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An efficient and convenient synthesis of 1,2,3-trisubstituted pyrroles via iodocyclization from ethyl acetoacetate

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Abstract

A novel and efficient methodology for the synthesis of 1,2,3-trisubstituted pyrroles by one-pot two-step reaction has been developed. The iodocyclization of series of β-enamino esters followed by dehyroiodination, led to the formation of corresponding pyrroles. This approach provides an easy access to a wide range of 1,2,3-trisubstituted pyrroles.

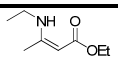
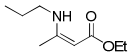
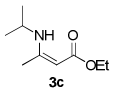
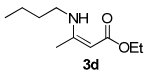
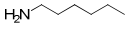
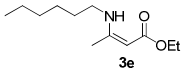
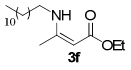
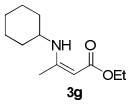
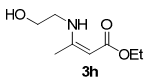
Keywords: Pyrroles; One-pot synthesis; Iodocyclization; Tandem reaction

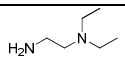
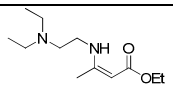
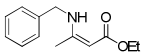
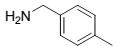
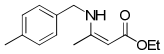
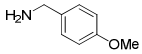
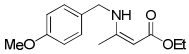
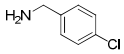
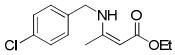
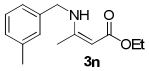
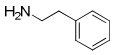
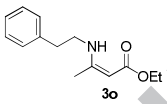
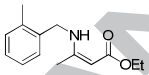
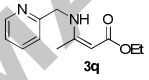
Substituted pyrroles represent an important class of organic compounds which have found in many bioactive molecules and natural products.[1-2] They have also been widely applied in medicinal and material science.[3] In view of their characteristic properties, a variety of methods for synthesis of substituted pyrroles have been developed. Paula and co-workers reported the efficient synthesis of 2,3,5-substituted pyrrole derivatives by treatment of 2,3-dihydrofuran derivatives with trifluoroacetic acid.[4] Recently, Lingaiah and co-workers developed a novel method to construct tetrasubstituted pyrrole ring utilize polyethylene glycol as reaction medium.[5] Abu and co-workers employed a four-component reaction catalyzed by nickel (II) chloride hexahydrate to construct the tetra-substituted pyrroles.[6] However, efficient and convenient methodologies for the synthesis of 1,2,3-trisubstituted pyrroles are not numerous in literature.[7-8] In another arena of iodine chemistry, the nontoxic, inexpensive and readily available iodine has emerged as a very attractive reagent for

various organic transformations.[9-11] Particularly, the area of iodine mediated cyclization reaction has got enormous progress. Several organic compounds such as *cis*-2,5-disubstituted furans,[12] *cis*-tetrahydrofurans,[13] oxazoles,[14] iodobenzenes[15] and indolizines[16] have been synthesized via iodocyclization. In this letter, we describe one-pot two-step efficient synthesis of 1,2,3-trisubstituted pyrroles via iodocyclization from ethyl acetoaceate.

Our initial studies focused on the development of the construction of β-enamino esters which is a versatile synthetic intermediate via iodine-catalyzed enamination in organic solvent. This method was successfully applied to enamination of ethyl acetoacetate with various amines in acetonitrile. To continue our interest in preparing substituted pyrroles, we have designed to construct 1,2,3-trisubstituted pyrroles from β-enaminones. To our satisfaction, 1,2,3-trisubstituted pyrroles were successfully prepared by using β-enaminones, acetaldehyde, iodine and piperidine at -15 ^{o}C via one-pot two-step procedure. To the best of our knowledge, this is the first protocol explored synthesis of 1,2,3-trisubstituted pyrroles using this method.

Table 1. Scope and generality of the synthesis of β-enaminones

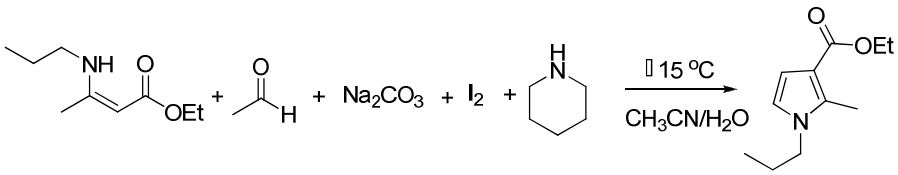
Entry	Amine	Product	Yield(%)[a]
1		 **3a**	96
2		 **3b**	97
3		 **3c**	97
4		 **3d**	96
5		 **3e**	96
6		 **3f**	78
7		 **3g**	95
8		 **3h**	87

9		 **3i**	89
10		 **3j**	93
11		 **3k**	92
12		 **3l**	93
13		 **3m**	91
14		 **3n**	92
15		 **3o**	94
16		 **3p**	88
17		 **3q**	85

[a] Yields are given for isolated product

We selected the reaction between ethyl acetoacetate and *n*-propylamine as a model reaction for optimizing the reaction conditions, such as solvent and reaction temperature (see supplementary data Table 1). Various β-enamino esters **3** were prepared in high yields as shown in Table **1**.

