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$BF_3{\cdot}OEt_2$-mediated alkenylation of pyrroles with α-oxo ketene dithioacetals

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ABSTRACT

$BF_3{\cdot}OEt_2$-mediated alkenylation of pyrroles with α-oxo ketene dithioacetals was efficiently realized, affording mono- and disubstituted ketene pyrrolyl acetals. In the cases of using *N*-unprotected pyrrole, the reactions gave ketene bipyrrolyl acetals as well as *N*,*O*-chelated BF_2 complexes. Diverse C–S transformations were achieved for the monosubstituted products, yielding *N*-heterocycles or multisubstituted olefins.

α-Oxo ketene dithioacetals[1] have recently been applied in diverse organic synthesis,[2] or used as odorless thiol equivalents under acidic conditions.[3] Very recently, transition metal-catalyzed C–H[4a–d] and C–S[4e–g] activation and functionalization of α-oxo ketene dithioacetals have also been explored. Pyrrole[5] is the important structural unit in many natural products and pharmaceuticals, so that efficient functionalization of pyrroles has been attracting much attention. As nucleophiles, pyrroles underwent Michael addition reactions with nitroolefins or enones,[6a,6b] and Friedel–Crafts alkylation.[6c–f] Arylation of pyrroles was well studied under various conditions.[7] However, alkenylation of pyrroles has not been paid considerable attention. Besides functional group-directed organic synthesis,[8] alkenylated pyrroles are usually accessed through transition metal-catalyzed alkenylation of pyrroles with alkenes[9] or addition of pyrrolyl C–H to alkynes.[10] Recently, we found that α-oxo ketene dithioacetals could react with indoles in the presence of trifluoroacetic acid (TFA) to form alkenylated indole derivatives under mild conditions (Scheme 1a).[11] Thus, we envisioned that pyrroles might undergo similar substitution reactions to produce alkenylated pyrroles. Unexpectedly, no target alkenylated products could be obtained from the reactions of pyrroles under similar conditions. To our delight, Lewis acid, that is, $BF_3{\cdot}OEt_2$ complex, could mediate the substitution reactions of α-oxo ketene dithioacetals with pyrroles, regioselectively giving mono- and bispyrrole products. Herein, we disclose $BF_3{\cdot}OEt_2$-mediated direct alkenylation of pyrroles with α-oxo ketene dithioacetals and the diverse transformations of the monosubstituted ketene pyrrolyl acetals.

Initially, the reaction of α-oxo ketene dithioacetal **1a** and *N*-benzylpyrrole (**2a**) was conducted to optimize the reaction conditions (Table 1). In the presence of one equivalent of $BF_3{\cdot}OEt_2$ the reaction of **1a** and **2a** in a 1:1 molar ratio underwent in acetonitrile at ambient temperature for 14 h to form pyrrolyl-substituted ketene thioacetal **3a** (63%) and bispyrrole **4a** (13%) (Table 1, entry 1). Increasing the loading of **1a** to 1.5 equiv enhanced the yield of **3a** to 79% (69% isolated yield) and lessened the formation of **4a**, while further increasing the amount of **1a** did not obviously improve the yield (Table 1, entries 2–5). Varying the Lewis acid amount only slightly influenced the reaction efficiency. Shortening the reaction time to 8–11 h lowered the product yields. It is notable that the reaction exclusively formed **3a** and **4a** as the products under the stated conditions. In order to get the bispyrrole product **4a** the amount of pyrrole **2a** was increased to 2 equiv. Thus, **4a** was obtained in 36% yield with **3a** (60%) as the major product (Table 1, entry 8). Using 2 equiv $BF_3{\cdot}OEt_2$ led to **4a** (47%), and further increasing the loading of **2a** to 3 equiv gave **4a** in 75% isolated yield (Table 1, entries 9–11). Keeping a higher concentration of $BF_3{\cdot}OEt_2$ (2.5 equiv) deteriorated formation of **4a** with formation of some unidentified side products (Table 1, entry 12). Nitromethane could also be used as the reaction medium, while toluene was not suitable solvent for the reaction. For easiness of the work-up procedures the conditions (condition A) for entry 3 and those (condition B) for entry 11 are considered as the optimal

