Metal- and solvent-free, iodine-catalyzed cyclocondensation and C–H bond sulphenylation: A facile access to C-4 sulfenylated pyrazoles via a domino multicomponent reaction

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ABSTRACT

We describe herein a green and efficient MCRs protocol to synthesize C-4 sulfenylated pyrazoles by iodine-catalyzed cyclocondensation and direct C–H bond sulphenylation reactions. Through this protocol, two new C–N bonds and one C–S bond are constructed simultaneously in a single step. This method provides a straightforward and sustainable way to construct valuable sulfenylated pyrazoles under metal- and solvent-free conditions.

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1. Introduction

Sulfur-containing compounds are ubiquitous in natural products and bioactive compounds, drugs, agrochemicals, and functional materials. Accordingly, seeking novel and efficient approaches for the formation of C–S bonds is an essential issue in modern organic chemistry and has received much attention. Transition-metal-catalyzed C–S bond forming reactions have been extensively investigated over the past decades, and have been demonstrated as an efficient synthetic strategy. In this respect, the palladium-, iron-, and copper-catalyzed cross-couplings of thiols or disulfides with aryl halides, pseudo halides or arylboronic acids, have become a versatile method for constructing of C–S bonds. In recent years, transition-metal or metal-free protocol for C–S bond formation via C–H bond sulphenylation reactions have also been intensively studied. In these transformations, various sulfenylating reagents such as aryl sulfonyl hydrazides, diaryldisulfides, arylsulfonyl chlorides, sulfinic acids, and sodium sulfinates have been widely used. However, these sulfenylating reagents either need for moisture-free conditions or need multi-steps for its synthesis. Hence, directly using thiols as sulfenylation reagents appears synthetically attractive.

Pyrazoles, standing for a class of significant N-heterocycles, have been received huge attention in recent years due to their wide applications in dyes, and agrochemicals. The pyrazole scaffold occurs in many biologically active natural products such as pyrazofurin (I), 4-methoxywithasomnine (II), and formycin (III) (Fig. 1). Importantly, pyrazoles are also highly valuable structural motifs in various commercially available drugs, such as Crizotinib (IV), Fipronil (V), and Celebrex (VI) (Fig. 1). The introduction of thiols into pyrazole in a regioselective fashion, could enhance or alter its biological and pharmacological activity. In 2016, Purohit and co-workers demonstrated a highly efficient synthetic approach to sulfenylated pyrazoles via palladium-catalyzed sulphenylation of pyrazolones with thiols [eqn (1), Scheme 1]. In 2014, Zhao and Lu developed an efficient I$_2$-catalyzed, p-toluenesulphonic acid-promoted sulphenylation of pyrazolones with sulphonyl hydrazides for the synthesis of sulfenylated pyrazoles at 120 °C [eqn (2), Scheme 1]. Very recently, our group also demonstrated a metal-free approach to sulfenylated pyrazoles through NaOH-promoted
direct sulfonylation of pyrazolones with aryl thiols under mild conditions [eqn (3), Scheme 1].

Seeking efficient, simple, and green methods for the construction of diverse and elaborated heterocycles from simple chemical raw materials has been of growing interest yet remains a continuing challenge. Multi-component reactions (MCRs) in which complex and diverse structures are created in a single operation, have emerged as a significant tool, and has received much attention. One-pot MCRs allows the creation of several bonds in a one-pot fashion and affords remarkable advantages, such as operational simplicity, convergence, facile automation, and hence maximization of yields and reduction of waste, rendering the transformations green. As a consequence, the design of new MCRs with a green protocol is still highly desired but full of challenge, especially in the areas of drug discovery, and material science. On the other hand, the development of mild and green catalytic conditions by using DMSO as an oxidant has been of increasing importance in view of the environmental concerns. Considering the importance of the pyrazole and thiol frameworks, and together with our growing interest in sulfur-containing compounds synthesis, herein we wish to report a novel and multi-component reaction strategy for the construction of thiol-substituted pyrazoles via iodine-catalyzed cyclocondensation and C–H bond sulphenylation under metal- and solvent-free conditions [eqn (4), Scheme 1].

