



## One-pot multistep synthesis of 3-aminoindolizine derivatives

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### ABSTRACT

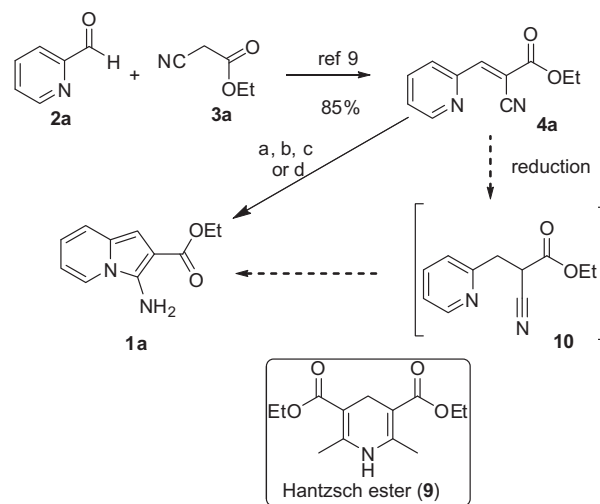
We have developed an efficient one-pot multistep sequence to the synthesis of 3-aminoindolizine derivatives by using Hantzsch ester (**9**) as a mild hydride transfer agent. The reaction scope was investigated and the effect of substrates on reaction outcomes was discussed.

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Improving efficiency is one of the main pursuits of modern organic synthesis research.<sup>1,2</sup> This is further reinforced by the increasing concerns of environmental protection and sustainability in past decades. To date the design, development, and utilization of efficient environmentally benign synthetic process has become a conscientious choice of synthetic chemists.<sup>3,4</sup> One attractive strategy is to design and develop a novel one-pot multistep synthesis that helps simplify reaction handling and product purification, improve synthetic efficiency, and reduce solvent consumption and disposal. This will ultimately help reduce consumption of natural resources, minimize the potential, harmful impact of various chemicals on environment, and increase sustainability.<sup>5</sup>

In one of our medicinal chemistry programs, we needed **1a** (Scheme 1) to prepare more complex analogs containing indolizine core. Indeed, indolizine can serve as an isosteric replacement for indoles<sup>6</sup> and other heterocycles,<sup>7</sup> and is found to possess interesting biological activities.<sup>8</sup> To the best of our knowledge, the synthesis of **1a** had previously been reported by two groups using a three-step sequence (Scheme 1). The first step involves the Knoevenagel condensation between 2-pyridylcarboxaldehyde (**2a**) and ethyl cyanoacetate (**3a**) to form product **4a**.<sup>9</sup> When **4a** was exposed to DIBAL reduction,<sup>9</sup> Raney-Ni catalyzed hydrogenation,<sup>9</sup> or electrochemical reduction in the presence of chlorotrimethylsilane,<sup>10</sup> **1a** was obtained in a moderate 45%, 43% or 47% yield from **4a**, respectively. We hypothesized that the formation of **1a** could proceed through intermediate **10**. The subsequent intramolecular cyclization reaction of **10** that involves the addition of pyridine nitrogen to cyanide followed or accompanied by some rearrangement

processes would deliver **1a**. Based on these reports and our reaction pathway analysis, we envisioned that under suitable reduction conditions it should be possible to run the whole sequence, including the Knoevenagel condensation between 2-pyridylcarboxaldehyde (**2a**) and ethyl cyanoacetate (**3a**), and the following transformation of **4a** into **1a**, in an environmentally benign one-pot manner. Literature search showed that Hantzsch ester (**9**), a versatile and mild hydride transfer reagent<sup>11,12</sup> used for the promotion of reductive alkylation reactions,<sup>13</sup> might serve this purpose.



**Scheme 1.** Reagents and conditions: (a) DIBAL, Ref. 9, 45%; (b) Raney-Ni in AcOH, Ref. 9, 43%; (c) e<sup>-</sup>, Me<sub>3</sub>SiCl, ref 10, 47%; (d) **9**, toluene, 105 °C, 3 h, 70%.

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As per our initial proof of concept, we heated **4a** with 1.1 equiv of Hantzsch ester (**9**) in toluene at 105 °C for 3 h and the desired compound **1a** was obtained in 70% yield (Scheme 1). This result suggested that Hantzsch ester (**9**) was an effective hydride transfer agent for the transformation and prompted us to investigate the possibility of running the sequence in a one-pot multistep manner.

