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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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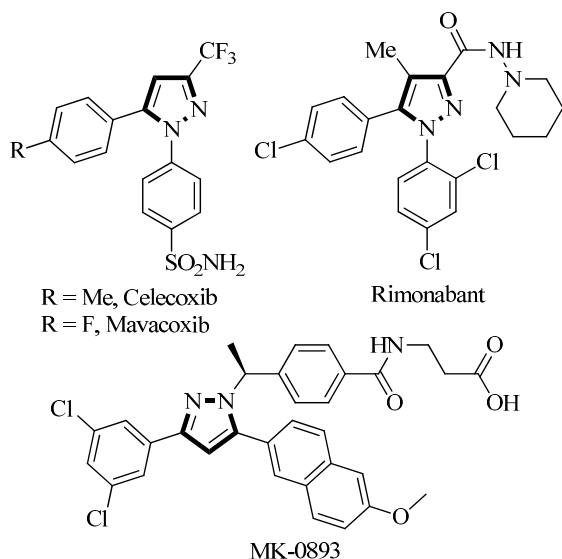


Fig. 1. Structures of some pharmacologically important pyrazoles.

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.

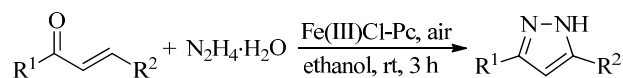
For many years, phthalocyanines (Pcs) have been extensively studied because of their macrocyclic 18π -electron conjugated ring systems [54]. Metallophthalocyanine complexes (MPcs), which are structurally similar to metal porphyrins, are easily accessible and more stable to degradation than porphyrins [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 $\text{C}_{15}\text{H}_{12}\text{N}_2$ [$\text{M} + \text{H}$] $^+$: 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 $\text{C}_{16}\text{H}_{14}\text{N}_2$ [$\text{M} + \text{H}$] $^+$: 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,

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