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Article

Iron(III) phthalocyanine chloride-catalyzed oxidation–aromatization of α,β -unsaturated ketones with hydrazine hydrate: Synthesis of 3,5-disubstituted 1*H*-pyrazoles

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ABSTRACT

We have developed an iron(III) phthalocyanine chloride-catalyzed oxidation–aromatization of α,β -unsaturated ketones with hydrazine hydrate. Various 3,5-disubstituted 1*H*-pyrazoles were obtained in good to excellent yields. This method offers several advantages, including room-temperature conditions, short reaction time, high yields, simple work-up procedure, and use of air as an oxidant. The catalyst can be recovered and reused five times without loss of activity.

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1. Introduction

Nitrogen heterocycles, which are widely known, are important scaffolds in many biological molecules and pharmaceutical products. Pyrazole derivatives have been extensively used as the core structures of biologically active compounds, e.g., anti-inflammatory [1], antitumor [2], antibacterial, [3] and analgesic [4] compounds. They are also vital building blocks in many pharmaceuticals and natural products [5–7], e.g., celecoxib, mavacoxib, rimonabant, and MK-0893 [8] (a potent glucagon receptor inhibitor, Fig. 1).

Pyrazoles are also used as building blocks in synthetic organic chemistry, versatile, pluripotent ligands in coordination chemistry [9–13], and in transition-metal cross-coupling and

polymerization reactions [14–17]. These heterocycles have also attracted much interest because of their technological impacts, e.g., as ultraviolet stabilizers, photoprotecting agents, and energetic materials [18–22]. However, although some natural products containing pyrazole ring systems are known, they are not widespread [23–27].

Because of the importance of pyrazole derivatives, significant efforts have been devoted to developing new methods for their synthesis. Pyrazoles are generally synthesized by (1) reacting hydrazines with 1,3-dicarbonyl compounds/unsaturated hydrocarbons [28–34], (2) 1,3-dipolar cycloaddition of diazoalkanes with alkenes or alkynes [35–42], (3) reacting α,β -unsaturated carbonyl with hydrazines [43–46], and various other strategies [47–53]. However, these methods often re-

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Fig. 1. Structures of some pharmacologically important pyrazoles.

quire harsh reaction conditions (stoichiometric strong base, high reaction temperature), precious-metal catalysts, and stoichiometric and environmentally unfriendly oxidants. The introduction of simple and efficient methods for the synthesis of pyrazole derivatives under mild and environmentally benign conditions is therefore needed.

For many years, phthalocyanines (Pcs) have been extensively studied because of their macrocyclic 18π -electron conjugated ring systems [54]. Metallophthalocyanine complexes (MPcs), which are structurally similar to metal porphyrins, are easily accessible and more stable to degradation than porphyrins [55–57]; they have been extensively used to catalyze various organic reactions [58–65]. Because MPcs are insoluble in common organic solvents, they can be easily separated from reaction mixtures by filtration and reused without further treatment. MPcs therefore behave like heterogeneous catalysts, without having the inherent disadvantage of leaching commonly associated with heterogeneous and heterogenized homogeneous catalysts.

Here, we report an efficient and heterogeneous method for the synthesis of 3,5-disubstituted 1*H*-pyrazoles under mild reaction conditions, using iron(III) phthalocyanine chloride as a recyclable catalyst (Scheme 1). The experimental procedure is simple and clean and uses environmentally friendly solvents, and the products are obtained in high yields.

2. Experimental

2.1. Materials and characterization

All reagents were purchased from commercial suppliers and were used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded at room temperature with a 400 MHz spectrometer (^1H at 400 MHz, ^{13}C at 100 MHz), using DMSO- d_6 or CDCl_3 as the solvent with tetramethylsilane (TMS) as the internal standard; chemical shifts are quoted rela-

Scheme 1. Preparation of 3,5-disubstituted 1*H*-pyrazoles.

tive to TMS. High-resolution electrospray ionization mass spectrometry (HRMS (ESI)) was performed using a Bruker micrOTOF-QII instrument.

