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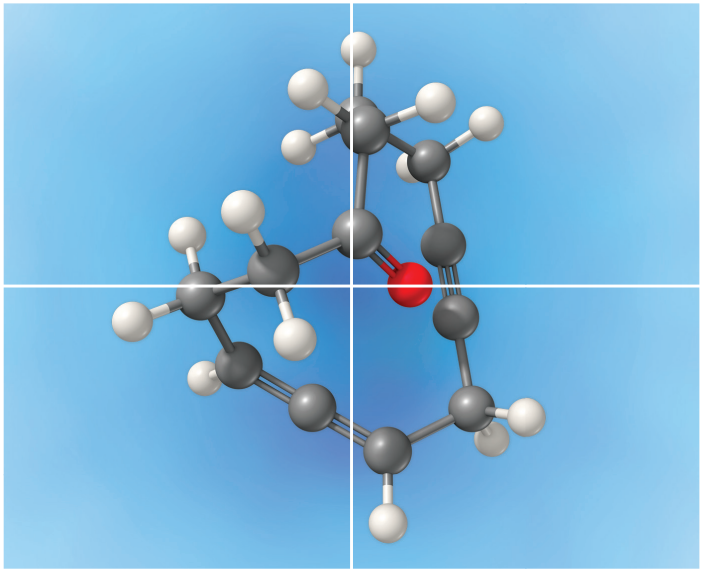

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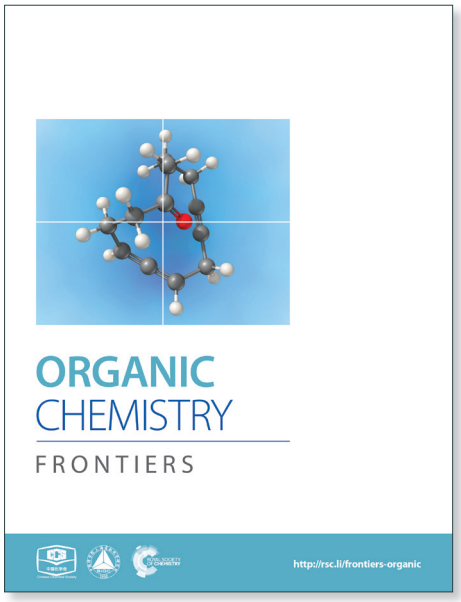

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Fe/S-catalyzed decarboxylative redox condensation of arylacetic acids with nitro arenes†

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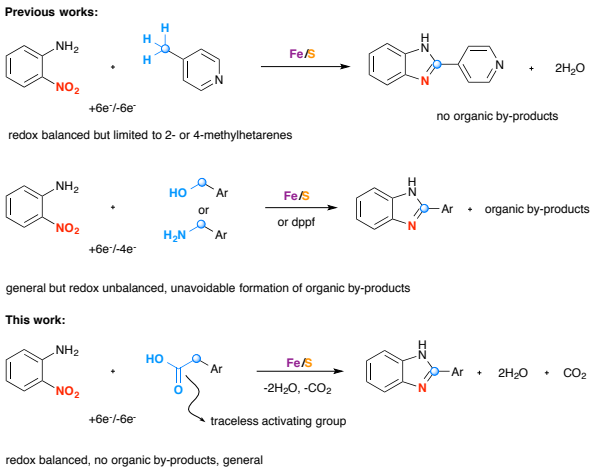
Fe/S clusters generated *in situ* from simple iron salts and sulfur S_8 were found to be highly efficient to catalyze the decarboxylative redox condensation of arylacetic acids with nitro arenes in the presence of *N*-methylpiperidine as a basic additive. A wide range of aza-heterocycles was obtained in an atom-, step-, and redox- economical manner with water and carbon dioxide as the only by-products.

Enzymatic transformations have been an inexhaustible source of inspiration for progress in organic synthesis and catalysis. Decarboxylative coupling reaction of carboxylic acids is a versatile method to create carbon-carbon and carbon-heteroatom bonds.[1] Although the process is thermodynamically favorable due to the formation of stable carbon dioxide by-product, the non-enzymatic reaction requires in general high temperatures and/or strong oxidizing agents in the presence of metal catalysts. Intriguingly, such transformations which are common and fundamentally important in biology can be conducted efficiently under physiologic conditions in the presence of some decarboxylases.[2] The active sites of some of these enzymes were found to contain iron-sulfur clusters.[3] The oxidation states of the iron atoms in these clusters change between +2 and +3, the effect being the charge and discharge process of multiple electrons of these biological capacitors. This way, the enzyme acts as electron transfer agents in biological redox reactions. Organic synthesis can take inspiration from Nature to design versatile assemblage for biomimetic transformations and catalysts.

