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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

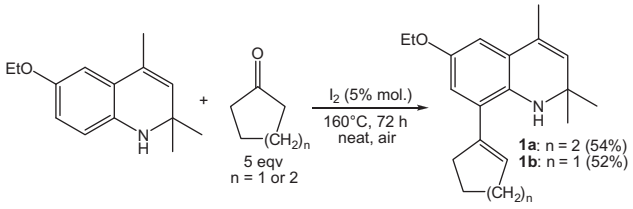
An iodine-catalyzed direct cycloalkenylation of dihydroquinolines and arylamines has been developed. This method consists of a Friedel–Crafts reaction between dihydroquinolines (or arylamines) and cyclic ketones in which the double bond is selectively generated throughout the course of the reaction resulting 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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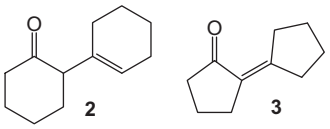
Table 1
Optimization of the reaction conditions

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.

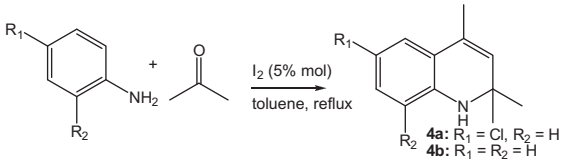
As we previously reported,[4a] cyclohexanone polymerizes when heated in the presence of a catalytic amount of iodine to yield predominantly β,γ-unsaturated ketone oligomers (**2**), while cyclopentanone reacts under the same conditions to produce mainly α,β-unsaturated ketone oligomers (**3**), with 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.



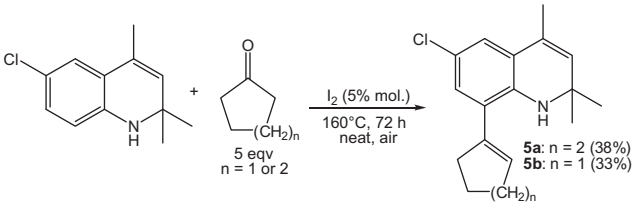
With the optimal reaction conditions in hand, we undertook to explore the scope of the reaction starting with a series of 1,2-dihydroquinolines prepared through the iodine-catalyzed version of the Skraup–Doebner–Von Miller synthesis.[6] Toward this goal, 4-chloroaniline or aniline was allowed to react 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.