2.2. General procedure for synthesis of α,β -unsaturated ketones

An aqueous solution of sodium hydroxide (20%, 5 mL) was slowly added to a stirred solution of ketones (1 mmol) and aldehydes (1 mmol) in ethanol (5 mL). The mixture was stirred at room temperature for 1 h and then poured into water (20 mL). The obtained solid was removed by filtration and washed with ice water and ethanol to nature. The crude product was purified by recrystallization from ethanol.

2.3. General procedure for synthesis of 3,5-disubstituted 1*H*-pyrazoles from α,β -unsaturated ketones and hydrazine hydrate

α,β -Unsaturated ketones (0.5 mmol), hydrazine hydrate (1.5 mmol, 3 equiv.), iron(III) phthalocyanine chloride (5 mol%), K_2CO_3 (0.5 mmol, 1 equiv.), and ethanol (3.0 mL) were added successively to a dry round-bottomed flask. The mixture was stirred at room temperature for 3 h under air. When the reaction was complete, as indicated by thin-layer chromatography, the reaction mixture was washed with saturated NaCl aqueous solution (2×10 mL) and extracted with ethyl acetate (2×10 mL); the organic layers were combined. After drying with anhydrous Na_2SO_4 and evaporation under reduced pressure, the crude product was purified by column chromatography on silica gel using petroleum ether:ethyl acetate (4:1) as the eluent to afford 3,5-disubstituted 1*H*-pyrazoles.

2.4. Spectroscopic data of products

3,5-Diphenyl-1*H*-pyrazole (**2a**). White solid, yield: 89%; ^1H NMR (400 MHz, CDCl_3) δ : 7.71 (d, $J = 7.2$ Hz, 4H), 7.39–7.30 (m, 6H), 6.82 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 148.7, 131.2, 128.8, 128.1, 125.6, 100.0; HRMS (ESI) m/z calcd. for $\text{C}_{15}\text{H}_{12}\text{N}_2$ [$M + \text{H}$] $^+$: 221.1073, found: 221.1073.

3-Phenyl-5-(*p*-tolyl)-1*H*-pyrazole (**2b**). White solid, yield: 84%; ^1H NMR (400 MHz, DMSO- d_6) δ : 13.29 (s, 1H), 7.85–7.71 (m, 4H), 7.44 (d, $J = 6.8$ Hz, 2H), 7.27 (d, $J = 7.8$ Hz, 2H), 7.12 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 151.5, 143.1, 137.6, 129.8, 129.3, 128.2, 127.7, 126.0, 125.6, 125.6, 99.7, 21.3; HRMS (ESI) m/z calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_2$ [$M + \text{H}$] $^+$: 235.1230, found: 235.1238.

5-(4-Nitrophenyl)-3-phenyl-1*H*-pyrazole (**2c**). Yellow solid, yield: 84%; ^1H NMR (400 MHz, DMSO- d_6) δ : 13.72 (s, 1H), 8.29 (d, $J = 8.0$ Hz, 2H), 8.13 (d, $J = 8.0$ Hz, 2H), 7.82 (d, $J = 6.8$ Hz, 2H), 7.49–7.39 (m, 4H); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 149.8, 146.9, 144.5, 140.5, 129.5, 129.4, 128.9, 126.3, 125.7, 124.6,

101.5; HRMS (ESI) m/z calcd. for $C_{15}H_{11}N_3O_2$ $[M + H]^+$: 266.0924, found: 266.0917.

5-(3-Nitrophenyl)-3-phenyl-1*H*-pyrazole (**2d**). White solid, yield: 87%; 1H NMR (400 MHz, $CDCl_3$) δ : 8.60 (s, 1H), 8.16–8.11 (m, 2H), 7.64 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.43–7.36 (m, 3H), 6.92 (s, 1H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 149.8, 148.8, 144.4, 135.8, 131.8, 130.8, 129.5, 129.2, 128.8, 125.6, 122.5, 119.7, 100.9; HRMS (ESI) m/z calcd. for $C_{15}H_{11}N_3O_2$ $[M + H]^+$: 266.0924, found: 266.0923.

