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Elements as Direct Feedstocks for Organic Synthesis: $Fe/I_2/O_2$ for Diamination of 2-Cyclohexenones with 2-Aminopyrimidine and 2-Aminopyridines

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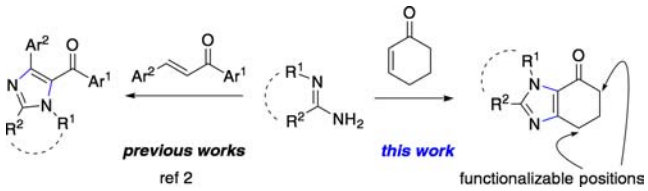
Supporting Information

ABSTRACT: Elements as feedstocks for organic synthesis, the trio of metallic iron, molecular iodine, and dioxygen, were found to be an excellent tool for oxidative regioselective diamination of conjugated enones with 2-aminopyrimidine (a guanidine surrogate) and 2-aminopyridines leading to unaromatized coupled products in moderate to good yields.

The fused imidazole core is found in various natural and unnatural biologically active molecules as well as synthetic intermediates.[1] Reports for efficient syntheses of these five-membered heterocycles by catalytic oxidative diamination of conjugated enones with 1,3-bis-azanucleophiles are limited in the used of chalcones[2] as oxidized partners (Scheme 1). In these cases, the chemoselectivity does not appear to pose a problem because the conjugated enone moiety is substituted by two aryl groups. A new, simple, and selective reaction for oxidative diamination of enolizable conjugated enones, especially further functionalizable ones, is therefore highly desirable and has practical synthetic interests.

Scheme 1. Diamination of Conjugated Enones



With growing concerns over natural resource depletion and waste emission, a shift toward more efficient and sustainable reactions for the manufacture of chemicals has emerged.[3] One of the answers to such challenging problems is the direct use of chemical elements as feedstocks (reagents, catalyst) while limiting or even avoiding the presence of unnecessary components (spectator counterions, crystallized water, and other molecules) in the reaction mixture.[4] Herein, we describe a successful example of applying this concept to the diamination reaction of conjugated enones using a metallic iron−molecular iodine−dioxygen catalytic oxidative system.

Iron(II,III) and iodide salts have been used extensively as (pre)catalysts for redox transformations. From the viewpoint of atom-, redox-, and cost-efficiency, this versatile chemistry suffers from some drawbacks. First, although these reactions rely basically on redox couples Fe^{2+}/Fe^{3+} and I^-/I_2, in most cases, these catalytically active species were used as salts whose counterions were not really involved in or necessary for the reactions. Second, the manipulation of some compounds is complicated because they are hygroscopic and/or readily oxidized (ferrous and iodide salts). The presence of water and oxidized products in undetermined amounts in such compounds can alter the reaction efficiency and reproducibility. In this context, metallic iron and molecular iodine, readily available as stable, nonhygroscopic solids with low prices, are good candidates to avoid all these issues. Finally, this catalytic redox chemistry using dioxygen, which is unquestionably the greenest and cheapest oxidant, once applied to C−H functionalization would be an ideal solution.

In connection with our ongoing project on the synthesis of the hexanitrogenated core of marine alkaloid benzosceptrins,[1b] we were looking for an efficient method to introduce successively two guanidine moieties into a cyclohexane derivative. One of the most promising approaches is using readily available 2-aminopyrimidine as a versatile guanidine source and 2-cyclohexenone as carbon skeleton (Scheme 2).

As a preliminary study targeting **3aa**, we employed unsubstituted cyclohexenone **1a** as the coupling partner (Table 1). Compared to the related oxidative coupling reaction between chalcones and 1,3-bis-nucleophiles,[5] the present reaction is more challenging because the 4- and 6- positions of the cyclohexenone are possibly also reactive (vide infra) but also provides valuable opportunities for further functionalization.

