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One-pot three-component synthesis of pyrazoles through a tandem coupling-cyclocondensation sequence

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Abstract

An efficient and general one-pot procedure for the synthesis of pyrazoles from acid chlorides, terminal alkynes and hydrazines was described via a coupling and cyclocondensation sequence. Acid chlorides coupled with terminal alkynes to give α,β-unsaturated ynones, and in situ converted into pyrazoles by the cycloaddition of hydrazines. The desired pyrazoles were obtained with 15–85% isolated yields.

Tandem reactions refer to two reactions operating in succession in the same reaction vessel.[1] Nowadays, tandem reactions have emerged as powerful tools to meet the demands of modern organic chemistry due to the synthetic efficiency, molecular diversity, low production costs, etc.[2] Perhaps the most synthetically useful version of tandem processes is to construct interesting cyclic compounds, a large family of the natural products with significant biological activities, synthetic intermediates with wide-ranging utility for drug candidates and fine chemicals.[3] In this context, we have recently developed tandem sequences for the synthesis of polysubstituted tetrahydropyrimidines or 2,5-dihydro-1,3-oxazin-6-ones.[4] Encouraged by these results, we are interested in investigating similar tandem reactions to broaden N-containing heterocycles.

Pyrazoles and its derivatives, which are a large class of N-containing heterocycles, possess important biological and pharmaceutical activities,[5] and are also useful synthetic building blocks and metal ligands in organic chemistry.[6,7] Therefore, a number of synthetic methods have been developed for the construction of this skeleton, including the cyclization of 1,3-diketones with hydrazine,[8] 1,3-dipolar cycloaddition of diazoalkanes with alkynes,[9] the reaction of hydrazines with α,β-unsaturated ketones[10] and several other methods.[11] Recently, great interest is focused on one-pot construction of heteroaromatic compounds, such as oxadiazoles,[12] pyrimidines,[13] *N*-sulfonyl pyrroles, indoles and carbazoles,[14] furan,[15] ethyl 3-hydroxyquinoxaline-2-carboxylates,[16] pyrano- and furanoquinolines,[17] and pyrazoles. Of these heterocycles, one-pot synthesis of pyrazoles has been developed based on these intermediates generated in situ including 1,3-diketones,[8a] diazo compounds[9] and ynones.[18] Unfortunately, some of the reagents used in these cases are toxic, sensitive to air, difficult to obtain and dangerous.

Thereby, the construction of pyrazoles with simple, cheap, safe and easily available organic molecules as the components in one-pot would be more facile and efficient. Many methods exist for the synthesis of ynones from the coupling of acid chlorides and terminal alkynes.[19] Herein, we report an efficient and general one-pot three-component procedure for the construction of pyrazoles via a tandem coupling-cyclocondensation sequence. Ynones were synthesized directly from acid chlorides and terminal alkynes, and were then converted in situ into pyrazoles by the cycloaddition of hydrazines.

Our first attempt at this one-pot transformation employed 2-furancarbonyl chloride (**1a**) as a substrate coupled with phenylacetylene (**2a**) and hydrazine hydrate (**3a**) (Table 1). Using CuI as a catalyst, the desired product 3-furan-5-phenyl-1*H*-pyrazole (**4aaa**) was obtained in only 25% isolated yield. The use of $PdCl_2(PPh_3)_2$/CuI[19c] could

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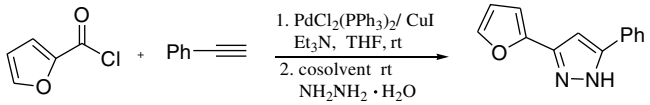
Table 1
Optimization of conditions for the synthesis of pyrazole **4a**[a]

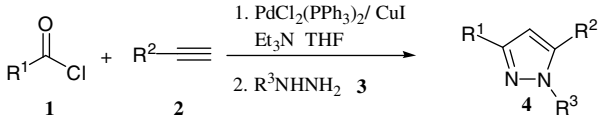


1a **2a** **3a** **4aaa**

Entry	Catalyst	NH_2NH_2 (mmol)	Cosolvent	Yield[b] (%)
1	CuI[c]	2	—	25
2	$PdCl_2(PPh_3)_2$/CuI	2	—	52
3	$PdCl_2(PPh_3)_2$/CuI	3	—	58
4	$PdCl_2(PPh_3)_2$/CuI	3	MeOH	67
5	$PdCl_2(PPh_3)_2$/CuI	3	EtOH	60
6	$PdCl_2(PPh_3)_2$/CuI	3	CH_3CN	73

[a] Reaction conditions: **1a** (1.5 mmol), **2a** (1.0 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol), CuI (0.03 mmol) and Et_3N (2.0 mmol) in THF (5 mL) at room temperature for 2 h. Then **3a** and consolvent (2 mL) were added at room temperature for 16 h.
[b] Isolated yields.
[c] The reaction was carried out with CuI (0.05 mmol) as a catalyst for 12 h.

