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Iodine-Mediated One-Pot Synthesis of C-3 Acylated Indolizines from Pyridines, Aryl Methyl Ketones and Acrylate Derivatives

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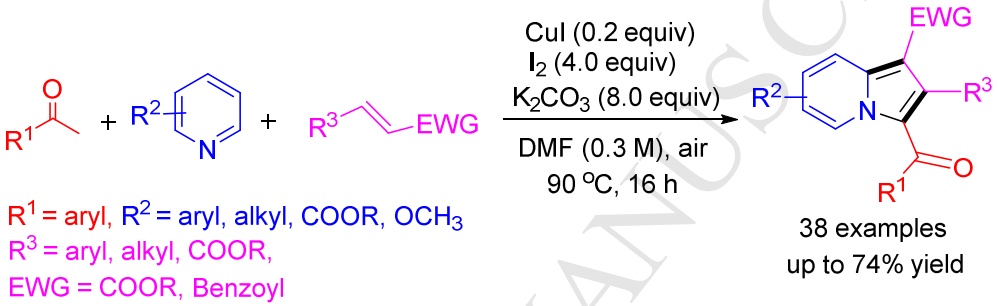

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Iodine-Mediated One-Pot Synthesis of C-3 Acylated Indolizines from Pyridines, Aryl Methyl Ketones and Acrylate Derivatives

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ABSTRACT

An I2/CuI-promoted multi-component reaction from pyridines, aryl methyl ketones and electrondeficient acrylates has been accomplished in a "one-pot" manner, which provides a straightforward and efficient access to C-3 acylated indolizines. The key intermediate of N-ylides is hypothesized to be generated in situ from pyridines and (hetero)aryl methyl ketones in the presence of iodine. This method has been applied in the synthesis of two molecules with anticonvulsant and anti-inflammatory activities.

1. Introduction

Indolizines are important bridgehead nitrogen heterocycles that have received great attention due to their interesting molecular structures featuring 10 π-delocalized electrons [1]. Indolizines exhibit a broad array of bioactivities, such as antibacterial [2], antimycobacterial [3], antioxidant [4], anticonvulsant [5], anti-inflammatory [5], and HIV inhibitory activities [6]. and thus, a number of synthetic approaches have been developed for the preparation of indolizines. The methods for producing indolizines include the Schmidt reaction [7], the Tschitschibabin reaction [8], 1,5-dipolar cyclizations [9], 1,3-dipolar cyclization [10], transition metal catalyzed intramolecular cyclization [11] and intermolecular cyclization [12]. Recently, the syntheses of indolizines involving iodine, which serves as an iodination reagent, have been reported. In particular, Wu and coworkers demonstrated a two-step preparation of indolizines in the presence of copper oxide [13]. The reaction requires a stoichiometric amount of copper oxide and reflux conditions to generate iodo-acetophenone for the second step, and the two steps require different solvents. Another example was demonstrated from Yavari and coworkers, which employed iodine as an iodination regent for the synthesis of indolizines via a 1,3-dipolar cycloaddition reaction of nitrogen ylides with alkynones [14]. However, the reaction requires the step by step addition of starting materials, and the substrate scope is limited to with onlyalkynones . Herein, we report our results of an iodine-mediated synthesis of C-3 acylated indolizines in which pyridine ylide was generated in situ in the presence of iodine, and this protocol was accomplished in a one-pot manner.

