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Synergistic I_2/Amine Promoted Povarov-Type Reaction for the Synthesis of 2-Acyl-3-aryl(alkyl)quinolines Using Aryl(alkyl)acetaldehydes as Alkene Surrogates

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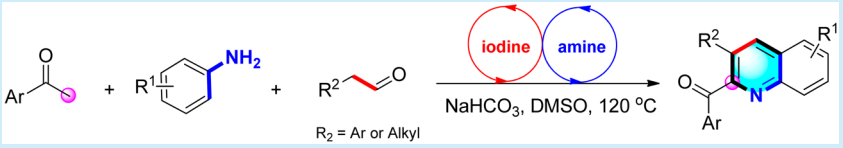
Supporting Information

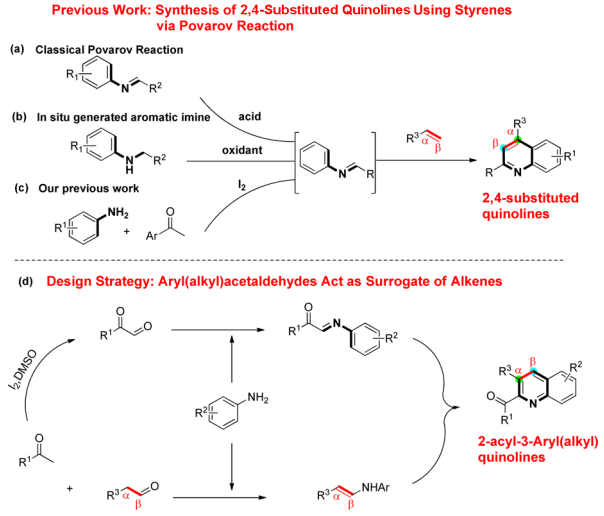


ABSTRACT: A synergistic I_2/amine promoted formal [4 + 2] cycloaddition of methyl ketones, arylamines, and aryl(alkyl)acetaldehydes as alkene surrogates has been established. This protocol allowed the modular synthesis of various 2-acyl-3-aryl(alkyl)quinolines, rather than 2,4-substituted quinolines. Notably, the arylamines not only participated as reactants in this reaction but also acted as indispensable catalysts to promote enamine formation. Moreover, mechanistic investigation suggested that the reaction occurred via an iodination/Kornblum oxidation/Povarov/aromatization sequence.

Quinoline subunits are widespread in natural products[1] and pharmaceutical molecules[2] and are important intermediates for asymmetric synthesis.[3] In past decades, numerous named reactions, including Skraup, Doebner−Von Miller, Friedländer, and Povarov reactions, have been reported for quinoline synthesis.[4] Among these methods, the Povarov reaction, which is catalyzed by either protic or Lewis acids and involves the formal [4 + 2] cycloaddition between 2-azadienes and dienophiles, is an efficient method for synthesizing quinolines (Scheme 1a). In recent years, good progress has been made in Povarov reactions.[5−7] The main strategy focused on the in situ generation of aromatic imines through the oxidation of sp^3 C−H bonds, followed by cycloaddition with alkenes. For example, novel strategies[6] have been developed for achieving sp^3 C−H bond oxidation of *N*-benzylanilines and glycine derivatives for the synthesis of 2,4-substituted quinoline derivatives with an alkene (Scheme 1b). In 2014, our group[7] took advantage of methyl ketones for building 2-acyl-4-arylquinolines with *p*-toluidine and an alkene via Povarov-type reactions (Scheme 1c). Despite progress in this area, most of the products remain restricted to 2,4-substituted quinolines because of the inherent regioselectivity of the alkene in the Povarov reaction. Direct construction of 2-acyl-3-aryl(alkyl)quinolines via the Povarov-type reaction has not yet been reported, as tuning the addition of an alkene to aromatic imines to be α-selective is much more difficult than making it β-selective. In this context, the investigation and development of suitable alkene surrogates to construct 2-acyl-3-aryl(alkyl)quinolines via a Povarov reaction are especially attractive. Inspired by synergistic enamine catalysis theory[8] and our previous work,[9] we envisaged that aryl(alkyl)acetaldehydes could act as alkene surrogates. Aryl(alkyl)acetaldehydes would generate enamines in situ via amine catalysis (Scheme 1d) and exhibit distinctly different regioselectivity compared with an alkene. Herein, we present a synergistic I_2/amine promoted Povarov-type reaction for preparing 2-acyl-3-aryl(alkyl)quinolines using methyl ketones and arylamines as precursors of aromatic imines, and aryl(alkyl)acetaldehydes as alkene surrogates.

