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SYNTHESIS OF PYRAZOLES THROUGH COPPER-CATALYZED THREE-COMPONENT COUPLING OF ALDEHYDES, ALKYNES, AND *p*-TOLUENESULFONYLHYDRAZIDE

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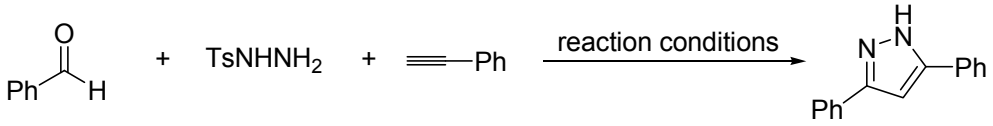
Abstract – A convenient one-pot synthesis of 3,5-disubstitued 1*H*-pyrazoles through copper-catalyzed three-component coupling of aldehydes, alkynes, and *p*-toluenesulfonylhydrazide has been developed. This method provides a flexible and rapid route to 3,5-disubstituted 1*H*-pyrazoles.

Substituted pyrazoles are important synthetic targets in the pharmaceutical industry because the pyrazole motif makes up the core structure of numerous biologically active compounds. Therefore, various approaches have been developed for their synthesis.[1,2] Two important methods are usually adopted: one is the reaction of reacting hydrazines with 1,3-dicarbonyl compounds, and the other is 1,3-dipolar cycloaddition of diazoalkanes or nitrilimines with olefins or alkynes.[1a,1c] However, the former often results in a mixture of regioisomers, while the latter has found only limited applications in pyrazole synthesis because 1,3-dipoles are often difficult to prepare and are potentially explosive. As a result, new approaches allowing for efficient assembly of different pyrazole skeletons with diverse substitution patterns are in high demand.

In recent years, three-component coupling reactions of an aldehyde, an alkyne and an amine, commonly called A^3-coupling, have received considerable attention due to their convenience in the organic synthesis.[3,4] Recently, Liu *et al*. described an efficient gold(III)-catalyzed multi-component reaction of heteroaryl aldehydes, amines and alkynes.[4a] This pioneer method allows for the facile synthesis of substituted aminoindolizines with high atom economy. Subsequently, in 2010, Gevorgyan and co-workers demonstrated a copper-catalyzed three-component coupling towards imidazoheterocycles.[4b] Fujii and Ohno also reported a gold-catalyzed three-component annulation for the dihydropyrazoles in 2012.[4c]

However, further development of three-component coupling reaction towards heterocycles is still an extremely attractive, yet challenging task. We herein wish to report an efficient three-component coupling reaction for the synthesis of pyrazoles from aldehydes, alkynes, and *p*-toluenesulfonylhydrazide.

Table 1. Screening of catalysts and solvents[a]



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

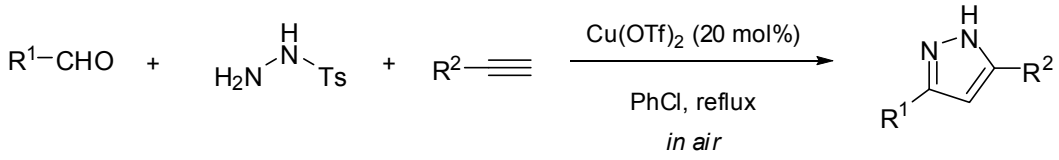
Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]
1	$FeCl_3$	MeCN	12	0
2	$ZnCl_2$	toluene	12	0
3	AgOTf	PhCl	24	38
4	$AgBF_4$	PhCl	24	33
5	AgOAc	PhCl	24	trace
6	**$Cu(OTf)_2$(20)**	**PhCl**	**3**	**60**
7	$Cu(OTf)_2$(10)	PhCl	15	45
8	CuCl	PhCl	24	trace
9	$Cu(OAc)_2$	PhCl	24	41
10	$Cu(OTf)_2$	$MeNO_2$	2	complex
11	$Cu(OTf)_2$	toluene	6	40
12	$InCl_3$	PhCl	24	0
13	$In(OTf)_3$	PhCl	24	0
14	$Zn(OTf)_2$	PhCl	24	complex
15	$Cu(OTf)_2$(10), CuCl(10)	PhCl	13	47

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.6 mmol), **3a** (1.5 mmol) and catalyst (20 mol%) in solvent (3 mL) at reflux for an appropriate time (Tf=triflyl).
[b] Isolated yields based on **1a**.

