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MULTICOMPONENT REACTION FOR THE SYNTHESIS OF 1,2,3,4,6-PENTASUBSTITUTED PIPERIDINES CATALYZED BY NIS

Liu Pengpeng*

School of Petroleum and Chemical Engineering, Dongying Vocational Institute, Dongying, 257091, China. E-mail: pengpeng8113@163.com

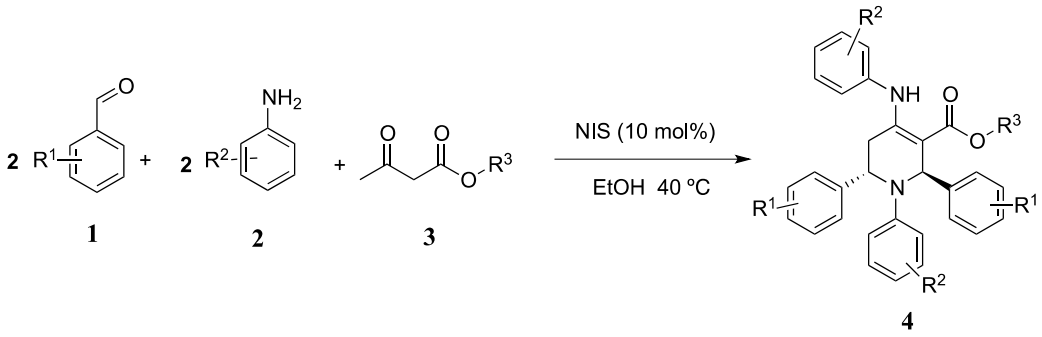
Abstract – An efficient, suitable and high yielding method has been developed for the synthesis of substituted piperidines via multicomponent, one-pot domino reaction of *β*-keto ester, aromatic amines, and aromatic aldehydes in the presence of catalytic amount of N-iodosuccinimide (NIS) in ethanol. Atom economy, mild reaction conditions, good to excellent yields, operational simplicity and easy work-up are some of the important features of this method.

The piperidine ring system is one of the most regular motifs found in many naturally occurring alkaloids,[1] synthetic pharmaceuticals, and a wide variety of biologically active compounds.[2] There are thousands of literature references, including patents, which utilize such compounds in medicinal research.[3] A large number of compounds bearing piperidine scaffold have entered preclinical and clinical trials over the last few years.[4] In particular, 1,4-disubstituted piperidine scaffolds find useful applications as established drugs,[5] and exhibit a wide range of biological activities such as anti-bacterial,[6] anti-malarial,[7] anti-inflammatory,[8] anti-convulsant,[9] and anti-hypertensive[10] activities.

Due to the broad spectrum of bioactivity, tetrahydropyridine derivatives became attractive synthetic target for medicinal and organic chemists. As a result, a variety of methodologies have been developed for their synthesis such as reaction of dihydropyran with anilines,[11] proline mediated cascade Mannich-type intramolecular cyclization,[12] amine catalyzed annulations of Morita-Baylis-Hillman acetate with 1,3-azadienes.[13] In the last two decades, the synthesis of highly functionalized piperidines have been widely reported via multicomponent reaction involving one molecule of *β*-keto ester, two molecules of substituted aniline and two molecules of aldehyde. Usually, acidic catalysts are used for such reactions, organic acids including picric acid,[14a] tartaric acid,[14b] citric acid,[14c] polystyrene sulfonic acid (PSSA),[14d] oxalic acid dihydrate,[14e] and camphor-10-sulfonic acid (CSA);[14f] as well as Lewis acids.[15] In addition, ionic liquids are also good catalyst for this type reaction, and many different kinds of ionic liquids have

been reported.[16] Previously literatures revealed that some bromine-containing reagents such as bromodimethylsulfonium bromide (BDMS),[17] tetrabutylammonium tribromide (TBATB),[18] Fe_2O_3-BIM tribromide,[19] PEG-embedded KBr_3,[20] and bis(1,3-dimethylimidazolidinone) hydrotribromide (DITB)[21] were efficient catalysts for the synthesis of functionalized piperidines. Very recently, Wu and co-workers reported that trimethyliodosilane (TMSI) was also an efficient catalyst for the synthesis of functionalized piperidines.[22] N-Iodosuccinimide (NIS) has been used widely as a useful catalyst in organic chemistry.[23] With these informations in hand, I speculate that NIS may be used to promote the substituted piperidines synthesis.