After successfully prepared a series of β-enamino esters, with the aim to construct 1,2,3-trisubstituted pyrroles, we selected **3b** as a model reaction to examine its behavior under different conditions. Upon treatment **3b** with acetaldehyde, iodine in basic condition, the reaction furnished the desired product, ethyl 2-methyl-1-propyl-1H-pyrrole-3-carboxylate (**Scheme 1**).



3b **4b**

Scheme 1. Multicomponent one-pot synthesis of 1,2,3-trisubstituted pyrroles

The optimization of the reaction conditions, including reaction temperature, base, and the equivalent of iodine were then investigated. First, various bases were screened (Table 2, entries 1-6), and sodium carbonate was proven to be preeminent for this reaction. Then, we observed the equivalent of iodine also have important influence on the reaction. A less amount of iodine (for example, 0.5 equiv) resulted in a low yield (55%). In contrast, when the equivalent of iodine increased to 1.5 equiv, a good yield was achieved (82%). Finally, we examined the influence of different temperatures and different equivalents of piperidine on this reaction (Table 2, entries 3 and 9-16). To our satisfaction, when the reaction was carried out at –15 °C, it proceeded smoothly and clean, furnishing **4b** in good yield (Table 2; entries 3 and 9-11). A series of experiments were performed to reveal that the optimal results were obtained: when the reaction of **3b** performed with acetaldehyde (8.0 equiv), iodine (1.5 equiv) sodium carbonate (1.2 equiv) and piperidine (1.0 equiv) in acetonitrile at –15 °C, whereby the yield of **4b** reached up to 82%.

Table 2. Optimization of the synthesis 1,2,3-trisubstituted pyrroles

Entry	Iodine	Piperidine	Base	Temp.°C	Yield(%)[a]
1	1.5 equiv	1.0 equiv	KOH	–15	53
2	1.5 equiv	1.0 equiv	LiOH	–15	44
3	1.5 equiv	1.0 equiv	Na_2CO_3	–15	82
4	1.5 equiv	1.0 equiv	Cs_2CO_3	–15	69
5	1.5 equiv	1.0 equiv	$NaHCO_3$	–15	63
6	1.5 equiv	1.0 equiv	DBU	–15	71
7	0.5 equiv	1.0 equiv	Na_2CO_3	–15	55
8	1.0 equiv	1.0 equiv	Na_2CO_3	–15	67
9	1.5 equiv	0 equiv	Na_2CO_3	–15	17
10	1.5 equiv	0.1 equiv	Na_2CO_3	–15	38
11	1.5 equiv	0.5 equiv	Na_2CO_3	–15	54
12	1.5 equiv	2.0 equiv	Na_2CO_3	–15	77
13	1.5 equiv	1.0 equiv	Na_2CO_3	–20	51

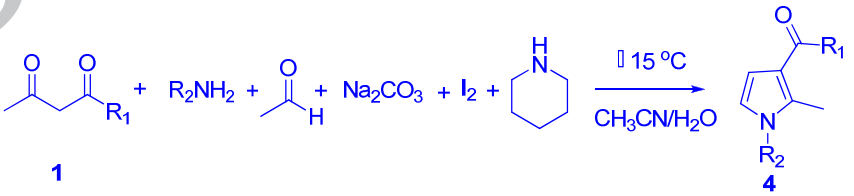
14	1.5 equiv	1.0 equiv	Na_2CO_3	0	65
15	1.5 equiv	1.0 equiv	Na_2CO_3	r.t.	49
16	1.5 equiv	1.0 equiv	Na_2CO_3	60	48

[a] Yields are given for isolated product.

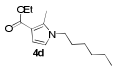
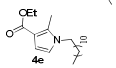
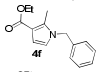
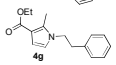
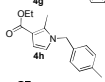
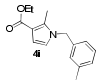
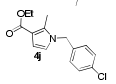
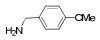
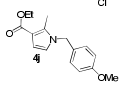
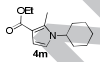
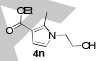
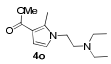
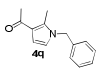
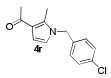
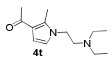
[b] Standardization of reaction conditions: **3b** (1.0 mmol), piperidine (1.0 mmol), and acetaldehyde (8.0 mmol).

