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A facile synthesis of isoindoline and Δ^1-pyrrolines from chalcone and glycine by a cascade of process involving addition, *in situ* decarboxylation and cyclization

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ABSTRACT

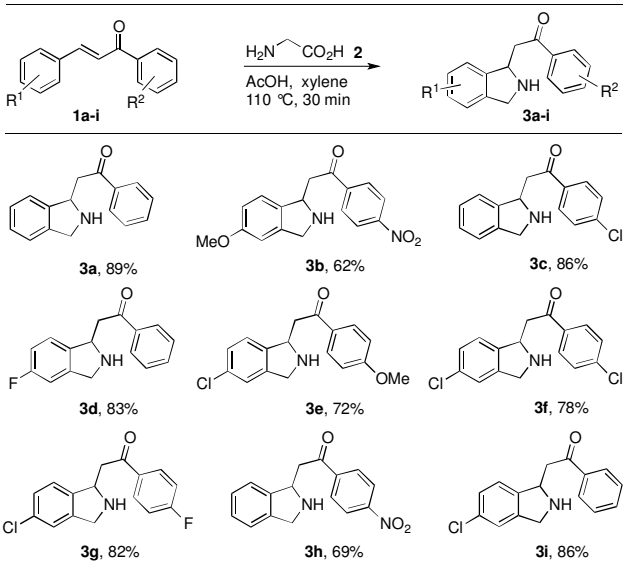
In this paper, we report a rapid one- step entry into isoindoline and Δ^1-pyrrolines from chalcone. The key step in the synthesis is the addition of glycine to chalcone. In acidic medium the reaction presumably goes through aza-Michael addition, whereas in basic medium the reaction proceeds through condensation followed by cyclization.

Isoindolines, Δ^1-pyrrolines and their derivatives are of interest as antitumor,[1] diuretic agents, selective serotonin uptake inhibitors and herbicides.[2] Hence, intensive research efforts are being continued to develop new and efficient synthetic methods.[3] Traditionally, the syntheses of isoindolines involve the use of metal or organocatalyst.[3c,4] Very recently, Zu et al,[5] reported the synthesis of polycyclic isoindolines using palladium catalyst.[3f,3h,,6] The expensive and moisture sensitive nature of the metal catalyst would restrict the use of the metal catalyzed reactions in large scale.

In search of simple methods to synthesize isoindolines, we turned our attention to chalcones. With α,β-unsaturated ketone as part of the chalcones substrate, it should be possible to introduce aza-Michael addition[7] more readily by employing acid and amino acids as the amine component. Decarboxylation would give carbanion and allow electro cyclization and give fused bicyclic amine product in one step. To test this desired chemistry, the investigation was initiated using 1 equiv. of chalcone **1a** and 1 equiv. of glycine **2** with 0.3 equiv. of acetic acid in xylene at 110 °C, and isoindoline product **3a** was obtained in good yield (Table 1). The starting material **1** was prepared by the Claisen-Schmidt condensation between ketones and aldehydes in the presence of sodium hydroxide in ethanol (see ESI for details).

The reaction with 1 equiv of glycine for 30 minutes afforded isoindoline **3a** in poorer yield (28 %). While adding 3 equiv of glycine, the reaction afforded the expected product **3a** in good yield. On decreasing the reaction temperature to 80 °C, the yields were considerably decreased. The use of strong acid like trifluoroacetic acid, trichloroacetic acid instead of acetic acid largely produces decomposed product. The desired product **3a** was not obtained in the absence of acetic acid. We reasoned that acetic acid would involve in sequence of steps: activation of chalcone α,β-unsaturated ketone as Michael acceptor which

Table 1 Synthesis of isoindolin-1-phenylethanone using acetic acid.