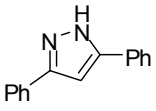
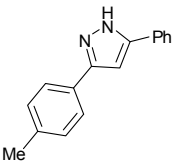
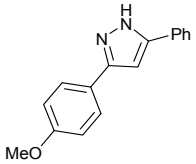
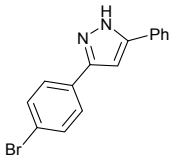
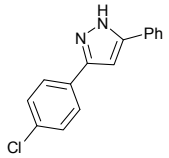
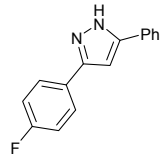
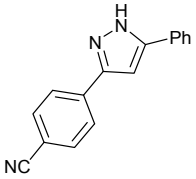
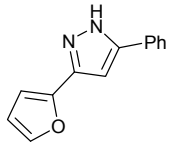
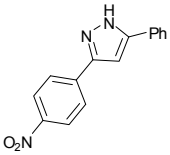
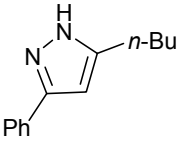
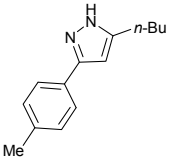
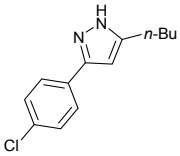
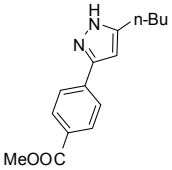
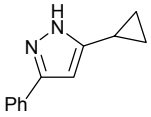
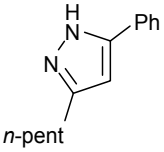
Our research began with the solvent and catalyst screening (Table 1). We attempted a range of metallic catalysts including Cu(I), Cu(II), Zn(II), In(III), Fe(III), and Ag(I). Notably, a low yield was obtained in the presence of both CuCl and $Cu(OTf)_2$ (Table 1, entry 15). In the work of Gevorgyan and co-workers,

the combination of CuCl and $Cu(OTf)_2$ worked very well.[4b] After careful screening, the optimal condition was determined as show in Table 1, entry 6, which using 20 mol% $Cu(OTf)_2$ as the catalyst in chlorobenzene at reflux, leading to the **4a** in 60% yield.

Table 2. Synthesis of 3,5-disustituted 1*H*-pyrazoles[a]



