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Regioselective synthesis of multisubstituted pyrazoles via cyclocondensation of β-thioalkyl-α,β-unsaturated ketones with hydrazines

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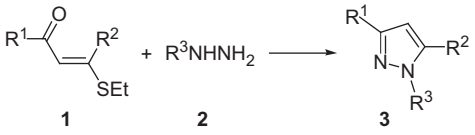
ABSTRACT

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

Pyrazoles and their derivatives usually possess vital pharmaceutical and biological activities,[1] 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,[3] 1,3-dipolar cycloaddition of diazo compounds with alkynes and alkyne equivalents,[4] and other procedures.[5] However, it remains a challenge to reach sufficient regioselectivity for the target pyrazoles in a synthetic task. Recently, Junjappa and co-workers reported the synthesis of substituted 1-aryl-5(or 3)-*N*-(cycloamino) pyrazoles by condensation of *N*,*S*-acetal precursors with unsymmetrical phenylhydrazines in a regiocontrolled fashion.[3a] Kimpe and co-workers documented the preparation of fluorinated pyrazoles with relatively poor regioselectivity by means of a similar strategy.[3c] A new access to 3,4-disubstituted pyrazoles from $FeCl_3$-catalyzed aminolysis of β-carbonyl-1,3-dithianes with hydrazine hydrate has also been developed.[3d] Very recently, our group realized an efficient palladium(0)-catalyzed, Cu(I)-mediated regio- and stereoselective approach to β-thioalkyl-α,β-unsaturated ketones via oxo directing Liebeskind–Srogl cross-coupling reactions of α-oxo ketene dithioacetals with aryl or alkenylboronic acids.[6] With their determined molecular structures in hand, we envisioned that β-thioalkyl-α,β-unsaturated ketones may be viewed as the equivalents of 1,3-diketones.

As part of our ongoing work on the development of pyrazole-based NNN ligands[7] and transformation of α-oxo ketene dithioacetals,[8] herein we report an efficient synthetic protocol to regioselectively multisubstituted pyrazoles by cyclocondensation of β-thioalkyl-α,β-unsaturated ketones[6] with hydrazines (Eq. (1)).



1 2 3 (1)

The reactions of β-thioalkyl-α,β-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, β-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 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-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 β-thioalkyl-α,β-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 1*H*-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

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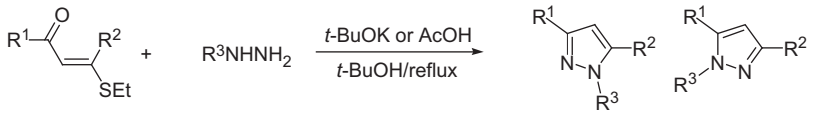
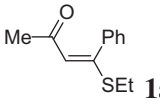
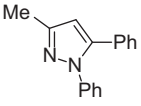
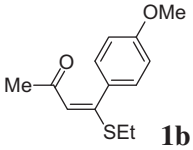
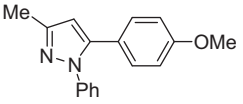
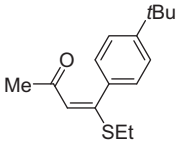
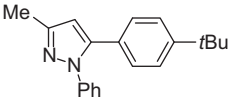
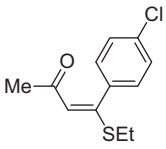
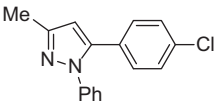
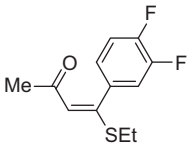
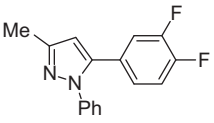
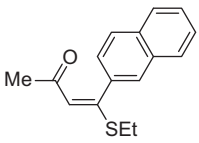
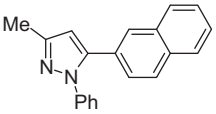
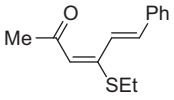
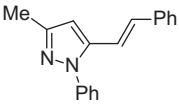
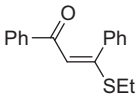
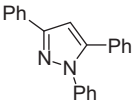
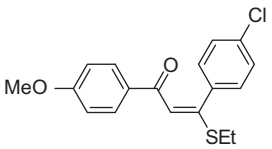
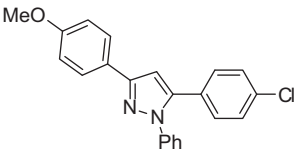
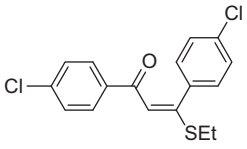
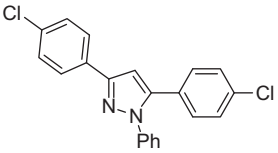
Table 1
Synthesis of pyrazoles (**3**)[a,b]