Recently, several groups[4-6] have begun to explore catalytic redox coupling reactions starting directly from aromatic nitro compounds as a convenient and direct method to aza heterocycles without prior reduction of the nitro group. In connection with the widespread interest in the development of a more sustainable redox chemistry, we are particularly interested in exploring the versatility of biomimetic catalysts based on iron/sulfur clusters generated from iron or its simple salts and elemental sulfur.[4,6] The idea behind is linked to the redox active iron-sulfur clusters due to their capacity of reversibly taking up electrons from a reducing partner and transfering them to an oxidant partner even delayed in time. Different reducing partners such as methylhetarenes, benzyl alcohols, and amines have been found to be successful substrates in these reactions (Scheme 1). Although methylhetarene substrates are efficient in term of number of electron transferred, the methyl group must be located at the 2- or 4- position of the aza-heterocycles for an efficient stabilization by resonance.[4a] The high inertness of the methyl group of other hetarenes or arenes (for example 3-picoline or toluene) required the use of other prefunctionalized compounds such as $ArCH_2OH$[5c] or RCH_2NH_2.[6a] Indeed, reaction of benzyl alcohols or amines with *o*-nitroanilines led to benzimidazoles. However, excess of alcohols/amines must be used to compensate the difference in electron numbers between the nitro group and $-CH_2OH$/$-CH_2NH_2$ group during the redox process. This unbalanced exchange led consequently to the formation of organic by-products issued from the oxidation of CH_2OH/CH_2NH_2 groups of the reducing partners.

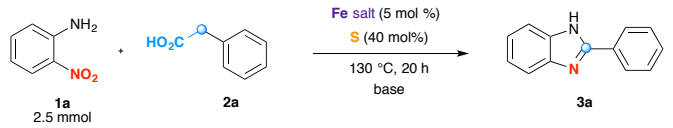


Scheme 1 Access to benzimidazoles by redox condensation

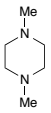
We reasoned that the use of an acetic acid function (HO_2CCH_2-), with a traceless activating carboxylic acid group, as a synthetic equivalent of a methyl group, would greatly expand the scope while maintaining a full electronic balance of the redox process. Moreover, this idea is supported by the fact that carboxylic acids are in general readily available starting materials in great structural diversity. As far as we are aware, no example of such a decarboxylative redox condensation has been reported prior to this study.

To test this idea, we chose *o*-nitroaniline and phenylacetic acid as prototypical substrates. Based on our previous experience on using Fe/S as redox condensation catalyst, $FeCl_3.6H_2O$ (5 mol %) and S (40 mol %) were used as precursors for catalyst.[7]

Table 1 Optimization of the reaction conditions[a]



1a 2.5 mmol 2a 3a

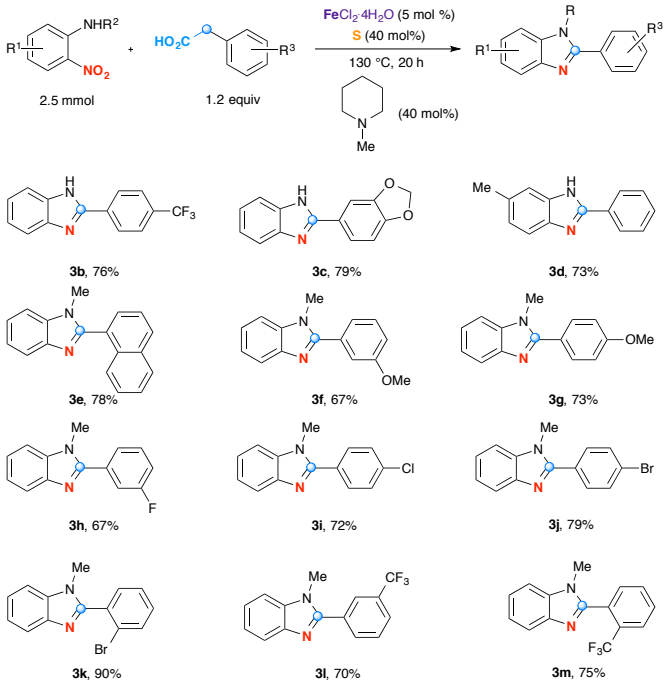
entry	**2a** equiv	base (equiv)	iron salt	conversion (%)[b]
1	2	 2	$FeCl_3{\cdot}6H_2O$	16
2	2	 2	$FeCl_3{\cdot}6H_2O$	16
3	2	 2	$FeCl_3{\cdot}6H_2O$	35
4	2	 2	$FeCl_3{\cdot}6H_2O$	87
5	2	 2	$FeCl_3{\cdot}6H_2O$	83
6	2	 2	$FeCl_3{\cdot}6H_2O$	74
7	2	 1.5	$FeCl_3{\cdot}6H_2O$	89(53)[c]
8	1.2	 1.5	$FeCl_3{\cdot}6H_2O$	91
9	1.2	 0.4	$FeCl_3{\cdot}6H_2O$	93
10	**1.2**	 **0.4**	**$FeCl_2{\cdot}4H_2O$**	**>95(82)[c]**