1 **2** **3** **4**

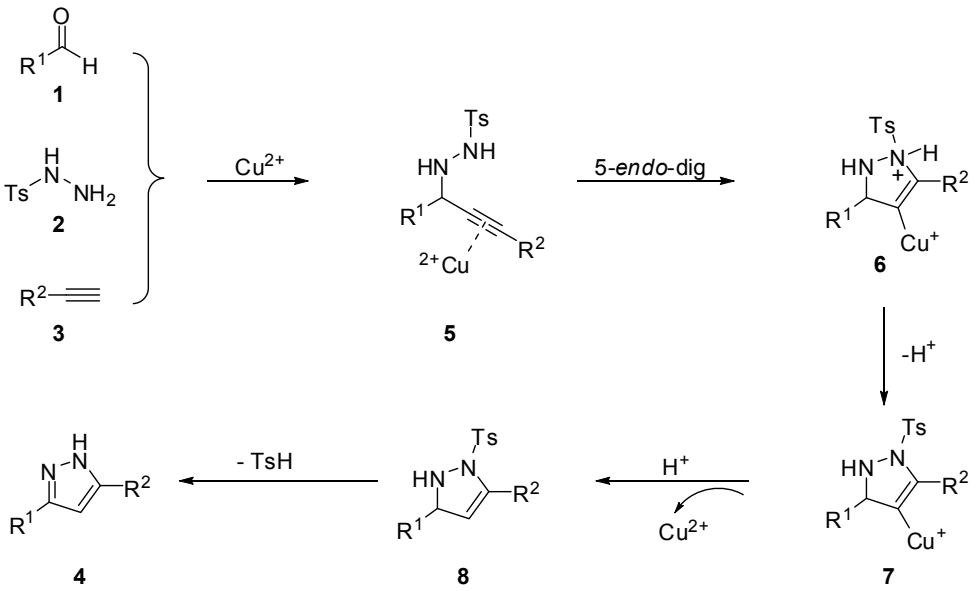
 **4a** - 3 h, 60% R^1 = Ph R^2 = Ph	 **4b** - 2 h, 61% R^1 = *p*-MePh R^2 = Ph	 **4c** - 2 h, 62% R^1 = *p*-MeOPh R^2 = Ph	 **4d** - 3h, 55% R^1 = *p*-BrPh R^2 = Ph
 **4e** - 1.5 h, 55% R^1 = *p*-ClPh R^2 = Ph	 **4f** - 1.5 h, 57% R^1 = *p*-FPh R^2 = Ph	 **4g** - 2 h, 32% R^1 = *p*-NCPh R^2 = Ph	 **4h** - 3.5 h, 30% R^1 = 2-furanyl R^2 = Ph
 **4i** - 1.1h, 38% R^1 = *p*-NO_2Ph R^2 = Ph	 **4j** - 6 h, 51%[b] R^1 = Ph R^2 = *n*-Bu	 **4k** - 5 h, 56%[b] R^1 = *p*-MePh R^2 = *n*-Bu	 **4l** - 7 h, 42%[b] R^1 = *p*-ClPh R^2 = *n*-Bu
 **4m** - 7.5 h, 35%[b] R^1 = *p*-MeOOCPh R^2 = *n*-Bu	 **4n** - 8.5 h, 45%[b] R^1 = Ph R^2 = cyclopropyl	 **4o** - 24 h, 0% R^1 = *n*-pent R^2 = Ph	

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), **3** (1.5 mmol) and $Cu(OTf)_2$ (20 mol%) in PhCl (3 mL) at reflux for an appropriate time. Isolated yields based on **1**.

[b] The reactions were performed in 25 mL sealed tube.

We next sought to evaluate the substrate scope of this three-component coupling reaction (Table 2). It was pleased to find that the reactions of aromatic aldehydes proceeded well, offering an easy access to 3,5-disubstituted 1*H*-pyrazoles with various substituents. In addition, a wide range of functional groups including F, Cl, Br, MeO, CN, NO_2 and COOMe could be well tolerated, leading to the products in moderate to good yields. In the examples of aromatic terminal alkynes (R^2 = aryl), both electron-donating and electron-withdrawing substituted aromatic aldehydes proceeded well (Table 2, **4b-4i**). On the other hand, relatively lower yields were obtained in the reactions of the aliphatic terminal alkyne (Table 2, **4j-4n**), possibly due to their decreasing acidity. It should be mentioned that the reaction of furanyl-substituted aldehyde also generated the pyrazole in 30% yield (Table 2, **4h**). We also investigate the reaction of aliphatic aldehyde, however, it was found that no corresponding pyrazole was produced (Table 2, **4o**).

As a working hypothesis, we proposed the following plausible mechanism (Scheme 1). First, a Cu(II)-catalyzed three-component coupling of aldehyde, *p*-toluenesulfonylhydrazide, and alkyne occurred to afford **5** via a Mannich-Grignard reaction.[3,5] Coordination of the triple bond in alkyne **5** to the copper catalyst enhanced the electrophilicity of the alkyne, and the subsequent nucleophilic attack of the nitrogen would produce the cation **6**. Cation **6** would undergo deprotonation to afford **7** which was followed by demetalation leading to **8**. Finally, pyrazoles **4** was afforded by the elimination of *p*-tolylsulfinic acid.



