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Povarov-Type Reaction Using Methyl as New Input: Direct Synthesis of Substituted Quinolines by I_2-Mediated Formal [3 + 2 + 1] Cycloaddition

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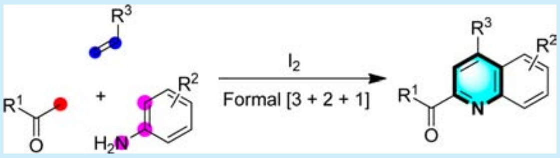
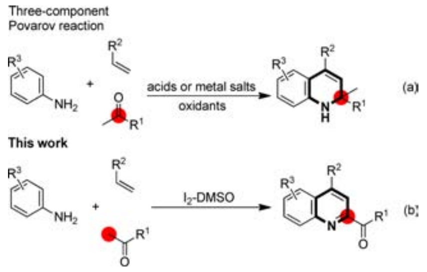
Ⓢ *Supporting Information*

ABSTRACT: A highly efficient molecular iodine mediated formal [3 + 2 + 1] cycloaddition reaction for the direct synthesis of substituted quinolines from methyl ketones, arylamines, and styrenes is developed. The methyl group of the methyl ketone represents uniquely reactive input in the Povarov reaction. A self-sequenced iodination/Kornblum oxidation/Povarov/aromatization mechanism has been proposed as a possible reaction sequence to account for the results observed in this study.



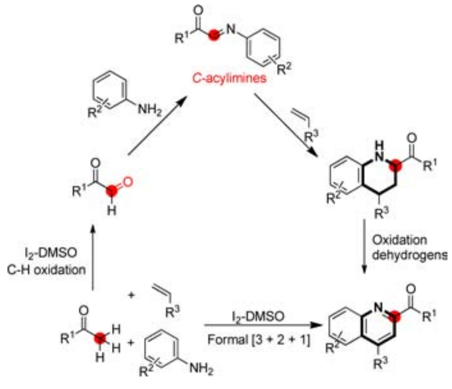
The quinoline nucleus is an important scaffold that is found in a wide range of biologically active compounds, including natural products and synthetic drugs.[1] For this reason, considerable research has been devoted to developing new methods for constructing substituted quinoline compounds.[2,3] The Povarov reaction,[4−6] which is a formal [4 + 2] cycloaddition reaction between an electron-poor 2-azadiene and an electron-rich dienophile, has recently emerged as one of the most efficient protocols for the preparation of quinolines. Notably, this reaction can be performed in a three-component fashion using a dienophile and an *N*-arylamine, generated in situ from a suitable arylamine and an aldehyde (or a ketone), to allow for the creation of three bonds in a single operation. The resulting tetrahydroquinolines can be transformed into the corresponding quinolines by treatment with an oxidant (Scheme 1a). Although significant progress has been made toward the development of Povarov reactions involving carbonyl groups, there have been no reports, to the best of our knowledge, concerning Povarov reactions with unactivated alkyl groups, such as a simple methyl group. Herein, we report the development of a reaction providing novel access to substituted quinolines via the oxidative cleavage of methyl C−H bonds under metal-free conditions (Scheme 1b).

Scheme 1. Povarov Reactions of Methyl Ketones



Continuing our research toward expanding the scope of named reactions,[7] we recently investigated the Povarov reaction of methyl ketones. Surprisingly, however, these reactions did not provide any trace of the classic Povarov products, with large amounts of acylation products being obtained instead. This indicated that we had discovered a fascinating new form of reactivity for the Povarov reaction, where the methyl group of the methyl ketone reacts instead of the carbonyl carbon. Mechanistically, the key step in our newly discovered Povarov reaction involves the cycloaddition reaction between a dienophile and an in situ generated *C*-acylimine intermediate (Scheme 2). Notably, some pioneering oxidative cleavages of methyl C−H bonds have been reported.[8] Liu and co-workers described CuI-catalyzed oxidation of methyl ketones to aldehydes in the presence of molecular oxygen, which proceeded via an arylglyoxal intermediate.[9] Furthermore, Kumar et al.

