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Synthesis of 1,3,4-Trisubstituted Pyrazoles from α-(1,3-Dithian-2-yl) Enamine Ketones via [4+1] Cyclization

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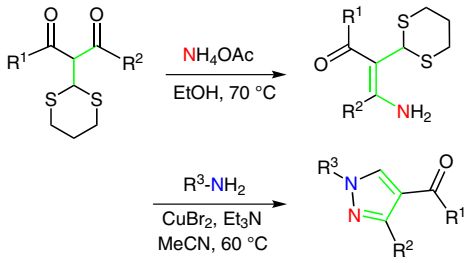

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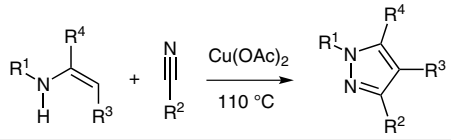
Abstract A novel method for the synthesis of 1,3,4-trisubstituted pyrazoles from α-(1,3-dithian-2-yl) enamine ketones and primary amines, involving copper(II)-catalyzed oxidative N–N coupling, has been developed. This unprecedented [4+1] approach is versatile in the synthesis of *N*-aryl, *N*-benzyl and *N*-alkyl pyrazoles, and provides an alternative to the conventional [3+2] methods.

Key words enamine ketones, primary amines, copper(II), catalysis, N–N coupling, [4+1] cyclization

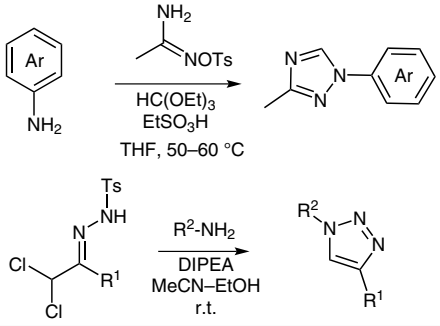
Substituted pyrazoles have shown a broad spectrum of pharmacological and biological activities.[1] For instance, 1,3,4-trisubstituted pyrazole derivatives can be utilized as antitumor and antiangiogenic agents;[2] 1,3,5-trisubsttuted pyrazole motif is adopted in inhibitors of mycobacteria tuberculosis and estrogen receptors;[3] Celebrex, Viagra and Acomplia, which have been successfully commercialized, are not exempt from pyrazole-containing compounds.[4]

The most commonly used approaches to the synthesis of pyrazoles, which involve the classical condensation of hydrazines with 1,3-dicarbonyl compounds and their equivalents,[5] the 1,3-dipolar [3+2] cycloadditions and the transition-metal-catalyzed C–N or C–C cross coupling on preformed pyrazoles[6–8] have been extensively studied. However, regioselective synthesis of the pyrazole ring remains a significant challenge.[9] Recently, Glorius and coworkers constructed a new method for the preparation of tetrasubstituted pyrazoles from enamines and nitriles involving a copper(II)-catalyzed oxidative N–N bond formation (Scheme 1).[10] The method has a broad substrate scope, and provides the products regiospecifically, but not escape from the conventional [3+2] cyclization.

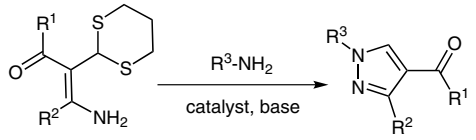


Scheme 1 Copper(II)-catalyzed oxidative N–N bond formation

Inspired by Glorius's work, synthesis of triazoles via [4+1] cyclization involving N–N coupling reactions were reported by Tam, Berkel and their co-workers (Scheme 2), respectively.[11,12] However, a similar breakthrough has still not been made in the synthesis of pyrazoles. Herein, we report an unprecedented N–N coupling strategy for the synthesis of 1,3,4-trisubstituted pyrazoles via [4+1] cyclization from α-(1,3-dithian-2-yl) enamine ketones and primary amines (Scheme 3).

