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Iodine-catalyzed cycloalkenylation of dihydroquinolines and arylamines through a reaction with cyclic ketones under neat conditions

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ABSTRACT

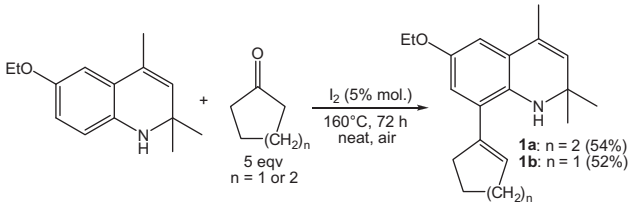
An iodine-catalyzed direct cycloalkenylation of dihydroquinolines and arylamines has been developed. This method consists of a Friedel–Crafts reaction between dihydroquinolines (or arylamines) and cyclic ketones in which the double bond is selectively generated throughout the course of the reaction resulting in a direct cycloalkenylation, under neat conditions.

Introduction

Charles Friedel and James Mason Crafts initially reported the alkylation and the acylation of aromatic rings using alkyl or acyl chlorides respectively, in the presence of aluminum chloride in 1877.[1] This breakthrough discovery has generated a lot of interest over the years resulting in the synthesis of a wide range of molecules through the modification of the original reaction conditions. Throughout these years, a large number of catalysts including Lewis acids such as BF_3, $BeCl_2$, $TiCl_4$, $SbCl_5$, or $SnCl_4$, Bronsted acids such as $HF{\cdot}SbF_5$ or $HSO_3F{\cdot}SbF_5$, and even nano-TiO_2/SO_4^{2-} or $Ph_3PAuCl/AgOTf$, to name a few, have been explored.[2] After more than a century of history, Friedel–Crafts reactions are still at the forefront of organic synthesis, with the emphasis geared toward the use of less toxic and non-corrosive catalysts. One of these catalysts is molecular iodine (I_2) which has been used in a wide variety of transformations including oxidative cyclization, cascade reactions, and direct C–H functionalizations, to name just a few.[3] Herein we report the iodine-catalyzed direct cycloalkenylation of arylamines, through a reaction between a cyclic ketone and an aromatic system in which the double bond is selectively generated throughout the reaction process, resulting in a direct C–H functionalization.

Results and discussion

As part of our continued effort to investigate the real mechanism of the iodine-catalyzed version of the Skraup–Doebner–Von-Miller quinoline synthesis,[4] we discovered that molecular iodine can catalyze a direct cycloalkenylation on dihydroquinolines. In fact, when reacting ethoxyquin with cyclohexanone or cyclopentanone in the presence of a catalytic amount of iodine, we obtained 8-cyclohexenyl-6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (**1a**, 54%) or 8-cyclopentenyl-6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (**1b**, 52%), respectively (see Scheme 1).[4a] Since these reaction conditions are unprecedented to the best of our knowledge, we undertook further investigations with a goal of expanding the scope of such a reaction.



Scheme 1. Reaction between ethoxyquin and cyclohexanone or cyclopentanone.[4a]

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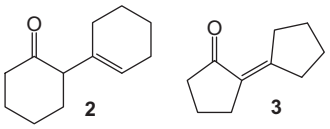
Table 1
Optimization of the reaction conditions

Entry[a]	Catalyst[b]	Cyclohexanone[b] (mol)	**1a**, Yield[c] (%)
1	I_2 (1% mol)	1	10
2	I_2 (1% mol)	3	38
3	I_2 (5% mol)	3	67
4	I_2 (5% mol)	5	69
5	I_2 (10% mol)	5	53
6	I_2 (100% mol)	5	39
7	I_2 (5% mol)	10	68
8	I_2 (5% mol) + DPPH (5% mol)	5	17
9	I_2 (5% mol) + DPPH (100% mol)	5	NR
10	KI (5% mol)	5	NR
11	CuI (5% mol)	5	NR
12	NIS (5% mol)	5	67
13	AIBN (5% mol)	5	NR
14	AIBN (100% mol)	5	NR
15	I_2 (5% mol), under nitrogen	5	NR
16	I_2 (5% mol), under oxygen	5	68

[a] Each reaction mixture was allowed to stir at 160 °C for 72 h.
[b] The percent mol and the mol equivalence are in relationship to 1 equiv of ethoxyquin.
[c] The percent yields refer to pure isolated products. NR = No Reaction.