2. Results and discussion

Initially, ethyl 3-oxobutanoate 1a, phenylhydrazine 2a, and 4-methylbenzenethiol 3d were chosen as the model substrates to optimize the reaction conditions, including the catalysts, solvents, and reaction temperatures under ambient air. As shown in Table 1, five catalysts such as NaI, KI, TBAI, I$_2$O$_5$, and I$_2$ were tested at 70 $^\circ$C in DMSO, and I$_2$ gave the highest yield (88%) (entries 1–5). No target product 4d was observed in the absence of I$_2$ catalyst (entry 6). Furthermore, the solvents including DMSO, DMF, CH$_3$CN, Toluene, THF, and H$_2$O were investigated by using I$_2$ as the catalyst at 70 $^\circ$C, and DMSO were found to be the most effective solvent (entries 5, 7–11). In addition, various temperatures were also tested (entries 6, 12–14), and 70 $^\circ$C was discovered to be more suitable for this transformation (entry 6). It should be noted that elevating the reaction temperature could lead to a lower yield of the product (entries 13 and 14), indicating that the temperature is crucial for this reaction. To our delight, the reaction can also proceed when the amount of DMSO lowered to 3 equiv. to 1a, which demonstrated that the present reaction can be performed under solvent-free conditions (entries 15–17). Furthermore, control experiments indicated that the amount of DMSO can be reduced to 3.0 equiv. (but not to 2.0 equiv.) (entries 13 and 14). After the optimization process of catalysts, solvents, and temperatures, the C-4 sulfenylated pyrazoles were synthesized under the optimized conditions: 5 mol % I$_2$ as the catalyst, in the presence of 3.0 equiv of DMSO at 70 $^\circ$C under an air atmosphere.

With the established optimal conditions in hand, the scope of this three-component sulphenylation reaction was investigated by conducting a variety of dicarbonyl compounds 1 to react with aryl hydrazines 2 and various simple thiols 3 (Table 2). We were pleased to find that the good to excellent yields were obtained under the standard conditions. In addition, the sulphenylation reaction could

### Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp. [°C]</th>
<th>Yield b (%)</th>
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<tr>
<td>1</td>
<td>NaI</td>
<td>DMSO</td>
<td>70</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>KI</td>
<td>DMSO</td>
<td>70</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>TBAI</td>
<td>DMSO</td>
<td>70</td>
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<td>4</td>
<td>I$_2$O$_5$</td>
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<td>15</td>
</tr>
<tr>
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<td>88</td>
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<td>DMF</td>
<td>70</td>
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</tr>
<tr>
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<td>I$_2$</td>
<td>CH$_3$CN</td>
<td>70</td>
<td>NR</td>
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<td>I$_2$</td>
<td>THF</td>
<td>70</td>
<td>19</td>
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<td>I$_2$</td>
<td>H$_2$O</td>
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<td>31</td>
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<td>50</td>
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<td>I$_2$</td>
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<td>65</td>
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<td>I$_2$</td>
<td>DMSO</td>
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<td>70</td>
<td>87$^c$</td>
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<tr>
<td>17</td>
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<td>70</td>
<td>79$^c$</td>
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<tr>
<td>18</td>
<td>I$_2$</td>
<td>None</td>
<td>70</td>
<td>0</td>
</tr>
</tbody>
</table>

a Reaction conditions: ethyl 3-oxobutanoate 1a (0.5 mmol), phenylhydrazine 2a (0.6 mmol), 4-methylbenzenethiol 3d (0.6 mmol), catalyst (0.025 mmol), solvent (2.0 mL), reaction time (24 h) under an air atmosphere. TBAI = (n-Bu)$_4$NI.

b Isolated yield.

c DMSO (6 equiv).

d DMSO (3 equiv).

e DMSO (2 equiv).
tolerate all kinds of substituted aryl hydrazines and thiols bearing both electron-donating groups (EDG) and electron-withdrawing groups (EWG) under the optimized conditions. Aryl hydrazines bearing EWGs such as chloride and trifluoromethyl generally provide the desired product (4h, 4i, 4m, and 4n) in lower yields compared to the ones bearing EDGs like methyl (4d, 4e, and 4f). Thiols possessing different groups were also evaluated, the electronic effect of the substituted groups including EDGs, neutral, and EWGs did not display an evident difference in the reactivity, as shown in Table 2. Also, naphthalene-2-thiol could be employed in the reaction to generate the desired products in good yields (4g, 4r and 4u). Of note, aromatic thiols and aromatic hydrazines showed the high reactivity, unfortunately, aliphatic ones were poor substrates. Under a similar condition, the methodology was extended to the synthesis of various C-4 sulfenylated pyrazoles from pentane-2,4-dione (6a-6f). The results are summarized in Table 3. Furthermore, some functional groups were tolerated in the present reactions, including methyl, methoxy, hydroxyl, and C–Cl bond, which provides the more options for the further modifications.