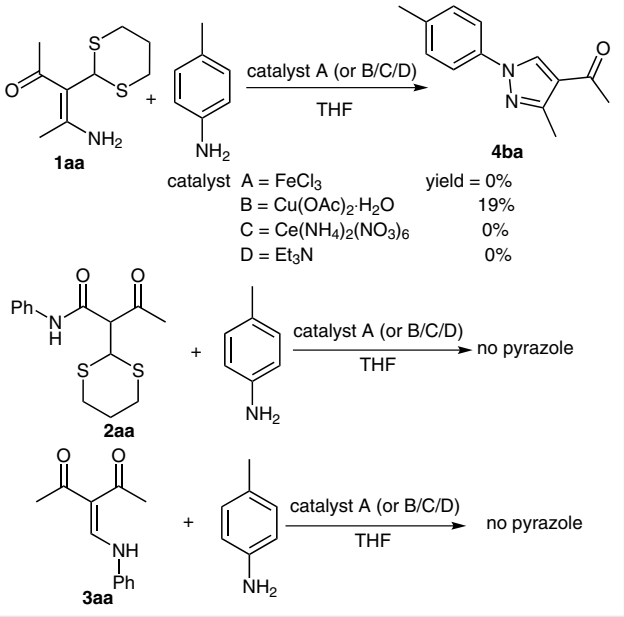


Scheme 2 Synthesis of triazoles via [4+1] cyclization involving N–N coupling reactions



Scheme 3 Synthesis of 1,3,4-trisubstituted pyrazoles via [4+1] cyclization involving N–N coupling reactions

A model study was initiated with α-(1,3-dithian-2-yl) enamine ketone **1aa** and 4-methylaniline as substrates to investigate competent substrates and catalysts. Encouragingly, a 19% yield of the desired pyrazole **4ba** was achieved after stirring for 12 hours at 60 °C in the presence of $Cu(OAc)_2·H_2O$ as the catalyst (Table 1). However, attempts to use other catalysts, such as $FeCl_3$, $Ce(NH_4)_2(NO_3)_6$ and Et_3N, were not as successful as $Cu(OAc)_2·H_2O$. Alternative substrates, such as 2-(1,3-dithian-2-yl)-3-oxo-*N*-phenylbutanamide (**2aa**) and 3-acetyl-4-(phenylamino)but-3-en-2-one (**3aa**), could not react with 4-methylaniline or failed to assemble pyrazole derivatives under attempted conditions (Scheme 4).



Scheme 4 Model study of catalysts and substrates

Further investigation showed that this transformation was highly solvent dependent. Higher yields were achieved in MeCN and THF (Table 1, entries 7 and 18), while other solvents, such as EtOH, $CHCl_3$ and DMF (entries 16, 17 and 19), led to no reaction or lower yield. It seems that the solubility of substrates was the key factor. When the reaction was conducted in DMF, it was observed that higher temperatures could not speed up the reactions and improve the yields apparently (entries 19–21). Consequently, the conditions in entry 18 were deemed the best, and they were chosen for further investigation.

Table 1 Optimization of Reaction Conditions

Entry	Catalyst	Base	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	$Cu(OAc)_2·H_2O$	–	THF	60	12	19
2	$Cu(OAc)_2·H_2O$	K_2CO_3	THF	60	12	55[b]
3	$Cu(OAc)_2·H_2O$	Et_3N	THF	60	20	72[c]
4	$Cu(OAc)_2·H_2O$	Et_3N	THF	60	20	78
5	$CuSO_4·5H_2O$	Et_3N	THF	60	24	32
6	$CuBr_2$	K_2CO_3	THF	60	12	–
7	$CuBr_2$	Et_3N	THF	60	6	90
8	$CuBr_2$	Et_3N	THF	60	6	90[d]
9	$CuBr_2$	Et_3N	THF	60	24	64
10	$CuCl_2$	Et_3N	THF	60	12	86[e]
11	CuO	Et_3N	THF	60	24	–
12	CuI	Et_3N	THF	60	24	44
13	$CuBr_2$	piperidine	THF	60	6	89
14	$CuBr_2$	Et_2N	THF	60	12	67
15	$CuBr_2$	pyridine	THF	60	12	–
16	$CuBr_2$	Et_3N	EtOH	60	12	–
17	$CuBr_2$	Et_3N	$CHCl_3$	60	12	–
18	**$CuBr_2$**	**Et_3N**	**MeCN**	**60**	**6**	**91**
19	$CuBr_2$	Et_3N	DMF	60	12	62
20	$CuBr_2$	Et_3N	DMF	80	12	56
21	$CuBr_2$	Et_3N	DMF	100	12	62