According to the above hypothesis, we commenced the study by treating model substrates, acetophenone (1.0 mmol), *p*-toluidine (1.0 mmol), and phenylacetaldehyde (1.0 mmol),

Scheme 1. Synthesis of Quinolines via Povarov Reaction



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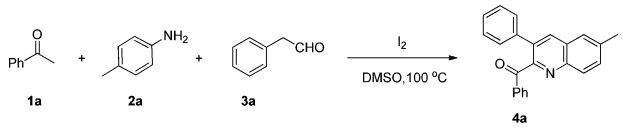
with I_2 (1.6 mmol) in DMSO at 100 °C. As expected, the reaction proceeded smoothly to afford the Povarov-type product **4a** in 52% yield (Table 1, entry 1) after 4 h. Based on this

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a 4a

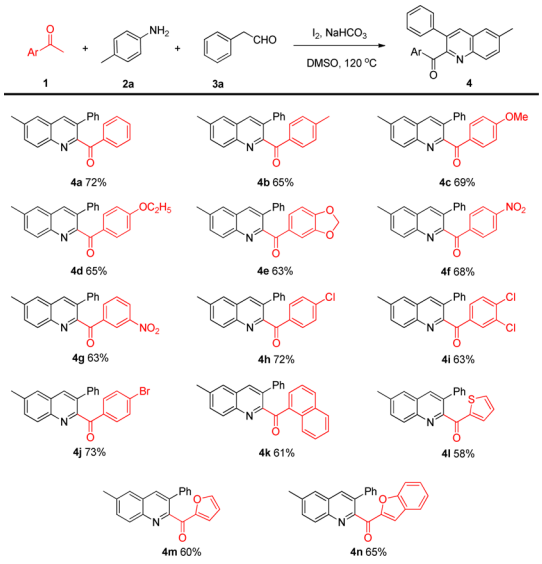
entry	I_2 (equiv)	1a:2a:3a	temp (°C)	yield (%)[b]
1	1.6	1:1:1	100	52
2	1.6	1:1:1	90	50
3	1.6	1:1:1	110	55
4	1.6	1:1:1	120	56
5	1.6	1:1:1	130	53
6	0.3	1:1:1	120	40
7	0.5	1:1:1	120	48
8	0.8	1:1:1	120	60
9	1.2	1:1:1	120	58
10	2.0	1:1:1	120	52
11	0.8	1:1:0.5	120	40
12	0.8	1:1:1.5	120	36
13	0.8	1:0.5:1	120	53
14	0.8	1:1.5:1	120	42
15[c]	0.8	1:1:1	120	69
16[d]	**0.8**	**1:1:1**	**120**	**72**
17[e]	0.8	1:1:1	120	58

[a]Reaction conditions: **1a** (1.0 mmol), **2a**, **3a**, I_2, heated in 3 mL of DMSO within 16 h unless otherwise noted. [b]Isolated yields. [c]With NaOH. [d]With $NaHCO_3$. [e]With Na_2CO_3.

encouraging result, we then examined various reaction conditions to improve the yield. First, different temperatures were applied to this Povarov-type reaction, with 120 °C giving the best yield (Table 1, entries 1−5). We subsequently investigated the effect of different amounts of iodine on the reaction outcome, finding that 0.8 equiv of iodine gave the optimum yield (Table 1, entries 6−10). We also investigated the effect of different molar ratios of **1a**/**2a**/**3a**, with no improvement obtained compared with 1/1/1 (Table 1, entries 11−14). Finally, the yield was further improved to 72% using $NaHCO_3$ (0.8 mmol) as an additive.