The scalability of the present method was also explored. As shown in Scheme 2, the proposed reaction between 1a, 2a and 3d was investigated under the standard conditions, which could give 1.01 g of 4d in 85% yield without any significant loss of reactive efficiency [eq (1)]. Besides, the sulfonyl product 7 as directly synthesized in 73% yield from 4d through oxidative reaction with m-chloroperbenzoic acid (m-CPBA). Obviously, this simple, metal-free protocol could be use as a practical approach for the synthesis of various C-4 sulfenylated or sulfonylated pyrazoles.

For the mechanistic studies of this transformation, several control experiments were performed (Scheme 3). First, treatment of ethyl 3-oxobutanoate 1a with phenylhydrazine 2a under the standard conditions led to 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one 8 in 96% yield, indicating that pyrazolone might be intermediate for this transformation [eq (1), Scheme 3]. It should be noted that the reaction of 1a with 2a was tested without iodine, and no conversion was observed [eq (2), Scheme 3]. Besides, treatment of benzenethiol 3a (0.6 mmol) only under the standard conditions, 1,2-diphenyldisulfane 9 was obtained in 98% yield, which implied that diaryldisulfides might act as an important intermediates in the present reactions [eq (3), Scheme 3]. Furthermore, direct coupling of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one 8 with 1,2-diphenyldisulfane 9 under the standard conditions, the desired

Table 2
I$_2$-Catalyzed synthesis of C-4 sulfenylated pyrazoles from 1,3-diketones, hydrazines and thiols.$^{a,b,c}$

<table>
<thead>
<tr>
<th>Reaction conditions: I$_2$ (0.025 mmol), DMSO (3.0 equiv.), under an air atmosphere.</th>
<th>Isolated yield.</th>
<th>Reaction time (24 h).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (0.5 mmol), phenylhydrazine, 2 (0.6 mmol), 3 (0.6 mmol),</td>
<td>4d (88%)</td>
<td>4a (78%)</td>
</tr>
<tr>
<td>DMSO (3.0 equiv.), under an air atmosphere.</td>
<td>4e (91%)</td>
<td>4b (84%)</td>
</tr>
<tr>
<td></td>
<td>4f (96%)</td>
<td>4c (62%)</td>
</tr>
</tbody>
</table>

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product 4b was obtained in 92% yield [eq (4), Scheme 3].

On the basis of the previous related literature,19 and our preliminary experimental findings, a possible reaction mechanism would be herein presented (Scheme 4). Initially, benzenethiol 3a was oxidized to 1,2-diphenyldisulfane 9 under the standard conditions. The reaction of 9 with I2 formed an electrophilic species PhSI 10.19 Then, the intermediate I reacted with electron-rich pyrazolone 8', generated in situ from I2-catalyzed cyclocondensation of ethyl 3-oxobutanoate 1a with phenylhydrazine 2a, to form carboxation III, which could be stabilized by the adjacent hydroxyl group. Then, intermediate III lost a proton to give the desired products 4a and HI. Finally, HI could be oxidized to I2 with DMSO to realize the radical chain growth.

3. Conclusion

In conclusion, a simple and environmentally friendly protocol has been newly developed for the synthesis of C-4 sulfenylated pyrazoles via I2-catalyzed domino multicomponent reaction of 1,3-diketones, hydrazines and thiols under metal- and solvent-free conditions. The chemistry simultaneously installs two C–N bonds and one C–S bond in one pot reaction, and a series of potentially biological C-4 sulfenylated pyrazoles could be efficiently obtained in good to excellent yields with good selectivity. Compared the previous protocols, this approach is more efficient and environmentally benign.

