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Zinc iodide: a mild and efficient catalyst for one-pot synthesis of aminoindolizines *via* sequential A^3 coupling/cycloisomerization†

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ZnI_2 was found to be an efficient catalyst for the synthesis of indolizine derivatives by a three-component coupling of pyridine-2-carboxaldehyde/quinoline-2-carboxaldehyde, secondary amines, and terminal alkynes in high yields. This protocol is compatible with a wide range of substrates and is expected to find broad applications due to its operational simplicity, shorter reaction time and low cost. A preliminary photophysical study showed that synthesized morpholinopyrrolo[1,2-*a*]quinolines represent a new class of fluorophore with high quantum yield.

Introduction

One-pot catalytic conversion of organic reactions with readily available, non-toxic, and inexpensive reagents has attracted significant research attention in recent years. Multicomponent reactions (MCRs) involve simple and flexible combination of three or more building units in a accessible one-pot reaction to form a product containing substantial elements of all the reactants.[1] The multicomponent synthesis of heterocycles allows structural diversity and complexity in a single operation and atom-efficient manner. So the MCRs become an important tool for both combinatorial chemistry and diversity-oriented synthesis (DOS), and play a significant role in the development of methodology for drug discovery.[2,3]

Indolizine is an important heterocycle, composed of an electron-rich pyrrole and an electron-poor pyridine, which has drawn considerable attention in past few years.[4] The indolizine nucleus is an important skeleton for many bioactive compounds, some of them are naturally occurring,[5] while others are only synthetically accessible and also important in pharmaceuticals. Indolizines and their derivatives have been allied with a broad range of biological activities such as antibacterial, antiviral, anti-inflammatory[6] and central nervous system (CNS) depressant activity.[7] They also serve as phosphatase inhibitors,[8] aromatase inhibitors,[9] antioxidant reagents,[10] and calcium entry blockers[11] (Fig. 1).

As a consequence, great attention has been drawn to the synthesis of indolizine derivatives and a number of elegant methods have been developed in recent years.[12] In most of the cases, transition metals are used to synthesize these moieties *via* C–C and C–N bond forming reactions. Three-component coupling reaction of 2-pyridine carboxaldehyde, secondary amine, and terminal alkyne (A^3) is one of the efficient strategies for the synthesis of these scaffolds.[13] However only few methodologies have been reported based on A^3 coupling reactions. But coinage metal based catalysts are used in almost all cases.[13a,b,d,e] Moreover, gold and silver catalysts are very expensive and additionally, sometimes inert atmosphere is required to carry out these transformations. Therefore, finding a new methodology for the synthesis of indolizines in terms of efficiency, operational simplicity and economic practicability is highly desirable.

Zinc salts are abundant, cheap, non-toxic, and exhibit environmentally benign properties. Therefore, organic chemists have been interested in using zinc salts as catalysts during the

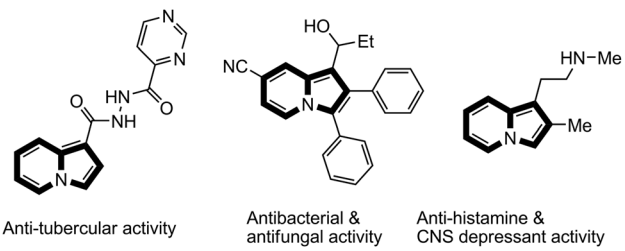

Fig. 1 Pharmacologically potent indolizine derivatives.

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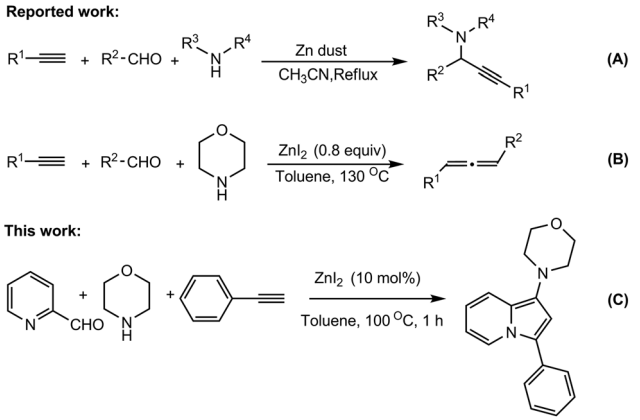


