³J = 4.6 Hz, 1H, 4-CH₂ pyrazole), 3.84 (dd, ²J = 16.8 Hz, ³J = 12.2 Hz, 1H, 4-CH₂ pyrazole), 5.96 (dd, ³J = 12.2 Hz, ³J = 3.1 Hz, 1H, 5-CH pyrazole), 6.96 (dd, J = 4.6 Hz, 3.1 Hz, 1H, H-4 thiophene), 7.06 (d, J = 3.1 Hz, 1H, H-3 thiophene), 7.23 (d, J = 4.6 Hz, 1H, H-5 thiophene), 7.44-7.54 (m, 3H, H-3,4,5 Ph), 7.56-7.65 (m, 2H, H-2,6 Ph), 8.14 (s, 1H, H-4 pyridine) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 22.1 (CH₃), 27.0 (COCH₃), 43.6 (4-CH₂ pyrazole), 55.0 (5-CH pyrazole), 124.8, 125.0, 125.1, 127.0, 128.3 (2C Ph), 128.8 (2C Ph), 130.1, 131.9, 135.8, 143.4, 143.7, 150.2, 151.5, 161.1, 169.1 (COCH₃) ppm.

1-[3-[4-(Furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-5-(3-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl]ethan-1-one (8d, C₂₇H₂₁N₅O₆) Beige crystals; m.p.: 165-168 °C (CH₂Cl₂-hexane); yield: 128 mg (50%); IR (KBr): = 1679 (C=O), 1534, 1345 (NO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 2.41 (s, 3H, COCH₃), 2.56 (dd, ²J = 18.3 Hz, ³J = 6.1 Hz, 1H, 4-CH₂ pyrazole), 2.77 (s, 3H, CH₃), 3.36 (dd, ²J = 18.3 Hz, ³J = 12.2 Hz, 1H, 4-CH₂ pyrazole), 5.64 (dd, ³J = 12.2 Hz, ³J = 6.1 Hz, 1H, 5-CH pyrazole), 6.43 (d, J = 3.0 Hz, 1H, H-4 furan), 6.69 (d, J = 3.1 Hz, 1H, H-3 furan), 7.35 (br. s, 1H, H-5 furan), 7.45-7.51 (m, 3H, H-3,4,5 Ph), 7.54-7.58 (m, 2H, H-5,6 Ar), 7.62 (d, J = 7.6 Hz, 2H, H-2,6 Ph), 8.06 (s, 1H, H-2 Ar), 8.18 (dd, J = 6.1 Hz, 3.1 Hz, 1H, H-4 Ar) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 21.9 (CH₃), 24.2 (COCH₃), 45.3 (4-CH₂ pyrazole), 59.2 (5-CH pyrazole), 112.4, 114.5, 120.5, 122.9, 124.3, 127.9 (2C Ph), 128.9 (2C Ph), 130.0, 130.3, 131.1, 132.0, 135.1, 143.2, 143.3, 143.4, 145.3, 148.6, 150.7, 151.8, 159.1, 169.4 (COCH₃) ppm.

1-[3-(2-Methyl-5-nitro-6-phenylpyridin-3-yl)-5-(3-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl]ethan-1-one (9d, C₂₃H₁₉N₅O₅) Beige crystals; m.p.: 181-182 °C (2-PrOH); yield: 171 mg (77%); IR (KBr): = 1679 (C=O), 1534, 1345 (NO₂) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 2.48 (s, 3H, COCH₃), 3.06 (s, 3H, CH₃), 3.29 (dd, ²J = 16.8 Hz, ³J = 6.1 Hz, 1H, 4-CH₂ pyrazole), 3.96 (dd, ²J = 18.3 Hz, ³J = 12.2 Hz, 1H, 4-CH₂ pyrazole), 5.71 (dd, ³J = 12.2 Hz, ³J = 6.1 Hz, 1H, 5-CH pyrazole), 7.47-7.54 (m, 3H, H-3,4,5 Ph), 7.54-7.64 (m, 4H, H-2,6 Ph, H-5,6 Ar), 8.10 (br. s, 2H, H-2 Ar, H-4 pyridine), 8.18 (d, J = 7.6 Hz, 1H, H-4 Ar) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 22.0 (CH₃), 27.2 (COCH₃), 43.6 (4-CH₂ pyrazole), 59.0 (5-CH pyrazole), 120.6, 123.1, 124.5, 128.3 (2C Ph), 128.8 (2C Ph), 130.2 (2C Ar), 132.0 (2C Ar), 135.7, 143.0, 143.6, 148.7, 150.1, 151.7, 161.2, 169.3 (COCH₃) ppm.

