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Graphical Abstract

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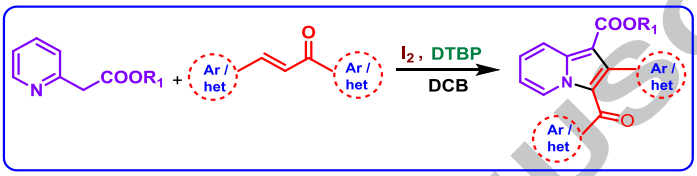

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Iodine–catalyzed [3+2] cyclization of 2-pyridylesters and chalcones: Metal-free approach for the synthesis of substituted indolizines

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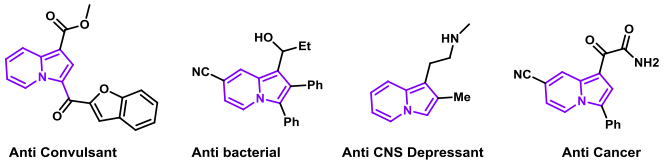
ABSTRACT

A transition metal-free iodine catalyzed synthesis of indolizine derivatives through [3+2] cyclization of 2-pyridylesters and chalcones has been described. The method is efficient to synthesize variety of substituted indolizines including hetero aromatic indolizines. Mechanistic studies reveal that, the reaction follows the radical pathway.

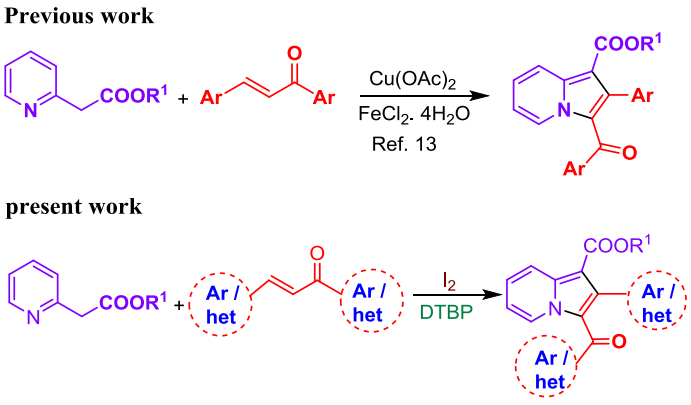
Introduction

The construction of azaheterocycles through direct functionalization of C−H bonds with simple and readily available starting substrates is of considerable interest in organic synthesis. This process accomplished under metal-free conditions becomes an advantageous, because it avoids the metal contamination in the final product. Among the azaheterocycles, the construction of indolizine derivatives are of significant importance due to their presence in a large variety of biologically active molecules,[1] naturalproducts,[2] and synthetic pharmaceuticals.[3] Many synthetic and naturally occurring indolizine derivatives found to exhibit outstanding biological activity for example; anti-inflammatory, antiviral, anti-bacterial, cardiovascular agents, anti-cancer and CNS depression agents (Scheme 1).[4, 5] Owing to their unique photo physical properties of substituted indolizines, they are used as organic materials for various applications.[6] Therefore, the development of synthetic methods to access indolizines paid much attention.



Scheme 1

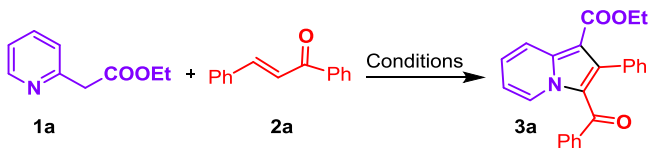
To our knowledge many reported methods involve transition metal catalyzed intra and/or inter molecular cyclisation of pyridine derivatives.[7-12] Recently we reported the synthesis of indolizine derivatives from 2-pyridylesters with chalcones, in which we used $Cu(OAc)_2$ as a catalyst and excess amount of $FeCl_2$ as an oxidant.[13] To avoid the use of metal, we continued our efforts to the development of metal-free conditions for this particular transformation (Scheme 2). Our previous experience on the synthesis of azaheterocycles[14] and by considering the advantages of iodine or their derivatives as an alternative to transition metal catalysis in organic transformations,[15] we described herewith the iodine-catalyzed synthesis of indolizines by [3+2] cyclization of 2-pyridylesters with chalcones.



Scheme 2

To check our hypothesis, we initially performed a reaction with 2-ethylpyridylacetate (0.4 mmol) **1a**, chalcone (0.2 mmol) **2a** and I_2 (0.05mmol) in DMF at 110 ºC for 24 h. To our delight, the expected product ethyl-3-benzoyl-2-phenylindolizine-1-carboxylate **3a** was obtained in 11% yield (Table 1, entry 1). On the basis of these initial findings we screened with other solvents such as DMSO, NMP, 1,2-dichlorobenzene (DCB) and toluene. A considerable improvement in the yield of **3a** was observed when DCB was used as a solvent (Table 1, Entry 2−5). Further, addition of DTBP (Di-tert-butyl peroxide) to the reaction mixture

Table 1: Optimization of reaction conditions for 3a[a]



