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Methyl ketone break-and-rebuild: a strategy for full α-heterofunctionalization of acetophenones

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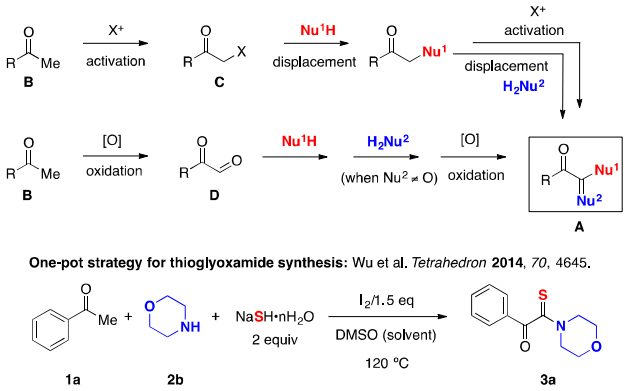
Willgerodt reaction under iron-catalyzed aerobic conditions was found to be an excellent tool for fully α-heterofunctionalization of acetophenones with sulfur and amines. Via this break-and rebuild strategy, a wide range of thioglyoxamides was synthesized in a four-component, highly atom-, step- and redox- economical manner with water as the only by-product.

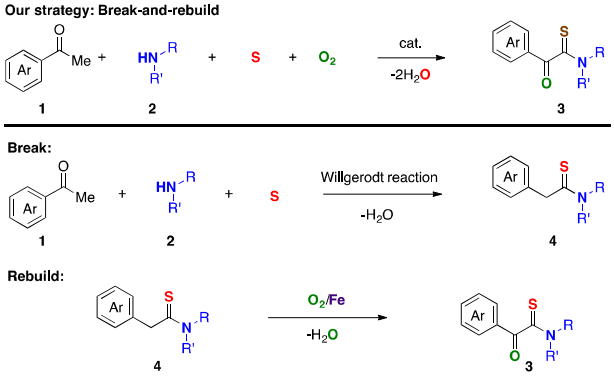
Fully α-heterosubstituted carbonyl motifs **A** are widely present among pharmaceutically active compounds as well as natural products.[1] Classical strategies to such scaffolds based on readily available methyl ketone **B** are summarized in Scheme 1. The first approach consists of an activation of the methyl moiety via α-halide[1a]/sulfonate[2] **C**, followed by nucleophilic displacement to introduce the first heterosubstituent. The sequence activation/displacement could be repeated to provide **A**. In the second approach, intermediate glyoxal **D** obtained from a $4e^-$ oxidation of **B** was subjected to nucleophilic attack and $2e^-$ oxidation. In both approaches, stoichiometric use of activating/oxidizing agents and multistep syntheses are required.

To simplify the transformation, one-pot protocols involving activating agents and nucleophiles were proposed. For example, thioglyoxamide **3a** could be obtained via one-pot reaction of acetophenone **1a** with morpholine **2a** and hydrated NaSH as nucleophiles and I_2/DMSO as oxidants, which implies that dimethyl sulfide, a volatile compound with unpleasant odor even at quite low concentrations, is among the by-products.[3] Moreover, the scope of aliphatic amines of the method is limited to the method is limited to six-membered ring amines such as morpholine, piperidine, cyclohexylamine and piperazine motifs. Although the global transformation **B** → **A** is simply a displacement of three hydrogen atoms by one sulfur atom and one amino group, all the above-mentioned approaches relied on stoichiometric use of oxidants other than dioxygen.[4]



Scheme 1. Fully α-heterosubstituted carbonyl motifs **A** from methyl ketone **B**

In this context, the direct formation of thioglyoxamides from an acetophenone **1**, elemental sulfur and an amine with oxygen as oxidizing agent would be an excellent and highly desirable solution, which exemplifies the principle of atom-, step- and redox economy (Scheme 2).



Scheme 2. Design of iron-catalyzed of oxidative Willgerodt reactions via break-and-rebuild strategy

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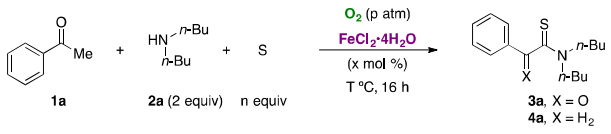
The expected reaction is similar to a typical Willgerodt-Kindler[5] reaction in the starting material, except for the presence of oxygen. In a classical Willgerodt-Kindler[6] reaction involving methyl ketone **1** as the ketone substrate, while its carbonyl function is reduced to the methylene group, its terminal methyl group is oxidized to thioamide function in **4** ("break" step). If the reaction is performed under aerobic conditions in the presence of an appropriate catalyst, the methylene moiety of **4**, thanks to its benzylic position, will be readily oxidized to regenerate the ketone function in **3** ("rebuild" step).

