

Direct C(sp²)-H chlorination of ketene dithioacetals using FeCl₃ as the chloride source and PhI(OAc)₂ as an oxidant

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The oxidant iodosobenzene diacetate was combined with the cheap, environment-friendly FeCl₃ as a chloride source to produce an efficient chlorinating agent for α -chlorination of ketene dithioacetals through direct C(sp²)-H chlorination. Furthermore, the synthetic utility of α -chlorinated ketene dithioacetals was verified by the intermolecular cyclization with hydrazine hydrate, leading to the synthesis of pyrazoles, in which a 1,2-sulfur migration was involved.

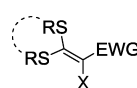
chlorination, FeCl₃, ketene dithioacetals, iodosobenzene diacetate

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Functionalized ketene dithioacetals have emerged as versatile intermediates in organic synthesis [1,2]. Among the various α -functionalized ketene dithioacetals, the α -halogenated ketene dithioacetals are especially attractive. Halogenated alkenes are important in fine chemical industry, and are used widely as intermediates in organic chemistry, for example, in transition-metal-catalyzed coupling reactions (Negishi coupling, Suzuki coupling, and Buchwald-Hartwig amination) [3]. However, exploration of the synthetic utility of α -halogenated ketene dithioacetals has been limited. Recently, De Kimpe and co-workers [4] reported the synthesis of α -fluorinated *N,S*-acetals through direct C(sp²)-H fluorination using 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) as the fluorinating reagent, followed by condensation with different hydrazines to afford 3-amino-4-fluoropyrazoles (Figure 1). Wang and co-workers [5] have developed an efficient method to prepare α -brominated and -iodinated ketene dithioacetals through bromo/iododecarbonylation or bromodeacetylation using bromine or iodine as the halogen source, but the reaction suffers from low efficiency and undesired side reactions. Recently, these draw-

backs were resolved by the same group, with CuBr₂, instead of bromine, used as the bromide source, and chemoselective direct C(sp²)-H α -bromination of ketene dithioacetals was achieved [6]. In contrast to α -fluorinated, brominated, and iodinated ketene dithioacetals, to our knowledge, the synthesis of α -chlorinated ketene dithioacetals has not been reported to date. In this paper, we wish to report the first synthesis of α -chlorinated ketene dithioacetals by direct C(sp²)-H chlorination of ketene dithioacetals using iodosobenzene diacetate (PhI(OAc)₂) as an oxidant [7] and FeCl₃, which is cheap and environmentally friendly, as the chloride source. Further, the cyclization reaction of α -chlorinated ketene dithioacetals with hydrazine hydrate was performed and produced pyrazoles, in which a 1,2-sulfur migration was involved [8].

Because iron is cheap, nontoxic, and abundant, iron-catalyzed organic reactions have attracted more attention than reactions with precious metal catalysts such as Pt, Rh,



X = Br, I Ref. [5]
X = F Ref. [4]
X = Cl This work

Figure 1 α -Halogenated ketene dithioacetals.

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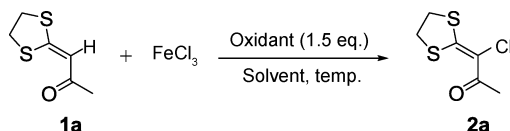
Ru, and Pd. Many organic transformations have been catalyzed or promoted by iron salts, and they have been used in the rapid development of direct C–H functionalization [9]. Some metal halides, such as CuBr₂, LiCl and CaCl₂, have been used in direct C–H halogenation [10], while FeX₃ (X = Br, Cl) was generally used as a halogen source in the halogenation of hydroxyl groups [11] and the addition/halogenation of alkenes and alkynes [12]. In our continued efforts to exploit iron salts as catalysts in organic reactions, we previously investigated several iron-catalyzed reactions for the synthesis of heterocycles [13]. In the present study, we investigated combining FeCl₃ with PhI(OAc)₂ to produce an efficient chlorinating agent. This agent was used in direct C(sp²)–H chlorination of ketene dithioacetals.

