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Iron-Catalyzed Aminolysis of β-Carbonyl 1,3-Dithianes: Synthesis of Stereodefined β-Enaminones and 3,4-Disubstituted Pyrazoles

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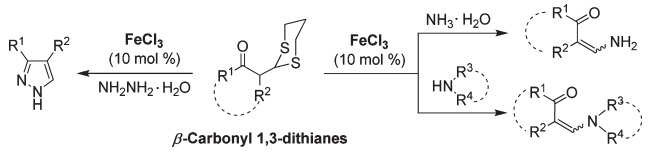
ABSTRACT



A novel iron-catalyzed aminolysis of β-carbonyl 1,3-dithianes with various amines including ammonia, primary and secondary amines, as well as hydrazine hydrate has been developed, leading to the synthesis of stereodefined β-enaminones and 3,4-disubstituted pyrazoles in good to high yields.

As a masked 1,3-dicarbonyl system, β-carbonyl 1,3-dithianes are easily prepared through the conjugate addition of dithiols to ynones, ynoates, and ynals[1] or by the reduction of α-oxo ketene-(*S*,*S*)-acetals using metal reduction systems such as Zn/HOAc, and Mg/Methanol.[2] Although β-carbonyl 1,3-dithianes are readily available, exploration of their synthetic utility is still rare. Ley and coworkers have done excellent pioneering work in this direction.[3] They developed an elegant methodology converting β-carbonyl 1,3-dithiane units to functionalized oxygen-containing heterocycles, useful in the synthesis of natural products such as lyngbouilloside, callipeltoside A,[3b] and fragments of the spongistatins.[3c,d] Recently, we reported a copper-promoted aminolysis of β-carbonyl 1,3-dithianes with amines, providing a new access to β-enaminones,[4] a class of important compounds known as versatile synthetic building blocks and therapeutic pharmacophores.[5,6] However, this methodology was hampered by some striking shortcomings which included the use of substoichiometric cupric salts and poor

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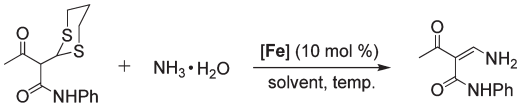
stereoselectivity of produced β-enaminones. To address these issues and achieve a catalytic process, after many attempts we found that the nontoxic and cheaper iron salts could efficiently catalyze the aminolysis of β-carbonyl 1,3-dithianes. Herein we wish to report the research details.

Table 1. Optimization of Iron Salt-Catalyzed Aminolysis of β-Carbonyl 1,3-Dithiane **1a** with Ammonia[a]



1a **2a**

entry	Fe source	solvent	temp (°C)	time (h)	yield[b] (%)
1	$FeCl_3$	DMF	25	9	90
2	**$FeCl_3$**	**DMF**	**60**	**0.6**	**91**
3	$FeBr_3$	DMF	60	1	90
4	$Fe(ClO_4)_3$	DMF	60	1.5	81
5	$FeCl_3$	THF	60	5	33
6	$FeCl_3$	DCE	60	5	25
7	$FeCl_3$	EtOH	60	5	67

[a] Reactions were performed with β-carbonyl 1,3-dithiane **1a** (1.0 mmol), ammonia (5.0 mmol), and [Fe] (10 mol %) in solvent (1 mL). [b] Isolated yields.

In the past few years, the study of the iron-catalyzed reactions has received great attention,[7] because compared with precious metal catalysts such as Pt, Rh, Ru, Pd, Au, and Ag, etc., iron is cheaper, nontoxic, and above all abundant on earth. In our continued efforts to exploit iron salts as catalyst in organic reactions, we previously have realized iron-catalyzed intramolecular aromatic C−H alkenylation of arenes with nonactivated ketones and the synthesis of polysubstituted pyrroles via [4C+1N] cyclization of 4-acetylenic ketones with primary amines.[8] We thus became interested in investigating iron-catalyzed aminolysis of β-carbonyl 1,3-dithianes. In this paper, we disclosed that the iron salts acted as efficient catalyst for the aminolysis of β-carbonyl 1,3-dithianes, featuring in a wide variety of applicable substrates and excellent stereoselectivity. When using hydrazine hydrate instead of amines, the pharmaceutically relevant 3,4-disubstituted pyrazoles were prepared in high yields.