With the optimized reaction conditions in hand, we next investigated the substrate scope of this reaction. As summarized in Scheme 2, a variety of acetophenone derivatives bearing different substituents were transformed into the desired 2-acyl-3-arylquinolines in moderate to high yields. For example, aryl methyl ketones bearing electron-neutral (4-H), electron-rich (e.g., 4-Me, 4-OMe, 4-OEt, and 3,4-OCH_2O), and electron-deficient (e.g., 4-NO_2 and 3-NO_2) groups were tolerated, affording the corresponding products in moderate to good yields (63−72%, **4a**−**g**). The optimized conditions were mild enough to be compatible with a broad range of halogenated (e.g., 4-Cl, 3,4-Cl_2, and 4-Br) substrates (63−73%, **4h**−**j**), which provided the possibility for further functionalization. Notably, 1-naphthyl methyl ketone also readily reacted in the reaction, giving the expected product (**4k**) in 61% yield. Furthermore, various heteroaryl ketones, including furanyl, benzofuryl, and thienyl methyl ketones, were tolerated under these conditions, giving the corresponding products in moderate yields (58−65%, **4l**−**n**).

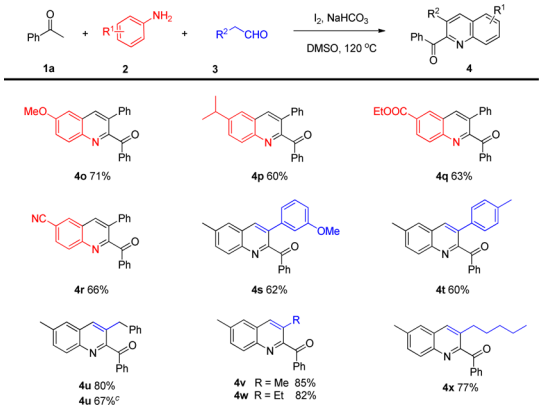
Scheme 2. Scope of Aryl Methyl Ketones[a,b]



[a]Reaction conditions: **1** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), and I_2 (0.8 mmol) and $NaHCO_3$ (0.8 mmol) in DMSO (3 mL) at 120 °C for 16 h. [b]Isolated yield.

Subsequently, the scope of the Povarov-type reaction was further explored using a variety of substituted anilines and aryl(alkyl)acetaldehyde (Scheme 3). Regarding the arylamine

Scheme 3. Scope of Anilines and Aryl(alkyl)acetaldehydes[a,b,c]



[a]Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), and I_2 (0.8 mmol) and $NaHCO_3$ (0.8 mmol) in DMSO (3 mL) at 120 °C for 16 h. [b]Isolated yield. [c]Gram reaction (5 mmol.)

substrates, both electron-rich (4-OMe and 4-$CH(CH_3)_2$) and electron-deficient (4-CO_2Et and 4-CN) substituents were tolerated on the phenyl ring of the aniline substrates, affording the corresponding products in satisfactory yields (60−71%; **4o**−**r**). Furthermore, arylacetaldehydes containing electron-rich groups (4-Me and 3-OMe) were transformed into the desired 2-acyl-3-arylquinoline products in moderate yields (60−62%, **4s**−**t**). Notably, alkylaldehydes were also employed, affording 2-acyl-3-alkylquinolines in high yields (77−85%, **4u**−**x**). Moreover, the structure of **4v** was unambiguously confirmed by X-ray crystallographic analysis (see Supporting Information).

To verify a possible mechanism, a series of control experiments associated with this transformation were performed.