Scheme 2. Povarov-Type Reaction via Oxidative Cleavage of Methyl C−H Bonds



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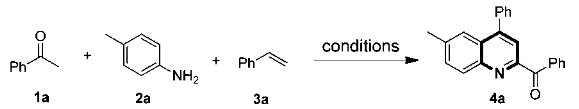
disclosed a copper(I)-catalyzed oxygenase reaction for the conversion of the allylic methyl group of 3-methylidene oxindole to the corresponding aldehyde.[10] Molecular oxygen can behave as an efficient oxidant in these types of reaction. However, to the best of our knowledge, the molecular iodine mediated formal [3 + 2 + 1] cycloaddition from methyl ketones, arylamines, and styrenes via the oxidative cleavage of methyl C−H bonds has not yet been reported, most likely due to the easy overoxidation of *C*-acylimines to the α-ketoamides.[11]

This cycloaddition process prompted us to investigate the reaction parameters in greater detail to evaluate their impact on the outcome of the reaction. The reaction of acetophenone (**1a**) with *p*-toluidine (**2a**) and styrene (**3a**) was selected as a model reaction for the current study and evaluated under various conditions. Pleasingly, the reaction proceeded smoothly over 4 h using 1.6 equiv of I_2 at 100 °C in DMSO to afford the Povarov cycloaddition product (**4a**) in 63% yield as a single regioisomer (Table 1, entry 1). The structure of this compound was unambiguously confirmed by X-ray crystallography analysis. On the basis of this encouraging result, several Lewis acid catalysts were also evaluated, including $FeCl_3$, $ZnCl_2$, $AlCl_3$, $InCl_3$, $Cu(OTf)_2$, and $Sc(OTf)_2$, but none of these catalysts had a positive impact on the outcome of the reaction (Table 1, entries 2−7). These results indicated that I_2 could also act as a Lewis acid to promote the direct cycloaddition step. A control experiment was conducted without I_2 to test this hypothesis and failed to provide any of the desired product (Table 1, entry 8). On the basis of this result, the reaction was further optimized using I_2 as the promoter. Interestingly, an increase in the loading of I_2 to 2.0 equiv gave **4a** in a higher yield (Table 1, entry 9), whereas a reduction in the charge of I_2 to 0.5 equiv resulted in a significant decrease in the yield (Table 1, entry 13). These results therefore demonstrated that catalytic amounts of I_2 could not be used to facilitate this reaction. The reaction could also proceed successfully when it was conducted in the presence of 2.0 equiv of I_2 at 80 °C (Table 1, entry 16).

Table 1. Optimization of the Reaction Conditions[a]

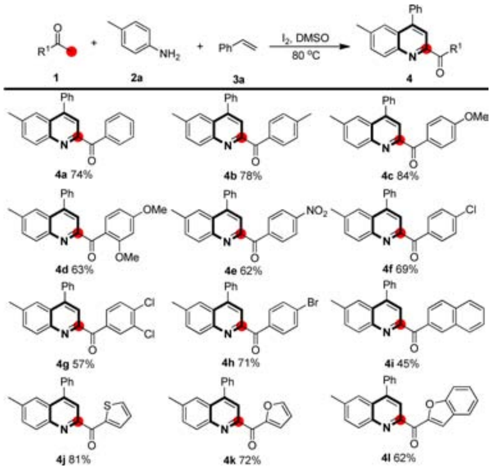


entry	I_2 (equiv)	Lewis acid	temp (°C)	yield[b] (%)
1	1.6		100	63
2	1.6	$FeCl_3$	100	62
3	1.6	$ZnCl_2$	100	58
4	1.6	$AlCl_3$	100	40
5	1.6	$InCl_3$	100	60
6	1.6	$Cu(OTf)_2$	100	44
7	1.6	$Sc(OTf)_2$	100	53
8			100	0
9	2.0		100	74
10	3.0		100	63
11	5.0		100	32
12	1.0		100	47
13	0.5		100	18
14[c]	2.0		100	74
15	2.0		60	10
16	**2.0**		**80**	**74**
17	2.0		110	74
18	2.0		130	74

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), Lewis acid (0.25 mmol), solvent (2 mL). [b]Isolated yields. [c]**3a** (1.0 mmol).

With the optimized conditions in hand, the generality and scope of the I_2-mediated formal [3 + 2 + 1] cycloaddition was next explored. To our delight, the reaction demonstrated wide substrate scope in terms of the aromatic ketone unit (Scheme 3).