Herein, I describe the synthesis of 1,2,3,4,6-pentasubstituted piperidines *via* one-pot multicomponent reactions of *β*-keto ester, aromatic amine and aromatic aldehyde catalyzed by NIS (Scheme **1**) in ethanol at 40 °C. The desired compounds crystallized directly from ethanol and were isolated through simple filtration and washing with ethanol.



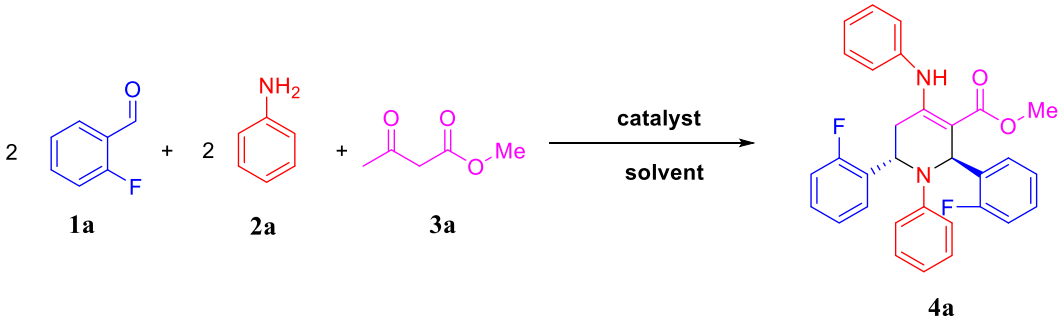
Scheme 1. The synthesis of 1,2,3,4,6-pentasubstituted piperidines

At the beginning, the multicomponent reaction between methyl acetoacetate with 2-fluorobenzaldehyde and aniline was chosen as the model reaction. Methyl acetoacetate **3a** (2 mmol) and aniline **2a** (4 mmol) were stirred at room temperature for 30 min to form the enamine intermediate followed by the addition of 2-fluorobenzaldehyde **1a** (4 mmol). The reaction mixture was further stirred till the formation of product **4a** completed.

Preliminary studies focused on the screening of catalyst type. I performed a blank experiment in ethanol as solvent, and no product was obtained even after prolonged reaction time (Table **1**, entry **1**). Other catalysts such as N-chlorosuccinimide (NCS) and N-bromosuccinimide (NBS) were also tested, but only trace of the desired products were obtained even after 24 h (Table **1**, entries**2 -3**). To my pleasure, 78% yield of the product was isolated when NIS was used as catalyst (Table **1**, entry **4**). Next, I examined the effect of different reaction solvents, which included MeOH, MeCN, THF and CH_2Cl_2 under the same reaction conditions (Table **1**, entries **5–8**). Moreover, the amount of catalyst was also tested, the yield got

decreased when the quantity of NIS was reduced from 10 mol% to 5 mol% (Table **1**, entry **9**). When 20 mol% of NIS was added, the reaction went smoothly and the desired product was obtained in 70% yield after 24 h of stirring at room temperature (Table **1**, entry **10**). Finally, I investigated the effect of reaction temperature on the experimental results and found that 40 °C was the best choice for the reaction.