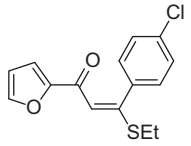
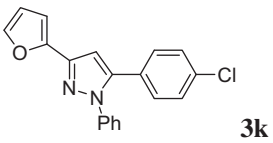
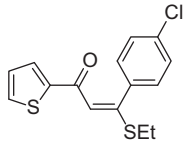
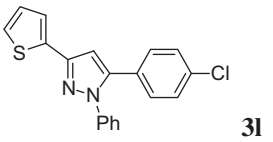
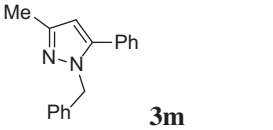
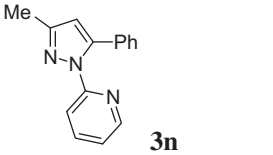
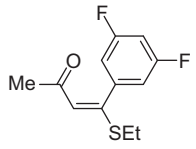
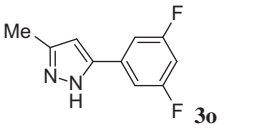
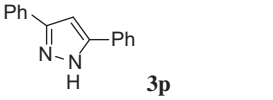
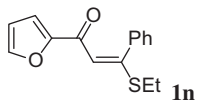
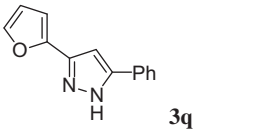
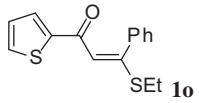
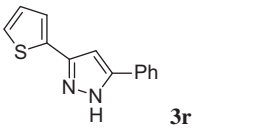


1 **2** **3** **3'**, not detected

Entry	**1**	R^4NHNH_2	Conditions	Product	Yield[b] (%)
1	 **1a**	$PhNHNH_2$ (**2a**)	A	 **3a**	87
2	 **1b**	**2a**	A	 **3b**	87
3	 **1c**	**2a**	A	 **3c**	92
4	 **1d**	**2a**	A	 **3d**	85
5	 **1e**	**2a**	A	 **3e**	82
6	 **1f**	**2a**	A	 **3f**	76
7	 **1g**	**2a**	A	 **3g**	83
8	 **1h**	**2a**	A	 **3h**	92
9	 **1i**	**2a**	A	 **3i**	79
10	 **1j**	**2a**	A	 **3j**	95

(*continued on next page*)

Table 1 (*continued*)

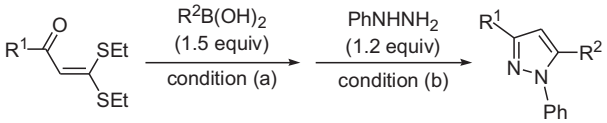
Entry	1	R^4NHNH_2	Conditions	Product	Yield[b] (%)
11	 **1k**	**2a**	A	 **3k**	78
12	 **1l**	**2a**	A	 **3l**	88
13	**1a**	$PhCH_2NHNH_2$ (**2b**)	B	 **3m**	96
14	**1a**	$2\text{-}C_5H_4NNHNH_2$ (**2c**)	B	 **3n**	75
15	 **1m**	$NH_2NH_2H_2O$ (**2d**)	B	 **3o**	80
16	**1h**	**2d**	B	 **3p**	91
17	 **1n**	**2d**	B	 **3q**	83
18	 **1o**	**2d**	B	 **3r**	95

[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.

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.[3a]

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 *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.