1a 2a 3a

entry	catalyst (mmol)	oxidant(mmol)	temp (°C)	solvent	**3a** yield (%)
1	I_2 (0.05)	-	110	DMF	11
2	I_2 (0.05)	-	110	DMSO	trace
3	I_2 (0.05)	-	110	NMP	trace
4	I_2 (0.05)	-	110	Toluene	26
5	I_2 (0.05)	-	110	DCB	56
6	I_2 (0.05)	O_2	110	DCB	37
7	I_2 (0.05)	TBHP(0.2)	110	DCB	trace
8	I_2 (0.05)	DTBP(0.2)	110	DCB	70
9	I_2 (0.05)	DTBP(0.2)	120	DCB	76
10	**I_2 (0.05)**	**DTBP(0.4)**	**120**	**DCB**	**87**
11	I_2 (0.1)	-	120	DCB	61
12	I_2 (0.3)	-	120	DCB	72

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), catalyst, oxidant, solvent (1.0 mL), 24 h, isolated yield.

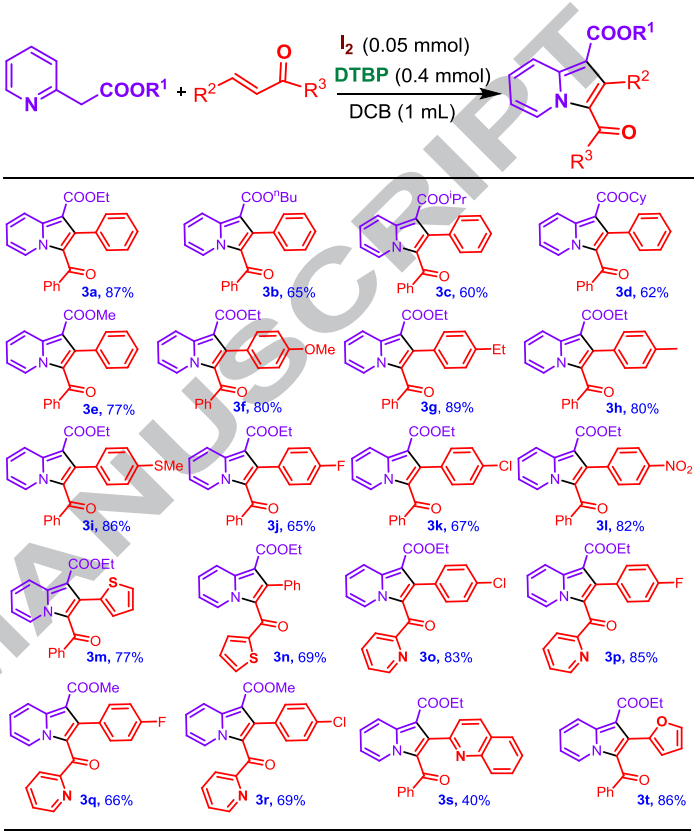
showed significant improvement in the yield of the product **3a**, whereas TBHP (tert-Butyl Hydroperoxide) and oxygen atmosphere were found inefficient oxidants for this transformation (Table 1, entries 6-9). The maximum yield of **3a**, (87 %) was observed at 120 ºC reaction temperature with two equivalents of DTBP as an oxidant w.r.t. **2a** (Table 1, entry 10). Increase in the amount of iodine (even more than stoichiometric amount w.r.t. **2a**) in absence of DTBP was found not efficient than the catalytic amount of iodine with DTBP (Table 1, entry 11&12). Finally the optimized conditions considered for this transformation are as follows: **1a** (0.4 mmol), **2a** (0.2 mmol), iodine (0.05 mmol), DTBP (0.4 mmol) and 1mL of DCB as a solvent at 120 ºC.

With the optimized conditions, the substrate scope of this iodine-catalyzed reaction was tested (Table 2). Different 2-pyridylesters (–COO^{n}Bu, –COO^{i}Pr, –COOcy and –COOMe groups) reacted well with chalcone **2a** and produced the corresponding indolizine esters **3b-3e** in moderate to good yields. Then, the reaction was extended to substituted chalcones with **1a**, both electron–donating and –withdrawing substituted groups containing chalcones were well tolerated under the optimized reaction conditions. The reaction of (**1a**) with electron donating groups (such as –OMe, –Et, –Me, –SMe) at *para* position of phenyl ring of chalcone provided the corresponding products **3f-3i** in good to excellent yields (80–89 %). The halogen (–F and –Cl) and nitro (–NO_2) substituted chalcones also underwent to the present transformation and gave the products **3j–3l** in good yields (65–82 %). Notably, hetero aromatic ring containing chalcones also well reacted under these conditions with **1a** and provided the corresponding products **3m–3t** with moderate to good yields (40–86 %). However the present conditions are not suitable for the reactants such as 2-(pyridin-2-yl) acetonitrile, N-methyl-N-phenylcinnamamide and ethylcinnamate to obtain corresponding products.

To validate the applicability of the present transformation in gram-scale preparation, we performed a gram scale reaction of **1a** and **2a** under the optimized conditions and the product **3a** was isolated in 81 % yield (Scheme 3).