[a] Reaction conditions: **1aa** (1.0 mmol), 4-methylaniline (1.0 mmol), base (1.5 mmol), catalyst (0.5 mmol), solvent (10 mL), 60 °C.
[b] Amount of K_2CO_3 used was 1.0 mmol.
[c] Amount of Et_3N used was 1.0 mmol.
[d] Amount of $CuBr_2$ used was 1 mmol.
[e] Amount of $CuBr_2$ used was 0.1 mmol.

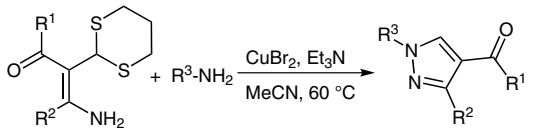
Having identified these optimal conditions, we then extended the substrate scope of this reaction. As illustrated in Table 2, a variety of anilines, regardless of the electron-donating or electron-withdrawing group on the aromatic ring, were broadly tolerated, giving the products in moderate-to-good yields (**4ba**–**4bm**). Valuable functional groups, such as methyl (**4ba**), methoxy (**4bc**), chloro (**4bm**), bromo (**4bd**), iodo (**4bk**) and nitro (**4be**), were also present in the corresponding products. Generally, electron-rich anilines showed higher reactivity to afford the 1,3,4-trisubstituted pyrazoles than those with electron-withdrawing groups at the same substitution position. It is easy to understand that the higher electron density at the nitrogen atom of anilines was beneficial to the initial nucleophilic substitution. Moreover, steric hindrance of both **1a** (**4bd**, **4bh**, **4bj**) and primary amines (**4ba**, **4bi**, **4bl**) had remarkable effect on this

transformation. It was verified that substituent R^3 could be alkyl and aryl, including heterocyclic groups like thienyl (**4bj**).

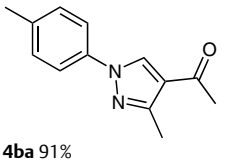
In addition, *N*-benzylpyrazole (**4bn**) could be obtained successfully through the method. Especially noteworthy was the regioselective synthesis of *N*-propylpyrazole (**4bo**), since *N*-alkylpyrazoles were difficult to synthesize by classical methods due to the limited availability and high cost of alkylhydrazine.[13] Points discussed above indicated a wide scope of the method unanimously.

To our surprise, neither excess catalysts[10a,14] nor suitable oxidants,[10b,15] which were essential conditions to an oxidative N–N bond formation, were loaded in this method. To confirm the mechanism of this N–N coupling, the cyclization was conducted under N_2 atmosphere. An 11% yield of pyrazole was obtained by the use of a 0.5 equivalent amount of $CuBr_2$ (Scheme 5,A). In contrast, reactions conducted under the same conditions without N_2 (Scheme 5,B) afforded the optimal reaction rate and conversion ratio (91% yield). Even a 0.1 equivalent amount of $CuBr_2$ could lead to a 64% yield under air atmosphere (Scheme 5,D). However, insufficient catalyst paralyzed the reaction completely when N_2 was filled (Scheme 5,C). Suitable oxidant was also indispensable to this N–N bond formation, and O_2 in the air was the only candidate.

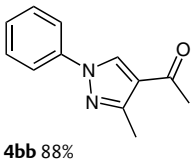
Table 2 Synthesis of 1,3,4-Trisubstituted Pyzoles[a]