As a starting point for these investigations, the reaction conditions described in Scheme 1 were optimized using the commercially available 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (ethoxyquin) and cyclohexanone as starting materials, and the obtained results are shown in Table 1. It appeared that the use of 3 to 5 equivalents of the ketones and 0.05 equivalent of iodine (entries 3 and 4) produced the best yield, and the use of a larger amount of ketone under the same conditions (entry 7) did not produce any further improvement of the yield. While the low amount of iodine is to be blamed for the low yield obtained in entry 2, the use of a larger amount of iodine (>5% mol) appeared to negatively impact the yield of the reaction (entries 5 and 6). Furthermore, the low amount of cyclohexanone (1:1 mol of ethoxyquin) is also to be blamed for the poor yield observed in entry 1 when compared to entry 2.

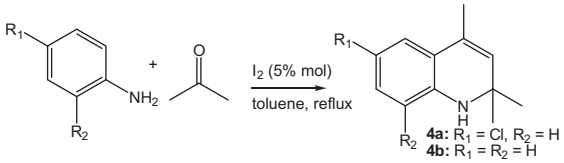
As we previously reported,[4a] cyclohexanone polymerizes when heated in the presence of a catalytic amount of iodine to yield predominantly β,γ-unsaturated ketone oligomers (**2**), while cyclopentanone reacts under the same conditions to produce mainly α,β-unsaturated ketone oligomers (**3**), with the dimer being the major product in each case. This polymerization is exacerbated by an increased amount of iodine,[4a] and this is consistent with the use of molecular iodine as a catalyst in aldol condensations.[5] As a result, a mixture of oligomer derivatives of **2** and **3** has always been observed as side products throughout the course of this work. In order to make sure that the self-polymerization of the cyclic ketones does not affect the reaction outcome, an excess of ketones (5:1 mol of ethoxyquin) was used throughout these investigations. On the other hand, the use of KI (entry 10) or CuI (entry 11) as a substitute for molecular iodine did not produce the expected product. However, the use of N-iodosuccinimide (NIS, entry 12) as a substitute for molecular iodine produces similar yield as in entries 3 and 4. As a result, the reaction conditions described in entry 4 were used as the standard conditions for subsequent reactions. It also appeared that the reaction does not take place under a nitrogen environment (entry 15) or when the system is closed to the atmospheric air, but proceeds just fine when run under an oxygen environment (entry 16). These data suggest that, although oxygen is needed for this reaction to proceed, atmospheric oxygen is enough to fulfill that requirement. As a result, the next series of reactions were run under an open air environment.



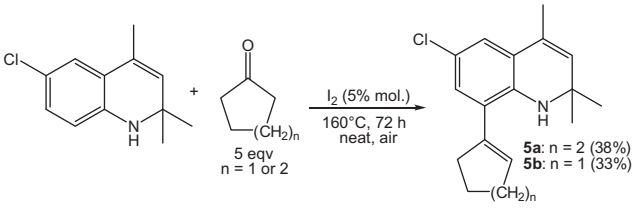
With the optimal reaction conditions in hand, we undertook to explore the scope of the reaction starting with a series of 1,2-dihydroquinolines prepared through the iodine-catalyzed version of the Skraup–Doebner–Von Miller synthesis.[6] Toward this goal, 4-chloroaniline or aniline was allowed to react with acetone in refluxing toluene to yield 6-chloro-1,2-dihydro-2,2,4-trimethylquinoline (**4a**, 38%) and 1,2-dihydro-2,2,4-trimethylquinoline (**4b**, 48%), respectively (see Scheme 2).

