Regioselective synthesis of multisubstituted pyrazoles via cyclocondensation of \( \beta \)-thioalkyl-\( \alpha,\beta \)-unsaturated ketones with hydrazines

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Multisubstituted pyrazoles were efficiently synthesized by cyclocondensation of \( \beta \)-thioalkyl-\( \alpha,\beta \)-unsaturated ketones with hydrazines under relatively mild conditions. A one-pot synthetic protocol through tandem Liebeskind–Srogl cross-coupling/cyclocondensation using \( \alpha \)-oxo ketene dithioacetals as the starting materials was also realized for the same purpose.

The reactions of \( \beta \)-thioalkyl-\( \alpha,\beta \)-unsaturated ketones (1) with hydrazines (2) were carried out in the presence of \( t \)-BuOK or HOAc in refluxing \( t \)-BuOH, efficiently affording multisubstituted pyrazoles (Table 1). When \( R_1^1 \) was methyl, the reactions of \( 1a-g \) with phenylhydrazine \((2a) \) underwent under the basic conditions (condition A), forming 1,3,5-trisubstituted pyrazoles \( 3a-g \) in 76–92% yields (entries 1–7). Methoxy, tert-butyl, chloro, and fluoro groups on \( R_2^1 \) substrates, that is, \( \beta \)-aryls in 1, can be tolerated during the reaction. Diene \( 1g \) reacted with \( 2a \) to give rare 3-styryl-pyrazole \( 3g \) (83%, entry 7). Altering \( R_1^1 \) to aryls and heteroaryls, the cyclocondensation reactions of \( 1h-l \) with phenylhydrazine were also efficiently carried out under condition A, forming the desired products \( 3h-l \) in 78–95% yields (entries 8–12). Under slightly acidic conditions (condition B), the reactions of \( 1a \) with benzylhydrazine \((2b) \) and 2-hydropyrindine \((2c) \) produced the target \( N \)-benzyl and 2-arylidene trisubstituted pyrazoles \( 3m \) and \( 3n \) in 96% and 75% yields, respectively, (entries 13–14). In order to obtain \( N \)-unprotected multisubstituted pyrazoles, hydrazide hydrate \((2d) \) was used to react with \( \beta \)-thioalkyl-\( \alpha,\beta \)-unsaturated ketones \((1) \). Thus, \( N \)-unprotected 3,5-disubstituted pyrazoles \( 3o-r \) were obtained in 80–95% yields (entries 15–18). Notably, the \((E)/(Z)\)-configurations of \( 1 \) did not affect the formation of pyrazoles \( 3 \), and the synthetic methodology was exclusively regioselective to afford \( N \)-protected 1,3,5-trisubstituted or 1H-3,5-disubstituted pyrazoles, forming no tautomers of the desired products \( 3 \), that is, \( 3 \). As compared to 1,3-diketones, the different electrophilicity of ethylthio from that of carbonyl toward hydrazines may facilitate such regioselective reactions of \( 1 \) with \( 2 \). It is proposed that the more acidic...
Table 1
Synthesis of pyrazoles (3)a,b

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>R1NHNH2</th>
<th>Conditions</th>
<th>Product</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>PhNHNH2 (2a)</td>
<td>A</td>
<td>3a</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2a</td>
<td>A</td>
<td>3b</td>
<td>87</td>
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<tr>
<td>3</td>
<td>1c</td>
<td>2a</td>
<td>A</td>
<td>3c</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2a</td>
<td>A</td>
<td>3d</td>
<td>85</td>
</tr>
<tr>
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<td>1e</td>
<td>2a</td>
<td>A</td>
<td>3e</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>2a</td>
<td>A</td>
<td>3f</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>2a</td>
<td>A</td>
<td>3g</td>
<td>83</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>2a</td>
<td>A</td>
<td>3h</td>
<td>92</td>
</tr>
<tr>
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<td>3i</td>
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</tr>
<tr>
<td>10</td>
<td>1j</td>
<td>2a</td>
<td>A</td>
<td>3j</td>
<td>95</td>
</tr>
</tbody>
</table>

(continued on next page)
N–H in 2 undergoes nucleophilic substitution with 1 to form an intermediate hydrazino-α,β-unsaturated ketone which is then dehydrated to give the pyrazole product.\(^3\)

Finally, a one-pot, two-step three-component tandem reactions via Liebeskind–Srogl cross-coupling\(^9\)/cyclocondensation sequence starting from 4\(^11\) was developed to prepare highly functionalized pyrazoles (Scheme 1). After the first step Liebeskind–Srogl cross-coupling reaction was completed by TLC monitoring, all the volatiles were pumped off under reduced pressure, and then \(\text{t}-\text{BuOK}\) base and a new solvent \(\text{t}-\text{BuOH}\) were added to initiate the next step transformation. Thus, trisubstituted pyrazoles 3b, 3h, and 3j–l were efficiently generated in 77–89% yields. Although a one-step condensation of symmetrical 1,3-diketones with hydrazines has been extensively applied for the synthesis of 3,5-disubstituted pyrazoles, unsymmetrical and functionalized 1,3-diketones are not readily available that no ready access has been developed for the preparation of multisubstituted pyrazoles. To the best of our knowledge, the present protocol has demonstrated an efficient regioselective route to highly functionalized pyrazoles.

