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Synthesis of highly functionalized piperidines via one-pot five-component reactions in the presence of $Cr(NO_3)_3 \cdot 9H_2O$

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Abstract: A simple and efficient method is described for one-pot five-component synthesis of highly functionalizaed piperidines from β-keto esters, aromatic aldehydes and various amines in the presence of a catalytic amount of $Cr(NO_3)_3.9H_2O$ in ethanol at room temperature. The main features of current protocol include mild reaction conditions, easy work up, and good yields.

Keywords: Piperidines, β-keto esters, Aldehydes, Amines, $Cr(NO_3)_3 \cdot 9H_2O$.

Introduction

As an important aspect of synthetic organic chemistry, multi-component organic reactions (MCRs) are among the most prosperity reaction classes. 1,3-Dicarbonyl compounds are one of the most multifaceted reagents to be used in MCRs because of the high reactivity of enaminones in both keto and enol forms, which are very advantageous to construct useful bioactive heterocycles [1-2].

The synthesis of highly functionalized piperidines is an important synthetic transformation as these scaffolds are found to form a very important core in numerous natural products [3]. The piperidines and their analogues are important heterocycles that are present in many naturally occurring alkaloids, biologically active synthetic molecules, and organic fine chemicals. Some of them also act as pharmaceutical agents. Compounds containing piperidine structural is one of the most common motifs found in numerous drugs, drug candidates and natural products such as alkaloids [4-6].They are also exhibit anti-hypertensive [7], antibacterial [8], neuro-protective agents[9-10], anticonvulsant and anti-inflammatory agents [11-12], and also antimalarial activities [13].

As a result, various synthetic approaches have been developed for the synthesis of piperidines based on intramolecular Mannich reaction onto iminium ions, imino Diels– Alder reaction, aza-Prins cyclizations, intramolecular Michael reaction, and cyclopropane ring-opening/Conia-ene cyclization [14]. Several types of catalysts were introduced previously for this purpose, such as $Bi(NO_3) \cdot 5H_2O$ [15], Cerium Ammonium Nitrate (CAN) [16], L-proline/TFA [13], $LaCl_3 \cdot 7H_2O$ [17], Iodine [18], $InCl_3$ [19], Bromodimethylsulfonium Bromide (BDMS) [20], acetic acid [21], VCl_3 [22], tetrabutylammonium tribromide (TBATB) [23], *p*-toluenesulfonic acid [14], picric acid [24]. However, some of these methods have drawbacks, such as long reaction times, unsatisfactory yields, difficult to prepare, heat reaction condition, or use of expensive catalysts. Hence, the development of a simple and high-yielding environmentally benign protocol for the one-pot multicomponent synthesis of piperidines without these problems.

Results and discussion

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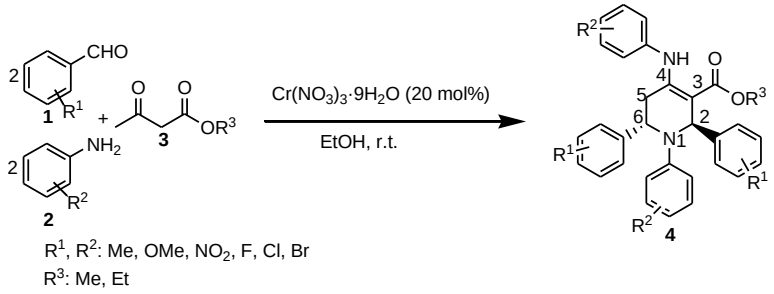
The compounds (1–29) were synthesized by reacting β-keto esters (1 equivalents), aromatic aldehydes and anilines (2.0 equivalents) in ethanol in the presence of $Cr(NO_3)_3{\cdot}9H_2O$ (20 mol%) at ambient temperature (Scheme **1**).



Scheme 1. Synthesis of highly functionalizaed piperidine **4**.

Various potential catalysts were tested for the direct synthesis of **4a** by the model reaction of 4-methylbenzaldehyde (2 mmol), aniline (2 mmol), and methyl acetoacetate (1 mmol) in varaiety solvent at room temperature, with results listed in Table **1**.

Table 1: Investigation of solvent effect.[a]

Entry	Solvent	Catalyst mol %	Time/ h	Yield %[b]
1	CH_3CN	20	7	80
2	MeOH	20	6	82
3	H_2O	20	24	25
4	EtOH/ H_2O (1:1)	20	20	46
5	EtOH	20	5	90
6	EtOH	15	8	82
7	EtOH	10	11	73
8	EtOH	5	16	60
9	EtOH	25	5	90
10	EtOH	-	48	-
11	-	20	24	31

[a] Experimental conditions: 4-methyl benzaldehyde (2 mmol), aniline (2 mmol), methyl acetoactate (1 mmol), $Cr(NO_3)_3{\cdot}9H_2O$ (20 mol %), and solvent (4 mL).
[b] Isolated yield.