5-(2,4-Dichlorophenyl)-3-phenyl-1*H*-pyrazole (**2e**). White solid, yield: 86%; 1H NMR (400 MHz, $DMSO-d_6$) δ : 13.43 (s, 1H), 7.87 (d, J = 7.2 Hz, 2H), 7.46 (t, J = 7.4 Hz, 5H), 7.34 (t, J = 7.2 Hz, 1H), 7.21 (s, 1H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 148.4, 143.5, 133.5, 132.4, 131.9, 130.1, 129.408, 128.5, 128.0, 125.9, 125.7, 125.4, 103.7; HRMS (ESI) m/z calcd. for $C_{15}H_{10}Cl_2N_2$ $[M + H]^+$: 289.0294, found: 289.0302.

5-(4-Chlorophenyl)-3-phenyl-1*H*-pyrazole (**2f**). White solid, yield: 90%; 1H NMR (400 MHz, $DMSO-d_6$) δ : 13.44 (s, 1H), 7.85 (d, J = 19.7 Hz, 4H), 7.48 (s, 4H), 7.36 (s, 1H), 7.23 (s, 1H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 151.9, 150.7, 144.0, 142.7, 133.0, 132.4, 129.4, 129.2, 128.7, 128.1, 127.3, 125.6, 100.3; HRMS (ESI) m/z calcd. for $C_{15}H_{11}ClN_2$ $[M + H]^+$: 255.0684, found: 255.0696.

5-(3-Bromophenyl)-3-phenyl-1*H*-pyrazole (**2g**). White solid, yield: 91%; 1H NMR (400 MHz, $CDCl_3$) δ : 7.80 (s, 1H), 7.60 (dd, J = 10.2 Hz, 4.4 Hz, 3H), 7.37 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 7.32–7.25 (m, 3H), 7.13 (t, J = 7.9 Hz, 1H), 6.74 (s, 1H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 150.3, 144.1, 136.5, 131.3, 130.6, 129.5, 129.2, 128.7, 128.0, 125.6, 124.5, 122.7, 100.6; HRMS (ESI) m/z calcd. for $C_{15}H_{11}BrN_2$ $[M + H]^+$: 299.0178, found: 299.0156.

5-(4-Methoxyphenyl)-3-phenyl-1*H*-pyrazole (**2h**). White solid, yield: 93%; 1H NMR (400 MHz, $CDCl_3$) δ : 7.69 (d, J = 7.0 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.36–7.25 (m, 3H), 6.85 (d, J = 8.8 Hz, 2H), 6.71 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 159.6, 151.6, 143.8, 129.4, 129.1, 128.5, 127.9, 126.9, 125.5, 114.9, 99.2, 55.6; HRMS (ESI) m/z calcd. for $C_{16}H_{14}N_2O$ $[M + H]^+$: 251.1179, found: 251.1188.

3-Phenyl-5-(thiophen-2-yl)-1*H*-pyrazole (**2i**). White solid, yield: 83%; 1H NMR (400 MHz, $CDCl_3$) δ : 7.68–7.66 (m, 2H), 7.43 (t, J = 7.4 Hz, 2H), 7.40–7.32 (m, 2H), 7.29 (d, J = 5.0 Hz, 1H), 7.08 (dd, J = 5.0 Hz, 3.6 Hz, 1H), 6.75 (s, 1H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 147.4, 143.9, 137.4, 129.5, 129.1, 128.8, 128.1, 125.6, 125.1, 124.2, 99.9; HRMS (ESI) m/z calcd. for $C_{13}H_{10}N_2S$ $[M + H]^+$: 227.0637, found: 227.0646.

3,5-Di-*p*-tolyl-1*H*-pyrazole (**2j**). White solid, yield: 92%; 1H NMR (400 MHz, $DMSO-d_6$) δ : 13.23 (s, 1H), 7.72 (dd, J = 24.5 Hz, 6.2 Hz, 4H), 7.29–7.24 (m, 4H), 7.08 (s, 1H), 2.33 (s, 6H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 151.7, 143.7, 138.0, 137.0, 131.4, 130.0, 129.6, 127.1, 125.5, 99.4, 21.3; HRMS (ESI) m/z calcd. for $C_{17}H_{16}N_2$ $[M + H]^+$: 249.1386, found: 249.1394.