In an initial run, we simply heated a mixture of equimolar amount of **2a** and **3a** with 1.1 equiv of Hantzsch ester (**9**) at 105 °C in toluene for 3 h and obtained compound **1a** in 12% yield (Table 1, entry 1). Interestingly, when the same reaction was performed again in the presence of 0.02 equiv of piperidinium acetate, a widely used Knoevenagel condensation catalyst, the formation of **1a** was increased to 56% yield (Table 1, entry 2). Encouraged by these results, we further explored the effect of the amount of piperidinium acetate used on the reaction, and found that with 0.05 and 0.1 equiv of the catalyst and we obtained **1a** in 74% and 71% yield (Table 1, entries 3 and 4), respectively. Compared to the 70% yield we obtained from the direct reduction of **4a** by Hantzsch ester (**9**), it seemed that the one-pot multistep reaction had an overall improved yield. Another commonly used Knoevenagel condensation catalyst, L-proline, was also employed at 0.05 equiv in the one-pot multistep process. However, the yield of **1a** was decreased to 45% (Table 1, entry 5). Based on these results, we decided to explore the reaction scope with a few other nitriles using our optimized conditions (Table 1, entry 3). The aim is to develop the method into a general approach for the synthesis of synthetically useful substituted 3-aminoindolizine analogs.<sup>14</sup> As

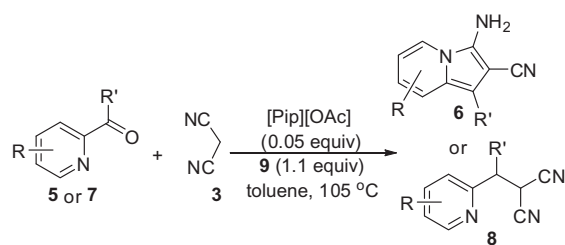
**Table 1**  
Reaction conditions optimization and reaction scope exploration of nitriles

Entry	3, EWG	Catalyst <sup>a</sup> (equiv)	Product	Yield <sup>b</sup> (%)
1	3a, EtOC(O)-	None		12
2	3a, EtOC(O)-	A (0.02)	<b>1a</b>	56
3	3a, EtOC(O)-	A (0.05)	<b>1a</b>	74
4	3a, EtOC(O)-	A (0.1)	<b>1a</b>	71
5	3a, EtOC(O)-	B (0.05)	<b>1a</b>	45
6	3b, <i>t</i> -BuC(O)-	A (0.05)		53
7	3c, MeS(O) <sub>2</sub> -	A (0.05)		34
8	3d, PhS(O) <sub>2</sub> -	A (0.05)		42
9	3e, NC-	A (0.05)		44

<sup>a</sup> A = piperidinium acetate; B = L-proline.

<sup>b</sup> Isolated yield.

**Table 2**  
Reaction scope exploration of 2-carbonylpyridine



Entry	Carbonyl	Yield <sup>a</sup>	Product
1		88%	
2		61%	
3		31%	
4		49%	
5		53%	
6		87%	
7		86%	
8		97%	
9		86%	
10		64%	

<sup>a</sup> Isolated yield.

shown in Table 1 (Table 1, entries 6–9), electron-withdrawing groups (EWGs) such as a ketone, sulfone, and cyano group were

tolerated under these conditions but the corresponding products were isolated with lower yields. It is noteworthy to point out that it is possible to further improve the yield if reaction conditions are carefully optimized for each of these EWGs.<sup>15</sup>