A survey of solvents revealed ethanol to be the best choice, used directly without rigorous drying. Low yields were obtained when acetonitrile or methanol or water was employed as the solvent. Some dependence was also observed on the amount of $Cr(NO_3)_3{\cdot}9H_20$ used. A satisfactory result was obtained in the presence of 20 mol % $Cr(NO_3)_3{\cdot}9H_2O$(Table **2**, entry 5). It is noteworthy that the increasing of catalyst loading to 25 mol% had no an improving effect on the yield of product.

Several reactions between substituted benzaldehydes, anilines, and methyl or ethyl acetoacetate were examined under the optimized conditions, and the results are summarized in Table **2**. Benzaldehydes with electronwithdrawing as well as electron-releasing groups reacted efficiently with anilines to give the corresponding piperidines in good to high yields. Various substituents on the benzene ring such as OMe, Me, NO_2, Cl, F and Br were tolerated during the reaction. In all cases, the reaction proceeded to afford piperidine derivatives in good yields.

In the case of 8- and 9-nitrobenzaldehydes the products were obtained in low yields, possibly due to the formation of more stable imines, having an extra conjugation in the presence of nitro group, which become less reactive and less soluble in ethanol.

A proposed reaction mechanism in the literature [16, 18, 23] for this five-component reaction is outlined in Scheme **2**. $Cr(NO_3)_3{\cdot}9H_20$ can serve as a Lewis acidic catalyst for the reaction of aniline and β-keto esters or benzaldehyde derivatives to give the β-enaminone [16] or imine [25], respectively. The intermolecular Mannich addition of the β-enaminone (**5**) to the imine (**6**) affords the intermediate **7**. Subsequently, the reaction of activated aldehyde with the intermediate **7** proceeds to afford the intermediate **8** by the elimination of H_2O. Then, tautomerization of **8** generates intermediate **9**, which immediately undergoes intramolecular Mannich-type reaction to give intermediate **10**. Finally, the intermediate **10** tautomerizes to generate the desired piperidine derivative **4** owing to conjugation with the ester group.

Conclusion

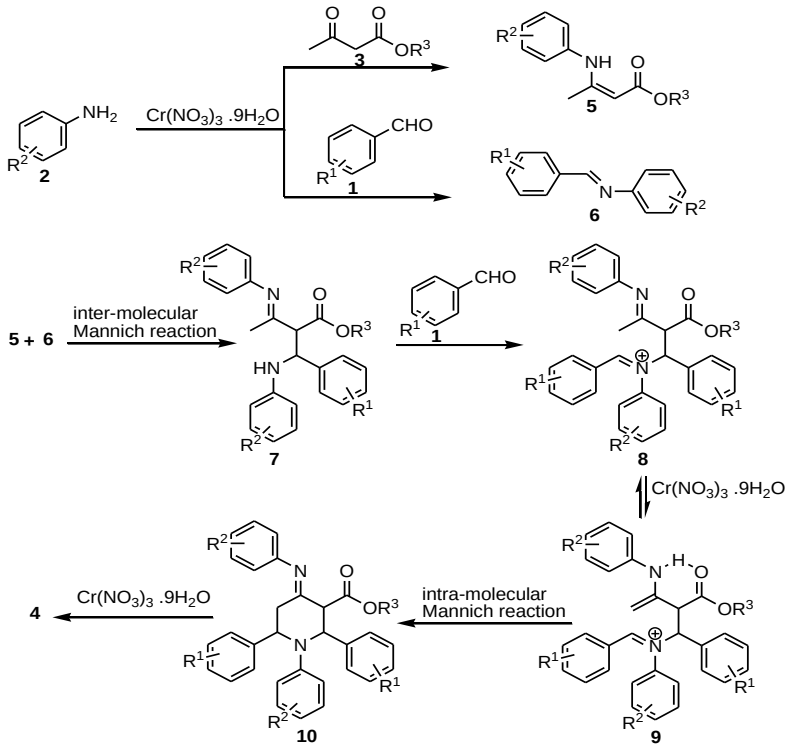
In summary, a novel and simple method for the formation of highly functionalizaed piperidines with $Cr(NO_3)_3 \cdot 9H_2O$ via one-pot five-component reaction from commonly available starting materials has been developed. In all cases, the easy workup procedure and good to high yields and the products can be collected easily by filtration.

Table 2: Synthesis of highly substituted piperidines 4a-4ac.