2. Results and Discussion

We performed the reaction of acetophenone **1a**, pyridine **2a** and methyl acrylate **3a** as model substrates for optimization (Table 1). It was found that no product was produced without the inclusion of additional base (Table 1, entry 1). To improve the yield of **4a**, different solvents were screened, and N,N-Dimethylformamide (DMF) was found to be the best solvent (Table 1, entries 3-5). Increasing or decreasing the reaction temperature caused a decrease in the yield of the product. (Table 1, entries 6-8). Attempts to increase the yield by adding various copper salts did not deliver better results (Table 1, entries 9-13). When replacing the copper salt with other Lewis acids, such as

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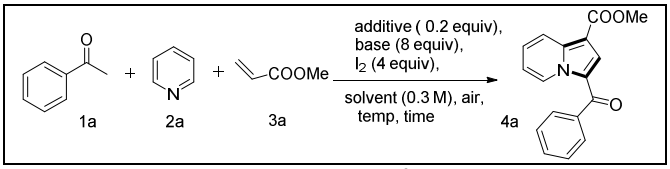
iron, zinc, or nickel, the results indicated that CuI was most effective (Table 1, entries 14-17). In addition to K_2CO_3, other bases were tested under the reaction conditions, but no improvement of yield was observed (Table 1, entries 18-24). Decreasing or increasing the amount of CuI did not improve the reaction (Table 1, entries 25-26). Finally, when the reaction was performed under inert conditions, no increased yield was obtained (Table 1, entry 27).

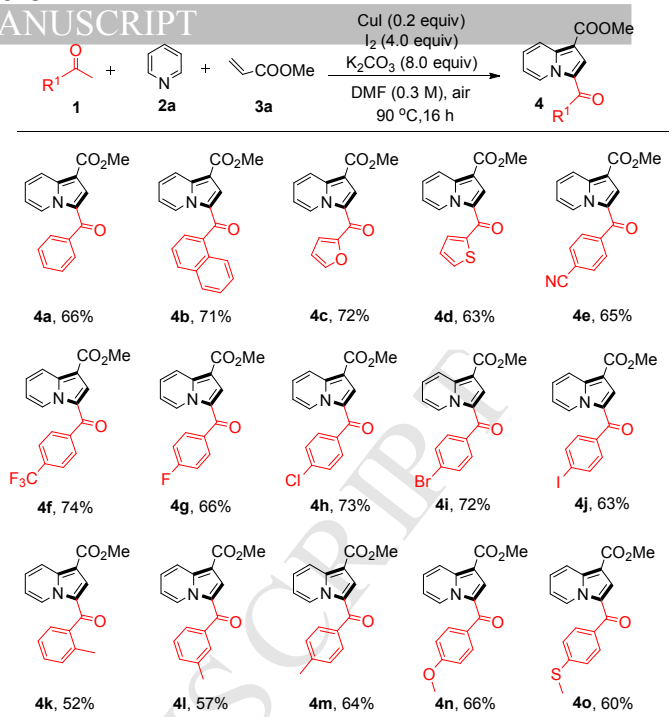
Table 1. Optimization of reaction conditions[a].



entry	solvent	additive (equiv)	T (°C)	base	Yield of 4a (%)
1	DMSO	-	100	-	N.R.
2	DMSO	-	100	K_2CO_3	18
3	NMP	-	100	K_2CO_3	30
4	DMF	-	100	K_2CO_3	34
5	DMA	-	100	K_2CO_3	28
6	DMF	-	110	K_2CO_3	32
7	DMF	-	90	K_2CO_3	40
8	DMF	-	80	K_2CO_3	36
9	DMF	CuCl (0.2)	90	K_2CO_3	52
10	DMF	CuBr (0.2)	90	K_2CO_3	49
11	DMF	CuI (0.2)	90	K_2CO_3	66
12	DMF	$Cu(OAc)_2$ (0.2)	90	K_2CO_3	47
13	DMF	CuO (0.2)	90	K_2CO_3	50
14	DMF	$FeCl_3$ (0.2)	90	K_2CO_3	60
15	DMF	$Zn(OAc)_2$ (0.2)	90	K_2CO_3	55
16	DMF	$NiCl_2$ (0.2)	90	K_2CO_3	59
17	DMF	$Zn(CF_3SO_3)_2$ (0.2)	90	K_2CO_3	64
18	DMF	CuI (0.2)	90	NEt_3	35
19	DMF	CuI (0.2)	90	DBU	30
20	DMF	CuI (0.2)	90	$NHEt_2$	N.R.
21[c]	DMF	CuI (0.2)	90	TMEDA	N.R.
22	DMF	CuI (0.2)	90	Na_2CO_3	41
23	DMF	CuI (0.2)	90	Cs_2CO_3	20
24	DMF	CuI (0.2)	90	KOAc	24
25	DMF	CuI (0.1)	90	K_2CO_3	51
26	DMF	CuI (0.4)	90	K_2CO_3	49
27[d]	DMF	CuI (0.2)	90	K_2CO_3	66