Scheme 3. Scope of Methyl Ketones[a,b]

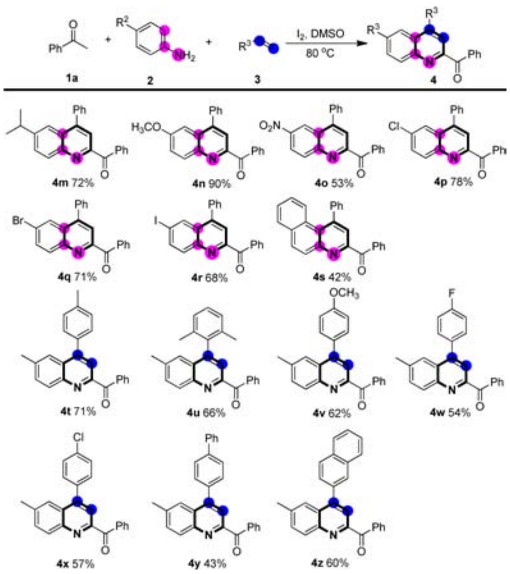


[a]Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), and I_2 (1.0 mmol) in DMSO (2 mL) at 80 °C. [b]Isolated yield.

Aryl methyl ketones bearing electron-neutral (4-H), electron-rich (e.g., 4-Me, 4-OMe, 2,4-OMe), and electron-deficient (e.g., 4-NO_2) phenyl rings were successfully converted to the corresponding products in moderate to good yields (62−84%; **4a−e**). The electronic and steric properties of the aromatic ketones had a little influence on the efficiency of this reaction. Furthermore, the optimized conditions were mild enough to be compatible with a broad range of halogenated (e.g., 4-Cl, 3,4-Cl_2, 4-Br) substrates (57−71%; **4f−h**), which provided the possibility for further functionalization. 2-Naphthyl methyl ketone also provided the expected product (**4i**) in 45% yield. Furthermore, the optimized conditions could be applied to various heteroaryl ketones, including furanyl, thienyl, and benzofuryl methyl ketones, which gave the corresponding products in moderate to good yields (62−81%; **4j−l**).

This strategy for oxidation of methyl C−H bonds was subsequently applicable to a variety of substituted anilines and styrenes, and the desired products were obtained in satisfactory yields (Scheme 4). Regarding the arylamine substrate, both electron-rich and electron-deficient anilines could be smoothly converted to the desired products (53−90%; **4m−o**). Interestingly, substrates bearing halogen substituents were well tolerated with the corresponding halo-substituted products being isolated in reasonable yields (68−78%; **4p−r**). β-Naphthylamine also reacted smoothly under the optimized conditions to give **4s** in 42% yield. The use of aniline unexpectedly resulted in the formation of a complex mixture of products. Regarding the styrenes, experimentation revealed that electron-rich styrenes (62−71%; **4t−v**) gave higher yields of the desired quinolines compared with weakly electron-deficient styrenes (43−57%; **4w−y**). Nevertheless, 4-cyanostyrene, which is a strong electron-deficient styrene, prevented the reaction from proceeding because of the decreased electron density on the aryl ring. Steric hindrance had a little influence on the efficiency of the reaction,

Scheme 4. Scope of Anilines and Styrenes[a]

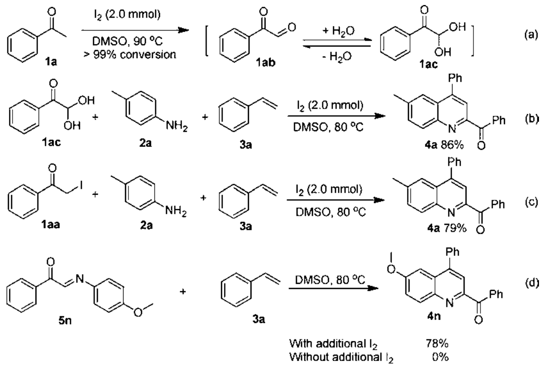


[a]Isolated yield.

as exemplified by *β*-vinylnaphthalene, which reacted under the optimized conditions to give the desired product (**4z**) in 60% yield.

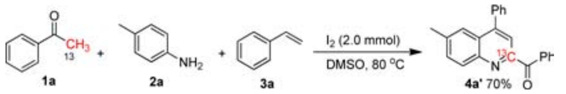
With the scope of the method established, the reaction mechanism was subsequently considered. Acetophenone (**1a**) was reacted with I_2 in DMSO at 90 °C to give phenylglyoxal (**1ab**) and the corresponding hydrated species (**1ac**) in quantitative yield (Scheme 5a). The hydrated species (**1ac**) was subjected to the optimized reaction conditions and gave **4a** in 86% yield (Scheme 5b). This result demonstrated that **1ac** was an intermediate in the current reaction. When the acetophenone substrate was replaced with *α*-iodo acetophenone (**1aa**), which was identified as a probable precursor of *α*-ketoaldehyde (**1ab**), the desired quinoline product was obtained in 79% yield (Scheme 5c). When *C*-acylimine (**5n**)[12] was used as a substrate in the reaction, the desired product **4n** was formed in 78% yield. However, the use of **5n** as a substrate did not result in the formation of **4n** when the reaction was conducted in the absence of I_2 (Scheme 5d). This suggested that iodine played an important role in the Povarov/oxidation process.