The choice of catalyst determines the success or failure of the transformation as the oxidation of the thioamide function in both **3** and **4** as well as of amine **2** must be taken into account. Moreover, due to high complexing capacity of both amine **2** and sulfide species (generated in the mixture of elemental sulfur and amine **2**), a metal catalyst involving in this reaction should be compatible.

As iron-sulfur clusters[7] are ubiquitous in living systems and responsible for a wide range of chemical transformations that sustain many fundamental life processes, iron was our first choice. The complexity of these catalytic systems complicates the synthesis, the study of their properties and the application in organic synthesis. We wondered if the addition of simple iron salt could perform this expected transformation, especially under aerobic conditions, which were known to be incompatible with iron-sulfur cluster.[8]

To address this question, we set up a model reaction of acetophenone **1a** with dibutylamine **2a** in the presence of elemental sulfur under solvent-free conditions (Table 1).

Table 1. Optimisation of reaction conditions

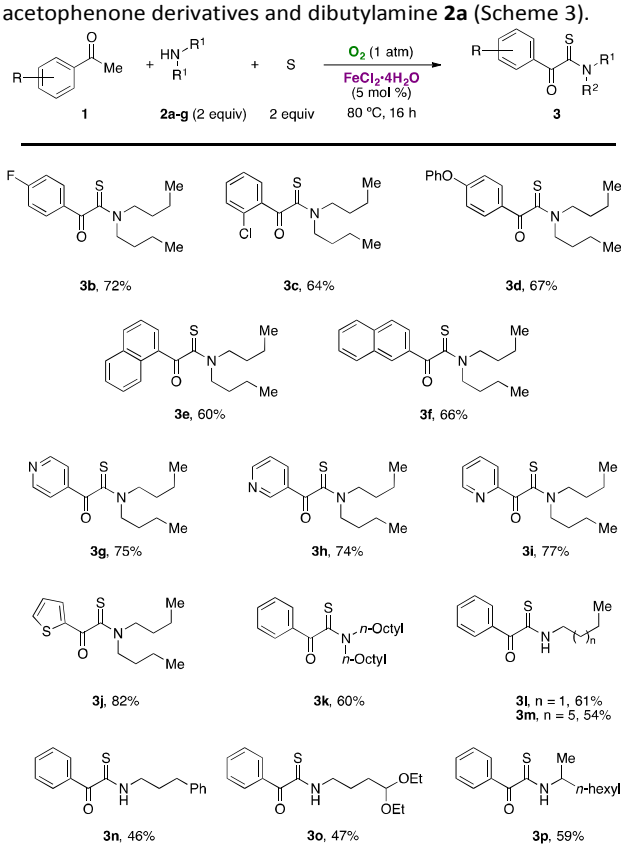


entry[a]	temp (°C)	n	x	p	**1a**:**3a**:**4a** ratio[b]	yield of **3a** (%)[c]
1	100	4	0	0	0:5:95	nd[d]
2	100	4	10	0	0:5:95	nd[d]
3	100	2	10	1	5:95:0	70
4	100	2	0	1	5:95:0	25
5	80	2	10	1	5:95:0	75
6	**80**	**2**	**5**	**1**	**5:95:0**	**78**
7	60	2	5	1	30:70:0	59
8	80	2	2	1	10:90:0	70

[a] Reaction conditions unless otherwise noted: **1a** (1 mmol), **2a** (2 mmol), S (n mmol, 32 mg.mmol-1), oxygen (p atm), $FeCl_2•4H_2O$ (x mol %). [b] Determined by 1H NMR of the crude reaction mixture. [c] Isolated yield. d Not determined.

The classical Willgerodt-Kindler conditions in the absence of both oxygen and iron catalyst was capable of transforming totally ketone **1a** efficiently the expected phenylthioacetamide **4a** along with a small amount of thioglyoxamide **3a** (entry 1). The reaction mixture was however unclean due to the oxidation of **2a** into *N*-butylthiobutyramide. Because oxygen was excluded from the reaction mixture, the oxygen atom of **3a** in this case was obviously issued from the starting acetophenone **3a**. Adding $FeCl_2•4H_2O$ (5 mol %) to the reaction mixture did not lead to any significant change in product ratio (entry 2). When the reaction was performed under an atmosphere of oxygen, the formation of **3a** was dramatically improved and **3a** could be isolated in good yield (entry 3). These aerobic conditions were found to be much less efficient to deliver **3a** in the absence of iron catalyst (entry 4). Indeed, most of acetophenone was oxidized into benzoate and the yield of thioglyoxamides **3a** was low. The system $Fe/O_2/S_8$ was shown to be more efficient at 80 °C (entry 5), even with lower catalyst loading (entry 6). Lower the reaction temperature to 60 °C resulted in a slower conversion of acetophenone **1a** (entry 5 *vs* 3). Interestingly, we found that the reaction performed with 5 mol % of iron salt leads to comparable ratio of product and pleasingly, the yield is improved to 78% (entry 6). Finally, **3a** could also be formed in lower yields when either sulfur content or iron catalyst loading was lowered (entries 7 and 8). We noted that thioamide **3a** could be readily oxidized into thioglyoxamide **4a** when **3a** was stirred with sulfur (1 equiv), $FeCl_2•4H_2O$ (1 mol %) and dibutylamine **2a** (1 equiv) under an atmosphere of oxygen.