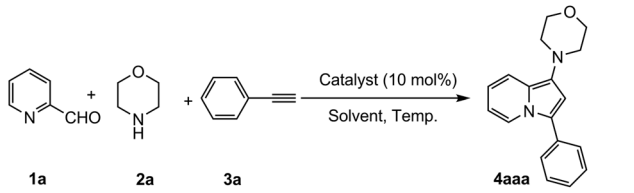
Scheme 1 Zn-catalyzed A^3 coupling reactions.

last three decades.[14] Various multicomponent reactions involving alkynes have been carried out employing zinc salts in recent times.[15] Kantam *et al.*[15a] reported a one-pot synthesis of propargylamines catalyzed by Zn-dust (Scheme 1, eq. **A**). Ma *et al.*[15b] reported ZnI_2-mediated synthesis of disubstituted allenes by a three-component coupling reaction involving alkynes, amines and aldehydes (Scheme 1, eq. **B**). Few cycloisomerization reactions catalyzed by Zn have also been reported for the synthesis of varieties of heterocycles.[16] Moreover, our own research found that Zn-salts are to be very efficient catalysts in promoting various chemical transformations.[17] Based on our own research experiences in Zn catalysis and C–H bond functionalization,[18] we thought that Zn could catalyze the three-component coupling and subsequent cycloisomerization to provide indolizine moiety. Herein we are pleased to report a simple and convenient approach to synthesize 1-amino-indolizines by a three-component coupling (A^3) of 2-pyridine carboxaldehyde, secondary amines, and terminal alkynes using ZnI_2 as a catalyst in toluene at 100 °C (Scheme 1, eq. **C**).

Results and discussion

We started our study by choosing pyridine-2-carboxaldehyde (**1a**), morpholine (**2a**), and phenylacetylene (**3a**) as the model substrates for this cascade reaction using 10 mol% ZnI_2 as the catalyst in toluene for 1 hour at 60 °C. To our delight, the desired product was obtained in 62% yield. Inspired by this result, we carried out the reaction employing various zinc salts in different solvents as well as varying temperature and the results are summarized in Table 1. When the temperature was increased to 80 °C and 100 °C, the yields of the reaction increased to 75% and 92% respectively (Table 1, entries 2, and 3). However, further increasing the temperature (under reflux) the yield of the reaction decreased to 82% (Table 1, entry 4). This may be due to the decomposition of the product at higher temperature. Other Zn salts like $ZnCl_2$, $ZnBr_2$ and $Zn(OTf)_2$ were not so effective like ZnI_2 (Table 1, entries 5–7). Toluene appeared to be the best choice among the common solvents such as EtOH, CH_3CN, 1,4-dioxane, THF, DMF, DMSO (Table 1, entries 8–13). 10 mol% ZnI_2 was necessary as the optimum

Table 1 Optimization of the reaction conditions[a]