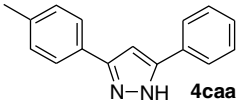
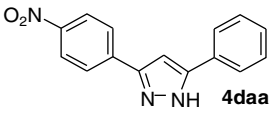
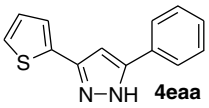
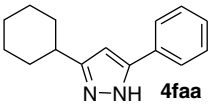
Table 2
One-pot synthesis of pyrazoles **4**[a]



1 **2** **4**

1	2	3	Product	Yield[b] (%)
1a	**2a**	**3a**	**4aaa**	73
1b	**2a**	**3a**	**4baa**	76
1b	**2b**	**3a**	**4bba**	15
1b	**2c**	**3a**	**4bca**	63
1b	**2d**	**3a**	**4bda**	41
1b	**2a**	**3b**	**4bab**	33[c]
1b	**2a**	**3c**	**4bac**	68

Table 2 (*continued*)

1	2	3	Product	Yield [b] (%)
1c	**2a**	**3a**	 **4caa**	68
1d	**2a**	**3a**	 **4daa**	52
1e	**2a**	**3a**	 **4eaa**	85
1f	**2a**	**3a**	 **4faa**	51

[a] Reaction conditions: **1** (1.5 mmol), **2** (1.0 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol), CuI (0.03 mmol) and Et_3N (2.0 mmol) in THF (5 mL) at room temperature for 2 h. Then, 3 (3.0 mmol) and CH_3CN (2 mL) were added at room temperature for 16 h.

[b] Isolated yields.

[c] 1 mL saturated aqueous Na_2CO_3 was added at the second step.

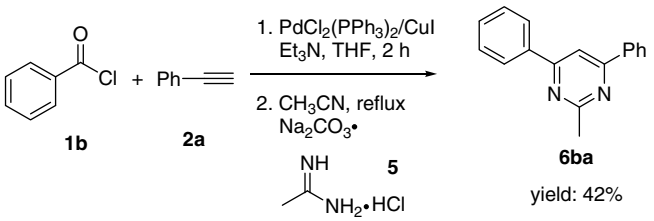
greatly increase the yield of **4aaa** (Table 1, entry 2). The amount of hydrazine hydrate (**3a**) affected the reaction to some extent. It was found that 3 equiv of 0.5 M hydrazine hydrate resulted in **4aaa** in 58% yield (Table 1, entry 3). In order to improve the conversion, a range of cosolvents were screened for the reaction of ynone with hydrazine, and acetonitrile was found to offer the highest yield (Table 1, entries 4–6).

The results in Table 1 revealed that 2-furancarbonyl chloride (**1a**) (1.5 mmol) smoothly reacted with phenylacetylene (**2a**) (1.0 mmol) in the presence of 1 mol % of Pd $(PPh_3)_2Cl_2$, 3 mol % of CuI and 2 mmol of triethylamine for 2 h in THF. Then, 3 mmol of 0.5 M hydrazine hydrate (**3a**) and acetonitrile (2 mL) were added and stirred for an additional 16 h, which gave pyrazole (**4aaa**) in 73% isolated yield (Table 1, entry 6).

Under the given optimized reaction conditions, we first conducted this one-pot tandem reaction of different terminal alkynes **2** with benzoyl chloride (**1b**) and hydrazine **3**.[20] As can be seen from Table 2, the corresponding pyrazoles **4baa** to **4bac** were obtained in 15–76% isolated yields. The use of aliphatic terminal alkyne (**2b**) led to **4bba** with only 15% yield. The reactivity of phenylhydrazine (**3b**) was much lower than that of hydrazine hydrate, and the addition of Na_2CO_3 could improve the yield of **4bab**. Subsequently, various acid chlorides **1** were investigated by coupling with **2a** and **3a**. The desired products **4caa** to **4faa** were obtained in 51–85% isolated yields.

The coupling of acid chloride and terminal alkyne could give ynone which may undergo dehydration reaction with hydrazine and subsequent 1,4-addition process to afford the desired pyrazole.

Encouraged by the successful one-pot procedure to the synthesis of the pyrazoles, we attempted this method to the one-pot three-component synthesis of pyrimidine (Scheme 1). It was found that pyrimidine **6ba** was obtained in 42% isolated yield.[21]



Scheme 1.

In conclusion, we have developed a convenient one-pot synthesis of pyrazoles via a three-component coupling-cyclocondensation sequence catalyzed by $Pd(PPh_3)_2Cl_2$/CuI. The protocol offers several advantages such as the use of commercially available materials, easy isolation, simple workup procedures and compatibility to various substrates making it an appealing alternative to construct heteroaromatic ring.