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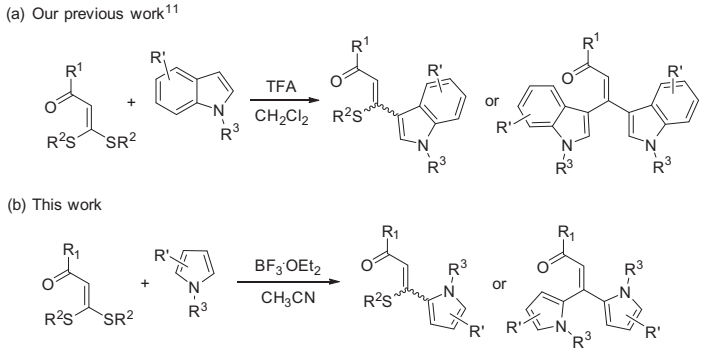
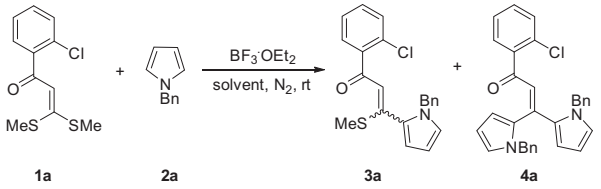


Scheme 1. Acid-mediated alkenylation of *N*-heterocycles with α-oxo ketene dithioacetals.

Table 1
Screening of reaction conditions[a]



1a **2a** **3a** **4a**

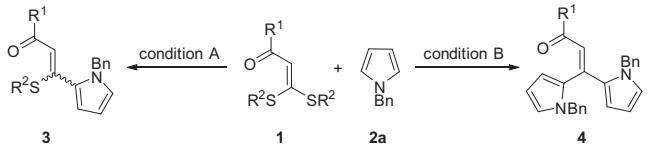
Entry	**1a**:**2a** (molar ratio)	$BF_3{\cdot}OEt_2$ (equiv)	Yield[b] (%)	
			3a[c]	**4a**
1	1:1	1.0	63	13
2	1.5:1	1.0	79	7
3	1.5:1	0.8	79 (69)[d]	7
4	1.5:1	0.6	76	6
5	1.8:1	0.8	80	5
6[e]	1.5:1	0.8	77	7
7[f]	1.5:1	0.8	74	6
8	1:2	1.0	60	36
9	1:2	2.0	50	47
10	1:2.5	2.0	40	60
11	1:3	2.0	(23)[d]	(75)[d]
12	1:3	2.5	(14)[d]	(71)[d]

[a] Conditions: **1a** (0.45 mmol for entries 1–7; 0.50 mmol for entries 8–12), CH_3CN (5 mL), 0.1 MPa N_2, rt, 14 h.
[b] Determined by ^1H NMR in $CDCl_3$.
[c] The molar ratio of *Z*/*E*-**3a** isomers was 2:1 by ^1H NMR analysis.
[d] Isolated yield in parentheses.
[e] 11 h.
[f] 8 h.

reaction parameters to prepare ketene pyrrolyl thioacetals of type **3** and bispyrroles of type **4**, respectively.

Next, the protocol generality was explored under the optimal conditions (Table 2). Under condition A or B α-oxo ketene dithioacetals **1a**–**1p** reacted smoothly with pyrrole **2a** to give products **3** (47–86%) and **4** (49–92%), respectively (Table 2), exhibiting good tolerance of the structural and electronic variations of the ketene dithioacetal substrates. In the cases of using dimethyl-thioacetals the substituent effects from the aryl moieties of **1** varied, giving **3a**–**3g** in 61–86% yields (Table 2, entries 1–7), while introduction of five-membered thienyl and furyl or bulky naphthyl to the molecular backbond led to lower yields for the target monosubstituted products **3h**–**3j** (50–57%) (Table 2, entries 8–10). In most cases, the bispyrrole products **4a**–**4j** were obtained in good to excellent yields (Table 2, entries 1–10). The diethylthioacetal substrates also reacted well with pyrrole **2a**, affording the corresponding monosubstituted ketene thioacetals **3k**–**3p** (47–77%) and bipyrroles **4k**–**4p** (64–81%) (Table 2, entries 11–16). The molecular structures of **4** were confirmed by the X-ray single crystal

Table 2
Substrate scope of α-oxo ketene dithioacetals (**1**)[a]