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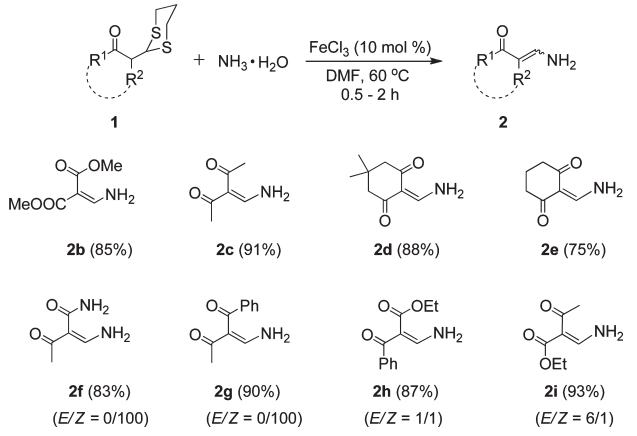
Initially, the survey on reaction parameters including iron catalysts, temperature, and solvents was performed using the reaction of β-carbonyl 1,3-dithiane **1a** with ammonia as a model reaction. This choice was based on the consideration that although β-enaminones bearing an unprotected amino group as synthetic building blocks were much more attractive, only a few synthetic methods are available,[9] necessitating a search for a simple and practical protocol for their synthesis. Some key results of the condition screening are summarized in Table 1. The reaction of **1a** with ammonia smoothly proceeded at room temperature in DMF, affording the desired product **2a** in 90% yield; once the reaction temperature was increased to 60 °C, the reaction time was dramatically reduced to 0.6 h, yet in a similarly high yield (entries 1 and 2). Other tested iron salts such as $FeBr_3$ and $Fe(ClO_4)_3$ all efficiently catalyzed this transformation and gave **2a** in good yields (entries 3 and 4). In comparison, the solvent types significantly influenced target yields. For example, the weakly polar, aprotic solvents such as THF and DCE gave poor yields of **2a** (33 and 25%, respectively) even within an extended reaction time, and most substrate **1a** was recovered (entries 5 and 6). EtOH as solvent resulted in a complete conversion but with a moderate yield of **2a** (entry 7). Consequently, the conditions in entry 2 were the best, and they were chosen for further investigation. Noticeably, the formation of **2a** in the above experiments was completely stereoselective, and only the (*Z*)-isomer was detected by ^{1}H NMR analysis of crude product mixture.

Scheme 1. Synthesis of β-Enaminones **2** with an Unprotected Amino Group[a−c]