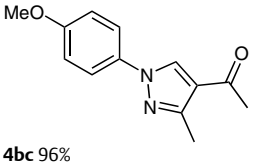
1a **4b**



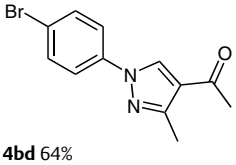
4ba 91%



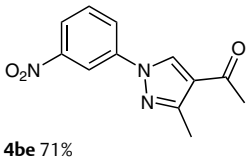
4bb 88%



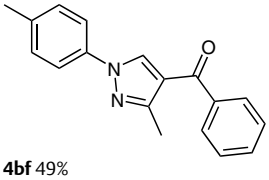
4bc 96%



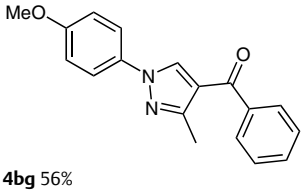
4bd 64%



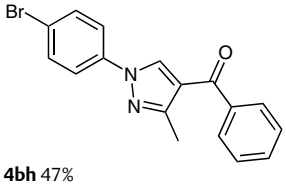
4be 71%



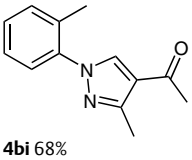
4bf 49%



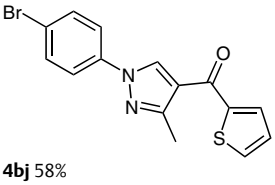
4bg 56%



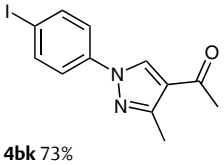
4bh 47%



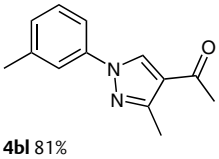
4bi 68%



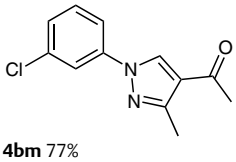
4bj 58%



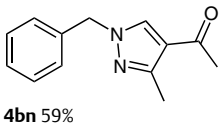
4bk 73%



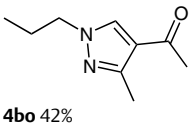
4bl 81%



4bm 77%

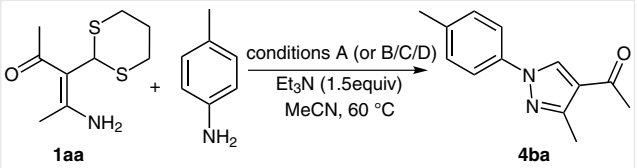


4bn 59%



4bo 42%

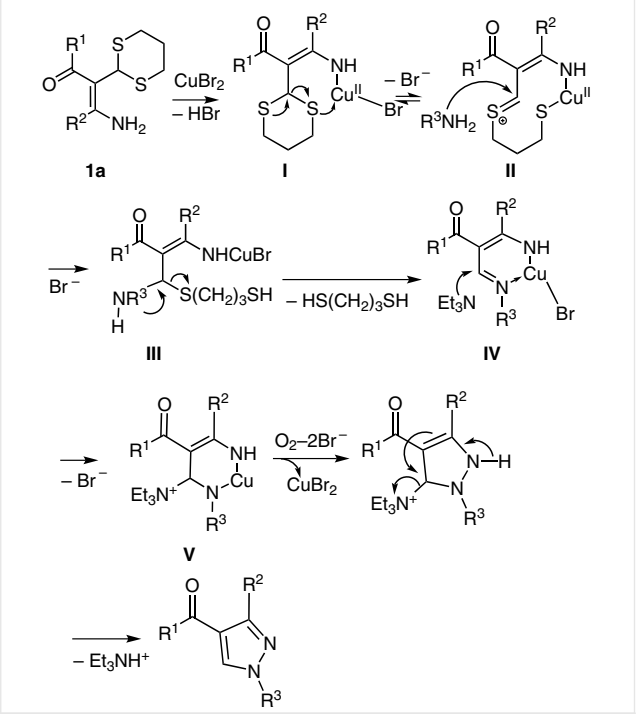
[a] Reaction conditions: **1a** (1.0 mmol), R^3NH_2 (1.0 mmol), Et_3N (1.5 mmol), $CuBr_2$ (0.5 mmol), MeCN (10 mL), 60 °C.