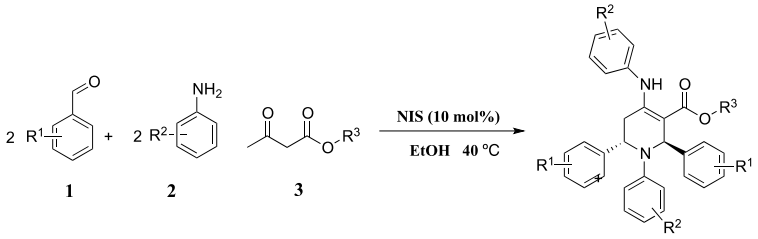
Table 1. Screening of optimal reaction conditions



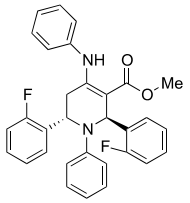
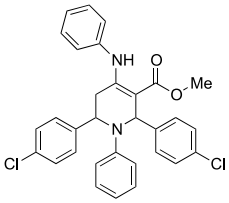
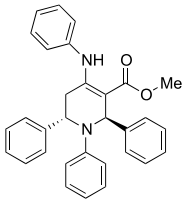
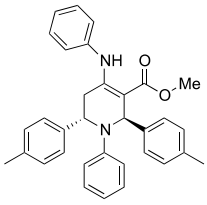
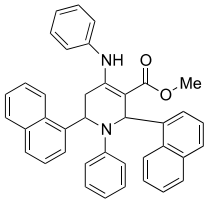
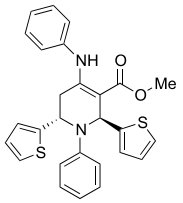
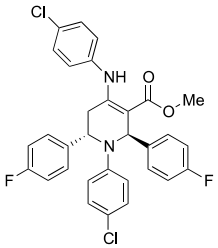
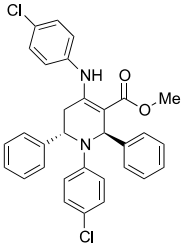
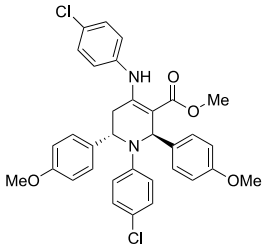
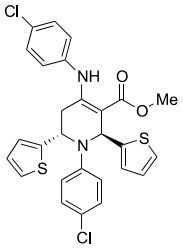
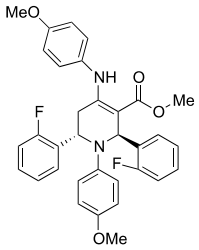
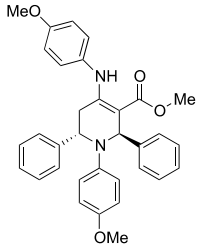
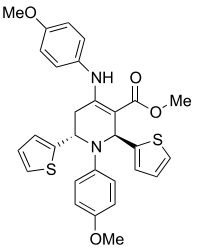
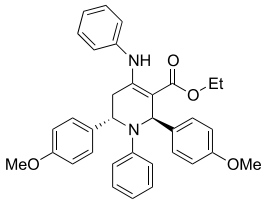
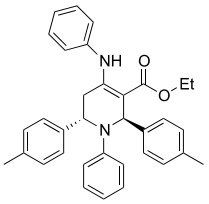
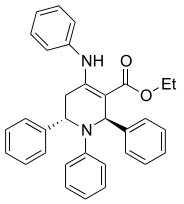
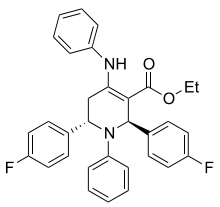
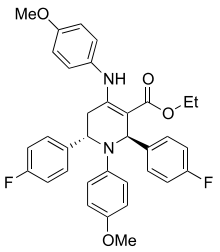
Entry	Catalyst (equiv.)	Solvent	Temperature (°C)	Time (h)	Isolated yield (%)
1	No catalyst	EtOH	rt	24	0
2	NCS(0.10)	EtOH	rt	24	trace
3	NBS(0.10)	EtOH	rt	24	trace
4	NIS (0.10)	EtOH	rt	24	78
5	NIS(0.10)	MeOH	rt	24	71
6	NIS(0.10)	MeCN	rt	24	55
7	NIS(0.10)	THF	rt	24	38
8	NIS (0.10)	CH_2Cl_2	rt	24	21
9	NIS(0.05)	EtOH	rt	24	58
10	NIS(0.20)	EtOH	rt	24	70
11	NIS(0.10)	EtOH	40	8	90
12	NIS(0.10)	EtOH	60	8	89