Entry	R^1	R^2	R^3	Product	Time/ h	Yield/ %[a]	M.p. / °C	Lit. m.p./ °C[b] [Ref.]
1	4-Me	H	Me	4a	5	90	215	212-214[20]
2	4-Me	H	Et	4b	6	80	227-230	228-231[18]
3	4-Me	4-Me	Et	4c	7	70	170-172	169-171[26]
4	4-OMe	H	Me	4d	8	81	185-187	187-188[27]
5	H	4-Br	Et	4e	4	92	198-200	196-198[26]
6	4-Cl	H	Me	4f	4	86	187-189	189-191[20]
7	4-Me	4-Cl	Me	4g	7	87	217-219	218-220[15]
8	3-NO_2	H	Me	4h	16	50	181-183	182-183[18]
9	4-NO_2	H	Me	4i	14	55	238-240	239-241[18]
10	H	H	Me	4j	7	82	172-173	169-171[20]
11	H	4-OMe	Et	4k	8	75	177-180	179-181[14]
12	H	4-Cl	Et	4l	4	84	201-203	202[13]
13	H	4-Me	Et	4m	6	78	195-197	196-198[15]
14	H	4-F	Me	4n	9	90	176-177	172-175[15]
15	4-Cl	4-Me	Et	4o	7	87	228	227-229[15]
16	4-OMe	4-Cl	Me	4p	7	82	193-195	194-195[16]
17	4-Me	4-Br	Me	4q	4	81	228-230	229-230[20]
18	4-Me	4-OMe	Me	4r	7	89	224-226	225-226[20]
19	4-Me	4-Me	Me	4s	7	80	206-207	206-208[18]
20	4-Me	4-F	Et	4t	10	88	185-186	183-185[14]
21	4-Cl	4-Br	Me	4u	8	70	191-192	190-192[15]
22	4-OMe	4-Cl	Et	4v	11	65	179-180	180-181[15]
23	4-OMe	H	Et	4w	13	62	166-168	166-168[14]
24	4-Cl	4-F	Et	4x	9	87	220-221	219-222[15]
25	H	H	Et	4y	8	70	174-176	174-175[20]
26	4-NO_2	H	Et	4z	15	68	245-248	247-250[16]

27	4-Me	4-OMe	Et	4aa	7	61	222-224	221-224[16]
28	4-NO_2	4-OMe	Me	4ab	10	72	197-199	198-199[27]
29	4-OMe	4-Br	Me	4ac	4	90	175-177	178[13]

[a] Isolated yield
[b] All known products reported previously in the literature were characterized by comparison of NMR spectra with those of authentic samples.



Scheme 2: Speculative Proposed mechanism for reactions between substituted benzaldehydes **1**, anilines **2** and methyl or ethylacetoacetate **3** for generation of piperidine 4.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus. The ^{1}H NMR spectra were recorded on a Bruker DRX-400 Avance instrument with $CDCl_3$ as solvent. All reagents were purchased from Merck (Darmastadt, Germany), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland), and used without further purification.

*General procedure for the synthesis of piperidines (**1-29**):*

A mixture of β-ketoester (1.0 mmol), aldehyde (2.0 mmol), amine (2 mmol), and $Cr(NO_3)_3{\cdot}9H_2O$ (0.20 mmol) in 4mL of ethanol was stirred at room temperature for an appropriate time (Table **2**). After completion of the reaction, as indicated by TLC, the thick precipitate was filtered off and washed with ethanol to give pure products. Specrtal data for selected data for compounds **4a** and **4e** are presented below:

Methyl 1-phenyl-4-(phenylamino)-2,6-di-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate **(4a):**

Solid; m.p. 215 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ / ppm): 2.25 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.75 (1H, dd, *J* = 15.2, 2.4 Hz, H'-5), 2.84 (1H, dd, *J* = 15.2, 5.6 Hz, H''-5), 3.93 (3H, s, OCH_3), 5.09 (1H, d, *J* = 3.1 Hz, H-6), 6.32 (2H, d, *J* = 8.0 Hz, ArH), 6.37 (1H, s, H-2), 6.48 (2H, d, *J* = 8.8 Hz, ArH), 6.60 (1H, t, *J* = 7.2 Hz, ArH), 7.00-7.12 (11H, m, ArH), 7.20 (2H, d, *J* = 8.0 Hz, ArH), 10.29 (1H, s, NH).

Ethyl 4-(4-bromophenylamino)-1-(4-bromophenyl)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate ***(4e):***

Solid; m.p. 198-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ ppm): 1.50 (3H, t, *J* = 6.8 Hz, $OCH_2C\mathit{H}_3$), 2.74 (1H, d, *J* = 15.2 Hz, H'-5), 2.89 (1H, dd, *J* = 15.2, 5.6 Hz, H''-5), 4.35-4.40 (1H, m, OCH_aH_b), 4.45-4.52 (1H, m,

OCH_aH_b), 5.13 (1H, d, *J* = 4.0 Hz, H-6), 6.14 (2H, d, *J* =8.0 Hz, ArH), 6.41 (1H, s, H-2), 6.42 (2H, d, *J* = 8.0 Hz, ArH), 7.14-7.34 (14H, m, ArH), 10.26 (1H, s, NH).

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