4. Experimental section

4.1. General remarks

All commercially available reagent-grade chemicals were purchased from chemical suppliers and used as received without further purification. Proton and carbon magnetic resonance spectra (1H NMR and 13C NMR) were recorded using either tetramethylsilane (TMS) as the internal standard in CDCl3 (1H NMR: TMS at 0.00 ppm, CDCl3 at 7.24 ppm; 13C NMR: CDCl3 at 77.0 ppm) or tetramethylsilane (TMS) as the internal standard in DMSO-d6.
6.88 (d, 2H, \( J = 10.0 \) Hz), 7.33 (d, 2H, \( J = 10.0 \) Hz), 7.27 (d, 2H, \( J = 10.0 \) Hz), 7.09 (d, 2H, \( J = 10.0 \) Hz), 2.32 (s, 3H), 2.12 (s, 3H).

13C NMR (DMSO-\( d_6 \), 125 MHz, ppm) \( \delta \) 162.0, 156.8, 142.8, 140.8, 140.4, 134.7, 134.6, 134.1, 131.8, 126.0, 92.2, 25.7, 17.4. HRMS calc. for \( \text{C}_{17} \text{H}_{16} \text{N}_2 \text{NaO}_5 [M+Na]^+ \) 353.0486, found 353.0483.

4.2.5. 4-(4-chlorophenylthio)-3-methyl-1-p-tolyl-1H-pyrazol-5-ol (4e)\textsuperscript{1a}

Eluent petroleum ether/ethyl acetate (15:1). 138 mg, 84% yield.

1H NMR (DMSO-\( d_6 \), 500 MHz, ppm) \( \delta \) 7.60 (d, 2H, \( J = 10.0 \) Hz), 7.33 (d, 2H, \( J = 10.0 \) Hz), 7.27 (d, 2H, \( J = 10.0 \) Hz), 7.09 (d, 2H, \( J = 10.0 \) Hz), 2.32 (s, 3H), 2.12 (s, 3H).

13C NMR (DMSO-\( d_6 \), 125 MHz, ppm) \( \delta \) 162.0, 156.8, 142.8, 140.8, 140.4, 134.7, 134.6, 134.1, 131.8, 126.0, 92.2, 25.7, 17.4. HRMS calc. for \( \text{C}_{17} \text{H}_{16} \text{N}_2 \text{NaO}_5 [M+Na]^+ \) 353.0486, found 353.0483.

4.2.6. 3-Methyl-1-p-tolyl-4-(4-tolylthio)-1H-pyrazol-5-ol (4f)

Eluent petroleum ether/ethyl acetate (15:1). 133 mg, 86% yield.

1H NMR (DMSO-\( d_6 \), 500 MHz, ppm) \( \delta \) 7.60 (d, 2H, \( J = 10.0 \) Hz), 7.27 (d, 2H, \( J = 10.0 \) Hz), 7.09 (d, 2H, \( J = 10.0 \) Hz), 2.32 (s, 3H), 2.12 (s, 3H).\textsuperscript{1c} HRMS calc. for \( \text{C}_{17} \text{H}_{16} \text{N}_2 \text{NaO}_5 [M+Na]^+ \) 353.0486, found 353.0483.

4.2.7. 3-Methyl-4-(naphthalen-1-ylthio)-1-p-tolyl-1H-pyrazol-5-ol (4g)

Eluent petroleum ether/ethyl acetate (15:1). 145 mg, 84% yield.

1H NMR (DMSO-\( d_6 \), 500 MHz, ppm) \( \delta \) 8.00 (d, 2H, \( J = 10.0 \) Hz), 7.72 (d, 2H, \( J = 10.0 \) Hz), 7.53 (d, 2H, \( J = 10.0 \) Hz), 7.13–7.09 (m, 3H), 2.18 (s, 3H), \textsuperscript{1c} HRMS calc. for \( \text{C}_{17} \text{H}_{16} \text{N}_2 \text{NaO}_5 [M+Na]^+ \) 353.0486, found 353.0483.

4.2.8. 1-(4-chlorophenyl)-3-methyl-4-(phenylthio)-1H-pyrazol-5-ol (4h)

Eluent petroleum ether/ethyl acetate (15:1). 124 mg, 79% yield.