5-(2-Fluorophenyl)-3-(*p*-tolyl)-1*H*-pyrazole (**2k**). Pale yellow solid, yield: 88%; 1H NMR (400 MHz, $DMSO-d_6$) δ : 13.43 (d, J = 66.9 Hz, 1H), 8.07–7.64 (m, 3H), 7.51–7.21 (m, 5H), 7.02 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 159.4 (d, $^1J_{CF}$ = 257 Hz), 151.7, 146.2, 143.9, 137.8, 129.9, 128.5, 126.9, 125.6, 125.2, 121.7, 116.7 (d, $^2J_{CF}$ = 22 Hz), 102.6 (d, $^4J_{CF}$ = 22 Hz), 21.3; HRMS (ESI) m/z calcd. for $C_{16}H_{13}N_3F$ $[M + H]^+$: 253.1136, found:

253.1149.

5-(4-Chlorophenyl)-3-(*p*-tolyl)-1*H*-pyrazole (**2l**). White solid, yield: 95%; 1H NMR (400 MHz, $CDCl_3$) δ : 7.69 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 7.8 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.26–7.22 (m, 2H), 6.78 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 150.6, 144.2, 138.1, 133.1, 132.3, 130.0, 129.1, 127.2, 126.9, 125.5, 99.8, 21.3; HRMS (ESI) m/z calcd. for $C_{16}H_{13}N_2Cl$ $[M + H]^+$: 269.0840, found: 269.0840.

5-(4-Nitrophenyl)-3-(*p*-tolyl)-1*H*-pyrazole (**2m**). Pale yellow solid, yield: 89%; 1H NMR (400 MHz, $CDCl_3$) δ : 13.65 (s, 1H), 8.30 (d, J = 8.4 Hz, 2H), 8.13 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 7.6 Hz, 2H), 7.37 (s, 1H), 7.31 (d, J = 7.6 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 154.5, 151.6, 149.3, 145.3, 143.1, 134.8, 131.4, 131.0, 130.3, 129.4, 105.9, 26.1; HRMS (ESI) m/z calcd. for $C_{16}H_{13}N_3O_2$ $[M + H]^+$: 280.1081, found: 280.1082.

5-(Thiophen-2-yl)-3-(*p*-tolyl)-1*H*-pyrazole (**2n**). Pale yellow solid, yield: 85%; 1H NMR (400 MHz, $CDCl_3$) δ : 7.52 (d, J = 8.0 Hz, 2H), 7.24 (s, 1H), 7.20 (d, J = 4.8 Hz, 1H), 7.11 (d, J = 7.6 Hz, 2H), 6.99–6.97 (m, 1H), 6.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 138.2, 135.3, 131.3, 130.7, 129.5, 127.5, 127.1, 125.4, 124.5, 123.9, 99.5, 21.3; HRMS (ESI) m/z calcd. for $C_{14}H_{12}N_2S$ $[M + H]^+$: 241.0794, found: 241.0809.

5-(Furan-2-yl)-3-(*p*-tolyl)-1*H*-pyrazole (**2o**). White solid, yield: 81%; 1H NMR (400 MHz, $DMSO-d_6$) δ : 13.34 (s, 1H), 7.79–7.68 (m, 3H), 7.29–7.24 (m, 2H), 6.92 (s, 1H), 6.84–6.58 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 142.8, 137.8, 132.0, 130.7, 129.9, 129.1, 125.6, 125.1, 112.1, 106.3, 99.2, 21.3; HRMS (ESI) m/z calcd. for $C_{14}H_{13}N_3O$ $[M + H]^+$: 225.1022, found: 225.1034.

5-(4-Methoxyphenyl)-3-(*p*-tolyl)-1*H*-pyrazole (**2p**). White solid, yield: 86%; 1H NMR (400 MHz, $CDCl_3$) δ : 7.58 (dd, J = 16.6 Hz, 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.67 (s, 1H), 3.80 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 159.3, 148.6, 148.2, 137.4, 129.3, 128.7, 126.9, 125.5, 124.2, 114.0, 98.8, 55.1, 21.3; HRMS (ESI) m/z calcd. for $C_{17}H_{16}N_2O$ $[M + H]^+$: 265.1335, found: 265.1340.