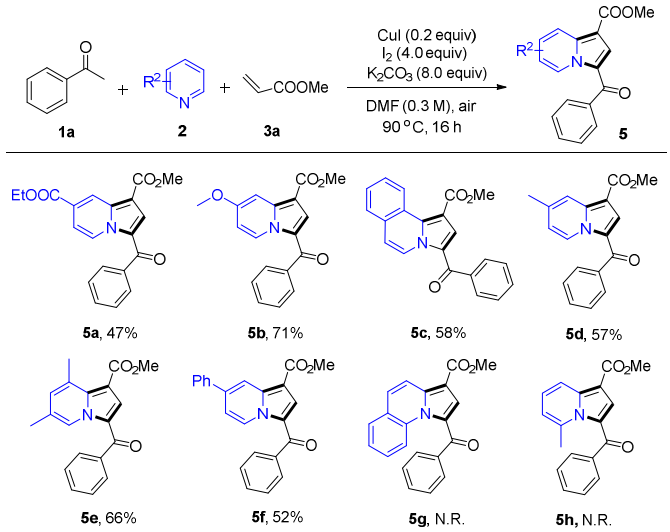
[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.6 mmol), **3a** (0.3 mmol), additive (0.2 equiv), base (8 equiv) and I_2 (4.0 equiv) in 1 mL of solvent for 16 h at 90 °C. [b]Isolated yields. [c]TMEDA: N,N,N',N'-Tetramethylethylenediamine. [d]Under nitrogen atmosphere in dry DMF.

To investigate the substrate scope of acetophenone derivatives, a series of different (hetero)aryl methyl ketones reacted with **2a** and **3a** in a one-pot fashion were studied under standard conditions (Scheme 1). The results indicated that most of the acetophenone derivatives reacted well under the reaction conditions. 1-(Naphthalen-1-yl)ethanone, 1-(furan-2-yl)ethanone and 1-(thiophen-2-yl)ethanone were compatible substrates in the reaction and delivered the corresponding products. Cyano-, trifluoromethyl-, fluoro-, chloro-, bromo- and even iodo-substituted indolizine derivatives could be prepared in moderate yields by this method. Among them, CF_3 group in the para position of the phenyl ring delivered the highest yield (74%). The steric effect was observed when substrates possessed a methyl-substituent on the *para*-position, this substrate produced a product with a 66% yield, while a methyl-substituent in the *meta*-position gave a 57% yield and a methyl-substituent in the *ortho*-position gave a 52% yield. Finally, acetophenones with -OMe and -SMe at the *para* position of phenyl ring were also employed in the reaction to produce the products with a 66% yield and a 60% yield, respectively.



Scheme 1: Synthesis of C-3 acylated indolizines from pyridine, methyl acrylate and different (hetero)aryl methyl ketones.