With the optimal reaction conditions in hand, I then examined the generality and scope of this five-component reaction using a variety of aromatic aldehydes, aromatic amines, and *β*-keto esters, and the outputs are summarized in Table **2**. In general, aromatic aldehydes bearing electron-donating or electron-withdrawing functional groups at different positions reacted with methyl acetoacetate smoothly in the presence of aniline to generate the corresponding products in good to excellent yields (Table **2**, 4a ~ 4e). Besides substituted benzaldehyde, aromatic heterocyclic aldehyde was also suitable for this reaction (Table **2**, 4f). In contrast, aliphatic aldehydes such as *n*-hexanal and isobutyraldehyde did not give their corresponding functionalized piperidines.

Table 2. Synthesis of highly functionalized piperidines catalyzed by NIS



1 2 3 4

				
4a (90%)	**4b (95%)[c]**	**4c (87%)**	**4d (84%)**	**4e (85%)[d]**
				
4f (80%)	**4g (92%)**	**4h (86%)**	**4i (81%)**	**4j (82%)**
				
4k (81%)	**4l (74%)**	**4m (69%)**		
				
4n (76%)	**4o (89%)**	**4p (78%)**	**4q (91%)**	**4r (79%)**

[a]reaction conditons: **1** (4 mmol), **2** (4 mmol), **3** (2 mmol), EtOH (30 mL), NIS (0.2 mmol);
[b]isolated yields; [c]compounds are obtained as diasteromeric mixture with *anti/syn* = 1.2 : 1.0;
[d]compounds are obtained as diasteromeric mixture with *anti/syn* = 1.4 : 1.0;

Several aromatic amines were examined to study the generality and scope of the present protocol. Aromatic amines were found to be effective substrates and afforded the corresponding tetrahydropyridine derivatives in moderate to good yields (Table **2**, 4g ~ 4m). Lastly, other *β*-keto ester such as ethyl acetoacetate was examined. The alkoxy moiety present had little or no influence on the reaction, and generally good yields were obtained (Table **2**, 4n ~ 4r).

In summary, I have developed an efficient protocol for the construction of 1,2,3,4,6-pentasubstituted piperidines by employing catalytic amount of NIS via multicomponent reaction of *β*-keto ester, aromatic amines, and aromatic aldehydes in ethanol. The attractive features of this procedure are the mild reaction conditions, operational simplicity, superior atom-economy, and eco-friendly catalyst.

EXPERIMENTAL

All reagents were purchased from Adamas (China), and were used as received without further purification. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with silica gel plates (60F-254) using UV light. Yields refer to pure compounds. Melting points were measured on an electro thermal 9100 apparatus. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 500 MHz spectrometer as indicated in the data list. The abbreviations s, d, dd, t, q, br, and m stand for the resonance multiplicity singlet, doublet, doublet of doublets, triplet, quartet, broad and multiplet, respectively.

Typical Procedure for the Synthesis of 1,2,3,4,6-Pentasubstituted Piperidines(4a-4r)

A mixture of *β*-keto ester (2 mmol), aromatic amines (4 mmol), NIS (0.2 mmol), and EtOH (30 mL) was stirred at room temperature for 30 min. After that, aromatic aldehydes (4 mmol) was added and the reaction stirred at 40 °C for another 8 h. The progress of the reaction was monitored by TLC. On completion of the reaction, cooled down to the room temperature the solid product was collected by simple filtration and washed with ethanol and dried.

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SUPPORTING INFORMATION

Supplementary data (analytical data for reaction products) associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27283/102/8.

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