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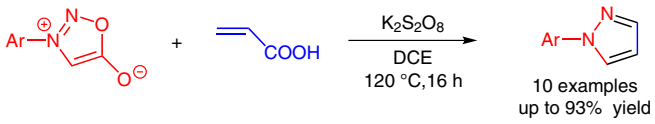
Facile Synthesis of 1-Arylpyrazoles

Yiwen Yang *[a]
Chunxiang Kuang *[b]

[a] College of Biological, Chemical Sciences, and Engineering, Jiaxing University, Jiahang Road 118, Jiaxing 314001, P. R. of China
yangyiwen@mail.zjxu.edu.cn
[b] Department of Chemistry, Tongji University, Siping Road 1239, Shanghai 200092, P. R. of China
kuangcx@tongji.edu.cn



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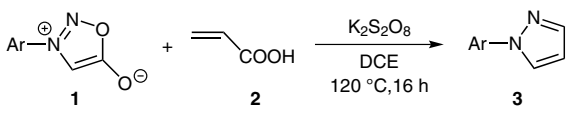
Abstract A convenient and transition-metal-free synthesis of 1-arylpyrazoles that involves the cycloaddition of 3-arylsydnones and acrylic acid is presented. The process proceeds smoothly to obtain the target products with moderate to high yields.

Key words pyrazoles, 1,3-dipolar cycloaddition, sydnones, acrylic acid, metal-free reactions

Pyrazoles belong to an important class of heterocyclic compounds with a wide range of pharmaceutical and biological activities, such as antiplatelet, antiallergenic,[1] anti-inflammatory, antimicrobial,[2] antifungal,[3] and anticancer.[4] 1-Arylpyrazoles, as an important branch of pyrazoles, have received considerable attention because of their prevalence in numerous agrochemicals and pharmaceuticals.[5] For example, arylpyrazoles can be used as key intermediates to prepare the potent and selective COX-2 inhibitor Celecoxib.[6] They are also key structural units in several leading agrochemicals, such as the insecticides chlorantraniliprole and fipronil.[7]

1-Arylpyrazoles can be synthesized through cross-coupling reaction,[8] condensation,[9] 1,5-dipolar cycloaddition,[10] and 1,3-dipolar cyclization.[11] Among these methods, the latter provides the most convenient synthetic route. However, the preparation of 1-arylpyrazoles through the 1,3-dipolar cycloaddition of sydnones with acetylene or acrylonitrile requires high temperature (170 °C) or excess acrylonitrile. Moreover, acetylene, which is a highly combustible gas, is difficult to manage. Therefore, the development of a practical synthetic route to prepare 1-arylpyrazoles is necessary.

In this paper, we report a convenient and transition-metal-free synthesis of a series of new 1-arylpyrazoles **3** with moderate to high yields. The 1,3-dipolar reaction of 3-arylsydnones with acrylic acid is illustrated in Scheme 1.

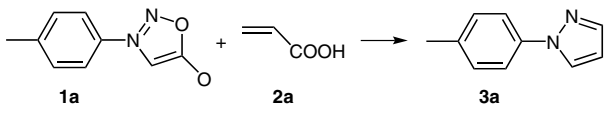


Scheme 1 Synthesis of 1-arylpyrazoles **3**

The reaction of *p*-tolylsydnone (**1a**) and acrylic acid (**2a**) using $K_2S_2O_8$ as oxidant in 1,2-dichloroethane was investigated to identify suitable reaction conditions (Table 1). The mixture was stirred in a sealed tube at 80 °C using an oil bath. After 16 hours, product **3a** was obtained in 51% yield (entry 1). The effects of different temperatures, solvents, and oxidants on the formation of **3a** were examined. At 100 and 120 °C, the yields increased to 62 and 90%, respectively (entries 2–3). When the temperature was decreased to 25 °C, the yield decreased to 5% (entry 4). When toluene, acetonitrile, dimethylformamide, or 1,4-dioxane was used as solvent, the yield decreased to 79, 72, 0, or 76%, respectively (entries 5–8).

The influence of other oxidants on the formation of **3a** was also tested. When $K_2S_2O_8$ was replaced with sublimed sulfur, benzoquinone, nitrobenzene, or O_2 (1 atm), the yield reduced to 63, 68, 60, or 43%, respectively (Table 1, entries 9–12). When no oxidant was used in the reaction, only 5% yield of **3a** was obtained (entry 13). At the end of the process, the optimum reaction conditions were determined to be a 1:2 mol ratio of **1a** to **2a**, $K_2S_2O_8$ oxidant (2.0 equiv), 1,2-dichloroethane solvent, 120 °C, and 16 hours under air atmosphere (entry 3).