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20. *A typical procedure for the preparation of compound* **4**. To a 25 mL round-bottomed flask, $PdCl_2(PPh_3)_2$ (0.01 mmol), CuI (0.03 mmol), Et_3N (2.0 mmol) acid chloride **1** (1.5 mmol) and terminal alkyne **2** (1.0 mmol) were added in THF (5 mL) at room temperature for 2 h under N_2. Then hydrazine **3** (3.0 mmol) and CH_3CN (2 mL) were added and reacted for an additional 16 h. Then the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (2×20 mL). The combined organic layers were dried with sodium sulfate, concentrated to dryness and isolated by preparative TLC or column chromatography to obtain pure products **4**. ***3-Furan-2-yl-5-phenyl-1H-pyrazole*** (**4aaa**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.48 (q, $J = 1.6$ Hz, 1H), 6.67 (d, $J = 2.4$ Hz, 1H), 6.78 (s, 1H), 7.35–7.46 (m, 4H), 7.70–7.72 (m, 2H); IR (KBr) ν: 3392 br s, 2946, 2837, 1609, 1552, 1460, 1115, 1026 cm^{-1}; MS (70 eV) m/z (%): 210 ($M^{\cdot+}$, 100), 181, 152, 127, 105, 79, 77. ***3,5-Diphenyl-1H-pyrazole*** (**4baa**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.86 (s, 1H), 7.33–7.45 (m, 6H), 7.74 (d, $J = 7.2$ Hz, 4H); IR (KBr) ν: 3096, 2921, 1639, 1565, 1457, 1084 cm^{-1}; MS (70 eV) m/z (%): 220 ($M^{\cdot+}$, 100), 191, 165, 110, 77, 51, 32. ***5-Hexyl-3-phenyl-1H-pyrazole*** (**4bba**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.87 (t, $J = 6.8$ Hz, 3H), 1.27–1.37 (m, 6H), 1.63–1.68 (m, 2H), 2.65 (t, $J = 7.6$ Hz, 2H), 5.40–6.20 (br s, 1H), 6.36 (s, 1H), 7.29–7.40 (m, 3H); 7.70–7.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 150.0, 147.9, 132.7, 128.6, 127.7, 125.7, 100.9, 31.5, 29.2, 28.9, 26.4, 22.5, 14.0; IR (KBr) ν: 3249, 2928, 2855, 1642, 1569, 1458, 1264 cm^{-1}; MS (70 eV) m/z (%): 228 ($M^{\cdot+}$), 213, 199, 171, 158 (100), 145, 128, 104, 91; Anal. Calcd for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 79.15; H, 8.60; N, 12.32. ***3-Phenyl-5-p-tolyl-1H -pyrazole*** (**4bca**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.39 (s, 3H), 6.82 (s, 1H), 7.23–7.45 (m, 5H), 7.61 (d, $J = 8$ Hz, 2H); 7.74 (d, $J = 4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 147.0, 138.3, 129.6, 128.9, 128.2, 125.5, 99.9, 21.3; IR (KBr) ν: 2957, 2923, 1647, 1459, 1097 cm^{-1}; MS (70 eV) m/z (%): 234 ($M^{\cdot+}$, 100), 219, 205, 189, 178, 165, 152, 130, 117, 104, 89, 77,63, 51. ***5-Naphthalen-2-yl-3-phenyl-1H-pyrazole*** (**4bda**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.86 (s, 1H), 7.31–7.52 (m, 6H), 7.57 (d, $J = 6.4$ Hz, 1H), 7.76–7.89 (m, 4H), 8.28 (d, $J = 8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 149.3, 146.6, 133.8, 131.8, 131.3, 129.0, 128.8, 128.4, 128.1, 127.1, 126.7, 125.7, 125.5, 125.3, 103.9; IR (KBr) ν: 3190 br s, 3056, 2961, 1645, 1565, 1460, 1269, 1171 cm^{-1}; MS (70 eV) m/z (%): 270 ($M^{\cdot+}$, 100), 241, 215, 191, 167, 152, 135, 119, 104, 95, 77, 63, 51; Anal. Calcd for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36. Found: C, 84.38; H, 5.50; N, 10.53. ***1,3,5-Triphenyl-1H-pyrazole*** (**4bab**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.81 (s, 1H), 7.27–7.42 (m, 13H), 7.90 (dd, $J_1 = 7.2$ Hz, $J_2 = 1.2$ Hz, 2H); IR (KBr) ν: 3057, 2924, 1598, 1549, 1494, 1364 cm^{-1}; MS (70 eV) m/z (%): 296 ($M^{\cdot+}$, 100), 268, 217, 192, 180, 165, 147, 134, 116, 77, 64, 51, 32. ***2-(3,5-Diphenyl-1H-pyrazol-1-yl)ethanol*** (**4bac**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.03 (t, $J = 4.0$ Hz, 2H), 4.26 (t, $J = 4.0$ Hz, 2H), 6.63 (s, 1H), 7.25–7.50 (m, 8H), 7.83 (d, $J_1 = 8.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 151.0, 145.6, 132.9, 130.2, 129.0, 128.8, 128.7, 127.9, 125.6, 103.3, 62.2, 50.9; IR (KBr) ν: 3063, 2926, 1640, 1549, 1461, 1071 cm^{-1}; MS (70 eV) m/z (%): 264 ($M^{\cdot+}$), 233 (100), 220, 206, 191, 179, 165, 130, 117, 104, 91, 77, 57; Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.32; H, 6.14; N, 10.55. ***5-Phenyl-3-p-tolyl-1H-pyrazole*** (**4caa**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.38 (s, 3H), 6.81 (s, 1H), 7.22–7.44 (m, 4H), 7.59–7.74 (m, 5H); IR (KBr) ν: 3184 br s, 2922, 1651, 1540, 1506, 1400, 1295 cm^{-1}; MS (70 eV) m/z (%): 234 ($M^{\cdot+}$, 100), 219, 205, 189, 178, 165, 152, 130, 117, 104, 89, 77, 63, 51, 32. ***3-(4-Nitro-phenyl)-5-phenyl-1H-pyrazole*** (**4daa**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36–7.40 (t, $J = 8.0$ Hz, 4H), 7.81 (s, 2H), 8.11 (d, $J = 4.0$ Hz, 2H); 8.29 (d, $J = 8.0$ Hz, 2H), 13.7 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 146.9, 129.5, 128.9, 126.3, 125.6, 124.7, 101.6; IR (KBr) ν: 3190, 2920, 1644, 1515, 1457, 1330, 1299 cm^{-1}; MS (70 eV) m/z (%): 265 ($M^{\cdot+}$, 100), 249, 235, 219, 207, 191, 178, 165, 152, 139, 116, 104, 89, 77, 63, 51, 30. ***5-Phenyl-3-thiophen-2-yl-1H-pyrazole*** (**4eaa**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.68 (s, 1H), 6.99–7.01 (m, 1H), 7.21–7.34 (m, 5H), 7.64 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 145.4, 135.0, 130.3, 128.9, 128.4, 127.5, 125.6, 124.8, 124.1, 100.2; IR (KBr) ν: 3096,