1H NMR (DMSO-\( d_6 \), 500 MHz, ppm) \( \delta \) 7.80 (d, 2H, \( J = 10.0 \) Hz), 7.72 (d, 2H, \( J = 10.0 \) Hz), 7.53 (d, 2H, \( J = 10.0 \) Hz), 7.13–7.09 (m, 3H), 2.14 (s, 3H), \textsuperscript{1c} HRMS calc. for \( \text{C}_{17} \text{H}_{16} \text{N}_2 \text{NaO}_5 [M+Na]^+ \) 353.0486, found 353.0483.

4.2.9. 1-(4-chlorophenyl)-4-(4-chlorophenylthio)-3-methyl-1H-pyrazol-5-ol (4i)

Eluent petroleum ether/ethyl acetate (15:1). 131 mg, 75% yield.

1H NMR (DMSO-\( d_6 \), 500 MHz, ppm) \( \delta \) 7.81 (d, 2H, \( J = 10.0 \) Hz), 7.53 (d, 2H, \( J = 10.0 \) Hz), 7.10 (d, 2H, \( J = 10.0 \) Hz), 3.07 (s, 3H), \textsuperscript{1c} HRMS calc. for \( \text{C}_{17} \text{H}_{16} \text{N}_2 \text{NaO}_5 [M+Na]^+ \) 353.0486, found 353.0483.

4.2.10. 1-(4-chlorophenyl)-4-(4-methoxyphenylthio)-3-methyl-1H-pyrazol-5-ol (4j)

Eluent petroleum ether/ethyl acetate (10:1). 138 mg, 80% yield.

1H NMR (DMSO-\( d_6 \), 500 MHz, ppm) \( \delta \) 7.86 (d, 2H, \( J = 10.0 \) Hz), 7.53 (d, 2H, \( J = 10.0 \) Hz), 7.10 (d, 2H, \( J = 10.0 \) Hz), 2.32 (s, 3H), 2.12 (s, 3H), \textsuperscript{1c} HRMS calc. for \( \text{C}_{17} \text{H}_{16} \text{N}_2 \text{NaO}_5 [M+Na]^+ \) 353.0486, found 353.0483.
1H NMR (DMSO-d$_6$, 500 MHz, ppm) $\delta$ 119.8 (s, br, 1H), 7.85--7.81 (m, 4H), 7.77 (d, 1H, $J = 5.0$ Hz), 7.52--7.40 (m, 5H), 7.31 (t, 1H, $J = 10.0$ Hz), 7.26 (d, 1H, $J = 10.0$ Hz), 1.32 (s, 9H).

$^{13}$C NMR (DMSO-d$_6$, 125 MHz, ppm) $\delta$ 160.9, 157.1, 139.1, 137.4, 133.8, 131.3, 129.4, 128.8, 128.1, 127.2, 126.4, 125.6, 124.1, 122.2, 121.8, 84.2, 34.1, 29.4. HRMS calc. for C$_{23}$H$_{22}$N$_2$NaOS [M + Na]$^+$ 397.1345, found 397.1346.

4.2.19. 3-tert-Butyl-4-(p-tolylthio)-1H-pyrazol-5-ol (4s)

Eluent petroleum ether/ethyl acetate (15:1). 146 mg, 72% yield.

1H NMR (DMSO-d$_6$, 500 MHz, ppm) $\delta$ 12.43 (s, br, 1H), 8.07 (d, 2H, $J = 10.0$ Hz), 7.85 (d, 2H, $J = 5.0$ Hz), 7.08 (d, 2H, $J = 10.0$ Hz), 6.95 (d, 2H, $J = 5.0$ Hz), 2.22 (s, 3H), 1.31 (s, 9H).

$^{13}$C NMR (DMSO-d$_6$, 125 MHz, ppm) $\delta$ 162.0, 157.9, 142.1, 135.7, 134.4, 130.0, 129.1 (q, $J = 204.3$ Hz), 126.6 (q, $J = 32.3$ Hz), 125.1, 123.6, 85.6, 34.2, 29.2, 20.8. HRMS calc. for C$_{22}$H$_{21}$F$_3$Na$_2$OS [M + Na]$^+$ 429.1219, found 429.1214.

4.2.20. 1,3-Diphenyl-4-(phenylthio)-1H-pyrazol-5-ol (4t)$^{136}$

Eluent petroleum ether/ethyl acetate (10:1). 120 mg, 70% yield.