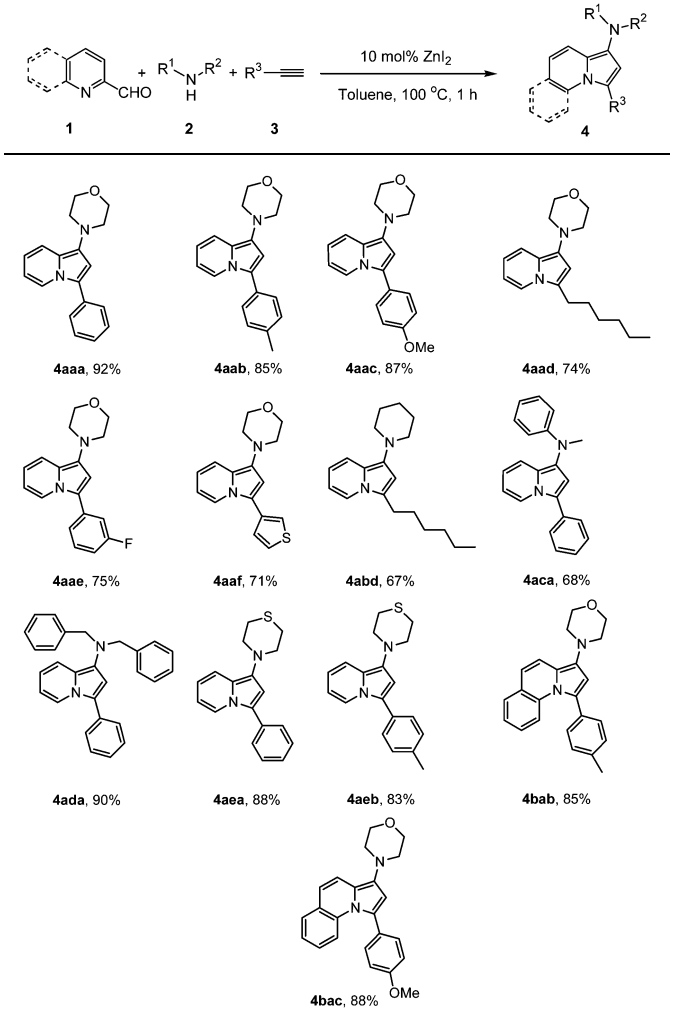
Entry	Catalyst	Mol%	Solvent	Temp. (°C)	Yield[b] (%)
1	ZnI_2	10	Toluene	60	62
2	ZnI_2	10	Toluene	80	75
3	ZnI_2	10	Toluene	100	92
4	ZnI_2	10	Toluene	Reflux	82
5	$ZnCl_2$	10	Toluene	100	72
6	$ZnBr_2$	10	Toluene	100	75
7	$Zn(OTf)_2$	10	Toluene	100	73
8	ZnI_2	10	Ethanol	Reflux	—
9	ZnI_2	10	Acetonitrile	Reflux	—
10	ZnI_2	10	1,4-Dioxane	100	Trace
11	ZnI_2	10	THF	Reflux	Trace
12	ZnI_2	10	DMF	100	<5
13	ZnI_2	10	DMSO	100	<5
14	ZnI_2	15	Toluene	100	90
15	ZnI_2	5	Toluene	100	78
16	$FeCl_3$	10	Toluene	100	—
17	$AlCl_3$	10	Toluene	100	—

[a] *Reaction conditions*: 1 mmol of **1a**, 1.1 mmol of **2a** and 1.2 mmol of **3a** in the presence of catalyst in solvent (3 mL) for 1 h. [b] Isolated yields.

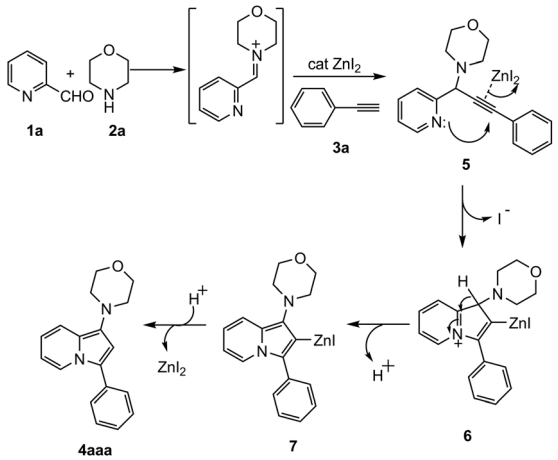
amount of catalyst and increasing the amount of catalyst (15 mol%) did not improve the yield, (Table 1, entry 14) whereas decreasing the amount of catalyst (5 mol%) decreased the yield (Table 1, entry 15). Use of inert atmosphere was not beneficial for this transformation. However other Lewis acids such as anhydrous $AlCl_3$ (10 mol%) and $FeCl_3$ (10 mol%) (Table 1, entries 16, and 17) did not afford the corresponding products. Finally optimized reaction conditions was achieved using pyridine-2-carboxaldehyde (1 mmol), morpholine (1.1 mmol) and phenylacetylene (1.2 mmol) in presence of 10 mol% of zinc iodide in toluene at 100 °C (Table 1, entry 3) under ambient air.