A: $CuBr_2$ (0.5 equiv), N_2, 24 h, 11% yield
B: $CuBr_2$ (0.5 equiv), air, 6 h, 91% yield (Table 1, entry 18)
C: $CuBr_2$ (0.1 equiv), N_2, 24 h, 0% yield
D: $CuBr_2$ (0.1 equiv), air, 24 h, 64% yield (Table 1, entry 9)

Scheme 5 Study of oxidants

On the basis of the above results and completed work,[10,16] a possible mechanism is proposed in Scheme 6. The Cu^{II} first coordinates to the nitrogen and sulfur atoms in α-(1,3-dithian-2-yl) enamine ketone **1a**, forming the intermediate **I**. Subsequently, one C–S bond is cleaved to give the intermediate **II**. After that, the amine attacking at the carbon atom of **II** leads to the desulfurization which results in the formation of 1,3-bisimine **IV**. Then, Cu^{II} coordinates to the nitrogen atom of amine to generate Cu^{II}-(1,3-imine-enamine) chelate **V**. With reductive elimination, the desired N–N bond is formed to generate the corresponding 1,3,4-trisubstituted pyrazoles. Reduced copper catalyst follows, is oxidized to Cu^{II} by oxygen molecules in the air and reenters the catalytic cycle.



Scheme 6 Proposed reaction mechanism

In summary, we have reported a novel copper-catalyzed approach for the synthesis of 1,3,4-trisubstituted pyrazoles from α-(1,3-dithian-2-yl) enamine ketones and primary amines, involving a copper(II)-catalyzed oxidative N–N coupling and a non-oxidative C–N bond formation.[17] Regioselective synthesis of *N*-arylpyrazoles, *N*-benzylpyrazoles and *N*-alkylpyrazoles using the same method was achieved. Furthermore, this unprecedented and highly practical [4+1] cyclization provides an alternative to the conventional [3+2] methods of pyrazole synthesis[5,6] with a broad substrate scope, high atom efficiency, without the need of carcinogenic hydrazines and with less formation of toxic by-products. Notably, air, the most environment friendly oxidant, was employed under mild reaction conditions. Studies are ongoing in our laboratory to investigate further synthetic applications.

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(17) **General Procedure for the Synthesis of α-(1,3-Dithian-2-yl)enamine Ketones (1a)**: To a 25.0-mL round-bottomed flask, dithiane (10.0 mmol), NH_4OAC (3.85 g, 50.0 mmol) and EtOH (5.0 mL) were added successively. The mixture was stirred at 70 °C. Solid in the flask dissolved into liquid gradually, and a clear solution was obtained. Continuous heating made the solution muddy, and finally solid was precipitated from the solution. The solvent was removed and the residue was cooled. The residue (crude product) was washed with cool EtOH to obtain pure product **1a**.

Selected Spectral Data of 4-Amino-3-(1,3-dithian-2-yl)pent-3-en-2-one (1aa): yield: 92%; white solid; mp 163–164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70–1.83 (m, 2 H), 2.39 (s, 3 H), 2.49 (s, 3 H), 2.81–2.86 (m, 2 H), 2.94–3.01 (m, 2 H), 5.22 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.40, 25.25, 28.74, 33.86, 48.14, 104.64, 167.15, 195.09.

General Procedure for the Synthesis of 1,3,4-Trisubstituted Pyrazoles (4b): To a solution of α-(1,3-dithian-2-yl) enamine ketones **1a** (1.0 mmol) and primary amine (1.0 mmol) in MeCN (10.0 mL), $CuBr_2$ (0.1116 g, 0.5 mmol) and Et_3N (0.1518 g, 1.5 mmol) were added. The reaction mixture was warmed to 60 °C and stirred until the staring material was consumed (monitored by TLC). Upon cooling to r.t., the reaction mixture was filtrated and washed with CH_2Cl_2. The filtrate was concentrated in vacuo and purified by column chromatography over silica gel to give product **4b**.

Selected Data:

1-[3-Methyl-1-(4-methylphenyl)-1*H*-pyrazol-4-yl]ethanone (4ba): 91% yield; white solid; mp 101–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 2.47 (s, 3 H), 2.57 (s, 3 H), 7.25–7.28 (d, *J* = 8.4 Hz, 2 H), 7.54–7.57 (d, *J* = 8.4 Hz, 2 H), 8.25 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.26, 20.98, 28.65, 119.38, 122.37, 130.08, 130.84, 136.99, 137.25, 151.71, 192.49. HRMS (ESI, TOF): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{15}N_2O$: 215.1186; found: 215.1179.