1-[5-(4-Fluorophenyl)-3-[4-(furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-4,5-dihydro-1H-pyrazol-1-yl]ethan-1-one (8e, C₂₇H₂₁FN₄O₄) Beige crystals; m.p.: 181-183 °C (2-PrOH); yield: 157 mg (65%); IR (KBr): = 1667 (C=O), 1535, 1345 (NO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 2.38 (s, 3H, COCH₃), 2.53 (dd, ²J = 18.3 Hz, ³J = 4.5 Hz, 1H, 4-CH₂ pyrazole), 2.73 (s, 3H, CH₃), 3.27 (dd, ²J = 18.3 Hz, ³J = 12.2 Hz, 1H, 4-CH₂ pyrazole), 5.56 (dd, ³J = 12.2 Hz, ³J = 4.5 Hz, 1H, 5-CH pyrazole), 6.40 (br. s, 1H, H-4 furan), 6.64 (d, J = 4.5 Hz, 1H, H-3 furan), 7.04 (t, J = 9.1 Hz, 2H, H-3,5 Ar), 7.11-7.15 (m, 2H, H-2,6 Ar), 7.26 (br. s, 1H, H-5 furan), 7.43-7.48 (m, 3H, H-3,4,5 Ph), 7.58-7.63 (m, 2H, H-2,6 Ph) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 21.9 (CH₃),

24.2 (COCH₃), 45.5 (4-CH₂ pyrazole), 59.0 (5-CH pyrazole), 112.2, 114.4, 115.8 (d, ²J_{C-F} = 22.1 Hz, 2C Ar), 124.7, 127.1 (d, ³J_{C-F} = 8.6 Hz, 2C Ar), 128.0 (2C Ph), 128.9 (2C Ph), 130.2, 131.0, 135.2, 136.8, 143.3, 143.4, 145.2, 150.5, 151.9, 159.1, 162.1 (d, ¹J_{C-F} = 246.3 Hz), 169.1 (COCH₃) ppm.

1-[5-(4-Fluorophenyl)-3-(2-methyl-5-nitro-6-phenylpyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl]ethan-1-one (9e, C₂₃H₁₉FN₄O₃) Yellow crystals; m.p.: 196-198 °C (2-PrOH); yield: 82 mg (39%); IR (KBr): = 1667 (C=O), 1511, 1409 (NO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 2.42 (s, 3H, COCH₃), 3.03 (s, 3H, CH₃), 3.21 (dd, ²J = 17.9 Hz, ³J = 4.6 Hz, 1H, 4-CH₂ pyrazole), 3.84 (dd, ²J = 17.9 Hz, ³J = 11.9 Hz, 1H, 4-CH₂ pyrazole), 5.59 (dd, ³J = 11.9 Hz, ³J = 4.6 Hz, 1H, 5-CH pyrazole), 6.97-7.09 (m, 2H, H-3,5 Ar), 7.15-7.23 (m, 2H, H-2,6 Ar), 7.42-7.51 (m, 3H, H-3,4,5 Ph), 7.54-7.62 (m, 2H, H-2,6 Ph), 8.07 (s, 1H, H-4 pyridine) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 22.1 (CH₃), 27.1 (COCH₃), 43.8 (4-CH₂ pyrazole), 59.0 (5-CH pyrazole), 116.0 (d, ²J_{C-F} = 22.0 Hz, 2C Ar), 124.9, 127.3 (d, ³J_{C-F} = 7.6 Hz, 2C Ar), 128.3 (2C Ph), 128.8 (2C Ph), 130.1, 131.9, 135.8, 136.9, 143.7, 150.2, 151.5, 161.1, 162.3 (d, ¹J_{C-F} = 244.4 Hz), 169.1 (COCH₃) ppm.

Declarations

Acknowledgements The reported study was funded by RFBR, project number 19-03-00376.

Spectrophotometric studies were performed on the basis of the Research Resource Center "Natural Resource Management and Physico-Chemical Research" Institute of Chemistry, Tyumen State University (with the financial support of the Ministry of Science and Higher Education of the Russian Federation (contract no. 05.594.21.0019, unique identification number RFMEFI59420X0019)).