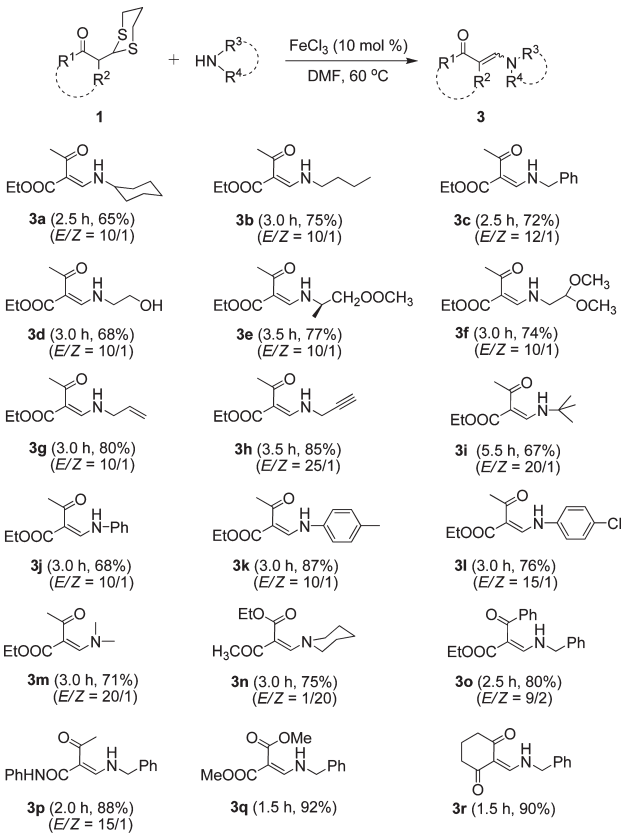


[a] Reactions were performed with β-carbonyl 1,3-dithianes (1.0 mmol), ammonia (5.0 mmol), and $FeCl_3$ (10 mol %) in DMF (2 mL) at 60 °C. [b] Isolated yields. [c] The isomer ratio of **2** was determined by ^{1}H NMR analysis of the crude product mixture, and the configuration was assigned by NOE experiment.

With the optimal conditions in hand (Table 1, entry 2), we sought to study the reaction scope for substrate applicability. As summarized in Scheme 1, β-enaminones **2** with an unprotected amino group were prepared in short reaction times (0.5−2.0 h) and with good to high yields (75

− 93%). In addition to the formation of acyclic, symmetric β-enaminones **2b** and **2c**, the cyclic β-enaminones **2d** and **2e** were also prepared in good yields. For the β-enaminones **2f**−**i** produced from unsymmetric substrates, the stereochemistry was worthy noting. Except for **2h** with an *E*/*Z* ratio of 1/1, the formation of β-enaminones **2f** and **2g** was completely (*Z*)-selective (*E*/*Z* = 0/100); as opposed to enaminone **2i** with the (*E*)-configuration being the major product (*E*/*Z* = 6/1). These results demonstrated that the iron-catalyzed aminolysis of β-carbonyl 1,3-dithiane with ammonia represented an efficient and stereoselective approach to β-enaminones bearing a free amino group.

Scheme 2. Synthesis of *N*-Protected β-Enaminones **3**[a−c]



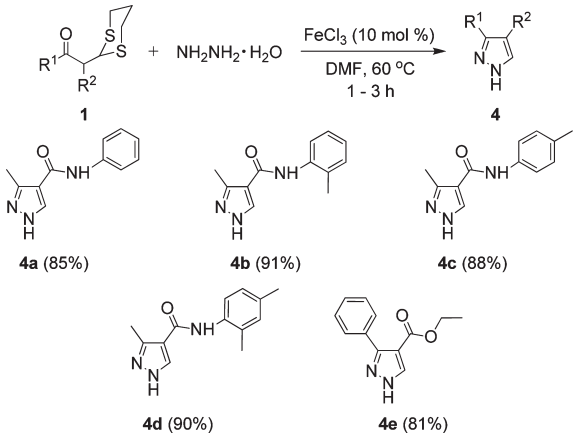
[a] Reactions were performed with β-carbonyl 1,3-dithianes (1.0 mmol), amines (2.0 mmol), and $FeCl_3$ (10 mol %) in DMF (1 mL) at 60 °C.

[b] Isolated yields.

[c] The isomer ratio of **3** was determined by ^1H NMR analysis of the crude product mixture, and the configuration was assigned by NOE experiment.

Next, the iron-catalyzed reaction between β-carbonyl 1,3-dithianes and primary/secondary amines was carried out aiming to prepare *N*-protected β-enaminones. As shown in Scheme 2, a range of aliphatic primary amines, even including the sterically hindered *tert*-butylamine, could be used and afforded the corresponding β-enaminones **3a**−**i** in moderate to high yields. Noticeably, a variety of functional groups were tolerant in this process, including alkyl, aryl, hydroxyl, ester, acetal, alkenyl, and alkynyl groups. Also, the aminolysis reaction involving aromatic primary amines with an electron-donating or electron-withdrawing group smoothly proceeded and gave β-enaminones **3j**−**l** in good yields. In addition to primary amines, the secondary amines such as dimethylamine and piperidine also proved to be suitable partners (**3m** and **3n**). Further, variations on the R^1 and R^2 groups on substrate **1** were tested, and to our dismay, no observable influence on the reaction efficiency was observed (**3o**−**r**). It seems the double carbonyl groups are essential for the aminolysis reaction because no reaction took place using the substrate (R^1 = Ph, R^2 = H) to react with benzylamine. Analysis of the stereochemistry of products **3a**−**p** showed that in most cases the (*E*)-isomer was dominant (the ratio of *E*/*Z* up to 25), except for **3n**.