These 1,2-dihydroquinoline derivatives were successively subjected to the reaction conditions described in entry 4, in the presence of cyclohexanone or cyclopentanone to yield the corresponding cycloalkenylated dihydroquinoline derivatives. In fact, under these conditions, 6-chloro-1,2-dihydro-2,2,4-trimethylquinoline (**4a**) reacts with cyclohexanone to yield 6-chloro-8-cyclohexenyl-1,2-dihydro-2,2,4-trimethylquinoline (**5a**) which totally decomposes regardless of the method of purification and preservation. Thus, this compound was never fully characterized, although the HRESI-MS spectrum was very decent. On the other hand, reacting **4a** with cyclopentanone yielded 6-chloro-8-cyclopentenyl-1,2-dihydro-2,2,4-trimethylquinoline (**5b**, 33%) which was very stable and was fully characterized (see Scheme 3). The yield in these cases was significantly lower than that obtained with ethoxyquin under the exact conditions, suggesting that the deactivating effect of the chlorine atom on the aromatic ring might be having a negative effect on the reaction.

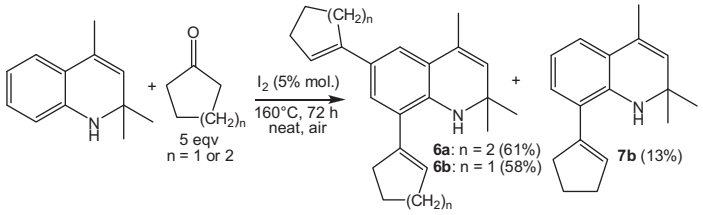
More importantly, 1,2-dihydro-2,2,4-trimethylquinoline (**4b**), a dihydroquinoline derivative in which the *ortho*- and the *para*-positions to the nitrogen are available, reacted under the same conditions with cyclopentanone or cyclohexanone to yield 6,8-dicyclohexenyl-1,2-dihydro-2,2,4-trimethylquinoline (**6a**, 61%) and 6,8-dicyclopentenyl-1,2-dihydro-2,2,4-trimethylquinoline (**6b**, 58%), respectively. These two compounds are cycloalkenylated at the *ortho*- and *para*-positions to the nitrogen of the dihydroquinoline ring as illustrated in Scheme 4. In the case of cyclopentanone, we also isolated a side product (7**b**) in which only the *ortho*-position to the nitrogen atom is substituted. This probably suggests that the *ortho*-position to the nitrogen atom in these molecules is more reactive than the *para*-position.



Scheme 2. Synthesis of dihydroquinoline derivatives.



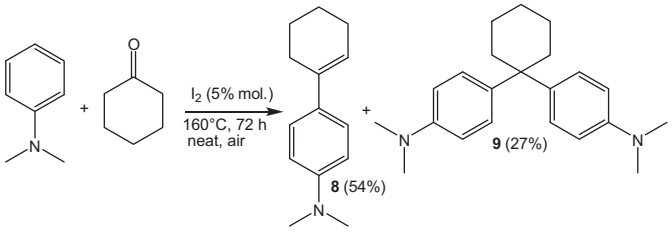
Scheme 3. Reaction between 6-chloro-1,2-dihydro-2,2,4-trimethylquinoline and cyclohexanone or cyclopentanone.



Scheme 4. Reaction between 1,2-dihydro-2,2,4-trimethylquinoline and cyclohexanone or cyclopentanone.

In order to further expand the scope of the reaction, a series of aniline derivatives were submitted to the same reaction conditions as a replacement for 1,2-dihydroquinolines. Under these conditions, reacting a primary arylamine with a cyclic ketone will result in a dihydroquinoline derivative as we previously reported.[4a] Thus, a series of *N*,*N*-dimethylaniline derivatives were used as starting materials instead. *N*,*N*-dimethylaniline reacted with cyclohexanone to yield mainly 4-cyclohexenyl-*N*,*N*-dimethylaniline (**8**, 54%) and 4-(1-(4-(dimethylamino)phenyl)cyclohexyl)-*N*,*N*-dimethylaniline (**9**, 27%), a compound in which two molecules of *N*,*N*-dimethylaniline are attached to the same carbon of the cyclohexane through the *para*-position to the nitrogen atom (Scheme 5). No *ortho*-cycloalkenylated derivative was obtained for this reaction. The structure of compound **9** was unambiguously determined by single crystal X-ray diffraction, and the obtained molecular formula is shown in Figure 1.