1H NMR (DMSO-d$_6$, 500 MHz, ppm) $\delta$ 12.44 (s, br, 1H), 7.90--7.88 (m, 4H), 7.54 (t, 2H, $J = 10.0$ Hz), 7.40--7.35 (m, 4H), 7.29 (t, 2H, $J = 5.0$ Hz), 7.14--7.11 (m, 3H).

$^{13}$C NMR (DMSO-d$_6$, 125 MHz, ppm) $\delta$ 157.1, 151.9, 150.2, 140.6, 139.1, 138.8, 136.8, 129.6, 128.9, 128.7, 127.5, 125.5, 125.2, 115.5, 85.6. HRMS calc. for C$_{21}$H$_{16}$N$_2$NaOS [M + Na]$^+$ 372.9940, found 372.9944.

4.2.21. 4-(Naphthalen-1-ylthio)-1,3-diphenyl-4-phenylthio)-1H-pyrazol-5-ol (4u)$^{136}$

Eluent petroleum ether/ethyl acetate (10:1). 148 mg, 75% yield.

1H NMR (DMSO-d$_6$, 500 MHz, ppm) $\delta$ 12.51 (s, br, 1H), 7.94--7.91 (m, 4H), 7.85 (t, 2H, $J = 10.0$ Hz), 7.77 (d, 1H, $J = 10.0$ Hz), 7.59--7.54 (m, 3H), 7.47--7.32 (m, 7H).

$^{13}$C NMR (DMSO-d$_6$, 125 MHz, ppm) $\delta$ 157.1, 152.1, 138.8, 133.9, 131.4, 129.5, 129.2, 128.9, 128.8, 128.1, 127.5, 127.3, 127.2, 125.0, 125.8, 124.2, 122.5, 122.2, 85.6. HRMS calc. for C$_{25}$H$_{18}$N$_2$NaOS [M + Na]$^+$ 417.1032, found 417.1035.

4.2.22. 3,5-Dimethyl-1-phenyl-4-(phenylthio)-1H-pyrazole (6a)$^{136}$

Eluent petroleum ether/ethyl acetate (15:1). 91 mg, 65% yield.

1H NMR (CDCl$_3$, 500 MHz, ppm) $\delta$ 7.52--7.51 (m, 4H), 7.42 (dd, 1H, $J = 10.0$ Hz), 7.27--7.44 (m, 4H), 7.14--7.09 (m, 3H), 2.38 (s, 3H), 2.33 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 125 MHz, ppm) $\delta$ 153.2, 144.2, 159.8, 138.3, 129.2, 128.9, 127.9, 125.4, 124.9, 124.7, 106.1, 12.1, 11.6. HRMS calc. for C$_{19}$H$_{15}$N$_2$NaOS [M + H]$^+$ 303.0926, found 303.0928.

4.2.23. 3,5-Dimethyl-1-phenyl-4-(p-tolylthio)-1H-pyrazole (6b)$^{136}$

Eluent petroleum ether/ethyl acetate (15:1). 103 mg, 70% yield.

1H NMR (CDCl$_3$, 500 MHz, ppm) $\delta$ 7.53--7.49 (m, 4H), 7.41 (dd, 1H, $J = 10.0$ Hz), 7.08 (d, 2H, $J = 10.0$ Hz), 7.01 (d, 2H, $J = 10.0$ Hz), 2.38 (s, 3H), 2.33 (s, 3H), 2.32 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 125 MHz, ppm) $\delta$ 153.2, 144.0, 139.8, 134.8, 134.7, 129.7, 129.2, 127.8, 125.8, 124.7, 106.7, 20.9, 12.1, 11.6. HRMS calc. for C$_{19}$H$_{15}$N$_2$NaOS [M + H]$^+$ 317.1083, found 317.1086.

4.2.24. 4-(2,4-dichlorophenyl)-3,5-dimethyl-1-phenyl-1H-pyrazole (6c)$^{136}$

Eluent petroleum ether/ethyl acetate (15:1). 102 mg, 59% yield.