Scheme 3. Synthesis of 3,4-Disubstituted Pyrazoles **4**[a,b]



[a] Reactions were performed with β-carbonyl 1,3-dithianes (1.0 mmol), hydrazine hydrate (2.5 mmol), and $FeCl_3$ (10 mol %) in DMF (1 mL) at 60 °C.

[b] Isolated yields.

The wide scope of substrates and excellent stereoselectivity authenticated this iron-catalyzed aminolysis of β-carbonyl 1,3-dithianes to be a general and stereoselective approach to β-enaminones. Noticeably, β-enaminones **2** and **3** structurally contained double carbonyl at α-position and one hydrogen at β-position; such β-enaminones have been found to modulate α7 nAChRs and the effect of γ-aminobutyric acid (GABA) on the GABA receptor complex.[10] We therefore developed a straightforward approach to this kind of β-enaminones.

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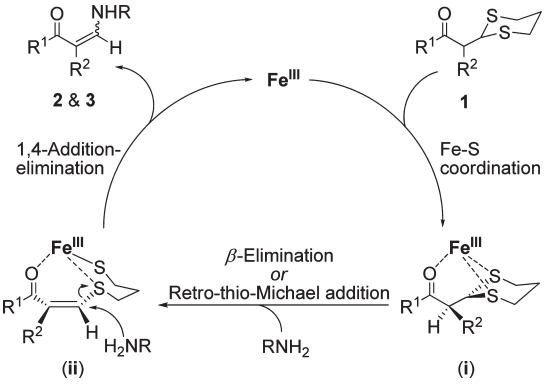
Further, synthetic access to the pyrazoles was achieved by using hydrazine hydrate instead of amines in the iron-catalyzed aminolysis of β-carbonyl 1,3-dithianes. Pyrazoles serve as important core structures in many pharmaceuticals and pharmaceutical leads with a wide range of biological activities,[11]in particular, the 3,4-disubstituted pyrazoles known as anticancer and anti-inflammatory agents.[12] As shown in Scheme 3, the 3,4-disubstituted pyrazoles **4a**−**e** were made in excellent yields (81−91%). This provided a new route to the medicinally important pyrazole derivatives.[13]

Scheme 4. Plausible Catalytic Mechanism



Although the mechanistic details of this transformation are not clear at the moment, we tentatively proposed a possible catalytic route as depicted in Scheme 4.[14] The Fe(III) first coordinated to the carbonyl and sulfur atoms in 1,3-dithioacetal moiety, forming the intermediate (**i**). Subsequently, one C−S bond cleaved to gave intermediate (**ii**) either through β-elimination reaction using the amine as a base to extract the α-hydrogen or via a Fe(III)-catalyzed retro-thio-Michael addition without the aid of amine as a base. Finally, the amine displaced the remaining alkylthio group via an 1,4-addition−elimination approach to furnish β-enaminones **2** and **3**, accompanying the generation of Fe(III) catalyst, during which time the stereoselectivity of products was influenced by the type of amines as well as the R^2 substituent.

In conclusion, a novel iron-catalyzed aminolysis of β-carbonyl 1,3-dithianes with various amines has been developed, leading to the synthesis of stereodefined β-enaminones and 3,4-disubstituted pyrazoles. This catalytic procedure is striking in terms of the wide range of applicable substrates, mild reaction conditions, and excellent stereoselectivity. Further studies in combination with theoretical calculation to elucidate the reason for the stereoselectivity and application of this methodology to synthesize other interesting heterocycles are underway.

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Supporting Information Available. Experimental procedures; $^1H/^{13}C$ NMR and NOE spectroscopic data for compounds **2**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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