Moving forward, we chose malononitrile (**3e**) as our standard nitrile partner to explore the reaction scope with different 2-carbonylpyridines. The results are summarized in Table 2. Overall, 11 carbonyl compounds were subjected to this study and only one aldehyde, isoquinoline-3-carbaldehyde (not listed in Table 2), gave a complicated mixture products. However, its regioisomers quinoline-2-carbaldehyde (**5f**) and isoquinoline-1-carbaldehyde (**5c**) were able to participate in the reaction and provide the corresponding 3-aminoindolizine derivative **6f** and **6c** in 87% and 31% yield (Table 2, entries 3 and 6), respectively. Compared to quinoline-2-carbaldehyde (**5f**), the replacement of a carbon with nitrogen as in **5e** led to a lower reaction yield (87% vs 53%, entry 6 vs entry 5, Table 2). Simple aldehydes such as **5a** and **5b** are good substrates for this one-pot sequence to 3-aminoindolizine derivatives **6a** and **6b** (in 88% and 61% yield, respectively, entries 1 and 2 of Table 2). It would appear that the intrinsic electronic property of the substituent at the 6-position of pyridyl ring played a critical role in controlling the product formation. While a 6-methyl group as represented by **5g** led to the formation of 3-aminoindolizine derivative **6g** in 86% yield (Table 2, entry 7), three other aldehydes with a substituent at its 6-position, such as 6-methoxy in **7a**, 6-bromo in **7b**, or 6-fluoro in **7c**, afforded only the uncyclized product **8a**, **8b**, or **8c** in 97%, 86% or 64% yield, respectively (Table 2, entries 8–10).<sup>16</sup> What in common with these three substituents is that they can all exert an electron inductive effect in 2-pyridylcarboxaldehyde system. There is a possibility that an electronic clash between the electron cloud of lone-pair electrons of oxygen, bromine or fluorine and of the cyanide prevented the cyclization from occurring. However, this was ruled out based on the fact that we could still obtain cyclized product **6e** from aldehyde **5e** in 53% yield (Table 2, entry 5). Finally, a methyl ketone **5d** was used to explore the possibility of using the process to synthesize 3-aminoindolizine derivative bearing a substituent at its 1-position and the desired cyclized product **6d** was obtained in 49% yield. This represents a slight improvement on product yield in comparison to the 44% yield of cyclized product **1e** obtained from the corresponding reaction of aldehyde **1a** with malononitrile.

The general procedure for the synthesis of the 3-aminoindolizine derivatives **1a–e**, **6a–g**, and uncyclized product **8a–c** is described below: To a reaction mixture of cyano substrate **3** (2.0 mmol), 2-carbonyl pyridine derivative (2.0 mmol), and piperidinium acetate (15 mg, 0.10 mmol) in toluene (6 ml), was added diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (**9**) (Hantzsch ester, 557 mg, 2.2 mmol) in one portion at room temperature. The resulting mixture was degassed with a stream of nitrogen and then stirred at 105 °C for 3 h. After cooling to room temperature, a minimum amount (ca 0.3–0.5 mL) of DMSO was added to the reaction mixture and the resulting solution was directly loaded to a silica gel column and purified by column chromatography using Teledyne Isco Combiflash system.

In summary, we have developed an efficient one-pot multistep sequence for the synthesis of 3-aminoindolizine derivatives by using Hantzsch ester (**9**) as a mild hydride transfer agent. The se-

quence has a wide reaction scope with respect to nitrile substrates; all the nitriles containing electronwithdrawing groups such as carboxylic acid ester, sulfone, ketone, and cyanide tested in our study provided corresponding 3-aminoindolizine derivatives. However, the reaction scope with various substituted 2-carbonylpyridines was dependent on their electronic properties. While most of the pyridine substrates used in our study provided 3-aminoindolizine derivatives, those groups with electron inductive effect substituted at 6-position of pyridine ring led to formation of only uncyclized products **8**.

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15. At the end of our study, we re-examined more closely the formation of **1e** from **2a** and **3e** (Table 1, entry 9). We found that under the original reaction conditions as described in Table 1, entry 9, an enamine **11** side product was formed (Fig. A) in ca. 20% yield. Compound **11** is stable to flash chromatography over silica gel column

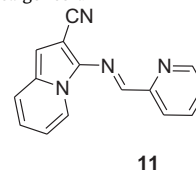
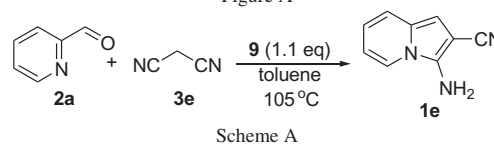


Figure A



We then found that without the use of Knoevenagel condensation catalyst piperidinium acetate, the formation of **11** was reduced but the reaction yield of **1e** was hardly effected (46% without vs 44% with piperidinium acetate). In order to further suppress the formation of **11**, we used 1.4 instead of 1.0 equiv of **3e** in the absence of a catalyst, and found that the yield of **1e** was improved from 46% to 59% (Scheme A).

16. Attempts to cyclize **8a** under a variety of conditions failed to provide any cyclized product. Further exploration needs to be done.