The screening experiments were initially examined in the presence of $FeCl_2{\cdot}4H_2O$ and molecular iodine as catalyst and dioxygen as the oxidant in DMF at atmospheric pressure (balloon) (entry 1). As we expected, this catalytic oxidizing system was effective to promote the oxidative coupling reaction,

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Scheme 2. Key Intermediate 3aa from 1a and 2a

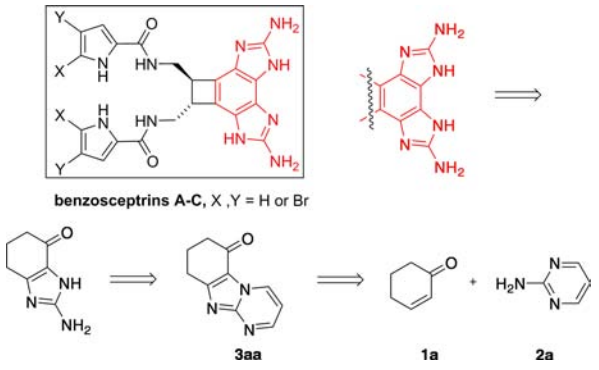
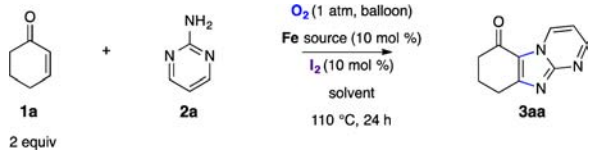


Table 1. Evaluation of Reaction Conditions[a]



entry	solvent	iron source	conversion[b] (%)
1	DMF	$FeCl_2{\cdot}4H_2O$	85
2	DMSO	$FeCl_2{\cdot}4H_2O$	89
3	HOAc	$FeCl_2{\cdot}4H_2O$	>95
4	HOAc	Fe	>95 (75% yield)

[a]Reaction conditions: **1a** (5 mmol), **2a** (2.5 mmol), iron source (0.25 mmol, 10 mol %), I_2 (0.25 mmol, 10 mol %), O_2 (1 atm, balloon), solvent (2 mL). [b]Determined by ^{1}H NMR.

leading to the desired product. Similar conversions were obtained in DMSO (entry 2) and HOAc (entry 3), but the purification is simpler in the latter case possibly because the formation of aromatized byproducts (2-anilinopyrimidine, hydroquinone) was limited in HOAc. When metallic iron was used as the iron source instead of $FeCl_2{\cdot}4H_2O$, the yield of the reaction was slightly improved to 75% (entry 4), which indicated that the chloride did not played any critical role in the reaction. In this case, iron was dissolved rapidly in the reaction medium and catalyzed the reaction.

The structure of **3aa** was unambigously confirmed by single-crystal X-ray diffraction as shown in Figure 1. This structure confirmed that the oxidative cross-coupling reaction led exclusively to the described regioisomer.

We next investigated the scope of the 2-aminopyridine substrates (**2b–j**) as this family of compounds is readily available in both quantity and structural diversity. As depicted

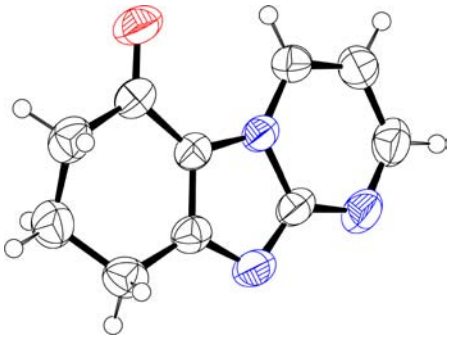
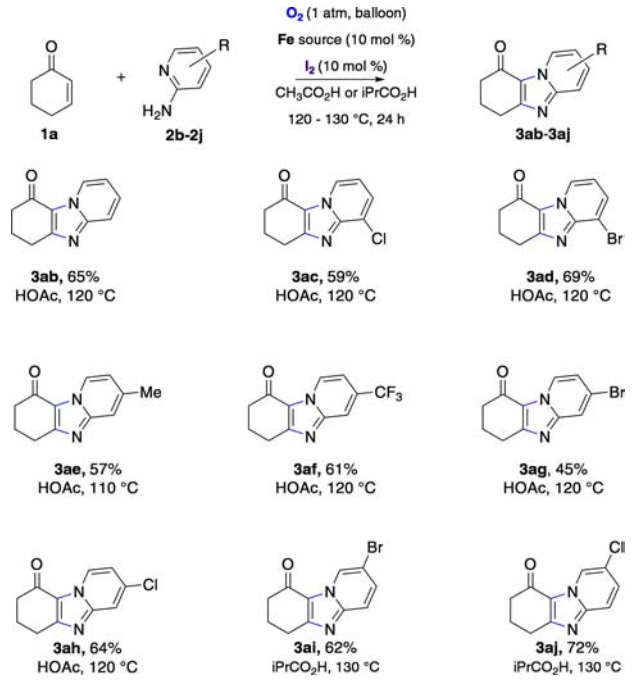