Table 1 Screening for Optimal Reaction Conditions[a]



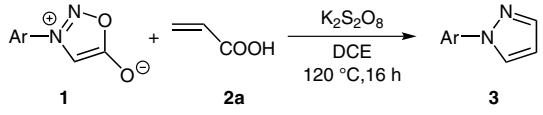
1a 2a 3a

Entry	Oxidant (2 equiv)	Solvent	Temp (°C)	Yield of **3a** (%)[b]
1	$K_2S_2O_8$	DCE	80	51
2	$K_2S_2O_8$	DCE	100	62
3	**$K_2S_2O_8$**	**DCE**	**120**	**90**
4	$K_2S_2O_8$	DCE	25	5
5	$K_2S_2O_8$	toluene	120	79
6	$K_2S_2O_8$	MeCN	120	72
7	$K_2S_2O_8$	DMF	120	0
8	$K_2S_2O_8$	1,4-dioxane	120	76
9	S	DCE	120	63
10	benzoquinone	DCE	120	68
11	nitrobenzene	DCE	120	60
12	O_2 (1 atm)	DCE	120	43
13	none	DCE	120	5

[a] Reaction conditions: **1a** (1.0 equiv) and **2a** (2.0 equiv), stirred, 16 h.
[b] Isolated yield.

A range of 3-arylsydnones were tested under the optimized reaction conditions. As shown in Table 2, the phenyl ring of 3-arylsydnones **1**, carrying either an electron-donating group such as methoxyl (**1b**) and methyl (**1c**) or an electron-withdrawing substituent including halogens (**1e**–**h**), trifluoromethyl (**1i**), and nitryl (**1j**) all proceeded smoothly with moderate to high yields. Compared with **1d**, higher yields were obtained when the phenyl ring of 3-arylsydnones **1** carried an electron-donating group (Table 2, entries 1–3). Conversely, the presence of an electron-withdrawing substituent on the phenyl ring of **1** provided 1-arylpyrazoles **3** in relatively low yields (entries 4–9). Lower yields were obtained when the substrates **1** had an electron-donating substituent at the *meta*-position (**1c**) than that at the *para*-position (**1a**). This result can be ascribed to the fact that an electron-donating group exerts a stronger electron-donating inductive effect at the *para*-position than at the *meta*-position (entry 2). This behavior is contrary to that of substrates **1** bearing electron-withdrawing groups (entries 5 and 6). We have also used 3-*o*-tolylsydnone as a substrate to react with acrylic acid under the optimized reaction conditions, but the desired product 1-*o*-tolyl-1*H*-pyrazole was not found; this result may arise because of steric hindrance. Heteroaryl-substituted sydnone derivatives proved to be very difficult to prepare, and they were not synthesized successfully by us; such substrates were therefore not examined for this reaction.

Table 2 Synthesis of 1-Arylpyrazoles[a]

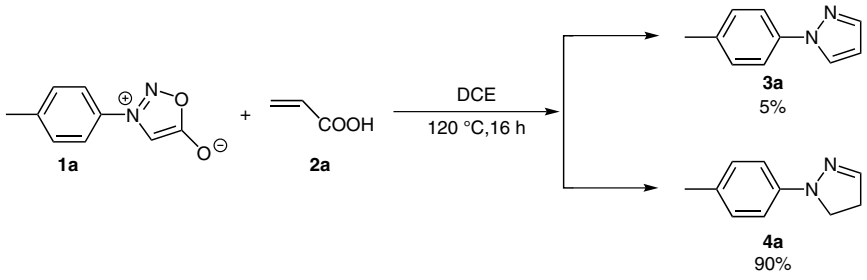


1 2a 3

Entry	Sydnone	R	Pyrazole	Yield of **3** (%)[b]
1	**1b**	4-$MeOC_6H_4$	**3b**	93
2	**1c**	3-MeC_6H_4	**3c**	88
3	**1d**	Ph	**3d**	86
4	**1e**	4-FC_6H_4	**3e**	63
5	**1f**	4-ClC_6H_4	**3f**	31
6	**1g**	3-ClC_6H_4	**3g**	52
7	**1h**	3-Cl-4-FC_6H_3	**3h**	36
8	**1i**	3-$F_3CC_6H_4$	**3i**	46
9	**1j**	3-$O_2NC_6H_4$	**3j**	43

[a] Reaction conditions: **1** (1.0 equiv), **2a** (2.0 equiv), $K_2S_2O_8$ (2.0 equiv), stirred, 16 h.
[b] Isolated yield.