The chlorination of α -acetyl ketene dithioacetal **1a** with FeCl₃ was used as a model reaction to optimize the reaction conditions. When iodobenzene diacetate was used as the oxidant, chlorination of **1a** occurred even at room temperature and produced **2a** in 81% yield (Table 1, entry 1). The reaction time was reduced to 20 min when the reaction temperature was increased to 60°C (entry 2). No reaction took place in the absence of iodobenzene diacetate (entry 3). Other solvents such as toluene, CH₂Cl₂, and methanol (MeOH) were tested, and it was found the highest yield (88%) of **2a** was obtained with MeOH (entries 4–6). A wide range of oxidants, including periodinanes (phenyliodine bis(trifluoroacetate), Dess-Martin periodinane), peroxides (*m*-chloroperoxybenzoic acid, di-*tert*-butyl peroxide), free radicals of nitroxides (2,2,6,6-tetramethylpiperidin-1-yl)oxyl,

5-nitroisophthalic acid), potassium peroxymonosulfates (K₂S₂O₈, Oxone), benzoquinones (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), fluorinating oxidative reagents (Selectfluor), and dioxygen (O₂), were screened in MeOH at room temperature (entries 7–17). The periodinanes gave the desired product in good yields, whereas other oxidants did not lead to chlorination of α -acetyl ketene dithioacetal **1a**. The exception was Selectfluor, which proved to be a little bit effective. Consequently, we chose PhI(OAc)₂ and FeCl₃ for the optimized chlorination of ketene dithioacetals.

Next, the reaction scope was studied. Representative ketene dithioacetals **1** were chlorinated under the optimal conditions (Table 1, entry 6). Variation of the R² group of cyclic ketene dithioacetals **1** containing the 1,3-dithiolan-2-ylidene structural unit was investigated (Table 2, entries 1–5). The corresponding α -chlorinated ketene dithioacetals **2a–2e** were produced in good yields (88%, 84%, 80%, 85% and 77%, respectively). With 1,3-dithian-2-ylidene-containing as the substrate under the same conditions, the desired product **2f** was isolated in 79% yield (Table 2, entry 6). In addition to the cyclic ketene dithioacetals, the acyclic ketene dithioacetals were also chlorinated by the same reaction, and produced chlorinated products **2g** and **2h** in 70% and 82% yields, respectively (Table 2, entries 7 and 8). The results listed in Table 2 illustrate that FeCl₃ and PhI(OAc)₂ combined can act as an efficient halogenating agent for α -chlorination of ketene dithioacetals through direct C(sp²)–H chlorination. This is the first report of an efficient synthetic method for α -chlorinated ketene dithioacetals.

Table 1 Optimization of reaction conditions



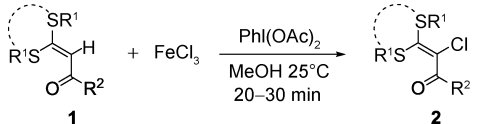
Entry	Solvent	Oxidant	T (°C)	Time (min)	Yield (%) ^{a)}
1	DMF	PhI(OAc) ₂	25	60	81
2	DMF	PhI(OAc) ₂	60	20	82
3	DMF	–	25	60	0
4	Toluene	PhI(OAc) ₂	25	60	0
5	CH ₂ Cl ₂	PhI(OAc) ₂	25	20	20
6	MeOH	PhI(OAc) ₂	25	20	88
7	MeOH	PIFA	25	20	48
8	MeOH	DMP	25	20	77
9	MeOH	<i>m</i> -CPBA	25	60	0
10	MeOH	DTBP	25	60	0
11	MeOH	TEMPO	25	60	0
12	MeOH	NIPH	25	60	0
13	MeOH	K ₂ S ₂ O ₈	25	60	0
14	MeOH	Oxone	25	60	0
15	MeOH	DDQ	25	60	0
16	MeOH	Selectfluor	25	20	46
17	MeOH	O ₂	25	60	0

a) Isolated yields.