Scheme 1. Proposed mechanism

EXPERIMENTAL

Unless otherwise noted, all reagents were obtained commercially and used without further purification. All reaction mixtures were stirred with a magnetic bar in flame-dried glassware. Thin layer

chromatography (TLC) was performed on Huanghai pre-coated glass-backed TLC plates and visualized by UV lamp (254 nm). Column chromatography on silica gel (300-400 mesh) was carried out using Technical Grade 60-90 ^{o}C v/v petroleum ether (distillated prior to use) and Analytical Grade EtOAc (without further purification). Concentration under reduced pressure was performed by rotary evaporation. Purified compounds were further addressed under high vacuum (3-5 mmHg). Yields referred to chromatographically purified compounds. ^{1}H and ^{13}C spectra were recorded on a Bruker AV-400 spectrometer. Chemical shifts were reported in ppm. ^{1}H-NMR spectra were referenced to TMS in $CDCl_3$ (0 ppm) or DMSO-d_6 (2.50 ppm), and ^{13}C-NMR spectra were referenced to $CDCl_3$ (77.0 ppm) or DMSO-d_6 (39.5 ppm). All ^{13}C-NMR spectra were measured with complete proton decoupling. Peak multiplicities were designated by the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; brs, broad singlet and *J*, coupling constant in Hz. Melting points were measured on a Bűchi Melting Point B-540 Apparatus using open glass capillaries and are uncorrected. IR spectra were recorded on a Nicolet AVATER FTIR360 spectrometer as thin film. Absorptions were given in wavenumbers (cm^{-1}). MS measurements were performed on Bruker Reflex III mass spectrometer. Data were obtained via Ultra-high Resolution Hybrid Qh-Fourier Transform Mass Spectrometer (En Apex ultra 7.0 FT-MS) operated by Department of Chemistry, Xiamen University.

General procedure for preparation of 3,5-disubstitued 1*H*-pyrazoles 4.

To a flame-dried 5-mL flask or 25-mL sealed tube equipped with a magnetic bar, aldehyde **1** (0.5 mmol, 1.0 equiv.), *p*-toluenesulfonylhydrazide **2** (0.6 mmol, 1.2 equiv.), alkyne **3** (1.5 mmol, 3.0 equiv.), Cu $(OTf)_2$ (20 mmol%, 0.1 mmol), and chlorobenzene (3 mL) were added successively. The mixture was stirred at room temperature until the **2** was dissolved, then heated to reflux for an appropriate time, and monitored periodically by TLC. Upon completion, the product was purified by column chromatography on silica gel to afford **4**.

Spectroscopic data for the new compounds 4k and 4m.

5-Butyl-3-*p*-tolyl-1*H*-pyrazole (4k): Prepared according to the general procedure and the reaction was performed for 5 h. The product (**4k**) was purified by column chromatography on silica gel to afford a yellow oil in 56% yield. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.6 Hz), 1.30-1.37 (m, 2H), 1.59-1.63 (m, 2H), 2.36 (s, 3H), 2.59 (t, 2H, J = 7.6 Hz), 6.32 (s, 1H), 7.16 (d, 2H, J = 8.0 Hz), 7.62 (d, 2H, J = 8.0 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 13.7, 21.2, 22.3, 26.1, 31.3, 100.6, 125.6, 129.2, 137.4; **IR** (film): 3420, 3092, 1598, 1517 cm^{-1}; **HRMS**(ESI): calc. for $C_{14}H_{18}N_2$ $[M+H]^+$: *m/z* (%) = 215.1548; found: 215.1541.

Methyl 4-(5-butyl-1*H*-pyrazol-3-yl)benzoate (4m): Prepared according to the general procedure and the reaction was performed for 7.5h. The product (**4m**) was purified by column chromatography on silica gel to afford a white solid in 35% yield (mp 87-89 ^{o}C). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, J = 7.6 Hz), 1.28-1.33 (m, 2H), 1.55-1.63 (m, 2H), 2.59 (t, 2H, J = 7.6 Hz), 3.91 (s, 3H), 6.39 (s, 1H), 7.78 (d, 2H, J = 8.4 Hz), 8.00 (d, 2H, J = 8.4 Hz); **^{13}C-NMR** (100MHz, $CDCl_3$): δ 13.7, 22.2, 25.8, 31.2, 52.0, 101.5, 125.4, 129.0, 130.0, 137.3, 147.4, 149.5, 166.9; **IR** (film): 3322, 3002, 1772, 1604, 1095 cm^{-1}; **HRMS**(ESI): calc. for $C_{15}H_{18}N_2O_2$ $[M+H]^+$: *m/z* (%) = 259.1447; found: 259.1442.

See Supporting Information for the spectroscopic data and corresponding references for the known compounds.

ACKNOWLEDGEMENTS

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