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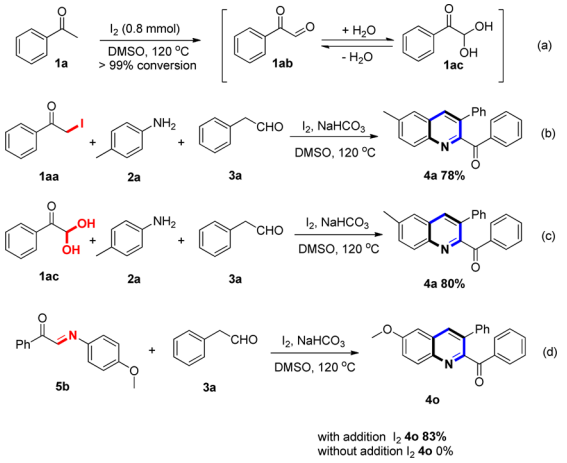
Aryl methyl ketone (**1a**, 1.0 mmol) was heated with I_2 (0.8 mmol) in DMSO at 120 °C to afford phenylglyoxal **1ab** and the corresponding hydrated species **1ac** in quantitative yield (Scheme 4a). When acetophenone **1a** was replaced by α-iodoacetophenone

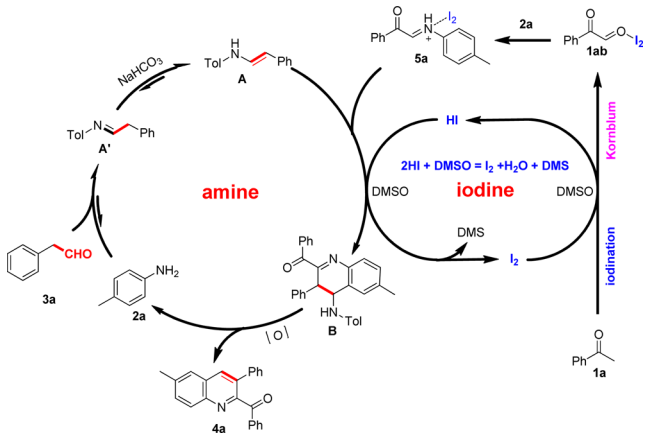
Scheme 4. Control Experiments



1aa under the optimized conditions with **2a** and **3a**, the desired product **4a** was afforded in 78% yield (Scheme 4b). Hydrated species **1ac** was also subjected to the optimized reaction conditions, affording **4a** in 80% yield (Scheme 4c). These results confirmed the intermediacy of phenacyl iodine **1aa** and phenylglyoxal **1ac** in this transformation. When C-acylimine **5b** was used as a substrate in the reaction, the desired product **4o** was formed in 83% yield under the standard conditions[10] (see Supporting Information), but no desired product was obtained in the absence of I_2 (Scheme 4d). These results implied the intermediacy of C-acylimine in the transformation and clearly suggested that iodine played an vital role in the Povarov/oxidation process.

Based on the outcome of the control experiments and previous studies,[11] a tentative mechanism for this transformation was proposed, as shown in Scheme 5. Acetophenone **1a** was converted into phenylglyoxal **1ab** via an iodination/Kornblum oxidation sequence. Next, iminium ion **5a** was formed via the condensation of intermediate **1ab** and *p*-toluidine **2a**. Meanwhile, *p*-toluidine **2a** could react with arylacetaldehyde to generate imine **A′**, which was then rapidly converted into intermediate

Scheme 5. Proposed Mechanism



enamine **A**[12] via base promoted tautomerization. Enamine **A** was then used as a dienophile in the Povarov-type reaction via a formal [4 + 2] cycloaddition with the in situ generated iminium ion **5a**, forming intermediate **B**. Finally, the desired product **4a** was obtained via deamination[13] of **B**. *p*-Toluidine **2a** then continued to participate in the reaction.

In summary, we have developed a synergistic iodine-amine promoted process for the synthesis of 2-acyl-3-aryl(alkyl)-quinolines via a Povarov-type reaction, in which aryl(alkyl)-acetaldehydes are used as useful alkene surrogates. Moreover, this protocol is an efficient method for enriching the scope of Povarov-type reactions. Notably, arylamines play dual pivotal roles in this reaction, promoting enamine formation and serving as a reactant. Further studies toward applications of this process are currently 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.7b01686.

Experimental procedures, product characterizations, crystallographic data, and copies of the ^{1}H and ^{13}CNMR spectra (PDF)

Crystallographic data for **4v** (CIF)

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Notes

The authors declare no competing financial interest.

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