AcOH = acetic acid, yields are calculated by after column purification.

directs aza-Michael addition with glycine to form the intermediate **a**. Then, it would mediate acid catalyzed decarboxylation to produce the carbanion intermediate **b**, which may preferentially undergo nucleophilic addition to aromatic

ring, subsequent oxidation to produce **3a** (Scheme 1). The proposed mechanism is based on the metal arene complex nucleophilic addition. The major difference in our methodology is the metal-free environment.[8] The required nucleophile was generated by acid-catalyzed decarboxyation.

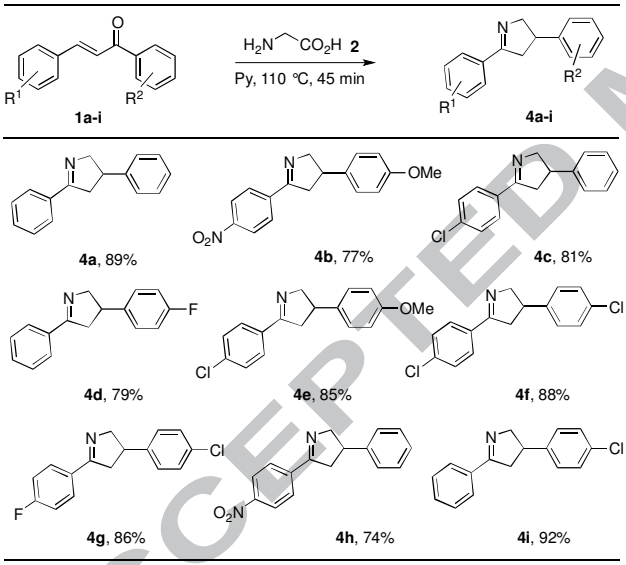
Table 2 Effect of solvent in the preparation of isoindoline.

Entry	Solvent	Time (h)	Temperature (°C)	Yield 3a[a]
1	CH_3CN	12	80	0
2	THF	12	70	0
3	DMF	8	110	0
4	DMSO	5	110	32
5	Toluene	4	110	58
6	Xylene	0.5	110	89
7	Benzene	1.5	80	52

[a]yields are calculated after column purification.

The viability of the reaction was tested in different high boiling solvents. The best yield was obtained with xylene. The reactions carried out at 110 °C in polar solvents resulted in decomposition of starting materials. Similarly, changes in the solvent polarity also affected the yield (Table 2). These results suggest that the less polar solvents are more suitable to produce the product **3a** in good yield. Using the optimized conditions, we next examined the reaction scope. Typical results are summarized in Table 1.

Table 3 Synthesis of Δ^1-pyrrolines using pyridine.



Py= pyridine, yields are calculated after column purification.

The success of the synthetic strategy encouraged us to test our methodology in the presence of base instead of acetic acid. Strikingly, the investigation initiated using chalcone **1a** and glycine **2** in pyridine at 110 °C yields Δ^1-pyrroline **4a**. We reasoned that the reaction proceeded by the formation of imine. The reactions of amine to carbonyl group have been extensively studied. Thus, the condensation would give an imine **c**[9] and decarboxylation would generate carbanion intermediate **d**. This intermediate undergoes thermal electrocyclization with the alkene and produces an intermediate **e**, which preferentially yields **4a** via 6π intramolecularcyclization (Scheme 1).[10] So far the available methods to synthesis Δ^1-pyrrolines involve multiple steps. Recently, Δ^1-pyrrolines were synthesized by Michael addition reaction of nitromethane to chalcone with subsequent reductive cyclization with Zn/HCl.[11] For the first time, we showed a single step approach involving imine formation and thermal electrocyclization[12] to get the desired Δ^1-pyrrolines product in good yield.

Scheme 1 Proposed mechanism for the formation of isoindoline and Δ^1-pyrrolines, respectively.