[a] Conditions: **1a** (2.5 mmol), **2a** (1.2-2 mmol), iron salt (5 mol %), sulfur (40 mol %, 1 mmol, 32 mg), base (0.4-2 equiv). [b] Determined by ^{1}H NMR of the crude mixture. [c] Yield of isolated **3aa**.

The reaction in 3-picoline at 130 °C resulted in the formation of 2-phenylbenzimidazole in low conversion (entry 1). The same result was observed with pyridine as an additive (entry 2). We hypothesized that basic conditions are necessary because the decarboxylation is initiated preferentially with carboxylate form. To improve the conversion, the screening of different basic additive was envisioned. A range of aza bases which are stable to the oxidation of elemental sulfur has been tested (entries 3-6). In all cases investigated, we noticed that all the bases stronger than 3-picoline are more efficient to promote this condensation.[8] Best result was observed with *N*-methylpiperidine (entry 4). Finally, strong inorganic bases such as NaOH, Na_2S were also tested but lower conversions were observed in theses cases (results not shown).

Encouraged by these results, we continued the optimization by lowering the quantity of base additive *N*-methylpiperidine. Interestingly, the conversion was improved (entry 7) but the purification remained inefficient due to the presence of base additive and excess phenylacetic acid. The reaction was thus conducted by lowering the quantities of both **2a** and *N*-methylpiperidine (entries 8-9) and led to higher conversions. Finally, replacing $FeCl_3{\cdot}6H_2O$ by $FeCl_2.4H_2O$ gave a slightly better conversion (entry 12) and the purification was simplified and more efficient (82%).[9]

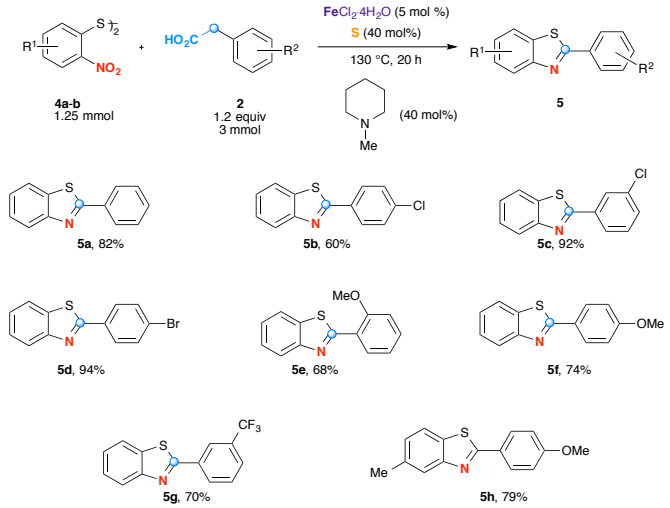
The next series of experiments evaluated the effect of substituents on the efficiency of the reaction. As shown in Scheme 2, this decarboxylative redox condensation can be applied to a variety of substrates to produce the corresponding 2-arylbenzimidazoles. In addition to NH benzimidazoles **3b-d**, *N*-methyl analogues could also be obtained in high yields **3e-m**. Functional groups such as OMe (**3f-g**), dioxymethylene (**3c**), F (**3h**), Cl (**3i**), Br (**3j-k**), CF_3 (**3b**,**l-m**) at different positions are well tolerated.