Having established the optimal conditions for the key cyclization process, we tried to explore the possibility of the synthesis of 1,2,3-trisubstituted pyrroles by one-pot reaction from ethyl acetoaceate. To our delight, we successfully established one-pot two-step three-component reaction in good yields. To a 25 mL round-bottom flask was added 1.0 mmol of ethyl acetoacetate, 1.2 mmol of various amines, 0.1 mmol of iodine and 6.0 mL of acetonitrile. The mixture was placed at room temperature for vigorous stirring. After ethyl acetoacetate was consumed (monitored by TLC), 6.0 mL of acetonitrile, 2.0 mL of water, 8.0 mmol of acetaldehyde, 1.2 mmol of sodium carbonate, 1.0 mmol of piperidine and 1.5 mmol of iodine were added . The reaction mixture was allowed to stir at 15 °C for special time. To explore the scope of this novel transformation, a variety of amines were tested under optimized conditions. In all of the cases, the transformation from ethyl acetoaceate to 1,2,3-trisubstituted pyrroles derivatives in moderate to good yields (Table 3). These results indicate that the present protocol is widely applicable for various amines.

Table 3. Scope and generality of the synthesis of 1,2,3-trisubstituted pyrroles



Entry	R_1	Amine	Product	Yield(%)
1	OEt		 4a	76
2	OEt		 4b	75
3	OEt		 4c	71

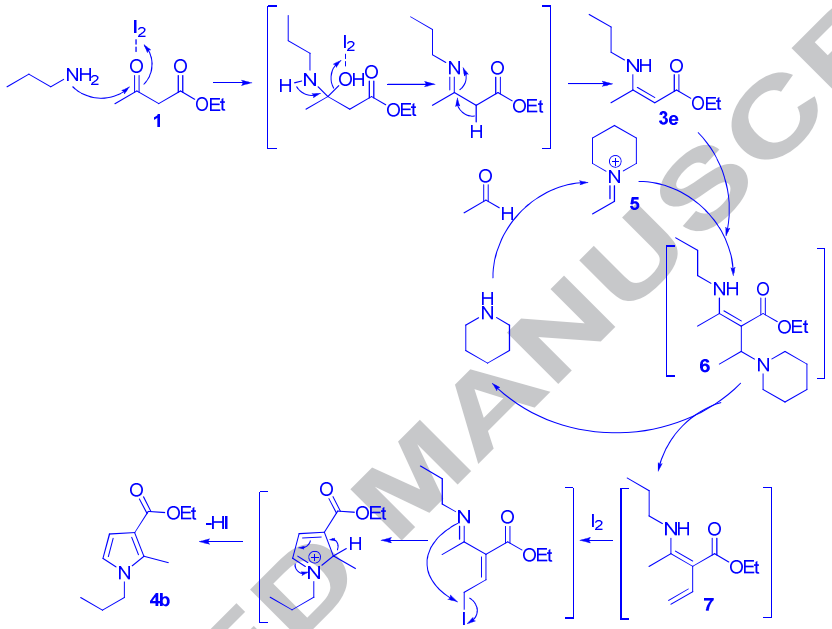
4	OEt				64
5	OEt				48
6	OEt				64
7	OEt			63	
8	OEt			64	
9	OEt			62	
10	OEt			62	
11	OEt			61	
12	OEt				63
13	OEt				65
14	OEt				51
15	OEt				46
16	Me				79
17	Me				71
18	Me				68
19	Me				70
20	Me				53

[a] Yields are given for isolated product

A plausible mechanism for the synthesis of 1,2,3-trisubstituted pyrroles is illustrated in Scheme 2. Initially, 3e was obtained from the condensation of ethyl acetoacetate **1** with *n*-propylamine, which is expected to proceed through an addition-elimination mechanism.[17] The intermediate **5**, generated by acetaldehyde and piperidine, reacts with **3e** to form **6** by

Knoevenagel condensation. Subsequently, the key intermediate **7** undergoes concomitant iodocyclization with elimination of HI and spontaneous aromatization to afford the final product **4b**. Similar reactions involving iodocyclization were already described in related literatures. [18-21]

Scheme 2. Proposed mechanistic pathway for one-pot synthesis of 1,2,3-trisubstituted pyrroles



In conclusion, we have developed an efficient and facile method to prepare 1,2,3-trisubstituted pyrrole derivatives by the treatments of acetaldehyde, ethyl acetoaceate, sodium carbonate, piperidine and iodine. The mild reaction conditions, low cost of reaction substrates, operational simplicity and good yields render this protocol very attractive.

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