2950, 2842, 1646, 1457, 1052 cm^{-1}; MS (70 eV) *m*/*z* (%): 226 ($M^{\cdot+}$, 100), 197, 171, 165, 113, 77, 40; Anal. Calcd for $C_{13}H_{10}N_2S$:C, 69.00; H, 4.45; N, 12.38. Found: C, 69.22; H, 4.28; N, 12.57. ***3-Cyclohexyl-5-phenyl-1H-pyrazole*** (**4faa**): ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.24–1.48 (m, 6H), 1.81–2.05 (m, 2H), 2.65–2.69 (m, 2H), 3.30–3.36 (m, 1H), 6.36 (s, 1H), 7.25–7.40 (m, 3H), 7.72–7.74 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 152.7, 150.0, 132.8, 128.7, 127.8, 125.6, 99.4, 35.9, 32.9, 26.1, 26.0; IR (KBr) *v*: 3007, 2927, 2854, 1647, 1568, 1459, 1029 cm^{-1}; MS (70 eV) *m*/*z* (%): 226 ($M^{\cdot+}$, 100), 211, 197, 185, 171, 158, 145, 128, 115, 104, 91, 77, 67, 55; Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.55; H, 8.28; N, 12.59.

21. *A typical procedure for the preparation of compound* **6ba**. To a 25 mL round-bottomed flask, $PdCl_2(PPh_3)_2$ (0.01 mmol), CuI (0.03 mmol), Et_3N (2.0 mmol), benzoyl chloride (1.5 mmol) and phenylacetylene (1.0 mmol) were added in THF (5 mL) at room temperature for 2 h under N_2. Then **5** (2.0 mmol), CH_3CN (2 mL) and Na_2CO_3 (2.5 mmol) were added and refluxed for 24 h. Then the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (2 × 20 m). The combined organic layers were dried with sodium sulfate, concentrated to dryness and isolated by preparative TLC to obtain pure products **6ba.** *2-Methyl-4,6-diphenylpyrimidine* (**6ba**): ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.86 (s, 3H), 7.50–7.52 (m, 6H), 7.88 (s, 1H), 8.10–8.13 (m, 4H); IR (KBr) *v*: 3061, 2955, 2924, 2853, 1574, 1532, 1459, 1368 cm^{-1}; MS (70 eV) *m*/*z* (%): 246 ($M^{\cdot+}$, 100), 236, 205, 195, 167, 152, 123, 102, 98, 76, 63, 51, 42.