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Communication

# A highly efficient heterogeneous palladium-catalyzed cascade three-component reaction of acid chlorides, terminal alkynes and hydrazines leading to pyrazoles

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ABSTRACT

In the presence of 0.5 mol% of 3-(2-aminoethylamino)propyl-functionalized MCM-41-immobilized palladium(II) complex [MCM-41-2N–Pd($OAc)_2$] and 1.0 mol% of CuI, acid chlorides were coupled with terminal alkynes in $Et_3N$ at 50 °C to give α,β-unsaturated ynones, which were converted *in situ* into pyrazoles by the cycloaddition of hydrazines at room temperature with acetonitrile as cosolvent. The cascade reactions generated a variety of pyrazole derivatives in moderate to good yields, and this heterogeneous palladium catalyst exhibited higher catalytic activity than $PdCl_2(PPh_3)_2$ and could be recovered and reused for at least 10 consecutive trials without any decreases in activity.

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## 1. Introduction

Pyrazoles and its derivatives are very important N-heterocyclic compounds since pyrazole scaffold is present in a plethora of biological relevant molecules displaying a variety of pharmaceutical properties [1–5] and also useful synthetic building blocks and metal ligands in organic chemistry [6–12]. Therefore, considerable effort has been made in the development of new pyrazole structures and new methods for their constructions [13–15]. The traditional methods for the synthesis of pyrazoles include the cyclization of 1,3-diketones with hydrazines [16,17], 1,3-dipolar cycloaddition of diazoalkanes with alkynes [18] and the reaction of α,β-unsaturated ketones with hydrazines [19]. Very recently, rhodium- or phosphine-catalyzed synthesis of pyrazole derivatives has also been reported [20–22].

Tandem reactions have emerged as powerful tools to meet the demands of modern organic synthesis due to the synthetic efficiency, molecular diversity, low production costs, etc [23–25]. Recently, tandem reactions have been widely applied to construct interesting heterocyclic compounds, a large family of the natural products with wide-ranging utility for drug candidates and fine chemicals [26,27]. Of these heterocycles, one-pot construction of pyrazole derivatives has been developed based on some intermediates generated *in situ* including 1,3-diketones [28], diazo compounds [18] and ynones [29–31]. For example, Jiang et al. described one-pot three-component synthesis of pyrazoles through a tandem coupling-cyclocondensation sequence of acid chlorides with terminal alkynes and hydrazines [30]. Unfortunately, some of the reagents used in these tandem reactions are toxic, sensitive to air and moisture, difficult to obtain and expensive. Therefore, one-pot synthesis of pyrazole derivatives starting from simple, cheap, safe and easily available materials via tandem reactions would be more facile and efficient.

α,β-Unsaturated ynones are usually prepared by the cross-coupling of acid chlorides with terminal alkynes in the presence of $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$ under mild conditions with high yields [32–34]. However, industrial applications of homogeneous palladium complexes remain a challenge because they are expensive, cannot be recycled, and difficult to separate from the product mixture, which is a particularly significant drawback for their application in the pharmaceutical industry. In contrast, heterogeneous catalysts can be easily separated from the reaction mixture by simple filtration and reused in successive reactions provided

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that the active sites have not become deactivated. Heterogeneous catalysis also helps to minimize wastes derived from reaction workup, contributing to the development of green chemical processes [35]. Therefore, the development of a stable heterogeneous palladium catalyst that allows for highly efficient synthesis of ynones from a wide range of substrates (acid chlorides and terminal alkynes) is worthwhile.

The discovery of mesoporous material MCM-41 has given an enormous stimulus to research in heterogeneous catalysis and provided a new possible candidate for a solid support for immobilizing homogeneous catalysts [36–38]. The hexagonally-ordered material MCM-41 has a regular pore diameter of *ca*.5 nm and a specific surface area >700 $m^2\ g^{-1}$ and rich silanol groups in the inner walls [39]. To date, some functionalized MCM-41-immobilized palladium, rhodium, and molybdenum complexes have been prepared and successfully used in organic reactions [40–47]. Recently, we reported the preparation of 3-(2-aminoethylamino)propyl-functionalized MCM-41-immobilized palladium(II) complex [MCM-41-2N–$Pd(OAc)_2$] and found that it is highly efficient heterogeneous palladium catalyst for the Suzuki–Miyaura reaction of aryl bromides with arylboronic acids [48]. In continuing our efforts to develop greener synthetic pathways for organic transformations, herein we wish to report a highly efficient and practical one-pot three-component procedure for the construction of pyrazoles via a tandem coupling-cyclocondensation reaction of acid chlorides with terminal alkynes and hydrazines in the presence of MCM-41-2N–$Pd(OAc)_2$ complex and CuI (Scheme 1).

## 2. Experimental

### 2.1. General remarks

All chemicals were reagent grade and used as purchased, unless otherwise noted. The MCM-41-2N–$Pd(OAc)_2$ complex was prepared according to our previous procedure [48], the palladium content was determined to be 0.26 mmol $g^{-1}$. All reactions were performed in dried solvent under an inert atmosphere of argon. All products were characterized by comparison of their spectra and physical data with authentic samples. IR spectra were determined on a Perkin–Elmer 683 instrument. $^1$H NMR spectra (400 MHz) were recorded on a Bruker Avance 400 MHz spectrometer with TMS as an internal standard in $CDCl_3$ as solvent. $^{13}$C NMR spectra (100 MHz) were recorded on a Bruker Avance 400 MHz spectrometer in $CDCl_3$ as solvent.