Figure 1. X-ray structure of **3aa**.

in Scheme 3, under the optimized conditions, a range of functional groups in **2** could tolerate the reaction conditions

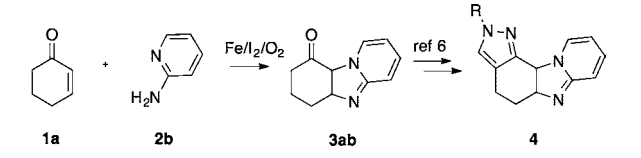
Scheme 3. Coupling Reaction between 1a and 2b–j



(Cl, Br, Me, CF_3), all of them gave the desired products as single regioisomer in moderate to good yields. The catalyst system is relatively insensitive to the electronic effect of substituents of 2-aminopyridines. These functional groups could afford an opportunity for further functionalization. In some case, acetic acid was replaced by isobutyric acid for higher temperature heating.

Product **3ab**, a precursor for the synthesis of a range of cytotoxic compounds **4** was previously prepared in a two-step sequence from cyclohexane-1,3-dione (Scheme 4).[6] By using our present method with both readily available and inexpensive starting materials **1a** and **2b**, **3ab** was obtained in only one step.

Scheme 4. 3ab as Precursor for Cytotoxic Heterocycles 4



Encouraged by the promising results obtained above, we turned our attention to the use of various cyclohexenones **2b–d** as coupling partner with 2-aminopyrimidine **2a** and 2-aminopyridine **2b** (Scheme 5). Satisfactory yields were obtained when methyl substituents were present in different positions 4, 5, or 6 of the cyclohexenone core.

It should be noted that under aerobic oxidative conditions one of the possible side reactions between a 2-cyclohexenone and an amino compound is the dehydrogenative aromatization leading to aniline.[7] Another possible complication is the 6- or 4-iodination of cyclohexenone followed by a cascade reaction with 2-aminopyridine. These kinds of transformation are well documented for enolizable ketones.[8] To our delight, under the

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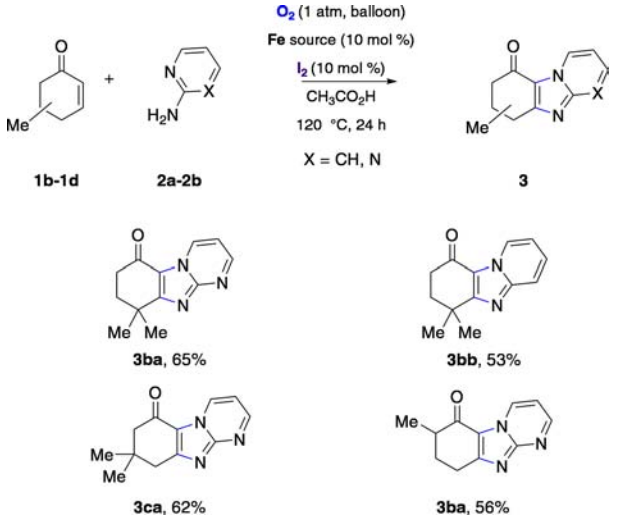
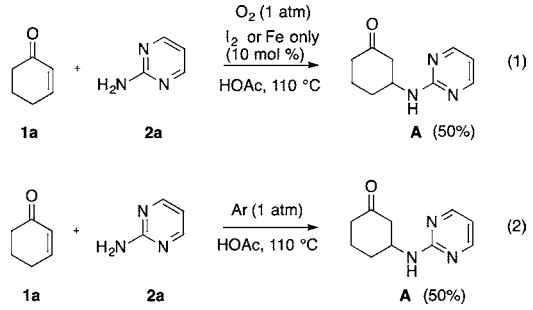
Scheme 5. Coupling Reaction between 1b−d and 2a,b