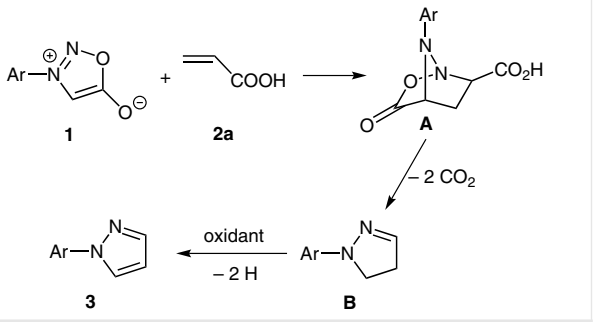
The reaction of *p*-tolylsydnone (**1a**) and acrylic acid (**2a**) in 1,2-dichloroethane at 120 °C was investigated to elucidate the probable reaction mechanism. After 16 hours, products **3a** and **4a** were obtained in 5 and 90% yields, respectively (Scheme 2). This result indicated that the synthesis of **3** may involve the following processes. First, 3-arylsydnone **1** reacts as a dipolar compound with acrylic acid (**2a**) through 1,3-dipolar cycloaddition to afford intermediate **A**. Subsequently, two molecules of CO_2 are lost,[12] and species **B** is generated; the CO_2 molecule from the ester



1a 2a

Scheme 2 Reaction of **1a** and **2a** without using $K_2S_2O_8$ as an oxidant

group may be lost faster than that from the carboxyl group.[11b] Finally, oxydehydrogenation occurs, and products **3** are formed (Scheme 3).



Scheme 3 Proposed mechanism for the synthesis of **3**

In conclusion, we have developed a convenient and transition-metal-free method for the synthesis of 1-arylpyrazoles **3** through the 1,3-dipolar cycloaddition of 3-arylsydnones and acrylic acid with moderate to high yields. 1-Arylpyrazoles are important heterocyclic compounds that are used in medicinal and biological research.

All commercially available reagents and solvents were obtained from commercial providers and used without further purification. Melting points were recorded with a WRS-2A melting-point apparatus and are uncorrected. IR spectra were obtained with a Nexus FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 400 MHz spectrometer. Chemical shifts are reported relative to internal tetramethylsilane (δ = 0.00 ppm) for ^{1}H and $CDCl_3$ (δ = 77.0 ppm) for ^{13}C. High-resolution mass spectra were recorded with a Finnigan-MAT GC/MS/DS 8430 spectrometer. Flash column chromatography was performed on 300–400 mesh silica gel. 3-Arylsydnones were prepared according to reported procedures.[13]

Synthesis of 1-Arylpyrazoles (3); General Procedure

A mixture of 3-arylsydnone (0.3 mmol), acrylic acid (0.6 mmol), and $K_2S_2O_8$ (0.6 mmol) in 1,2-dichloroethane (3 mL) was placed in a sealed tube. The tube was heated at 120 °C for 16 h by using an oil bath. Upon completion of the reaction (as monitored by thin-layer chromatography), the mixture was cooled to r.t. and the solvent was evaporated in vacuum. The resulting residue was purified by flash column chromatography (petroleum ether–EtOAc, 2:1) to give 1-arylpyrazoles **3**.

1-*p*-Tolyl-1*H*-pyrazole (3a)[8k]

Yield: 43 mg (0.270 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 6.47 (t, *J* = 2.0 Hz, 1 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 0.8 Hz, 1 H), 7.91 (d, *J* = 2.4 Hz, 1 H).

1-(4-Methoxyphenyl)-1*H*-pyrazole (3b)[8k]

Yield: 49 mg (0.279 mmol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 6.46 (t, *J* = 1.8 Hz, 1 H), 6.99 (d, *J* = 8.8 Hz, 2 H), 7.61 (d, *J* = 9.2 Hz, 2 H), 7.72 (s, 1 H), 7.85 (d, *J* = 2.4 Hz, 1 H).

1-*m*-Tolyl-1*H*-pyrazole (3c)[8b]

Yield: 42 mg (0.264 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 6.48 (t, *J* = 1.8 Hz, 1 H), 7.12 (d, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 7.8 Hz, 1 H), 7.48 (d, *J* = 8.4 Hz, 1 H), 7.58 (s, 1 H), 7.75 (d, *J* = 0.8 Hz, 1 H), 7.93 (d, *J* = 2.0 Hz, 1 H).

