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

Weiwei Jia, Haifeng Yua,b, Zhengkun Yua,a,*

Abstract

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 \(R^1\) 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 \(R^2\) substituents, that is, \(\beta\)-aryl in 1, can be tolerated during the reaction. Dienic 1g reacted with 2a to give rare 3-styryl-pyrazole 3g (83%, entry 7). Altering \(R^1\) to aryls and heteroaryls, the cyclocondensation reactions of 1b–l with phenylhydrazine were also efficiently carried out under condition A, forming the desired products 3b–l in 78–95% yields (entries 8–12). Under slightly acidic conditions (condition B), the reactions of 1a with benzhydrazine (2b) and 2-hydrazinopyridine (2c) produced the target N-benzyl and 2-pyridyl trisubstituted pyrazoles 3m and 3n in 96% and 75% yields, respectively, (entries 13–14). In order to obtain N-unprotected multisubstituted pyrazoles, hydrazine 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

Pyrazoles and their derivatives usually possess vital pharmaceutical and biological activities, and are also widely used in coordination and materials chemistry. Versatile synthetic routes have been developed for the synthesis of pyrazoles, including cyclocondensation of 1,3-diketones and related derivatives with hydrazines, developed for the synthesis of pyrazoles, including cyclocondensation of 1,3-diketones and related derivatives with hydrazines, and are also widely used in coordination and materials chemistry.2 Versatile synthetic routes have been developed for the synthesis of pyrazoles, including cyclocondensation of 1,3-diketones and related derivatives with hydrazines, and are also widely used in coordination and materials chemistry.2

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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.

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**Equation (1)**

\[
\begin{align*}
R^1 & \quad \xrightarrow{\text{condensation}} \\
R^2 & \quad \xrightarrow{\text{hydrazine}} \quad \text{3}
\end{align*}
\]
Table 1
Synthesis of pyrazoles (3)a,b

\[
\begin{array}{cccccc}
\text{Entry} & \text{1} & \text{R}^3&\text{NHNH}_2 & \text{Conditions} & \text{Product} & \text{Yield}^\circ (%)\\
1 & \text{MeO} \& \text{Ph} & \text{PhNHNH}_2 (\text{2a}) & \text{A} & \text{3a} & 87 \\
2 & \text{MeO} \& \text{Ph} & \text{2a} & \text{A} & \text{3b} & 87 \\
3 & \text{MeO} \& \text{Ph} & \text{2a} & \text{A} & \text{3c} & 92 \\
4 & \text{Cl} \& \text{Ph} & \text{2a} & \text{A} & \text{3d} & 85 \\
5 & \text{F} \& \text{Ph} & \text{2a} & \text{A} & \text{3e} & 82 \\
6 & \text{F} \& \text{Ph} & \text{2a} & \text{A} & \text{3f} & 76 \\
7 & \text{Ph} \& \text{Ph} & \text{2a} & \text{A} & \text{3g} & 83 \\
8 & \text{PhO} \& \text{Ph} & \text{2a} & \text{A} & \text{3h} & 92 \\
9 & \text{MeO} \& \text{Cl} & \text{2a} & \text{A} & \text{3i} & 79 \\
10 & \text{Cl} \& \text{Ph} & \text{2a} & \text{A} & \text{3j} & 95 \\
\end{array}
\]

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

Finally, a one-pot, two-step three-component tandem reactions via Liebeskind–Srogl cross-coupling9/cyclocondensation sequence starting from 411 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 $t$-BuOK base and a new solvent $t$-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.

In summary, an efficient regioselective synthetic route to multisubstituted pyrazoles has been developed by cyclocondensation of

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<th>Entry</th>
<th>$R^4$NHNH$_2$</th>
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$^a$ Condition (A): 1 (0.5 mmol), 2 (0.6 mmol), $t$-BuOK (1.0 mmol), $t$-BuOH (5 mL), reflux, 7–16 h. Condition (B): 1 (0.3 mmol), 2 (0.45 mmol), AcOH (18 μL), $t$-BuOH (3 mL), reflux, 5–9 h.

$^b$ Isolated yields.
β-thioalkyl-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 Liebeschütz–Srogl cross-coupling/cyclocondensation sequence using α-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

8. A general synthetic procedure—synthesis of 5-(4-tert-butylyphenyl)-3-methyl-1-phenyl-1H-pyrazole (3c): A mixture of 1c (131 mg, 0.55 mmol), PhNHNH2 (2a) (65 mg, 0.66 mmol), t-BuOK (112 mg, 1.0 mol) in 5 mL t-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 purified by silica gel column chromatography (elucent: petroleum ether (60–90 °C)/EtOAc = 20:1, v/v), affording 3c as a yellow crystalline solid (134 mg, 92% yield). Mp: 54–56 °C. 1H NMR (CDCl3, 23 °C, 400 MHz): δ 7.30 (m) and 7.14 (d, J = 8.0 Hz) (72 Hz, aromatic CH), 6.29 (s, 1 H, pyrazolyl CH), 2.38 (s, 3 H, CH3N), 1.30 (s, 9 H, (Bu)2), 13C (CD3) NMR (CDCl3, 23 °C, 100 MHz): δ 153.1 (Cq, C–N), 149.5 (Cq, C–N), 143.9, 140.5 and 127.9 (Cq each), 128.9, 128.3, 127.1, 125.4 and 125.3 (aromatic CH), 107.7 (pyrazolyl CH), 34.8 (Cq (CH3)2), 31.4 (Cq (CH3)), 13.7 (CH3 (CHN)). HRMS calculated for C12H15N2: 200.1783; Found: 200.1783.
9. A general procedure for one-pot synthesis of pyrazoles—synthesis of 5-(3,5-difluorophenyl)-3-methyl-1H-pyrazole (3b): Under nitrogen atmosphere a mixture of 5-α-oxo ketene dithioacetals (4a) (95 mg, 0.50 mmol), aryboronic acid 5a (114 mg, 0.75 mmol), Pd(PPh3)4 (43 mg, 0.0375 mmol), CuCl (191 mg, 1.0 mmol) and Cs2CO3 (326 mg, 1.0 mmol) in 5 mL THF was stirred at 50 °C for 2 h. All the volatiles were pumped off under reduced pressure, and then hydrazine PhNHNH2 (2a) (65 mg, 0.66 mmol), t-BuOK (112 mg, 1.0 mmol) and t-BuOH (5 mL) were added and the mixture was further stirred under refluxing conditions for 12 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 purified by silica gel column chromatography (elucent: petroleum ether (60–90 °C)/EtOAc = 20:1, v/v), affording 3b as a yellow crystalline solid (106 mg, 80% yield). All the new products were characterized by NMR and HRMS determinations. The known compounds 3a, 3b, and 3d14b 3d, 3s14b 3i and 3j14b 3s, 3m14b 3e and 3f14 were identified by comparison of their NMR features with those of the authentic samples or the reported NMR data.