3 **1** **2a** **4**

Entry	**1**		Condition	Product	Yield[b] (%)
1	**1a**	R^1 = 2-ClC_6H_4	A	**3a**	69 (2:1)[c]
		R^2 = SMe	B	**4a**	75
2	**1b**	R^1 = 2-BrC_6H_4	A	**3b**	76 (2:1)[c]
		R^2 = SMe	B	**4b**	49
3	**1c**	R^1 = 2-MeC_6H_4	A	**3c**	71 (3.4:1)[c]
		R^2 = SMe	B	**4c**	87
4	**1d**	R^1 = 3-ClC_6H_4	A	**3d**	61 (3.7:1)[c]
		R^2 = SMe	B	**4d**	65
5	**1e**	R^1 = 3-BrC_6H_4	A	**3e**	86 (3.6:1)[c]
		R^2 = SMe	B	**4e**	70
6	**1f**	R^1 = 3-MeC_6H_4	A	**3f**	63 (4:1)[c]
		R^2 = SMe	B	**4f**	80
7	**1g**	R^1 = 4-BrC_6H_4	A	**3g**	66 (4.4:1)[c]
		R^2 = SMe	B	**4g**	74
8	**1h**	R^1 = 2-thienyl	A	**3h**	51 (3.1:1)[c]
		R^2 = SMe	B	**4h**	92
9	**1i**	R^1 = 2-furyl	A	**3i**	57 (2.4:1)[c]
		R^2 = SMe	B	**4i**	90
10	**1j**	R^1 = 2-naphthyl	A	**3j**	50 (4:1)[c]
		R^2 = SMe	B	**4j**	80
11	**1k**	R^1 = Ph	A	**3k**	70 (3.5:1)[c]
		R^2 = SEt	B	**4k**	81
12	**1l**	R^1 = 4-FC_6H_4	A	**3l**	77 (3.6:1)[c]
		R^2 = SEt	B	**4l**	79
13	**1m**	R^1 = 4-ClC_6H_4	A	**3m**	75 (3.6:1)[c]
		R^2 = SEt	B	**4m**	70
14	**1n**	R^1 = 4-IC_6H_4	A	**3n**	76 (3.7:1)[c]
		R^2 = SEt	B	**4n**	64
15	**1o**	R^1 = 4-MeC_6H_4	AB	**3o**	47 (3.7:1)[c]
		R^2 = SEt	B	**4o**	84
16	**1p**	R^1 = 4-$MeOC_6H_4$	A	**3p**	69 (3.7:1)[c]
		R^2 = SEt	B	**4p**	64

[a] Condition A: **1** (0.45 mmol), **2a** (0.30 mmol), $BF_3{\cdot}OEt_2$ (0.24 mmol); condition B: **1** (0.50 mmol), **2a** (1.50 mmol), $BF_3{\cdot}OEt_2$ (1.00 mmol); CH_3CN (5 mL), 0.1 MPa N_2, rt, 14 h.
[b] Isolated yield.
[c] Molar ratio of *Z*/*E*-**3** isomers determined by ^1H NMR analysis.

structural determination of **4o** (Fig. 1). It is noteworthy that the reactions of α-acetyl, trimethylacetyl, and EtO(C=O) ketene di(ethylthio)acetals were complicated, resulting in no separable target products, both α-cyanoketene and cyclic α-oxoketene dimethylthioacetals did not react under the same conditions.

The scope of pyrrole substrates was then investigated (Table 3). The reaction of *N*-methylpyrrole (**2a**) with **1k** under condition A

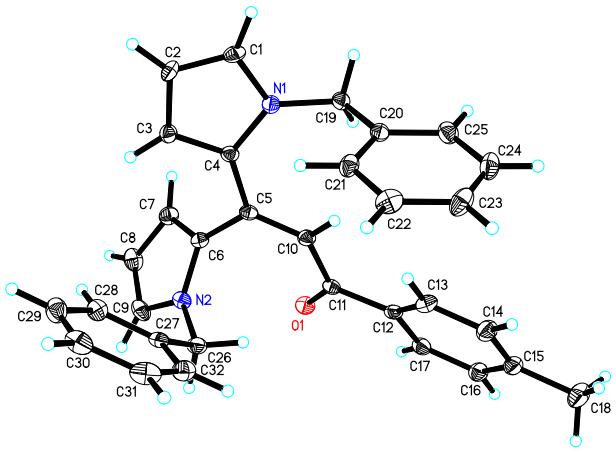
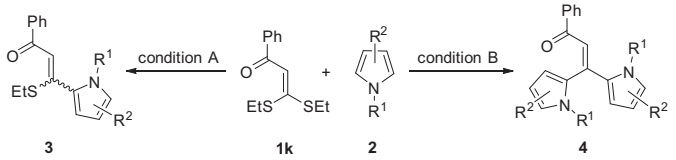
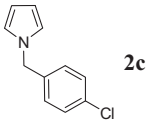
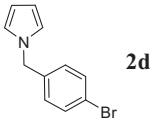
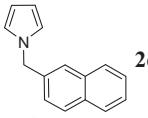
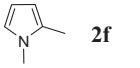
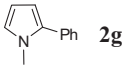
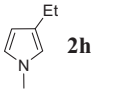


Figure 1. Molecular structure of **4o**.