### 2.2. General procedure for the synthesis of pyrazole derivatives

To a 25 mL round-bottomed flask, MCM-41-2N–$Pd(OAc)_2$ (19 mg, 0.005 mmol), CuI (2 mg, 0.01 mmol), acid chloride (1.3 mmol), terminal alkyne (1.0 mmol) and $Et_3N$ (3 mL) were added under argon. The mixture was stirred at 50 °C for 2 h and cooled to room temperature. Then hydrazine (3.0 mmol) and MeCN (2 mL) were added and the reaction mixture was stirred at room temperature for an additional 16 h. The reaction mixture was diluted with dichloromethane (20 mL), and filtered. The MCM-41-2N–$Pd(OAc)_2$ complex was washed with ethanol (2 × 5 mL) and diethyl ether (2 × 5 mL) and reused in the next run. The filtrate was washed with water (2 × 5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1 to 2:1) to provide the desired product.

#### 2.2.1. 3,5-Diphenyl-1H-pyrazole, **4a** [49]

White solid. IR (KBr): $\nu_{max}/cm^{-1}$ 3010, 2922, 1635, 1496, 1462, 975, 753, 688. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 7.74 (d, $J$ = 7.2 Hz, 4H), 7.43 (t, $J$ = 7.2 Hz, 4H), 7.36 (t, $J$ = 7.2 Hz, 2H), 6.89 (br, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 148.8, 131.3, 128.8, 128.2, 125.6, 100.1.

#### 2.2.2. 5-Phenyl-3-(p-tolyl)-1H-pyrazole, **4b** [49]

White solid. IR (KBr): $\nu_{max}/cm^{-1}$ 3185, 2921, 1639, 1508, 1458, 1140, 1068, 952. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 7.74 (d, $J$ = 7.2 Hz, 2H), 7.61 (d, $J$ = 7.6 Hz, 2H), 7.40 (t, $J$ = 7.4 Hz, 2H), 7.33 (t, $J$ = 7.2 Hz, 1H), 7.21 (d, $J$ = 8.0 Hz, 2H), 6.81 (s, 1H), 2.38 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 138.2, 131.6, 129.6, 129.0, 128.8, 128.3, 128.2, 126.4, 125.6, 125.5, 99.8, 21.3.

#### 2.2.3. 3-(4-Chlorophenyl)-5-phenyl-1H-pyrazole, **4c** [49]

White solid. IR (KBr): $\nu_{max}/cm^{-1}$ 3227, 2923, 1611, 1567, 1492, 1095, 1053, 967, 765. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 7.73–7.67 (m, 4H), 7.48–7.38 (m, 5H), 6.84 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 137.9, 133.7, 130.4, 129.0, 128.6, 126.9, 125.6, 125.5, 120.9, 100.3.

#### 2.2.4. 3-(4-Methoxyphenyl)-5-phenyl-1H-pyrazole, **4d** [49]

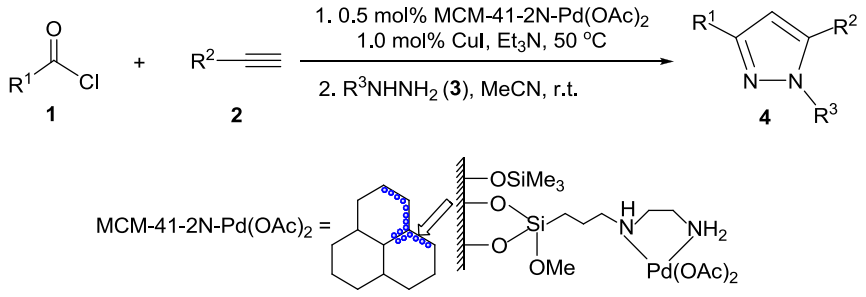
White solid. IR (KBr): $\nu_{max}/cm^{-1}$ 3135, 2917, 1619, 1509, 1460, 1255, 1036, 832, 766. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 7.74 (d, $J$ = 7.6 Hz, 2H), 7.65 (d, $J$ = 8.4 Hz, 2H), 7.43 (t, $J$ = 7.2 Hz, 2H), 7.35 (t, $J$ = 7.2 Hz, 1H), 6.96 (d, $J$ = 8.4 Hz, 2H), 6.80 (br, 1H), 3.85 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 159.8, 131.5, 128.9, 128.3, 126.9, 125.6, 123.9, 114.3, 99.9, 55.4.

#### 2.2.5. 3-(Furan-2-yl)-5-phenyl-1H-pyrazole, **4e** [49]

White solid. IR (KBr): $\nu_{max}/cm^{-1}$ 3393, 2943, 1614, 1492, 1460, 1115, 1026. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 7.72 (d, $J$ = 7.4 Hz, 2H), 7.45–7.34 (m, 4H), 6.77 (s, 1H), 6.66 (d, $J$ = 3.3 Hz, 1H), 6.48 (dd, $J$ = 3.3, 1.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ (ppm): 142.1, 128.9, 128.4, 125.6, 111.5, 106.4, 99.4.

#### 2.2.6. 5-Phenyl-3-(thiophen-2-yl)-1H-pyrazole, **4f** [49]

White solid. IR (KBr): $\nu_{max}/cm^{-1}$ 3094, 2948, 1645, 1458, 1054. $^1$H




**Scheme 1.** Synthesis of pyrazole derivative.

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