3-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1*H*-pyrazole (**2q**). White solid, yield: 89%; 1H NMR (400 MHz, $DMSO-d_6$) δ : 13.30 (s, 1H), 7.81 (d, J = 44.0 Hz, 4H), 7.50 (s, 2H), 7.12 (s, 1H), 7.03 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 159.6, 150.5, 144.0, 133.1, 132.5, 129.2, 127.2, 127.0, 122.4, 114.7, 99.5, 55.6; HRMS (ESI) m/z calcd. for $C_{16}H_{13}N_2OCl$ $[M + H]^+$: 285.0789, found: 285.0782.

3,5-Bis(4-chlorophenyl)-1*H*-pyrazole (**2r**). White solid, yield: 91%; 1H NMR (400 MHz, $DMSO-d_6$) δ : 13.51 (s, 1H), 7.85 (d, J = 8.0 Hz, 4H), 7.53 (d, J = 8.0 Hz, 4H), 7.28 (s, 1H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 150.8, 142.9, 132.8, 129.4, 127.3, 100.6; HRMS (ESI) m/z calcd. for $C_{15}H_{10}N_2Cl_2$ $[M + H]^+$: 289.0294, found: 289.0294.

3-(Naphthalen-2-yl)-5-(*p*-tolyl)-1*H*-pyrazole (**2s**). White solid, yield: 87%; 1H NMR (400 MHz, $CDCl_3$) δ : 8.20 (s, 1H), 7.89–7.83 (m, 4H), 7.63 (d, J = 8.0 Hz, 2H), 7.49–7.48 (m, 2H), 7.23 (s, 2H), 6.95 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 151.6, 144.1, 138.0, 137.2, 133.6, 132.9, 131.7, 130.0, 128.6, 128.4, 128.1, 126.9, 126.3, 125.5, 124.2, 123.9, 100.0, 21.3; HRMS (ESI) m/z calcd. for $C_{20}H_{16}N_2$ $[M + H]^+$: 285.1386, found: 285.1392.

3-(*o*-Tolyl)-5-(*p*-tolyl)-1*H*-pyrazole (**2t**). White solid, yield: 85%; ^1H NMR (400 MHz, CDCl_3) δ : 7.62 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 7.6 Hz, 1H), 7.25–7.15 (m, 5H), 6.65 (s, 1H), 2.43 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ : 149.3, 147.1, 137.8, 136.1, 130.9, 130.8, 129.5, 129.2, 129.0, 128.4, 126.0, 125.6, 102.8, 21.3, 20.9; HRMS (ESI) m/z calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2$ [$\text{M} + \text{H}$] $^+$: 249.1386, found: 249.1388.

5-(4-Methoxyphenyl)-3-methyl-1*H*-pyrazole (**2u**). Yellow oil, yield: 82%; ^1H NMR (400 MHz, CDCl_3) δ : 7.62 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.27 (s, 1H), 3.82 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (400 MHz, CDCl_3) δ : 159.5, 149.4, 143.4, 126.9, 125.0, 114.1, 101.6, 55.3, 11.8; HRMS (ESI) m/z calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$ [$\text{M} + \text{H}$] $^+$: 189.1022, found: 189.1026.

3-Hydrazinyl-1,3-diphenylpropan-1-one (**1**). Yellow oil; ^1H NMR (400 MHz, CDCl_3) δ : 7.99–7.92 (m, 2H), 7.58 (m, 1H), 7.50–7.42 (m, 5H), 7.40–7.36 (m, 3H), 7.32–7.30 (m, 1H), 5.35 (t, J = 6.0 Hz, 1H), 3.38 (d, J = 1.2 Hz, 1H), 3.37 (s, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ : 200.2, 143.0, 136.6, 133.7, 128.7, 128.6, 128.2, 127.7, 125.8, 70.1, 47.4; HRMS (ESI) m/z calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$ [$\text{M} + \text{H}$] $^+$: 241.1335, found: 241.1338.