Table 3
Scope of pyrroles **2**[a]



3 1k 2 4

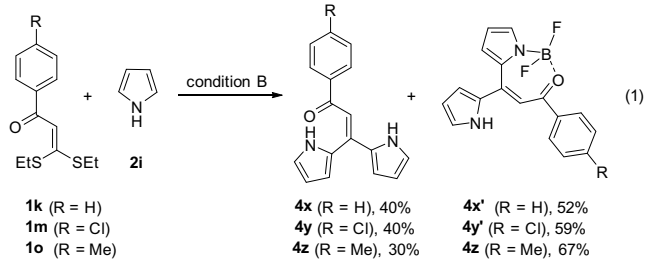
Entry	2	Condition	Product	Yield[b] (%)
1	 **2b**	A B	**3q** + **4q** **4q**	26 (1.9:1)[c] + 24 76
2	 **2c**	A B	**3r** **4r**	60 (3:1)[c] 75
3	 **2d**	A B	**3s** **4s**	60 (3:1)[c] 74
4	 **2e**	A B	**3t** **4t**	63 (3.4:1)[c] 95
5	 **2f**	A B	**3u** + **4u** **4u**	50 (1.9:1)[c] + 36 82
6	 **2g**	A B	**3v** **4v**	71 (2:1)[c] 96
7	 **2h**	A B	**3w** **4w**	41 (2.5:1)[c,d] 70

[a] Condition A: **1k** (0.45 mmol), **2** (0.30 mmol), $BF_3{\cdot}OEt_2$ (0.24 mmol); condition B: **1k** (0.50 mmol), **2** (1.50 mmol), $BF_3{\cdot}OEt_2$ (1.00 mmol); CH_3CN (5 mL), 0.1 MPa N_2, rt, 14 h.
[b] Isolated yield.
[c] Molar ratio of *Z*/*E*-**3** isomers determined by ^1H NMR analysis.
[d] 40 h.

only formed **3q** in 26% yield with production of **4q** (24%). Using *N*-arylmethyl-substituted pyrroles **2c**–**2e** led to the products in 60–63% yields. 1,2-Dimethylpyrrole (**2f**) reacted under condition A to give bispyrrole **4u** (36%) as the side product, whereas 1-methyl-2-phenylpyrrole (**2g**) reacted efficiently to afford **3v** (71%). However, 1-methyl-3-ethylpyrrole (**2h**) only exhibited a low reactivity. All the pyrrole substrates efficiently underwent these reactions to generate the bispyrrole products **4q**–**4w** (70–96%) under condition B.

When *N*-unprotected pyrrole (**2i**) reacted with **1** under condition B, bispyrroles **4x**–**4z** were formed in 30–40% yields with borondifluoride complexes **4x**′–**4z**′ (52–67%) formed as the major products (Eq. 1). Detailed investigation demonstrated that work-up with saturated aqueous $NaHCO_3$ solution caused the transformation of **4x**–**4z** to **4x**′–**4z**′. These results have demonstrated the synthesis of new types of organic N,O-borondifluoride complexes.[12] The molecular structure of **4x**′ was further confirmed by the X-ray single crystal determination (Fig. 2). It is noted that from the above reactions of pyrrole **2i** under condition A the desired monosubstituted products could not be collected.

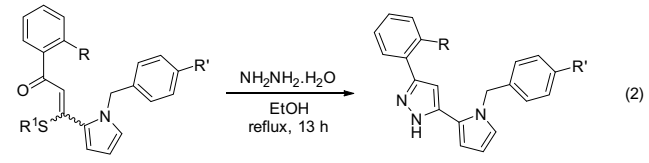
The resultant monosubstituted ketene thioacetals **3** were tested by condensation with hydrazine (Eq. 2) and guanidine (Eq. 3), or by palladium-catalyzed desulfurative cross-coupling with arylboronic acid in the presence of Cu(I) agent, that is, CuTC[4e] (Eq. 4). Thus, multifunctionalized 1*H*-pyrazoles **5a** and **5b** (91–97%), pyrimidines **6a** and **6b** (61–68%), and olefins **7a** and **7b** (93–94%) were obtained, respectively. These results have demonstrated the potential application of the present synthetic protocol in pyrrole-relevant organic synthesis.



