Organic LETTERS

Letter

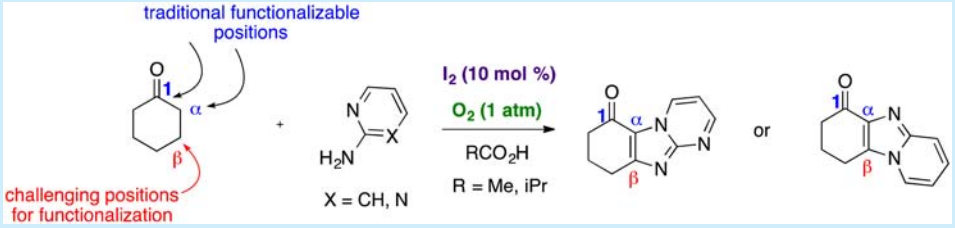
pubs.acs.org/OrgLett

Molecular Iodine-Catalyzed Aerobic α,β-Diamination of Cyclohexanones with 2-Aminopyrimidine and 2-Aminopyridines

Thanh Binh Nguyen,* Ludmila Ermolenko, Pascal Retailleau, and Ali Al-Mourabit*

Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Univ. Paris-Sud, Université Paris-Saclay, 1, av. de la Terrasse, 91198 Gif-sur-Yvette, France

Supporting Information



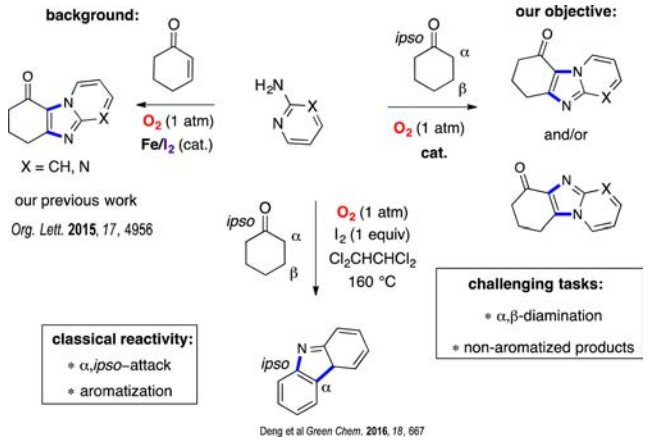
ABSTRACT: Molecular iodine is shown to be an excellent catalyst for aerobic oxidative α,β-diamination of cyclohexanones with 2-aminopyrimidine/2-aminopyridines. This α,β-C−H functionalization is remarkable for its simplicity in both substrates and conditions, involving one and a half oxygen molecules and releasing three water molecules as the only byproduct. In addition, the functionalized products including protected 2-aminoimidazoles introduced without aromatization can serve as useful building blocks for natural product synthesis and medicinal chemistry.

The C−H bond is a quasi-omnipresent structural motif in organic skeletons. Direct C−H functionalization approaches have recently received particular attention due to the atom economy and step efficiency associated with such transformations, especially when the reactions were carried out in many weakly activated or unactivated C−H bonds under aerobic conditions.

During the course of our study aiming at selective diamination of the C═C bond of cyclohexenones to provide polyaromatic heterocycles fused with cyclohexanones, we noted the fact that starting materials 2-cyclohexenones are commercially available in only a limited range of structures and are expensive (apart from the simplest 2-cyclohexenone) (Scheme 1).[1] It also seems much more difficult to synthesize some of them due to several reasons: low polarity, high volatility, high reactivity, and their propensity to aromatize/isomerize during preparation, purification, and further reaction processes.

In this context, the use of the corresponding cyclohexanones as surrogates for related 2-cyclohexenones for these reactions appears to be very advantageous. Cyclohexanones are much more readily obtainable synthetically and more available commercially with low prices and wide structural diversity, but their α,β-functionalizations are extremely challenging. Indeed, although structurally similar at first glance, these two families of compounds are chemically very distinct. As an example, 2-cyclohexenones can be functionalized selectively at the C═C bond while leaving the C═O bond intact. On the other hand, oxidative coupling reactions of cyclohexanones with diazanucleophiles have been described to occur at the α and *ipso* positions of the cyclohexanones with concomitant aromatization to give fused polyheteroaromatic systems.[2]