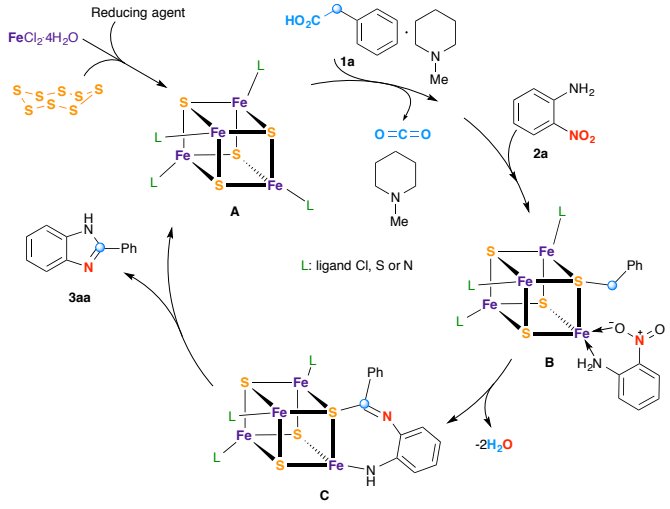
Scheme 2 Access to benzimidazoles **3**

The method was further successfully extended to the formation of benzothiazole analogues (Scheme 3). Although *o*-nitrothiophenols are not stable and readily oxidatively dimerized into 2,2'-dinitrodiphenyl disulfides **4**, the latter, commercially available can be used conveniently as oxidizing partners. Gratifyingly, while this redox process is unbalanced (each moiety of 2,2'-dinitrodiphenyl disulfide molecule **4** receives 7 electrons), excellent yields were observed in all cases tested even arylacetic acids were used only in slight excess quantities (1.2 equiv). Benzothiazoles are less polar and more soluble in organic solvents than benzimidazoles **3**, consequently the purifications by column chromatography are easier.

As for 2-arylbenzimidazoles **3**, in addition to the simplest **5a**, arylacetic acids bearing Cl-, Br-, MeO- and CF_3- functional groups also served as good substrates to yield the benzothiazoles efficiently.



Scheme 3 Access to benzothiazoles **5**



Scheme 4 Proposed mechanism

Although the mechanism of the transformation is not clear at this moment, some important observations may be discussed. First, an aryl group is necessary for the decarboxylative redox condensation of acetic acid derivatives **2**, suggesting its role as a stabilizing group. Second, the presence of a base is required. A plausible mechanism for this redox condensation reaction is proposed in Scheme 4 on the basis of the experiments described above and literature examples.[4-6] Since in the absence of either iron salt or elemental sulfur, the reaction does not proceed, the presence of Fe/S cluster plays a central role in this reaction. First, iron-sulfur clusters are produced from iron salts, elemental sulfur and a reducing agent. Redox flexible, these clusters can possess a wide range of oxidation states. One of the oxidized forms of these clusters can oxidize phenylacetate anion into phenylacetyloxy radical which next underdoes a decarboxylation into benzyl radical fixed to one of the sulfur atoms of the cluster. In parallel with this process, the reduction of the nitro group of *o*-nitroaniline was effected with one of the reduced forms of Fe/S clusters. Subsequent redox and condensation steps, catalyzed by Fe/S clusters thank to their redox flexible and acido-basic nature, led to final product 2-phenylbenzimidazole. Although iron and sulfur appear to function cooperatively in the redox system, the question regarding how it mediates between the decarboxylation and reduction reactions leading to benzazoles is under investigation.

Conclusions

In summary, we have developed an efficient decarboxylative redox condensation between nitro arenes and arylacetic acids. This straightforward and simple route to a wide range of valuable aza-heterocycles relies on the complex interplay between four critical components: *N*-methylpiperdine base and low-cost Fe/S catalyst generated *in situ* from simple iron salts and S. This approach is a nice example of atom-, step- and redox economical transformation. We continue to expand the scope of Fe/S catalyst for the synthesis of complex molecules from readily available starting materials.

Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental procedures, compounds characterization data, and copies of NMR spectra. See DOI: 10.1039/c000000x/

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7 Without either iron salt or sulfur as a catalyst in the absence/presence of a base additive (*vide infra*) no conversion at all or low conversions (< 5%) were observed.

8 ^{1}H NMR study of an equimolar mixture of phenylacetic acid and an organic base (*N*-methylpiperidine or 3-picoline) in deuterated methanol (0.2 M) showed that while *N*-methylpiperidine resulted in total deprotonation, 3-picoline did not lead to any change (See Supporting Information).

9 Iron chlorides $FeCl_2.4H_2O$ and $FeCl_3.6H_2O$ as well as other chloride salts of the first row transition metals such as $MnCl_2.4H_2O$, $CoCl_2.6H_2O$, $NiCl_2.6H_2O$, CuCl, $CuCl_2.2H_2O$ were also tested as catalysts (5 mol %) under standard conditions without sulfur and did not lead to any trace of **3a**. With the concomitent presence of chloride salts (5 mol %) and sulfur (40 mol %), low conversions were obtained with $MnCl_2.4H_2O$ (23%), $NiCl_2.6H_2O$ (5%), CuCl (9%).