The optimized conditions were next applied to a range of acetophenone derivatives and dibutylamine **2a** (Scheme 3).



Scheme 3. Reaction scope with open chain aliphatic amines

Although this kind of open chain secondary amine has never been tested under previously described oxidative conditions,[3a] it was found to be an excellent amine substrate. Halogen and phenoxy substituted products **3b**-**d**, including *o*-substituted

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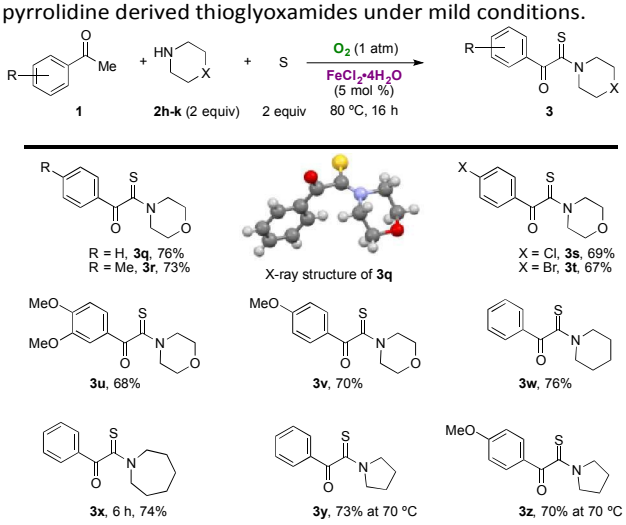
one **3c**, were also obtained without any difficulty. Polyaromatic (such as acetonaphthones) and heteroaromatic (acetylpyridines, acetylthiophene) ketone substrates also underwent the aerobic oxidative condensation to afford the corresponding thioglyoxamides **3e**-**i**. Highly lipophilic thioglyoxamide **3k** bearing two long chains could be synthesized by our strategy.

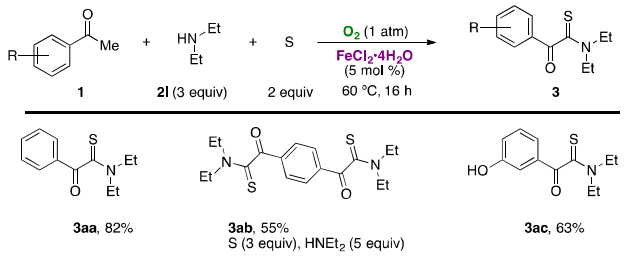
We next attempted the reaction conditions to primary amines. The expected secondary thioamides **3l**-**p** were formed in acceptable yields, including thioglyoxamide **3l** derived from low boiling butylamine and thioglyoxamide **3o** with a protected aldehyde function.

Morpholine as well as other cyclic analogs such as piperidine, pyrrolidine and hexamethyleneimine were also competent amine substrates (Scheme 4). In all cases tested, the corresponding thioglyoxamides were obtained in moderate to good yields. The halogen substituents are potentially useful for further functionalization. We noted that due to high nucleophilicity of pyrrolidine (bp 89 °C), its reactions with acetophenones could be performed at temperature as low as 70 °C and gave rise to the corresponding thioamides **3i**-**j** in high yields. Compared to the previously reported methods[3,4c,6b] in which the temperatures were in the range 100-130 °C, our strategy provided a first direct access to pyrrolidine derived thioglyoxamides under mild conditions.



Scheme 4. Reaction scope with cyclic secondary amines

Finally, with a highly volatile amine such as diethylamine (bp 55.5 °C), the reaction could be carried out at temperature as low as 60 °C (Scheme 5). To compensate the loss of diethylamine due to its volatility, the reaction was performed with 3 equiv of this amine. Interestingly, good yields of thioglyoxamides (**3ac**-**3aa**) were obtained for all three representative substrates. To fully functionalize 1,4-diacetylbenzene, a mixture of sulfur (5 equiv) and diethylamine (5 equiv) was used with the same iron catalyst loading and oxygen pressure. Our conditions were found to be efficient also to provide phenolic thioglyoxamides **3ac**, although the phenol function is known to coordinate strongly with iron(III).



Scheme 5. Selected reactions with diethylamine

Conclusions

In conclusion, a simple but effective and green synthesis of thioglyoxamides based on Willgerodt reaction under iron-catalyzed aerobic conditions has been described. This ketone break-and-rebuild strategy complements nicely the existing methods based on one-pot α-functionalization of methyl ketones followed by sulfuration and amination. It is likely that the catalytic activities of Fe/S system may be applied to other heterofunctionalizations, even under aerobic conditions, and such investigations are in progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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