**Scheme 1.** One-pot synthesis of pyrazoles via Liebeskind–Srogl cross-coupling/cyclocondensation reactions. Reagents and conditions: (a) 4 (0.50 mmol), 5 (0.75 mmol), \(\text{Pd(PPh}_3\text{)}_4\) (7.5 mol%), \(\text{PhLi}\) (7.5 mmol), copper(I) thiophene-2-carboxylate (CuTC\(^{10}\), 1.0 mmol), \(\text{Cs}_2\text{CO}_3\) (1.0 mmol), \(\text{THF}\) (5 mL), 50 °C, 2 h; (b) \(\text{t}-\text{BuOK}\) (1.0 mmol), \(\text{t}-\text{BuOH}\) (5 mL), reflux, 9–16 h.

In summary, an efficient regioselective synthetic route to multi-substituted pyrazoles has been developed by cyclocondensation of...
β-thioalkyl-α,β-unsaturated ketones with hydrazines.12–14 The present methodology has exhibited exclusive regioselectivity for the target products, generating no pyrazole tautomers. The one-pot synthetic procedure via tandem Liebeskind–Srogl cross-coupling/cyclocondensation sequence using 3-oxo ketene dithioacetals as the starting materials has also shown promising potentials in the preparation of highly functionalized pyrazoles.

Acknowledgments

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Supplementary data


References and notes


3. A general synthetic procedure—synthesis of 5-(3,5-difluorophenyl)-3-methyl-1-phenyl-1H-pyrazole (3c): A mixture of 1 (131 mg, 0.55 mmol), PPh3, 23

4. A general synthetic procedure—synthesis of 5-(3,5-difluorophenyl)-3-methyl-1-phenyl-1H-pyrazole (3b) and 5-(4-fluoro-3-methoxyphenyl)-3-methyl-1-phenyl-1H-pyrazole (3a): Products were characyerized by NMR and HRMS determinations. All the new compounds are characterized by comparison of their NMR features with those of the authentic samples or the reported NMR data.

5. A general procedure for one-pot synthesis of pyrazoles—synthesis of 5-(4-hydroxy-3-methyl-1-phenyl-1H-pyrazole (3b): Under nitrogen atmosphere a mixture of 3-oxo ketene dithioacetal (4a) (95 mg, 0.50 mmol), arylboronic acid (5a) (114 mg, 0.75 mmol), Pd(PPh3)4 (43 mg, 0.0375 mmol), CuI (112 mg, 1.0 mmol) and t-BuOH (112 mg, 0.75 mmol) were added in 5 mL THF. The mixture was stirred at 50 °C for 2 h. All the products were recovered by filtration, and then purified by gel column chromatography (eluent: petroleum ether/acetone = 20:1, v/v). The combined filtrate was evaporated all the volatiles under reduced pressure. The resultant mixture was purifed by silica gel column chromatography (eluend: petroleum ether (60–90 °C)/acetone = 10:1, v/v), affording 3c as a yellow crystalline solid (34 mg, 92% yield). The obtained 5-(4-fluorophenyl)-3-methyl-1-phenyl-1H-pyrazole (3a) (65 mg, 0.66 mmol), r-BuOH (112 mg, 1.0 mmol) in 5 mL r-BuOH was refluxed for 9 h. After cooled to ambient temperature, the resulting mixture was filtered through a short pad of celite and rinsed with 10 mL CH2Cl2. The combined filtrate was evaporated all the volatiles under reduced pressure. The resultant residue was purifed by silica gel column chromatography (eluend: petroleum ether (60–90 °C)/acetone = 10:1, v/v), affording 3c as a yellow crystalline solid (46 mg, 86% yield). The obtained 5-(4-fluorophenyl)-3-methyl-1-phenyl-1H-pyrazole (3a) (65 mg, 0.66 mmol), r-BuOH and water (2 mL) were added in 5 mL THF. The mixture was stirred at 50 °C for 2 h. All the products were recovered by filtration, and then purified by gel column chromatography (eluent: petroleum ether/acetone = 20:1, v/v). The combined filtrate was evaporated all the volatiles under reduced pressure. The resultant mixture was purifed by silica gel column chromatography (eluend: petroleum ether (60–90 °C)/acetone = 10:1, v/v), affording 3c as a yellow crystalline solid (34 mg, 92% yield). The obtained 5-(4-fluorophenyl)-3-methyl-1-phenyl-1H-pyrazole (3a) (65 mg, 0.66 mmol), r-BuOH (112 mg, 0.75 mmol) and t-BuOH (5 mL) were added in 5 mL THF. The mixture was stirred at 50 °C for 2 h. All the products were recovered by filtration, and then purified by gel column chromatography (eluent: petroleum ether/acetone = 20:1, v/v). The combined filtrate was evaporated all the volatiles under reduced pressure. The resultant mixture was purifed by silica gel column chromatography (eluend: petroleum ether (60–90 °C)/acetone = 10:1, v/v), affording 3c as a yellow crystalline solid (34 mg, 92% yield). The obtained 5-(4-fluorophenyl)-3-methyl-1-phenyl-1H-pyrazole (3a) (65 mg, 0.66 mmol), r-BuOH and water (2 mL) were added in 5 mL THF. The mixture was stirred at 50 °C for 2 h. All the products were recovered by filtration, and then purified by gel column chromatography (eluent: petroleum ether (60–90 °C)/acetone = 10:1, v/v), affording 3c as a yellow crystalline solid (34 mg, 92% yield).

6. All the new compounds are characterized by comparison of their NMR features with those of the authentic samples or the reported NMR data.