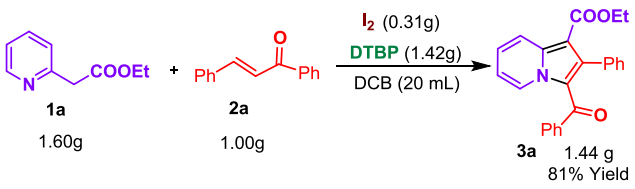
To get insight in to the reaction mechanism, additional experiments were performed (Scheme 4). It was observed that the reaction under argon atmosphere does not have considerable effect on the overall yield of the product (scheme 4. eq. 1). It indicates the molecular oxygen is not the driving force for this reaction. The addition of radical trapping reagent TEMPO to the reaction, it does not leads to the formation of **3a** or TEMPO

Table 2: Scope of indolizines from 2-pyridylesters and chalcones[a]



[a] 2-Pyridylester **1a** (0.4 mmol), chalcone **2a** (0.2 mmol), I_2 (0.05 mmol), DTBP (0.4 mmol), DCB (1.0 mL) in an oil bath at 120 ºC, for 24 h, isolated yields.

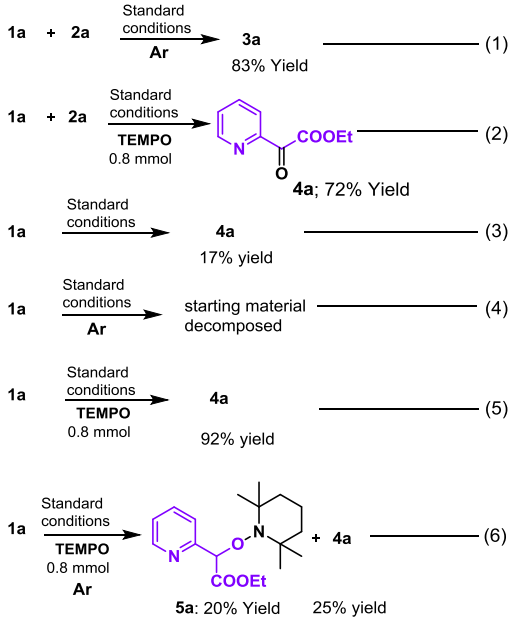
adduct, instead a keto product **4a** was isolated in 72 % yield (Scheme 4. eq. 2). Next **1a** was subjected to the optimized conditions without chalcone, only 17 % of **4a** was isolated (Scheme 4. eq. 3). Further, conducting the reaction of **1a** under argon atmosphere, the decomposition of **1a** was observed (Scheme 4. eq. 4). Reaction of **1a** with TEMPO under the optimized conditions, 92 % of **4a** was isolated (scheme 4. eq. 5). These experiments suggests the oxidation of **1a** to **4a** is efficient



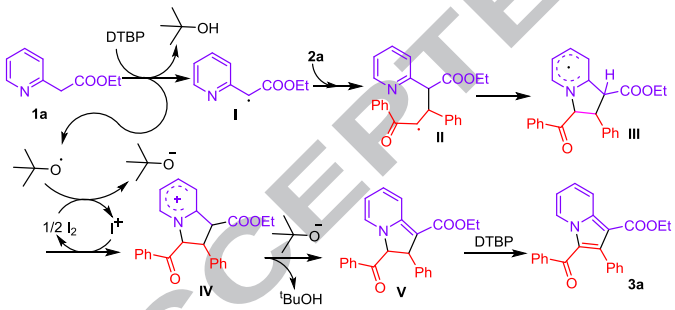
Scheme 3. Gram scale preparation of **3a**

only in presence of TEMPO. To confirm the role of the TEMPO, **1a** was treated with TEMPO under argon atmosphere, 20 % of TEMPO-adduct **5a** and 25 % of **4a** were isolated along with inseparable mixture of **4a** and **5a** (Scheme 4. eq. 6). Therefore, the formation of **5a** suggests the reaction may proceed through a radical intermediate **I**.

Based on experimental observations and reported literature a radical mechanism has been proposed.[15g] Initially **1a** in presence of DTBP forms a radical intermediate **I** and **I** up on reaction with **2a**, generate another radical intermediate **II**. This undergoes intra molecular radical addition followed by oxidation to yield intermediate **IV**. Proton elimination from **IV** and its subsequent aromatization yield the final product **3a**.



Scheme 4. Control Experiments



Scheme 5. Proposed Mechanism

In conclusion we have developed a transition metal-free indolizine synthesis through [3+2] cyclisation of 2-pyridylesters and chalcones using iodine as a catalyst. Wide range of substituted indolizines efficiently synthesized including hetero aromatic ring containing products. Mechanistic studies support a radical mechanism for the present transformation.

Acknowledgments

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Supplementary Material

Supplementary data (detailed experimental procedure and spectroscopic data) associated with this article can be found, in the online version, at

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Highlights:

Transition metal-free,

Iodine catalyzed,

Efficient Synthesis of indolizines,

Wide substrate scope,

Mild conditions