The substrate scope of pyridine derivatives was studied under the optimal reaction conditions (Scheme 2). Pyridines containing electron-withdrawing groups delivered the corresponding products with lower yields (**5a** in 47% yield) than those with electron-donating groups (**5b** with methoxy group in 71% yield, **5d** with methyl group in 57% yield and **5f** with phenyl group in 52% yield). It is noteworthy that isoquinoline as a substrate delivers the corresponding product **5c** in a 58% yield, while no product was obtained when quinoline was subjected to the same reaction conditions. Furthermore, 2-methylpyridine and quinoline were employed in this reaction to examine the effect of an occupied *ortho*-position. The results showed that no product was obtained (**5g**, N.R.; **5h**, N.R.). Pyridines with a 3,5-dimethyl



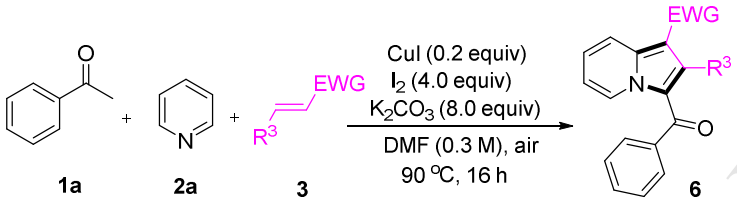
Scheme 2: Synthesis of C-3 acylated indolizines from acetophenone, methyl acrylate and substituted pyridines.

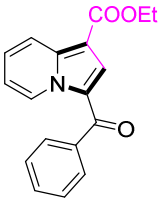
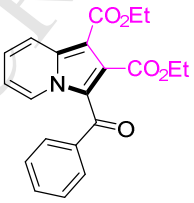
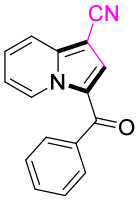
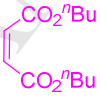
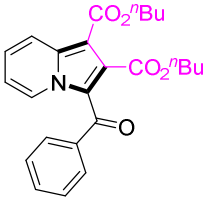
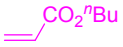
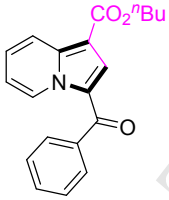
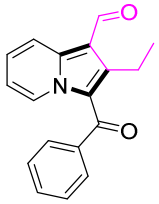
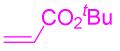
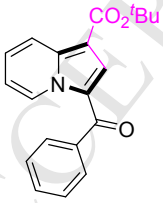
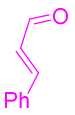
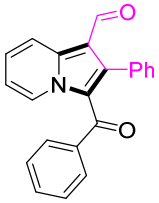
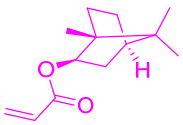
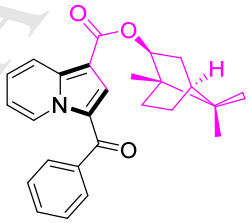
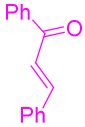
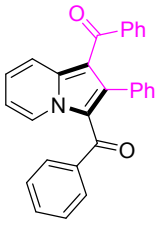
substituted substrate reacted well using this method for producing the indolizine product **5e** with a 68% yield.

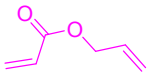
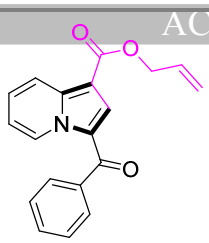
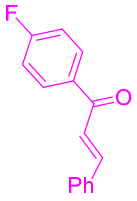
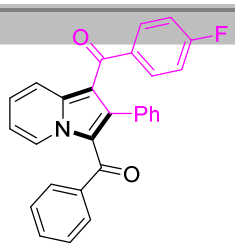
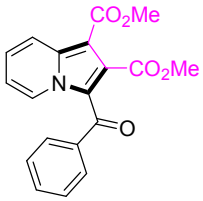
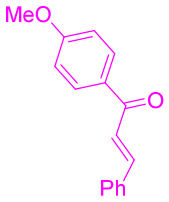
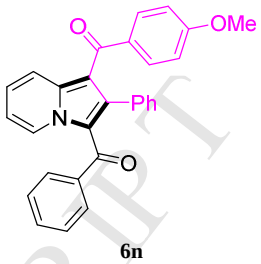
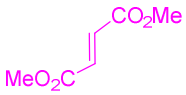
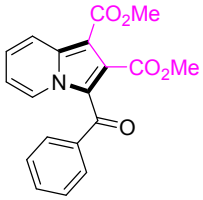
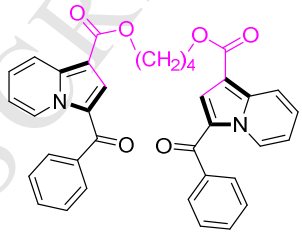
To study the substrate scope of electron-deficient alkenes, different substrates were employed in the reaction under optimal