R^1 =: Me (**4a**)	R^2 =: 4-$MeOC_6H_4$ (**5a**)	**3b**, 80%
Ph (**4b**)	Ph (**5b**)	**3h**, 85%
4-ClC_6H_4 (**4c**)	4-ClC_6H_4 (**5c**)	**3j**, 89%
2-furyl (**4d**)	4-ClC_6H_4 (**5c**)	**3k**, 78%
2-thienyl (**4e**)	4-ClC_6H_4 (**5c**)	**3l**, 77%

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), $Pd(PPh_3)_4$ (7.5 mol %), copper(I) thiophene-2-carboxylate (CuTC[10], 1.0 mmol), Cs_2CO_3 (1.0 mmol), THF (5 mL), 50 °C, 2 h; (b) *t*-BuOK (1.0 mmol), *t*-BuOH (5 mL), reflux, 9–16 h.

In summary, an efficient regioselective synthetic route to multisubstituted 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 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

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.168.

References and notes

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12. A general synthetic procedure—synthesis of 5-(4-*tert*-butylphenyl)-3-methyl-1-phenyl-1*H*-pyrazole (**3c**): A mixture of **1c** (131 mg, 0.5 mmol), $PhNHNH_2$ (**2a**) (65 mg, 0.6 mmol), *t*-BuOK (112 mg, 1.0 mmol) 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 CH_2Cl_2. The combined filtrate was evaporated all the volatiles under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: 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 ($CDCl_3$, 23 °C, 400 MHz): δ 7.30 (m) and 7.14 (d, J = 8.0 Hz) (7:2 H, aromatic CH), 6.29 (s, 1 H, pyrazolyl CH), 2.38 (s, 3 H, CH_3C=N), 1.30 (s, 9 H, *t*Bu); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 23 °C, 100 MHz): δ 151.3 (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, $C(CH_3)_3$), 31.4 ($C(CH_3)_3$), 13.7 (CH_3C=N). HRMS cacld for $C_{20}H_{22}N_2$: 290.1783; Found: 290.1783.
13. A general synthetic procedure—synthesis of 5-(3,5-difluorophenyl)-3-methyl-1*H*-pyrazole (**3o**): A mixture of **1m** (58 mg, 0.3 mmol), 80% $NH_2NH_2{\cdot}H_2O$ (**2d**) (28 mg, 0.45 mmol), AcOH (18 μL) in 3 mL *t*-BuOH was refluxed for 5 h. After cooled to ambient temperature, the resulting mixture was evaporated all the volatiles under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60–90 °C)/EtOAc = 20:1, v/v), affording **3o** as a yellow crystalline solid (46 mg, 80% yield). Mp: 123–125 °C. ^1H NMR ($CDCl_3$, 23 °C, 400 MHz): δ 7.61 and 7.27 (d each, J = 1.7 and 1.6 Hz, 2:1 H, aromatic CH), 6.33 (s, 1 H, pyrazolyl CH), 2.32 (s, 3 H, CH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 23 °C, 100 MHz): δ 149.2 (Cq, C=N), 141.9 (Cq, C–N), 136.2 (Cq, *i*-C of $C_6H_3F_2$), 135.4 (Cq, C–F), 127.6 and 124.2 (aromatic CH), 102.6 (pyrazolyl CH), 11.3 (CH_3). HRMS cacld for $C_{10}H_8N_2F_2$ [M−1]: 193.0577; Found: 193.0358.
14. A general procedure for one-pot synthesis of pyrazoles—synthesis of 5-(4-methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazole (**3b**): Under nitrogen atmosphere a mixture of α-oxo ketene dithioacetal (**4a**) (95 mg, 0.50 mmol), arylboronic acid **5a** (114 mg, 0.75 mmol), $Pd(PPh_3)_4$ (43 mg, 0.0375 mmol), CuTC (191 mg, 1.0 mmol) and Cs_2CO_3 (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 $PhNHNH_2$ (**2a**) (65 mg, 0.6 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 CH_2Cl_2. The combined filtrate was evaporated all the volatiles under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: 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 characyerized by NMR and HRMS determinations. The known compounds **3a**, **3b**, and **3h**,[15a] **3d**,[15b] **3i** and **3j**,[15c] **3l**,[15d] **3m**,[15e] **3n**,[15f] **3p–r**[3h] were identified by comparison of their NMR features with those of the authentic samples or the reported NMR data.
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