1k (R = H)
1m (R = Cl)
1o (R = Me)

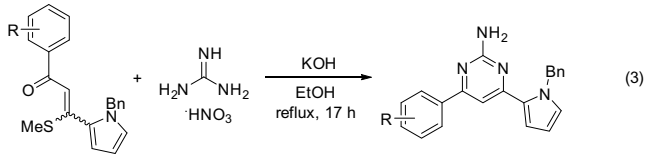
4x (R = H), 40%
4y (R = Cl), 40%
4z (R = Me), 30%

4x' (R = H), 52%
4y' (R = Cl), 59%
4z (R = Me), 67%



3a (R^1 = Me, R = Cl, R' = H)
3r (R^1 = Et, R = H, R' = Cl)

5a (from **3a**), 97%
5b (from **3r**), 91%



3a (R = 2-Cl)
3g (R = 4-Br)

6a (from **3a**), 61%
6b (from **3g**), 68%

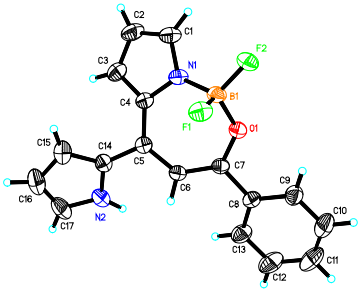
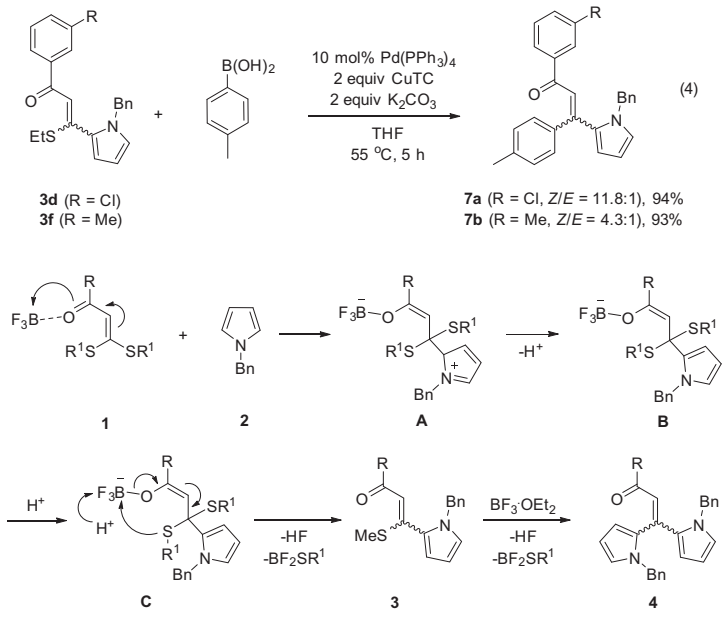


Figure 2. Molecular structure of **4x**′.



Scheme 2. Proposed mechanism.

A reaction mechanism is proposed in Scheme 2. The reaction is presumably initiated by the activation of the carbonyl oxygen atom in α-oxo ketene dithioacetal **1** with Lewis acid BF_3, followed by nucleophilic attack of the C2 of pyrrole **2** at the terminal carbon of the $C(SR)_2$ moiety to generate intermediate **A**. Species **A** readily transforms to species **B** by loss of a proton. β-(2-Pyrrolyl)-substituted ketene monothioacetal **3** is thus formed via further interaction of **B** with the proton by means of elimination of HF and BF_2SR^1. Compound **3** underwent a similar process to result in bispyrrole **4** as the final product.

In conclusion, $BF_3{\cdot}OEt_2$-mediated alkenylation of pyrroles was efficiently realized through the reactions of pyrroles with α-oxo ketene dithioacetals, giving mono- and bipyrrolyl-substituted ketene acetals or *N*,*O*-chelated BF_2 complexes. The present protocol provides a route to access pyrrolyl-based multifunctionalized olefins.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.102.

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