Scheme 1. Literature Background and Our Objective



More generally, for α,β-difunctionalization of cyclohexanones, copper(II) chloride[3] and 2-alkylidene-4-oxothiazolidine vinyl bromide/Br_2[4] were found to be effective stoichiometric oxidizing reagents to promote a cascade initiated by an attack on the α-carbon in cyclohexanones leading to 3-halocyclohexane-1,2-diones with various degrees of polychlorination for the first case.[3] Recently, new methods of β-functionalization with aryl ketones,[5] benzaldimines,[6] and benzonitriles[7] via photoredox catalysis or aryl iodides via palladium catalysis have been developed. To the best of our knowledge, there is no method available for the direct α,β-diamination of cyclohexanones by

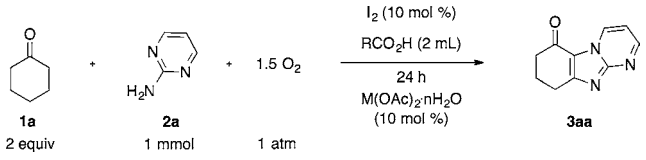
Received: March 21, 2016
Published: April 18, 2016

DOI: 10.1021/acs.orglett.6b00823
Org. Lett. 2016, 18, 2177−2179

any mode of activation. Herein, we demonstrate that a very simple catalytic system of molecular iodine is capable of realizing this transformation under aerobic conditions.

To initiate our investigation, we set up a model reaction between cyclohexanone **1a**, aminopyrimidine **2a** in acetic acid in the presence of molecular iodine (10 mol %), and a first-row transition metallic acetate as cocatalyst (10 mol %) for regeneration of molecular iodine under an atmosphere of oxygen (Table 1).

Table 1. Optimization of α,β-Diamination of Cyclohexanone



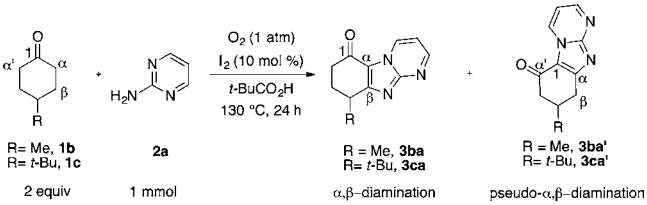
entry	M	*n*	R	temp (°C)	*t* (h)	conversion (%)[a]
1	Mn	4	Me	110	24	36
2	Fe	0	Me	110	24	–
3	Co	4	Me	110	24	33
4	Ni	4	Me	110	24	–
5	Cu	1	Me	110	24	32
6	Zn	2	Me	110	24	–
7	–	–	Me	110	24	35
8	–	–	Me	120	24	50
9	–	–	*i*Pr	120	24	65(60)[b]
10	–	–	***i*Pr**	**130**	**24**	**78 (70)**[b]

[a]Determined by ^{1}H NMR of the crude mixture. [b]Isolated yield.

While the reaction with iron(II), nickel(II), and zinc(II) acetates resulted in complex mixtures (entries 2, 4, and 6), a clean conversion was observed with manganese(II), cobalt(II), and copper(II) acetates (entries 1, 3, 5), giving rise to cyclohexanone fused heterocycle **3aa**. Comparable results were observed when lowering the metal catalyst loading (2, 1, 0.5, and 0.25 mol %) (not shown). To our surprise, the same reaction proceeded cleanly even in the absence of metal catalyst (entry 7). The reaction was further optimized by increasing temperature (entry 8) or using isobutyric acid as reaction solvent (entry 9). Finally, a good yield (70%) was obtained in isobutyric acid at 130 °C (entry 10).

At this stage, we wanted to confirm if the reaction was a real α,β-diamination instead of a formal one (as a result of a 1,α-diamination and subsequent/concomitant α′-oxygenation). For this purpose, 4-alkylcyclohexanones **1b,c** were evaluated (Scheme 2). Formation of ketone **3ba** as the major product (**3ba**:**3ba**′ = 10:1) suggested that the predominant pathway was effectively an α,β-diamination. This prevalence was also

Scheme 2. α,β-Diamination of 4-Substituted Cyclohexanones with 2a and Side Reactions