Furthermore, the reaction between 4-methoxy-*N*,*N*-dimethylaniline, 4-bromo-*N*,*N*-dimethylaniline, or 4,*N*,*N*-trimethylaniline with either cyclopentanone or cyclohexanone under the same conditions yielded only the starting material and the polymerized derivatives of the cyclic ketone used; no cycloalkenylation was observed in any of these cases. Since the *para*-position in all these aniline derivatives is also substituted, we concluded that steric hindrances resulting from the presence of two methyl groups on the nitrogen of the aniline must have precluded the *ortho*-cycloalkenylation. To further examine this hypothesis, 3-methoxy-*N*-methylaniline and 2-methoxy-*N*-methylaniline, two molecules bearing only one methyl group on the nitrogen atom, were allowed to react with cyclopentanone under the conditions described above. In these cases, the nitrogen and the *para*-position to the nitrogen appeared to be systematically cyclopentenylated, but no *ortho*-cyclopentenylation was observed. In fact, the reaction between 2-methoxy-*N*-methylaniline and cyclopentanone yielded *N*,4-dicyclopentenyl-2-methoxyaniline (**10a**, 42%) while the reaction with 3-methoxy-*N*-methylaniline yielded *N*,4-dicyclopentenyl-3-methoxy-*N*-methylaniline (**10b**, 36%), respectively, as illustrated in Scheme 6. It appeared that the reaction between the monosubstituted nitrogen atom and the ketone resulting in a cycloalkenylated arylamine is faster than any *ortho* or *para*-alkenylation of the benzene ring. This situation creates more steric hindrances at the *ortho*-positions than that observed with *N*,*N*-dimethylaniline and thus makes any *ortho*-alkenylation impossible. In fact, the reaction between the nitrogen atom of an aniline derivative and the carbonyl of a ketone resulting in the formation of a Schiff base is considered to be the very first step toward the preparation of dihydroquinoline through a Skraup–Doebner–Von Miller reaction.[4,6] However, since the nitrogen is mono-methylated in this case, a Schiff base cannot be produced, and instead, a *N*-cyclopentenylaniline derivative is generated. Furthermore, in the case of *N*,4-dicyclopentenyl-2-methoxyaniline (**10a**), an unexpected demethylation on the nitrogen atom was observed.



Scheme 5. Reaction between *N*,*N*-dimethylaniline and cyclohexanone.

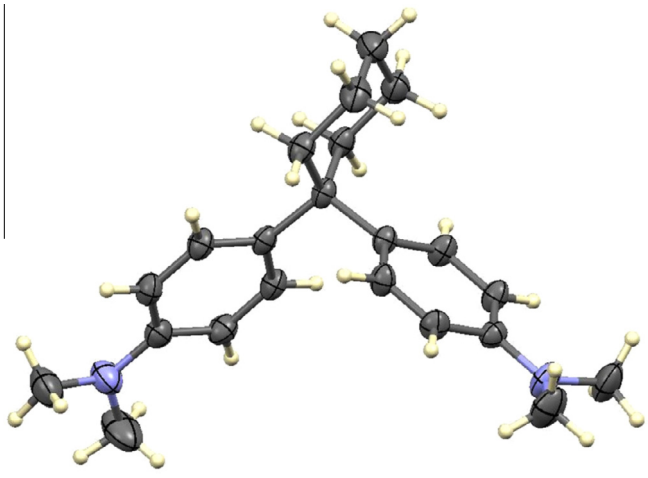
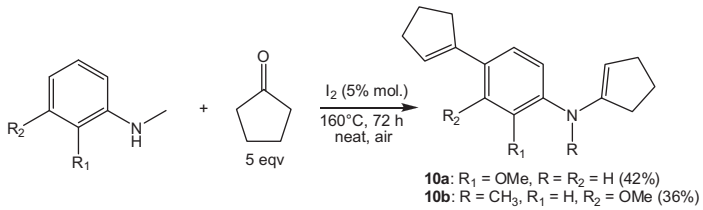