Keeping the optimized reaction conditions in hand a series of experiments were performed to verify the general applicability of the present methodology, which are summarized in Table 2. Various phenylacetylene having different substituents such as –Me (**4aab**, **4aeb**, **4bab**), –OMe (**4aac**, **4bac**), –F (**4aae**) led to the corresponding products in good to excellent yields. Aliphatic alkyne like 1-octyne gave the corresponding indolizines with moderate yields (**4aad**, **4abd**). It might be due to the instability of the compounds which decomposed quickly during column chromatography. Heteroaryl alkyne, 3-ethynyl thiophene (**4aaf**) also reacted under the present reaction conditions without any difficulties. Various cyclic and acyclic secondary amines, such as piperidine (**4abd**), dibenzylamine (**4ada**), and *N*-methylaniline (**4aca**) successfully gave the desired product with moderate to excellent yields. Interestingly, thiomorpholine afforded the indolizine derivatives (**4aea**, **4aeb**) in high yields

Table 2 ZnI_2-catalyzed synthesis of aminoindolizines[a]



[a] *Reactions conditions*: 1 mmol of **1**, 1.1 mmol of **2** and 1.2 mmol of **3** in the presence of ZnI_2 (10 mol%) in 3 mL of toluene at 100 °C for 1 h. Isolated yields.



Scheme 2 Proposed mechanism.

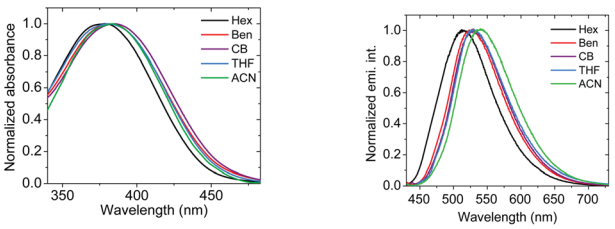


Fig. 2 Absorbance and fluorescence emission spectra of 4bac in various solvents (concentration ~ 10^{-4} mol L^{-1}). Hex = hexane, Ben = benzene, CB = chlorobenzene, ACN = acetonitrile.

without deactivation of catalyst. Moreover, quinoline-2-carboxaldehyde was also reacted successfully under the optimized reaction conditions to give the corresponding pyrrolo[1,2-*a*]-quinoline derivatives (**4bab**, **4bac**).

A proposed mechanism for this cyclization reaction is represented in Scheme 2. The first step is the A^3 coupling of pyridine-2-carboxaldehyde, morpholine and phenylacetylene in presence of catalytic amount of zinc iodide to form the corresponding propargylic pyridine **5** through the iminium intermediate.[15b] Zn co-ordinates with the triple bond of alkyne to enhance the electrophilicity. As a result nucleophilic attack by lone pair on nitrogen atom takes place resulting the formation of **6** which on subsequent deprotonation and demetallation giving rise to the corresponding 1-amino indolizine.

Organic compounds exhibiting intense fluorescence are always in demand as these are used as biological markers,[19] functional organic devices and sensors,[20] dyes[21] as well as in organic light emitting devices (OLEDs). On seeing the long conjugation of pyrrolo[1,2-*a*]quinoline moiety, we took interest in doing photophysical study. Therefore, a preliminary survey of the photophysical activity of few compounds (**4aaa**, **4bab**, **4bac**) was carried out (see, ESI†). The absorption spectra and emission spectra of **4bac** were recorded in various solvents (Fig. 2). In absorption spectra, there is no significant shifting. The characteristic emission band was observed with the maximum varying between 514 and 541 nm. This morpholinopyrrolo[1,2-*a*]-quinoline fluorophore exhibited high quantum yield (0.47) in chlorobenzene and also showed large Stokes shift which is an attractive property for biological probes. Moreover a distinct bathochromic (red) shift of the emission maxima was observed with increasing the polarity of the solvents. This solvatochromic behaviour which results from the stabilization of polar emitting state by polar solvents is characteristic for molecules showing internal charge transfer on excitation.[22]

Conclusions

In summary, we have developed a facile and economic protocol for the one-pot synthesis of the biologically potent indolizine derivatives by a three-component coupling of pyridine-2-carboxaldehyde/quinoline-2-carboxaldehyde, secondary amines, and terminal alkynes. The key features of the present protocol are wide substrate scope, operational simplicity, shorter

reaction times, low cost of the catalyst and good to excellent isolated yields. We believe that our present protocol is the simplest and a convenient way to synthesize indolizine scaffolds. Furthermore, morpholinopyrrolo[1,2-*a*]quinolines represent a new class of fluorophore with high quantum yields.

Acknowledgements

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