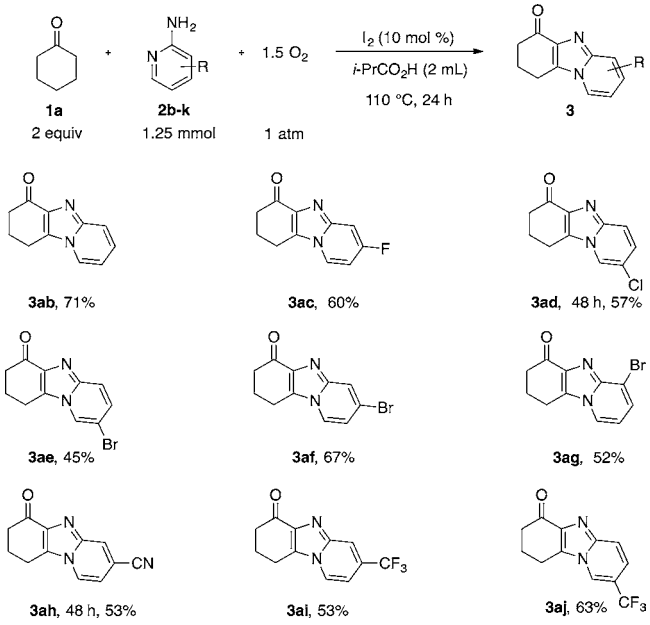


R = Me, 75%, **3ba**: **3ba'** = 10:1
R = *t*-Bu, 52%, **3ca**:**3ca'** > 99:1

accentuated with a more sterically hindered *t*-Bu group. The expected α,β-diamination ketone **3ca** was the only detectable regioisomer.

Having identified the optimal conditions for 2-aminopyrimidine with cyclic ketones, we wished to extend the reaction to a broad range of 2-aminopyridines, readily obtained from different commercial sources (Scheme 3). All tested derivatives provided moderate to good yields of the coupled product as a single isomer with inverse regiochemistry to that derived from 2-aminopyrimidine.

Scheme 3. α,β-Diamination of Cyclohexanones 1 with 2-Aminopyridines 2b–k



The structure was confirmed unambiguously by X-ray diffraction (product **3aj**, Figure 1). In general, reactions with 2-aminopyridines required a lower temperature than in the case with 2-aminopyrimidine **2a**.

Concerning the cycloalkanone ring size, our oxidative diamination conditions suffered however from some limitations

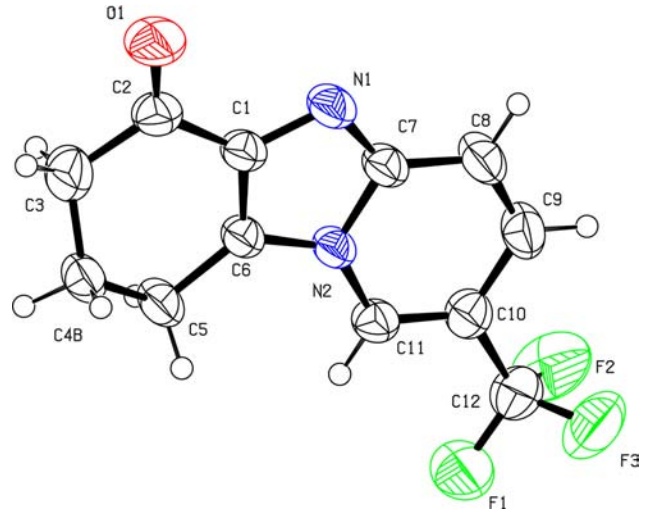
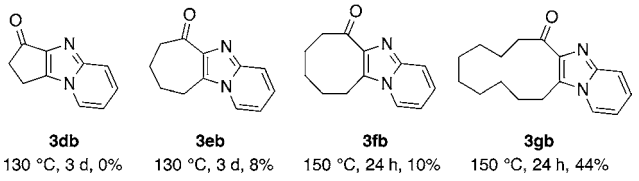


Figure 1. X-ray crystal structure of **3aj**.

DOI: 10.1021/acs.orglett.6b00823
Org. Lett. 2016, 18, 2177–2179

(Scheme 4). The reaction between cyclopentanone with 2-aminopyridine resulted in only a trace amount of the

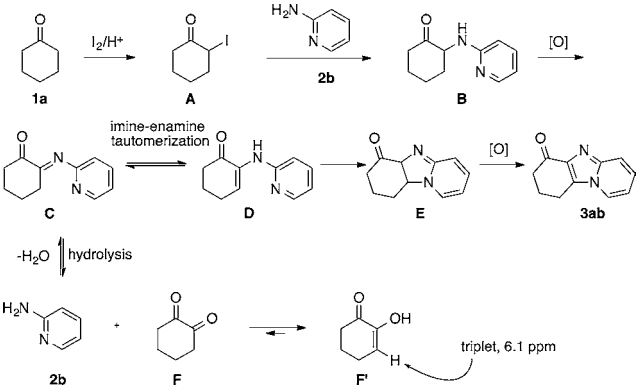
Scheme 4. Scope and Limitations of of Cycloalkanones



corresponding condensed product **3db** despite prolonged heating (3 d). An increase in the ring size led to better reactivity, and a moderate yield was observed with dodecanone.[8] These results demonstrated that the ring conformation of cycloalkanones, which is directly dependent on the ring size, is of vital importance to the success of the present method.