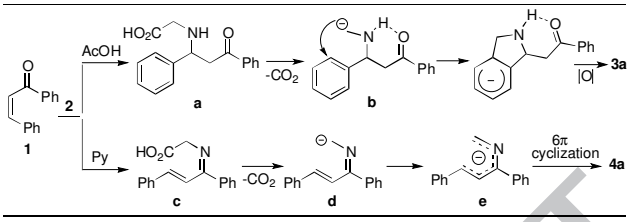
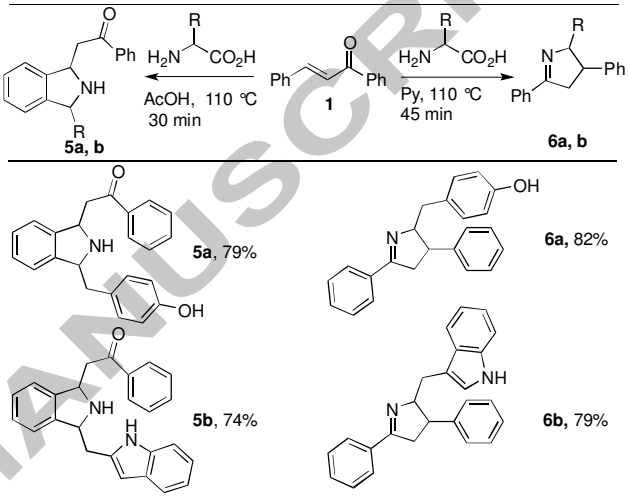


Table 4 Synthesis of isoindoline and Δ^1-pyrrolines employing other amino acids.



yields are calculated by after column purification.

Subsequently, the scope of the reaction was explored with other bases like sodium hydroxide, sodium methoxide and triethylamine, but the best result was obtained with pyridine (pK_a 5.25). As an alternate to pyridine, we tested the reaction in lutidine, a moderate base with pK_a 6.6. The reaction offered the desired products in good yield as similar to pyridine. So, further studies have been performed with pyridine considering the cost-effectiveness. To test the scope of the method, a series of chalcone **1a-i** and glycine **2** were subjected to the conditions described above. The reaction of **1a-i** with glycine **2** proceeded smoothly, affording the corresponding substituted Δ^1-pyrrolines **4a-i**, within 45 minutes, in good yields (Table 3). As summarized in Table 4, the proposed methodology is indeed possible with amino acids, such as tyrosine and tryptophan.

In conclusion, we have developed a rapid single- step method to prepare isoindoline and Δ^1-pyrrolines from chalcone. The acetic acid initiates a sequential azaMichael addition, decarboxylation and electrocyclization reaction, leading to efficient synthesis of isoindoline. On the other hand, pyridine initiates a sequential iminization, decarboxylation and electrocyclization reaction, leading to efficient synthesis of Δ^1-pyrrolines. To the best of our knowledge in chalcone chemistry, for the first time an amino acid was employed to generate carbanion and electrocyclization to form new carbon-carbon bond. Further, the simple manipulation of the reaction conditions to obtain two different products from the same chalcone makes our method very attractive. Further studies on the expansion of the substrate scope and the application of this methodology with other amino acids are currently underway in our laboratory and will be reported in due course.

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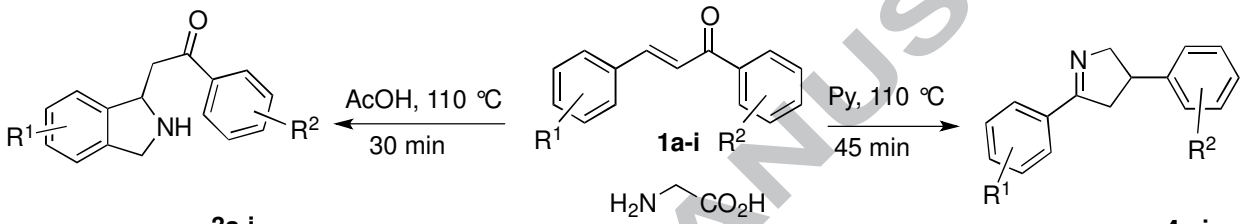

3a-i
62-89% yield

4a-i
74-89% yield