Scheme 5. Control Experiments



A ^{13}C-labeling experiment was also conducted under the optimized conditions using acetophenone-*β*-^{13}C as a substrate, which gave the desired product (**4a′**) in 70% yield (Scheme 6). Taken together, these experimental results indicated that *C*-acylimines were the key intermediates in the current reaction.

Scheme 6. ^{13}C Labeling Experiment



The reaction of **1a** (0.2 mmol) with **2c** (0.2 mmol) and **3a** (0.2 mmol) in the presence of I_2 (0.4 mmol) in DMSO-d_6 was monitored by ^{13}C NMR spectroscopy to develop a deeper understanding of the reaction mechanism (Figure 1). The results of this study also revealed that phenacyl iodine (**1aa**), phenylglyoxal (**1ab**), and *C*-acyl imine (**5n**) were important intermediates in the overall transformation.

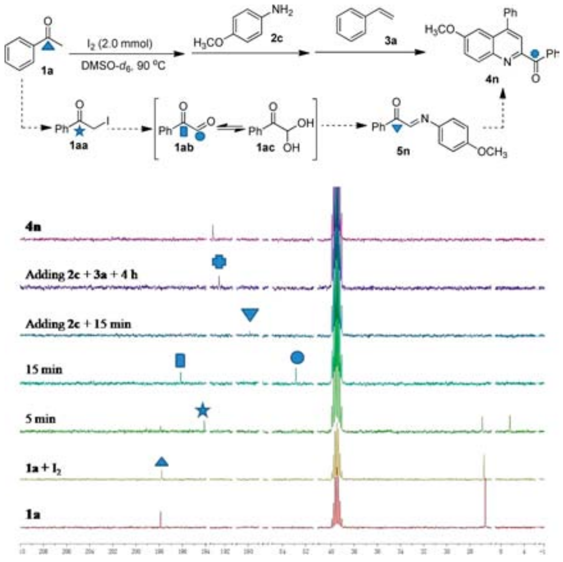
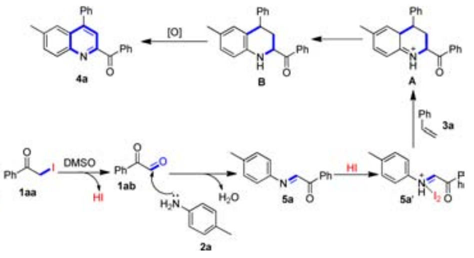


Figure 1. Progress of the reaction of **1a** (0.2 mmol), **2c** (0.2 mmol), and **3a** (0.2 mmol) with I_2 (0.4 mmol) at 90 °C by ^{13}C NMR (150 MHz, DMSO-d_6, 298 ± 0.5 K).

On the basis of the results of the current study as well as previous reports,[13] a possible mechanism was proposed using acetophenone (**1a**), *p*-toluidine (**2a**), and styrene (**3a**) as the substrates (Scheme 7). The initial reaction of molecular iodine with **1a** would result in the formation of the *α*-iodo ketone (**1aa**), which would be converted to phenylglyoxal by a subsequent Kornblum oxidation. The reaction of *p*-toluidine (**2a**) with the aldehyde group of **1ab** would then give the *C*-acyl imine **5a**, which would react with HI to give the activated *C*-acyl imine ion **5a′**. This activated species would be involved in the key step of

Scheme 7. Possible Mechanism



the Povarov-type reaction, and would react smoothly with styrene (**3a**) to give intermediate **B** in the presence of an excess or regenerated iodine.[14] Intermediate **B** would then undergo sequential oxidation and aromatization reactions to give the desired product **4a**.

In summary, a highly efficient I_2-mediated formal [3 + 2 + 1] cycloaddition for the direct synthesis of substituted quinolines using methyl ketones, arylamines, and styrenes has been developed. This synthetic pathway represents a fascinating new form of reactivity for the Povarov reaction, where the methyl group of the methyl ketone reacts instead of the carbonyl carbon. Initial studies of the mechanism suggested that this reaction proceeded through a self-sequenced iodination/Kornblum oxidation/Povarov/aromatization cascade reaction. Furthermore, this autotandem catalytic process was easy to operate and could sequentially promote three mechanistically distinct reactions in a single reactor using molecular iodine. Further studies of the application of this I_2-mediated formal cycloaddition are currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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