conditions (Table 2). The result was that most of the electron deficient alkenes reacted and gave the corresponding products ef Furthermore ficiently. Ethyl acrylate, acrylonitrile, butyl acrylate and *tert*-butyl acrylate were used in this reaction and delivered the corresponding products **6a-6d** (Table 2, entries 1-4). It is noteworthy that both *E*- and *Z*-dimethyl fumarate reacted well in the optimal conditions to deliver the same product **6g** in moderate yields (Table 2, entries 7-8). Furthermore, diethyl fumarate and di-tert-butyl fumarate resulted with a products **6h** and **6i** in 63% yield and 61% yield, respectively (Table 2, entries 9-10). When the substrates were aliphatic unsaturated aldehydes or chalcones, the yield decreased under standard reaction conditions b(Table 2, entries 11-15). When butane-1,4-diyl diacrylate was subjected to the properly tuned condition, product **6o,** containing two indolizine scaffolds, was isolated in a 63% yield (Table 2, entry 16).

Table 2. Synthesis of C-3 acylated indolizines from acetophenone, pyridine, and different electron deficient alkenes.

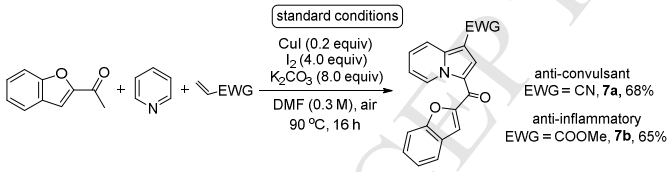


Entry	Alkene	Product	Yield(%)	Entry	Alkene	Product	Yield(%)
1		 **6a**	74	9		 **6h**	63
2		 **6b**	62	10		 **6i**	61
3		 **6c**	70	11		 **6j**	35
4		 **6d**	68	12		 **6k**	30
5		 **6e**	70	13		 **6l**	38

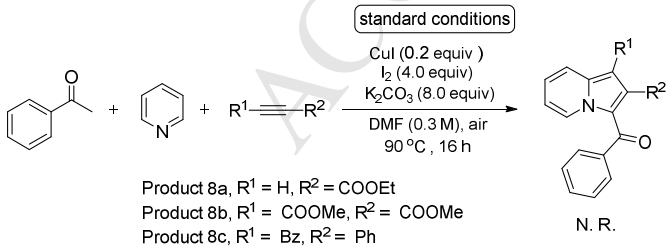
6		 **6f**	50	14		 **6m**	34
7		 **6g**	58	15		 **6n**	37
8		 **6g**	54	16		 **6o**	63[a]

[a] Reaction conditions: **1a** (1.2 mmol), **2a** (1.2 mmol), **3** (0.3 mmol), CuI (0.12 mmol), I_2 (2.4 mmol), K_2CO_3 (4.8 mmol), DMF (1.0 mL), air, 90 °C, 16 h.

To further prove the potential of this method, We utilized this protocol for the synthesis of two biologically active compounds (**7a** and **7b**) (Scheme 3) [5]. When electron-deficient alkynes, such as methyl propiolate, dimethyl but-2-ynedioate, and 1,3-diphenylprop-2-yn-1-one, were subjected to this reaction under optimal conditions, no product was detected (Scheme 4). Possible explanation could be that the side reaction of iodine with alkynes which consumed the alkynes. After the reaction employing alkynes, we have detected the complete consumption of alkynes, while no expected product was found.