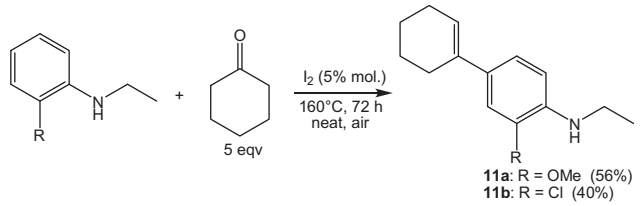
Figure 1. Anisotropic representation of compound **9** drawn at 50% probability level.

On the other hand, when reacting 2-chloro-*N*-ethylaniline or 2-methoxy-*N*-ethylaniline with cyclohexanone under these conditions, 2-chloro-4-cyclohexenyl-*N*-ethylaniline (**11a**) and 4-cyclohexenyl-*N*-ethyl-2-methoxyaniline (**11b**) were obtained, respectively (Scheme 7). Unlike with cyclopentanone, no reaction (cycloakenylation) was observed on the nitrogen atom although it was also monosubstituted. The structural difference between cyclopentanone and cyclohexanone might be the key factor behind the observed difference in reactivity, with cyclohexanone being more hindered than cyclopentanone.

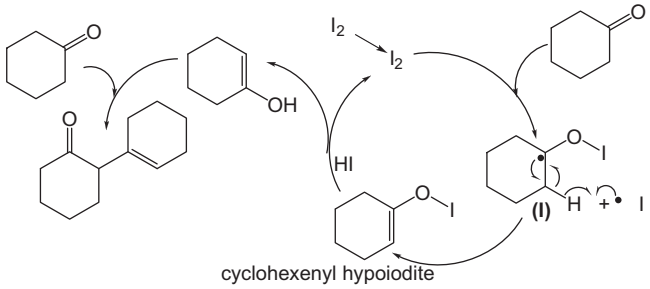
Several control experiments were conducted to gain some insights into the mechanism of this reaction. The addition of 5% mol of 1,1-diphenyl-2-picrylhydrazyl (DPPH)—a radical inhibitor—to the reaction mixture resulted in a significantly lower yield for **1a**, dropping from 69% (Table 1, entry 4) to just 17% (Table 1, entry 8), while the addition of 100% mol of DPPH (Table 1, entry 9) totally shut down the reaction. In fact, the GC–MS analysis of the mixture obtained in entry 9 showed no sign of the product. These observations suggest a possible involvement of radical intermediates in the mechanism of this reaction. It is then not surprising that the substitution of I_2 in the reaction mixture by KI (Table 1, entry 10) or CuI (Table 1, entry 11) did not produce any product. Interestingly, the substitution of I_2 by azobisisobutyronitrile (AIBN) which is a free radial initiator (Table 1, entries 13 and 14) even at a ratio of 100% mol in relationship with 1 equivalent of ethoxyquin, under the same reaction conditions, failed to produced the



Scheme 6. Reaction between 2-methoxy-*N*-methylaniline or 3-methoxy-*N*-methylaniline and cyclopentanone.



Scheme 7. Reaction between 2-chloro-*N*-ethylaniline or 2-metoxy-*N*-ethylaniline and cyclohexanone.



Scheme 8. A tentative mechanism for the observed cyclic ketone self-aldolization.