3. Results and discussion

The optimum reaction conditions were determined using the reaction of chalcone (**1a**) with hydrazine hydrate as a model. A series of experiments were performed to study the effects of various reaction parameters such as the catalyst, solvent, additives, and temperature; the results are summarized in Ta-

Table 1

Optimization of reaction conditions for synthesis of 3,5-disubstituted 1*H*-pyrazole **2a**.

Entry	Catalyst	Solvent	Base	Yield ^a (%)
1	—	EtOH	—	18
2	$\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$	EtOH	—	22
3	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	EtOH	—	25
4	Fe(III)Cl-Pc	EtOH	—	43
5	Fe_2O_3	EtOH	—	31
6	$\text{Fe(NO}_3)_3 \cdot 9\text{H}_2\text{O}$	EtOH	—	22
7	Fe(III)Cl-Pc	EtOH	K_2CO_3	93
8	Fe(III)Cl-Pc	EtOH	NaOH	80
9	Fe(III)Cl-Pc	EtOH	K_3PO_4	82
10	Fe(III)Cl-Pc	EtOH	Et_3N	54
11	Fe(III)Cl-Pc	Dioxane	K_2CO_3	75
12	Fe(III)Cl-Pc	THF	K_2CO_3	58
13	Fe(III)Cl-Pc	CH_3CN	K_2CO_3	33
14 ^b	Fe(III)Cl-Pc	EtOH	K_2CO_3	90
15 ^{b,c}	Fe(III)Cl-Pc	EtOH	K_2CO_3	71
16 ^{b,d}	Fe(III)Cl-Pc	EtOH	K_2CO_3	48
17 ^{b,e}	Fe(III)Cl-Pc	EtOH	K_2CO_3	87
18 ^{b,f}	Fe(III)Cl-Pc	EtOH	K_2CO_3	0

Reaction conditions: **1a** (0.5 mmol), hydrazine hydrate (1.5 mmol), catalyst (5 mol%), solvent (3.0 mL), additive (1.0 equiv.), under an air atmosphere, at refluxing temperature for 3 h.

^a Isolated yield. ^b Room temperature. ^c Hydrazine hydrate (1.0 mmol).

^d Hydrazine hydrate (0.75 mmol). ^e Catalyst (10 mol%).

^f Under nitrogen atmosphere.

ble 1. Initially, the reaction of chalcone (**1a**) with hydrazine hydrate was performed in the absence of an iron catalyst in ethanol at reflux temperature for 3 h in air. The desired product **2a** was obtained in only 18% yield (Table 1, entry 1). When 5 mol% Fe(III)Cl-Pc was added, the yield improved to 43% (Table 1, entry 2). Next, we screened various iron catalysts using air as the oxidant in the model reaction (Table 1, entries 2–6). The highest yield of the desired product was obtained using Fe(III)Cl-Pc (Table 1, entry 2) and was therefore used for further studies. The addition of K_2CO_3 (1.0 equiv.) to this system substantially improved the product yield to 93% (Table 1, entry 7). It is suggested that the base assisted the transformation by serving as a proton shuttle [46]. Other additives, namely NaOH , K_3PO_4 , and Et_3N , were also screened, but K_2CO_3 was found to be the most suitable (Table 1, entries 7–10). Other solvents, namely 1,4-dioxane, tetrahydrofuran (THF) and CH_3CN , were used instead of ethanol under these conditions; ethanol was the best solvent (Table 1, entries 11–13). An excellent yield was obtained even at room temperature (Table 1, entry 14). Lowering the amount of hydrazine hydrate to 2.0 equiv. significantly affected the reaction outcome, affording **2a** in 71% yield (Table 1, entry 15); however, a further reduction to 1.5 equiv. of hydrazine hydrate gave **2a** in only 48% yield (Table 1, entry 16). Increasing the amount of Fe(III)Cl-Pc did not improve the yield (Table 1, entry 17). The reaction was also performed under nitrogen; the desired product was not formed, indicating that oxygen is necessary for this reaction (Table 1, entry 18). Based on all these experiments, the optimum reaction conditions were identified as 5 mol% Fe(III)Cl-Pc and K_2CO_3 (1 equiv.) in ethanol at room temperature for 3 h.