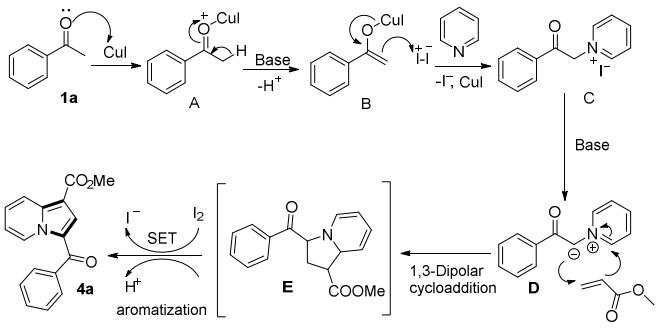


Scheme 3: Synthesis of anti-convulsant and anti-inflammatory indolizines.



Scheme 4: Reactions with electron-deficient alkynes under optimal conditions.

Based on previous reports [13, 14] and the above results, a plausible mechanism of this reaction is proposed in Scheme 5. Initial complexation of acetophenone and CuI forms intermediate **A**, which undergoes deprotonation to give intermediate **B**. Addition of iodine to intermediate **B** which reacts with pyridine generates pyridine ylide intermediate **C** in situ. Deprotonation of intermediate **C** in the presence of base delivers intermediate **D**, which undergoes 1,3-dipolar cycloaddition with methyl acrylate to form intermediate **E**, followed by further dehydrogenative aromatization in the presence of iodine to form the product indolizine.



Scheme 5: A plausible mechanism of the multiple-component reaction.

3. Conclusion

A one-pot method for the synthesis of multisubstituted indolizines was developed from acetophenones, pyridines and electron deficient alkenes. The substrate scope of this method was broad, since various (hetero)aryl methyl ketones, pyridines, and electron deficient alkenes were successfully applied using this protocol. We have also utilized the methodology to synthesize two biologically active compounds, which may attract the interests of many medicinal chemists. Further exploration and application of this methodology are currently ongoing in our laboratory.

4. Experimental section

Melting points were measured in a WRX-4 melting point apparatus purchased from Shanghai YICE Instrumental Company; ^{1}H and ^{13}C NMR spectra were recorded at 400 (500, 600) and 100 (125, 150) MHz, respectively using $CDCl_3$ as the solvent. (INOVA 400 MHz NMR Spectrometer, WNMR-I 500 MHz NMR Spectrometer, Bruker Avance NEO 600 MHz NMR Spectrometer) HRMS data were recorded on an agilent 6540 mass spectrometer with electro spray ionization and TOF mass analyzer. All column chromatography was performed using silica gel (200-300 microns). Unless otherwise noted, commercially available chemicals were used as received.

General Procedure for the Product:

A test tube was loaded with acetophenone (**1a**, 0.6 mmol, 72.1 mg), pyridine (**2a**, 0.6 mmol, 47.5 mg), methyl acrylate (**3a**, 0.3 mmol, 25.8 mg), K_2CO_3 (2.4 mmol, 331.7 mg) , I_2 (1.2 mmol, 304.6 mg), CuI (0.06 mmol, 11.4 mg) and 1 mL DMF. The reaction mixture was stirred at 90 °C for 16 h. After completion of the reaction, the reaction mixture was diluted with EtOAc, and washed with 10% $Na_2S_2O_3$ solution (50 mL). Then, the mixture was extracted with EtOAc (20 mL×3), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The remaining crude product was then purified through column chromatography using silica gel (EtOAc/petroleum ether = 1/10) to produce **4a** as a yellow solid with a 66% yield.

Acknowledgments

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Supplementary Material

Supporting Information File 1:

Experimental part and copies of NMR spectra data.

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