1-Phenyl-1*H*-pyrazole (3d)[8i]

Yield: 37 mg (0.258 mmol, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.49 (t, *J* = 2.0 Hz, 1 H), 7.31 (t, *J* = 7.4 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 2 H), 7.68–7.79 (m, 3 H), 7.96 (d, *J* = 2.4 Hz, 1 H).

1-(4-Fluorophenyl)-1*H*-pyrazole (3e)[8i]

Yield: 31 mg (0.189 mmol, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.49 (t, *J* = 2.0 Hz, 1 H), 7.16 (t, *J* = 8.6 Hz, 2 H), 7.60–7.70 (m, 2 H), 7.74 (d, *J* = 0.8 Hz, 1 H), 7.88 (d, *J* = 2.0 Hz, 1 H).

1-(4-Chlorophenyl)-1*H*-pyrazole (3f)[8i]

Yield: 17 mg (0.093 mmol, 31%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.51 (s, 1 H), 7.44 (d, *J* = 8.8 Hz, 2 H), 7.66 (d, *J* = 8.8 Hz, 2 H), 7.75 (s, 1 H), 7.92 (s, 1 H).

1-(3-Chlorophenyl)-1*H*-pyrazole (3g)[8k]

Yield: 28 mg (0.156 mmol, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.51 (t, *J* = 2.0 Hz, 1 H), 7.25–7.30 (m, 1 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 7.60 (dd, *J* = 1.2, 8.0 Hz, 1 H), 7.70–7.80 (m, 2 H), 7.94 (d, *J* = 2.0 Hz, 1 H).

1-(3-Chloro-4-fluorophenyl)-1*H*-pyrazole (3h)

Yield: 21 mg (0.108 mmol, 36%); yellow solid; mp 63.0–64.2 °C.

IR (KBr): 3069, 1692, 1659, 1581, 1548, 1513, 1482, 1263, 722, 653 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.51 (t, *J* = 2.0 Hz, 1 H), 7.25 (t, *J* = 8.6 Hz, 1 H), 7.53–7.62 (m, 1 H), 7.74 (d, *J* = 0.8 Hz, 1 H), 7.82 (dd, *J* = 2.6, 6.2 Hz, 1 H), 7.88 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 108.2, 117.4 (d, *J* = 22.0 Hz, 1 C), 118.6 (d, *J* = 7.0 Hz, 1 C), 121.6, 122.0 (d, *J* = 19.0 Hz, 1 C), 126.8, 136.9, 141.6, 156.5 (d, *J* = 247.0 Hz, 1 C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_7{}^{35}Cl^{19}FN_2$: 197.0277; found: 197.0276.

1-[3-(Trifluoromethyl)phenyl]-1*H*-pyrazole (3i)[14]

Yield: 29 mg (0.138 mmol, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.54 (t, *J* = 2.0 Hz, 1 H), 7.53–7.65 (m, 2 H), 7.79 (s, 1 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 8.00 (d, *J* = 2.4 Hz, 1 H), 8.02 (s, 1 H).

1-(3-Nitrophenyl)-1*H*-pyrazole (3j)[15]

Yield: 24 mg (0.129 mmol, 43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.57 (t, *J* = 2.2 Hz, 1 H), 7.67 (t, *J* = 8.2 Hz, 1 H), 7.80 (d, *J* = 1.2 Hz, 1 H), 8.05 (d, *J* = 2.4 Hz, 1 H), 8.09–8.18 (m, 2 H), 8.58 (t, *J* = 2.0 Hz, 1 H).

4,5-Dihydro-1-*p*-tolyl-1*H*-pyrazole (4a)

Prepared by following the general procedure ($K_2S_2O_8$ was not used).

Yield: 43 mg (0.270 mmol, 90%); tan solid; mp 51.5–52.6 °C.

IR (KBr): 3042, 2962, 2848, 1659, 1572, 1549, 1529, 1467, 1384, 1280, 815 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 2.87–2.98 (m, 2 H), 3.65 (t, *J* = 10.2 Hz, 2 H), 6.85 (s, 1 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 7.11 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 33.5, 47.1, 113.2 (2C), 128.5, 129.6 (2C), 140.7, 144.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{13}N_2$: 161.1073; found: 161.1070.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-34-1380658.

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