The substrate scope was investigated under the optimized conditions, and the generality of the reaction was examined using diversely substituted α,β -unsaturated ketones and hydrazine hydrate; the corresponding 3,5-disubstituted 1*H*-pyrazoles were obtained in reasonably high yields. The results are summarized in Table 2. The reactions went smoothly using α,β -unsaturated ketones with various aromatic substituents. The presence of electron-withdrawing or -donating groups at the *ortho*, *meta*, or *para* positions of the benzene rings of various α,β -unsaturated ketones had no significant impact on the reaction, and the ketones were conveniently transformed to their corresponding 3,5-disubstituted 1*H*-pyrazoles in excellent yields.

After the reaction was complete, the catalyst was separated from the reaction mixture by filtration and reused in subsequent experiments (up to four cycles). The data in Table 3 show that the product yields were comparable to those obtained with the fresh catalyst, indicating that the catalyst does not lose its activity and can be recycled without further treatment.

We investigated the mechanism of the reaction of α,β -unsaturated ketones with hydrazine hydrate. We performed the reaction under nitrogen (Table 1, entry 18). The target product, **2a**, was not detected, but a new compound, namely intermediate **I**, was isolated. ^1H and ^{13}C NMR spectroscopies, and HRMS (ESI) showed that **I** is formed by Michael addition of chalcone with hydrazine hydrate. Next, we added

Table 2

Reaction scope and versatility.

Entry	Product	Yield ^a (%)	Entry	Product	Yield ^a (%)
1		89	12		95
2		84	13		89
3		84	14		85
4		87	15		81
5		86	16		86
6		90	17		89
7		91	18		91
8		93	19		87
9		83	20		85
10		92	21		82
11		88			

Reaction conditions: **1** (0.5 mmol), hydrazine hydrate (1.5 mmol), catalyst (5 mol%), ethanol (3.0 mL), K₂CO₃ (1.0 equiv.), room temperature, under an air atmosphere, 3 h. ^a Isolated yield.

intermediate **I** to the reaction mixture under general conditions; a high yield of **2a** was obtained (Scheme 2).

The mechanism shown in Scheme 3 is proposed based on our experimental observations and literature reports [66–69]. First, the chalcone reacts with hydrazine hydrate via a Michael addition to form intermediate **I**, followed by dehydration ring

closure to give pyrazoline **II**. Catalyst **A** combines with oxygen to form complex **B**. In the next step, complex **B** combines with another catalyst, **1**, followed by oxidative cleavage to give **C**. Finally, pyrazoline oxidation by compound **C** forms product **2a**, and catalyst **A** is regenerated by reductive elimination of a water molecule, to close the catalytic cycle.

Table 3

Results of reusability of iron(III) phthalocyanine chloride.

$\text{Ph}-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{Ph} + \text{N}_2\text{H}_4\cdot\text{H}_2\text{O} \xrightarrow[\text{EtOH, rt, 3 h, air}]{\text{Fe(III)Cl-Pc, K}_2\text{CO}_3} \text{Ph}-\text{C}(\text{N}=\text{NH})=\text{CH}-\text{Ph}$		
	1a	2a
Entry	Catalyst (mol%)	Isolated yield (%)
1	5	90
2	Cycle 1	89
3	Cycle 2	91
4	Cycle 3	89
5	Cycle 4	91

Reaction conditions: **1a** (0.5 mmol), ethanol (3.0 mL), K₂CO₃ (1.0 equiv.), room temperature, under an air atmosphere, 3 h. **Scheme 2.** Control experiment. **Scheme 3.** Proposed mechanism.

4. Conclusions

We have developed a simple, highly efficient, and environmentally friendly method for the synthesis of 3,5-disubstituted 1H-pyrazoles from α,β -unsaturated ketones and hydrazine hydrate in ethanol at room temperature, using iron(III) phthalocyanine chloride as an inexpensive, recyclable catalyst. Air is used as the oxidant, which makes the transformation practical and economical. The reaction system tolerates various functional groups and gives the desired product in excellent yields. This reaction has potential applications in the large-scale synthesis of 3,5-disubstituted 1H-pyrazoles.