For the mechanism of this α,β-diamination of cyclohexanones, the first step is most likely the α-iodination of cyclohexanone **1a** to **A** followed by a nucleophilic attack of 2-aminopyridine **2b** to provide **B** (Scheme 5).

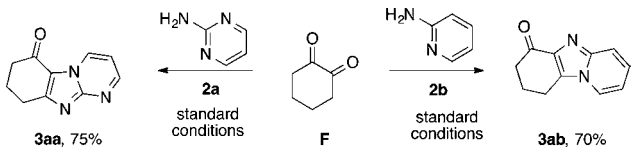
Scheme 5. Proposed Mechanism for the Formation of 3ab from 1a and 2b



The reaction is followed by an oxidation of the newly formed C−N bond to give an imine or iminium type intermediate **C**/**D** which facilitates a sequence β-amination−oxidative aromatization to provide the corresponding cross-coupling product. It is possible that the regiochemistry of the reaction is defined in the first step of α-amination of cyclohexanone **A** → **B**. However, it can also be redefined once the α-C−N bond is oxidized into α-C═N. Indeed, **C** can be hydrolyzed into **2b** and 1,2-cyclohexadione **F**. In some cases, we could detect the presence of **F** in the crude mixtures due to a very characteristic olefinic proton signal of its enol tautomer **F′** (~6.1 ppm).[9]

To confirm this hypothesis, we applied the standard conditions for F with **2a** and **2b** (Scheme 6). In both cases, the desired corresponding products **3aa** and **3ab** were formed

Scheme 6. Controlled Experiments of F with 2a and 2b



in comparable yields, and with exclusively the same regiochemistry in the experiments of cyclohexanone **1a**.

In conclusion, an unprecedented molecular iodine-catalyzed aerobic α,β-diamination reaction of cyclohexanones with 2-aminopyridines and 2-aminopyrimidine has been developed. The optimized reaction conditions allow the total regioselective formation of coupled products. Two different regiochemistries have been observed depending on the starting 2-aminoazine substrates. These results clearly demonstrate that this molecular iodine-catalyzed aerobic direct α,β-diamination of simple cyclohexanones **1** prevails in relation to the several limitations encountered with classical α,*ipso*-diamination/aromatization of cyclohexanones **1**.[2] It has significant advantages over the conventional diamination of conjugated cyclohexenones[1] because this approach not only avoids the use of conjugated enones, which are not readily available and require additional steps, but also is complementary in terms of regiochemistry of condensed products with 2-aminopyridines. Furthermore, this methodology, which involves up to one and a half oxygen molecules and releases three water molecules as the only byproduct, is obviously environmentally friendly. Although still in its very early stages, this approach has shown great potential for inexpensive and rapid access to pharmacologically relevant molecules. Efforts in understanding the reaction mechanism as well as enhancing the catalyst activity and enlarging the scope are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00823.

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

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

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: nguyen@icsn.cnrs-gif.fr.

*E-mail: ali.almourabit@cnrs.fr.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Nguyen, T. B.; Corbin, M.; Retailleau, P.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2015**, *17*, 4956.

(2) Xie, Y.; Wu, J.; Che, X.; Chen, Y.; Huang, H.; Deng, G. *Green Chem.* **2016**, *18*, 667.

(3) Nishizawa, K.; Satoh, J. Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1276.

(4) Baranac-Stojanovic, M.; Markovic, R.; Stojanovic, M. *Tetrahedron* **2011**, *67*, 8000.

(5) Petronijevic, F. R.; Nappi, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 18323.

(6) Jeffrey, J. L.; Petronijevic, F. R.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 8404.

(7) Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. *Science* **2013**, *339*, 1593.

(8) In the case of cyclododecanone, although the ^{1}H NMR showed a total conversion of 2-aminopyridine into the condensed product, the yield is low because of difficult purification.

(9) 1,2-Cyclohexadione exists exclusively as the enol form **F′** in $CDCl_3$.

DOI: 10.1021/acs.orglett.6b00823
Org. Lett. 2016, 18, 2177−2179