optimized conditions in acetic or isobutyric acid, this occurred only to a small extent compared to other aprotic solvents.

Although the detailed mechanism of this transformation, complicated by high reaction concentrations, cannot be elucidated at this stage, important observations may be discussed based on some selected controlled experiments (Scheme 6). First, treatment with iron or iodine alone only led

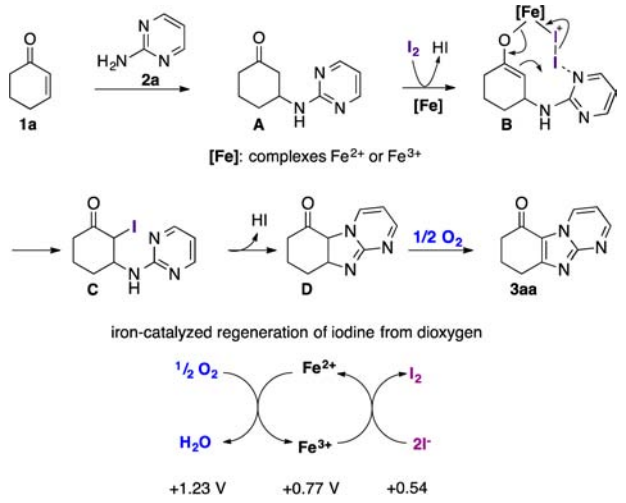
Scheme 6. Coupling Reaction between 1b−d and 2a,b



to the Michael adduct **A** and not the desired product **3** (eq 1). This observation demonstrated the cooperative role of iron/iodine system for the success of the reaction. Second, only one regioisomer **3** was obtained in all cases. Third, heating a mixture of only **1a** and **2a** in acetic acid only led rapidly to a nearly equimolar and equilibrium mixture of **2a** and **A** (eq 2) even after 1 h of heating and remained unchanged after 24 h.

Based on the observed regiochemistry, we proposed a possible pathway involving as a first step a Michael addition of the amino group of 2-aminopyrimidine to 2-cyclohexenone (Scheme 7). This was demonstrated by the formation and consumption of the Michael adduct **A** in the reaction mixture. The next step would be the regioselective iodination of the 2-position of adduct **A** followed by a cyclization and aromatization. Iron plays a vital role to the success of the reaction by complexing with both endocyclic nitrogen and enol oxygen atoms of **B** for a selective 2-iodination to provide **C**. Finally, when compared standard electrode potentials of three redox couples $1/2O_2,2H^+/H_2O$, $I_2/2I^-$, and Fe^{3+}/Fe^{2+}, we noticed that iron could catalyze the regeneration of iodine from iodide by dioxygen.

Scheme 7. Proposed Mechanism



In summary, we have developed an extremely simple catalytic system based on three elements $Fe/I_2/O_2$ for an oxidative coupling reaction between 2-aminopyrimidine or 2-aminopyridines with conjugated cyclohexenones. The unaromatized fused polycyclic azaheterocycles with a valuable aliphatic cyclohexenone function for further derivatization have been obtained in moderate to good yields. The oxidative C−H/N−H cross-coupling has displayed a broad substrate scope for both 2-aminopyridines and conjugated cyclohexenones as well as good functional group tolerance. Application of this procedure to other substrates and to the synthesis of bioactive polynitrogenated molecules is well underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02340.

General experimental procedure, characterization data of the compounds (PDF)

X-ray crystallographic data for **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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