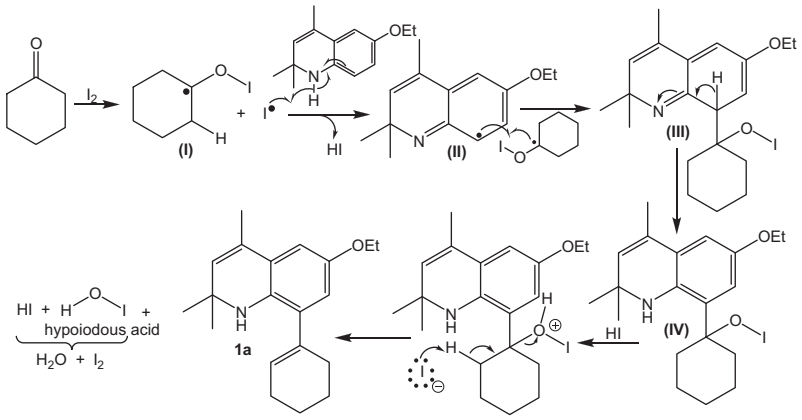
expected product as indicated by GC–MS analysis of the reaction mixture. This latter observation suggests that I_2 is doing more than just initiating the formation of radical intermediates in the reaction mixture.

Based on these experimental observations and considering the amount of dimerized cyclic ketone present in the reaction mixture throughout the entire investigations, we hypothesized that during the course of this reaction, I_2 reacts first with the ketone to generate a free radical intermediate (**I**) which reacts with the iodine radical generated in the same step, to produce a cyclohexenylhypoiodide. This latter entitity then reacts with hydriodic acid produced in the previous steps to restore the catalyst and generate the enol needed for the aldolization reaction as illustrated in Scheme 8. This hypothesis is consistent with the use of molecular iodine as a catalyst in aldol condensations.[5]

Alternatively, the radical intermediate (**I**) can react with dihydroquinoline (or arylamine) derivatives to generate the cycloalkenylated product as illustrated in Scheme 9. In this case, the iodine radical produced in the first step of the reaction reacts with the dihydroquinoline (or arylamine) intermediate to generate an imine radical (**II**) which couples with the cyclohexyl hypoiodite radical (**I**) to generate intermediate **III**. This latter intermediate will aromatize through a standard sigmatropic rearrangement ([1,3]-H shift), resulting in **IV**. The involvement of free radical intermediate similar to **II** in iodine-catalyzed reactions has previously been reported.[3d] The reaction between **IV** and HI followed by the elimination leads to the product **1a**. Finally, the hydriodic acid and the hypoiodic acid react in the presence of oxygen to restore the catalyst. This is a tentative mechanistic pathway, with several parameters that still need to be proven through much deeper investigations.

Conclusion

A straightforward iodine-catalyzed regioselective cycloalkenylation of dihydroquinolines and arylamines through a direct reaction between a cyclic ketone and an aromatic system resulting in a direct C–H functionalization has been developed. The major challenge for this work has been the auto-oxidation of some of the products as they turned into dark gummy substances regardless of the method of purification and preservation. This behavior is consistent with previous reports on the stability of dihydroquinoline derivatives.[4a,6] Nevertheless, we were able to obtain decent ^{1}H NMR, ^{13}C NMR, and HRESI-MS spectra for almost all these compounds (see Supplementary data). This reaction offers an easy and metal-free method for direct cycloalkenylation on arylamines in which the double bond is selectively generated throughout the



Scheme 9. A tentative reaction mechanism.

reaction process. This reaction also enables easy structural diversifications through the appropriate selection of starting materials, which will be of interest in medicinal chemistry. Further investigations into the mechanism of the reaction that can help in broadening the scope of this reaction and turn it into a versatile catalytic system are ongoing.

Acknowledgment

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Supplementary data

The reaction procedures and the characterization of all the compounds, the ^{1}H NMR and the ^{13}C NMR spectra of all the compounds described in this report, the HRESI-MS of **1a**, **1b**, **2**, **3**, **5a**, **5b**, **6a**, **6b**, **8**, **9**, **10b**, **11a** and **11b**, and the EI-MS (GC-MS) of **7b** and **10a** are provided assupplemental data. This material is available free of charge via the internet at http://www.journals.elsevier.com/tetrahedron Letters/. CCCDC 950965 contains the supplementary crystallographic data for **9**. Copies of these materials can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, Fax. (+44) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.081.

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