1H NMR (CDCl$_3$, 500 MHz, ppm) $\delta$ 7.54--7.50 (m, 4H), 7.45--7.42 (m, 4H), 7.30 (s, 1H), 7.09 (d, 1H, $J = 10.0$ Hz), 6.01 (d, 1H, $J = 5.0$ Hz), 2.35 (s, 3H), 2.29 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 125 MHz, ppm) $\delta$ 153.3, 144.6, 139.6, 136.3, 130.6, 130.7, 129.4, 129.3, 128.1, 127.4, 126.1, 124.7, 104.1, 12.0, 11.5. HRMS calc. for C$_{17}$H$_{13}$Cl$_2$Na$_2$OS [M + Na]$^+$ 371.0147, found 371.0149.
4.2.25. 3,5-Dimethyl-4-(naphthalen-1-ythio)-1-phenyl-1H-pyrazole (6d)

Eluent petroleum ether/ethyl acetate (15:1). 104 mg, 63% yield.

1H NMR (CDCl3, 500 MHz, ppm) δ 7.80 (d, 1H, J = 5.0 Hz), 7.75 (d, 1H, J = 5.0 Hz), 7.70 (d, 1H, J = 4.8 Hz), 7.65–7.52 (m, 4H), 7.48–7.42 (m, 4H), 7.28 (d, 1H, J = 10.0 Hz), 2.41 (s, 3H), 2.37 (s, 3H). 13C NMR (CDCl3, 125 MHz, ppm) δ 148.9, 140.0, 139.4, 134.3, 133.5, 132.5, 129.0, 127.8, 127.5, 127.2, 126.8, 126.6, 126.3, 125.6, 124.7, 106.9, 13.5, 12.4. HRMS calc. for C24H19N3SNa [M + Na]+ 353.1083, found 353.1086.

4.2.26. 3,5-Dimethyl-4-(naphthalen-1-ythio)-1-phenyl-1H-pyrazole (6f)①

Eluent petroleum ether/ethyl acetate (15:1). 91 mg, 56% yield.

1H NMR (CDCl3, 500 MHz, ppm) δ 7.80 (d, 2H, J = 10.0 Hz), 7.45 (d, 2H, J = 10.0 Hz), 7.07 (d, 2H, J = 10.0 Hz), 7.00 (d, 2H, J = 10.0 Hz), 2.37 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H). 13C NMR (CDCl3, 125 MHz, ppm) δ 153.5, 144.0, 138.3, 135.0, 134.9, 129.7, 129.3, 125.9, 125.8, 107.4, 20.9, 12.1, 11.6. HRMS calc. for C29H23N3S [M + Na]+ 351.0693, found 351.0697.

4.2.27. 4-(4-bromophenylthio)-3,5-dimethyl-1-p-tolyl-1H-pyrazole (6d)

Eluent petroleum ether/ethyl acetate (15:1). 107 mg, 58% yield.

1H NMR (CDCl3, 500 MHz, ppm) δ 7.37–7.35 (m, 4H), 7.30 (d, 2H, J = 10.0 Hz), 6.94 (d, 2H, J = 10.0 Hz), 2.44 (s, 3H), 2.33 (s, 3H), 2.30 (s, 3H). 13C NMR (CDCl3, 125 MHz, ppm) δ 152.9, 144.1, 138.0, 137.8, 137.2, 131.8, 129.8, 126.9, 124.6, 118.4, 105.2, 212, 12.1, 11.5. HRMS calc. for C31H27BrN3S [M + Na]+ 395.0188, found 395.0192.

4.2.28. 3-Methyl-1-phenyl-1H-pyrazol-5-ol (7)

Eluent petroleum ether/ethyl acetate (15:1). 107 mg, 58% yield.

1H NMR (CDCl3, 500 MHz, ppm) δ 9.34 (s, br, 1H), 7.84 (d, 2H, J = 10.0 Hz), 7.39 (t, 2H, J = 10.0 Hz), 7.19 (t, 1H, J = 10.0 Hz), 3.40 (s, 2H), 2.17 (s, 3H). 13C NMR (CDCl3, 125 MHz, ppm) δ 152.9, 144.1, 138.0, 137.8, 137.2, 131.8, 129.8, 126.9, 124.6, 118.4, 105.2, 212, 12.1, 11.5. HRMS calc. for C14H13N3O3S [M + Na]+ 219.0297, found 219.0290.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.02.046.
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