Previously, Wang et al. [14] found that the intermolecular cyclization between cyclic α -brominated ketene dithioacetals and hydrazine hydrate produced 1,2-sulfur migration products. To compare the cyclization reaction of α -brominated and -chlorinated ketene dithioacetals with hydrazine hydrate, we studied representative α -chlorinated ketene dithioacetals **2**, including cyclic and acyclic alkylthio groups-containing substrates. These dithioacetals were used in the cyclization reaction with hydrazine hydrate. Cyclic ketene dithioacetal **2** reacted smoothly with five equivalents of hydrazine hydrate in DMF at 100°C, and produced annulated and 1,2-sulfur migrated product **3a** in 68% yield (Figure 2). When the acyclic ketene dithioacetals **2g** and **2h** were reacted with hydrazine hydrate under the same conditions, the 1,2-sulfur migrated products **3b** and **3c** were obtained in 73% and 86% yields, respectively. These results prove there is no difference between the reactions of α -brominated and -chlorinated ketene dithioacetals in the cyclization with hydrazine hydrate.

A possible reaction mechanism for the formation of pyrazoles **3** is proposed with **3a** as an example (Figure 3).

Table 2 Direct C(sp²)-H α -chlorination of ketene dithioacetals **1**



Entry	R ¹	R ²	2	Yield (%) ^{a)}
1	CH ₂ CH ₂	Me	2a	88
2	CH ₂ CH ₂	Et	2b	84
3	CH ₂ CH ₂	PhCH=CH	2c	80
4	CH ₂ CH ₂	4-CH ₃ OPhCH=CH	2d	85
5	CH ₂ CH ₂	4-ClPhCH=CH	2e	77
6	CH ₂ CH ₂ CH ₂	Me	2f	79
7	<i>n</i> Bu	Me	2g	70
8	Et	Me	2h	82

a) Isolated yields.

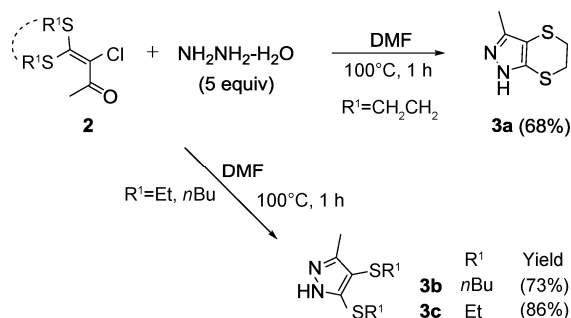


Figure 2 1,2-Sulfur migration during the intermolecular cyclization between α -chloride ketene dithioacetals **2** and hydrazine hydrate (isolated yields).

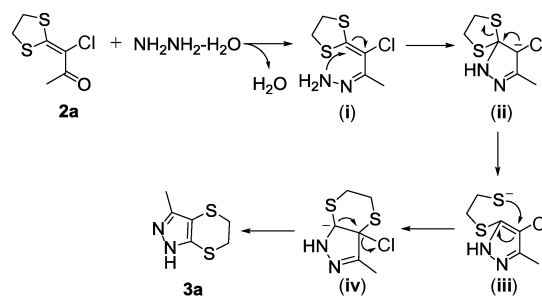


Figure 3 A possible reaction mechanism for formation of pyrazoles **3**.

First, intermolecular amination occurs between the carbonyl group of **2a** and hydrazine hydrate to produce imide intermediate (i). Subsequent intramolecular aza-Michael addition takes place and gives intermediate (ii) which then transforms into intermediate (iii) through retro thio-Michael addition. Finally, the chloride substituent is displaced by the sulfur anion through tandem thio-addition and β -elimination reactions, which forms the formal 1,2-sulfur migration product **3a**.

In summary, combining PhI(OAc)₂ as an oxidant with FeCl₃ as chloride source produced an efficient chlorinating agent. This agent was used for the first α -chlorination of ketene dithioacetals through direct C(sp²)-H chlorination. The synthetic utility of α -chlorinated ketene dithioacetals was verified by intermolecular cyclization with hydrazine hydrate, which produced pyrazoles by a 1,2-sulfur migration. Studies on the reaction mechanism and application of PhI(OAc)₂ and FeCl₃ as a chlorinating agent to other molecular systems are underway, and will be reported in due course.

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