References

1. Nowakowska Z (2007) Eur J Med Chem 42:125
2. Horley NJ, Beresford KJ, Chawla T, McCann GJ, Ruparelia KC, Gatchie L, Sonawane VR, Williams IS, Tan HL, Joshi P, Bharate SS, Kumar V, Bharate BS, Chaudhuri B (2017) Eur J Med Chem 129:159
3. Robinson MW, Overmeyer JH, Young AM, Erhardt PW, Maltese WA (2012) J Med Chem 55:1940
4. Bhambra AS, Ruparelia KC, Tan HL, Tasdemir D, Burrell-Saward H, Yardley V, Beresford KJM, Arroo RR (2017) Eur J Med Chem 128:213
5. Kozmík V, Lhoták P, Odlerová Ž, Paleček J (1998) Collect Czech Chem Commun 63:698
6. Sahu NK, Balbhadra SS, Choudhary J, Kohli DV (2012) Curr Med Chem 19:209
7. Fua ZY, Jinb QH, Qua YL, Guana LP (2019) Bioorg Med Chem Lett 29:1909
8. Bhambra AS, Ruparelia KC, Tan HL, Tasdemir D, Burrell-Saward H, Yardley V, Beresford LJM, Arroo RRJ (2017) Eur J Med Chem 128:213
9. Chauhan SS, Singh AK, Meena S, Lohani M, Singh A, Arya RK, Cheruvu SH, Sarkar J, Gayen JR, Datta D, Chauhan, PMS (2014) Bioorg Med Chem Lett 24:2820
10. Robinson MW, Overmeyer JH, Young AM, Erhardt PW, Maltese WA (2012) J Med Chem 55:1940

11. Ciupa A, Paul A, Mahon MF, Wood PJ, Caggiano L (2013) *Med Chem Comm* 4:956
12. Blackburn C, Duffey MO, Gould AE, Kulkarni B, Liu JX, Menon S, Nagayoshi M, Vos TJ, Williams J (2010) *Bioorg Med Chem Lett* 20:4795
13. Kumar N, Chauhan A, Drabu S (2011) *Biomed Pharmacother* 65:375
14. Shringare SN, Chavan HV, Bhale PS, Dongare SB, Mule YB, Patil SB, Bandgar BP (2018) *Med Chem Res* 27:1226
15. Adib M, Rajai-Daryasarei S, Pashazadeh R, Jahani M, Amanlou M (2018) *Synlett* 29:1583
16. Krasovitsky BM, Afanasiadi LM (1997) *Preparative Chemistry Organic luminophores (in Russian)*. Kharkov, Folio, p 117
17. Liu XH, Cui P, Song BA, Bhadury PS, Zhu HL, Wang SF (2008) *Bioorg Med Chem* 16:4075
18. ElBordiny HS, El-Miligy MM, Kassab SE, Daabees H, Ali WAM, El-Hawash SAM (2018) *Eur J Med Chem* 145:594
19. Abdel-Latif NA, Sabry NM, Mohamed AM, Abdulla MM (2007) *Monatsh Chem* 138:715
20. Sondhi SM, Kumar S, Kumar N, Roy P (2012) *Med Chem Res* 21:3043
21. Sowmya PV, Poojary B, Revanasiddappa BC, Vijayakumar M, Nikil P, Kumar V (2017) *Res Chem Intermed* 43:7399
22. Lone IH, Khan KZ, Fozdar BI (2014) *Med Chem Res* 23:363
23. Oleshchuk AL, Karbainova AA, Krivoruchko TN, Shulgau ZT, Seilkhanov TM, Kulakov IV (2019) *Chem Heterocycl Compd* 55:47
24. Oleshchuk AL, Shulgau ZT, Seilkhanov TM, Vasilchenko AS, Talipov SA, Kulakov IV (2020) *Synlett* 31:165
25. Koveza VA, Kulakov IV, Shulgau ZT, Seilkhanov TM (2018) *Chem Heterocycl Compd* 54:1127
26. Kulakov IV, Oleshchuk AL, Koveza VA, Palamarchuk IV (2020) *Synth Commun* 50:2432

Table

Table 1 Yields of compounds 6-9

Comp.	Ar
		6, R =	7, R = H	8, R =	9, R = H
		Yield/%			
a		92	96	59	48
b		94	71	30	30
c		95	71	47	83
d		98	59	50	77
e		99	80	65	39

Figures

Figure 1

Starting 3-acetyl-5-nitropyridines 4, 5

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [GraphicalAbstract.png](#)
- [Scheme1.png](#)
- [Scheme2.png](#)
- [SupplementarydataMonatsheftefurChemie06.02.21.docx](#)