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Graphical Abstract

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Iron(III) phthalocyanine chloride-catalyzed oxidation–aromatization of α,β -unsaturated ketones with hydrazine hydrate: Synthesis of 3,5-disubstituted 1*H*-pyrazolesJunlong Zhao*, Jun Qiu, Xiaofeng Gou, Chengwen Hua, Bang Chen
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Iron(III) phthalocyanine chloride-catalyzed oxidation–aromatization of α,β -unsaturated ketones with hydrazine hydrate was achieved, to give 3,5-disubstituted 1*H*-pyrazoles under mild conditions. The catalyst was recycled five times without loss of activity.

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氯化酞菁铁(III)催化 α,β -不饱和酮与水合肼氧化芳构化合成3,5-二取代1*H*吡唑

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摘要: 吡唑是含有两个相邻氮原子的五元杂环化合物, 因其广泛而优良的生物活性而备受化学家关注. 在过去几十年中, 药物学和农药学领域对吡唑类衍生物进行了广泛研究. 据文献报道, 吡唑类衍生物具有镇痛、杀菌、消炎、抗抑郁、抗病毒、抗癌、减肥、降脂、降压和降糖等生物活性. 不仅如此, 吡唑化合物在有机化学中也非常有用, 作为合成构件, 在配位化学中被用作多功能配体, 也在过渡金属交叉偶联反应和聚合反应中有所应用. 近几年研究发现, 吡唑类衍生物还可应用于紫外线稳定剂、含能材料和智能材料等领域. 因此, 探索简便高效的方法合成吡唑类化合物成为研究热点. 目前合成吡唑环的方法很多, 但多存在溶剂不环保、催化剂毒性大费用高、反应条件苛刻及产率低等缺点.

酞菁是一类具有18电子共轭二维平面芳香体系的大环化合物, 与天然卟啉的结构极其相似. 二者都易于利用光能进行

光化学反应, 环内有4个氮原子易与金属原子或离子配位形成金属配合物. 研究表明, 金属卟啉常作为氧化酶的活性位点而广泛存在于天然体系中, 充当氧化还原反应的催化剂. 因此, 作为其类似物, 金属酞菁被用作反应体系催化剂的研究成为热门. 此外, 金属酞菁具有高的热和化学稳定性, 易于制备, 无毒无味, 可根据反应进行修饰改性等特点, 非常适合用作催化剂.

考虑到金属酞菁在催化氧化反应上的良好效果, 本文将其应用于催化 α,β -不饱和酮与水合肼氧化芳构化反应. 选用查尔酮与水合肼作为模板底物对反应条件进行优化. 实验发现, 使用氯化酞菁铁配合物作催化剂时, 在碱存在下, 室温下反应即可高效转化为3,5-二取代1*H*吡唑. 在获得的最佳反应条件下拓展了底物范围, 发现无论芳香环上的取代基是给电子基团还是吸电子基团, 均能顺利地以较高收率得到相应吡唑衍生物. 此外, 由于氯化酞菁铁在乙醇中并不溶解, 因此进行了催化剂回收套用实验. 反应完成后, 将催化剂过滤并用少量乙醇洗涤, 然后以查尔酮与水合肼为反应模板进行催化剂循环实验, 发现催化剂回收使用4次后, 其催化活性并未降低. 最后, 对该反应机理进行了探究, 在氮气气氛中得到并分离出了反应中间体. 在确定了中间体结构后, 将其在优化的反应条件下进行反应, 也顺利得到了吡唑化合物. 结合文献提出了可能的反应机理, 即 α,β -不饱和酮先与水合肼发生迈克尔加成, 然后关环得到吡唑啉化合物, 再经由氯化酞菁铁活化空气中氧分子氧化下, 得到最终的3,5-二取代1*H*吡唑化合物.

总而言之, 本文发展了一例氯化酞菁铁催化 α,β -不饱和酮与水合肼的氧化芳构化反应, 以较高收率实现了3,5-二取代吡唑化合物的合成. 该方法具有反应条件温和、反应时间短、可循环使用5次、操作简易和利用空气作为氧化剂等优点.

关键词: 氯化酞菁铁; 芳构化; 吡唑; 迈克尔加成; 可循环催化剂; 绿色化学

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