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Trichloroacetic Acid as an Efficient Catalyst for One-pot Synthesis of Highly Functionalized Piperidines via multi-component Reaction

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Abstract

Trichloroacetic Acid (TCA) was used as an efficient catalyst for the synthesis of highly functionalized piperidines via a one-pot five-component reaction of aromatic amines, aromatic aldehydes and *β*-keto esters in MeOH at room temperature. The remarkable advantages offered by this method are good yields, simple procedure, short reaction times, no need to column chromatography and an easy work-up.

Keywords: *Piperidines, Trichloroacetic Acid, Multi-component Reaction, β-keto esters.*

Introduction

Multicomponent reactions (MCRs) are one-pot processes in which three or more reactants come together in a single reaction vessel to form a product containing substantial elements of all the reactants [1-3]. In recent years, there has been a growing interest in MCRs in the chemical and pharmaceutical industries, as MCRs not only lower production costs due to their high convergence and atom efficiency, but also reduces the environmental burden , which is the major principle of green chemistry.

The piperidines and their analogues are important heterocycles that are present in many naturally occurring alkaloids, biologically active synthetic molecules, and organic fine chemicals [4-6]. Some of them also act as pharmaceutical agents [7]. Compounds containing piperidine structural motif exhibit anti-hypertensive [8], antibacterial [9], antimalarial [10], anticonvulsant, and anti-inflammatory activities [11]. Furthermore, these compounds are intricately involved in the MAO based mechanism of Parkinson's disease [12-13] and as inhibitors of farnesyltransferase [14-15], and dihydroorate

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dehydrogenase (Figure 1) [16]. In this respect, substituted piperidines have been identified as an important class of therapeutic agents in the treatment of influenza infection [17-18], cancer metastasis [19-20], viral infections including AIDS [21], and diabetes [22].

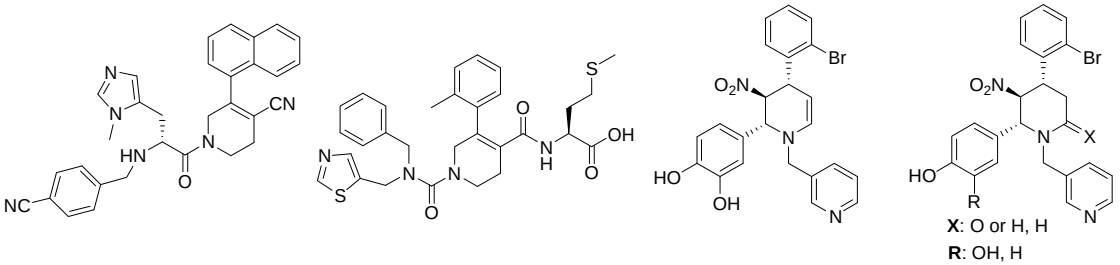


Figure 1. Farnesyltransferase active compounds containing piperidine framework [14-15].

The functionalized piperidines have been reported using MCRs strategy by employing bromodimethylsulfonium bromide (BDMS) [23], $InCl_3$ [24-25], iodine [26], cerium ammonium nitrate (CAN) [27], L-proline/ TFA [10], picric acid [28], lanthanum chloride heptahydrate ($LaCl_3.7H_2O$) [29], VCl_3 [30] and $ZrOCl_2.8H_2O$ [31]. However, some of these methods have drawbacks, such as long reaction times, unsatisfactory yields, highly toxic catalysts, 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.

This study is a part of our current studies on development of efficient multi-component reactions for the preparation of interesting bioactive molecules [32-33] and especially on the synthesis of piperdine [34-41]. Here, we reported a new method for the synthesis of highly functionalized piperidines via a one-pot five-component reaction of aromatic amines, aromatic aldehydes and β-keto esters in MeOH at room temperature using Trichloroacetic Acid as a catalyst.

Experimental

Material and methods

Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and a JASCO FT/IR-460 plus spectrometer, respectively. The ^1H NMR spectra were recorded on a Bruker DRX-400 Avance instrument with $CDCl_3$ as solvent at 400 MHz. The aromatic aldehydes, anilines, β-ketoesters, and Trichloroacetic Acid were obtained from Merck (Darmstadt, Germany), Acros (Geel, Belgium), and Fluka (Buchs, Switzerland), and used without further purification.

General procedure for the synthesis of highly functionalized piperidine **4**

A solution of aromatic amine 2 (2.0 mmol) and β-ketoester 3 (1.0 mmol) in MeOH (5

mL) was stirred for 20 min in the presence of trichloroacetic acid at room temperature. Next, the aromatic aldehyde 1 (2.0 mmol) was added and the reaction mixture was stirred for the time indicated in Table 2. The progress of the reaction was monitored by thin-layer chromatography (TLC), and the solvent system was used for the TLC ethyl acetate/n-hexane (2:7). After completion of the reaction, the thick precipitate was filtered off and washed with ethanol (3 × 2 mL) to give the pure product **4**.

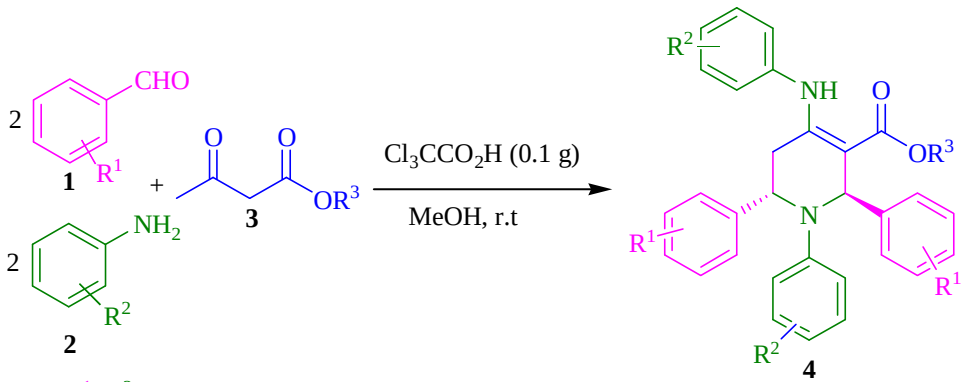
Spectral data of selected products are represented below:

Compound **4p**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.78 (1H, dd, *J*= 15.2, 2.4 Hz, H'-5), 2.87 (1H, dd, *J*= 15.2, 5.6 Hz, H"-5), 3.97 (3H, s, OCH_3), 5.14 (1H, d, *J*= 5.6 Hz, H-6), 6.40 (1H, s, H-2), 6.45 (2H, d, *J*= 7.2 Hz, ArH), 6.50 (2H, d, *J*= 8.0 Hz, ArH), 6.69 (1H, t, *J*= 7.2, ArH), 7.09-7.28 (13H, m, ArH), 10.30 (1H, s, NH).

Compound **4g**: ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.51 (3H, t, *J*=7.2 Hz, OC-CH_3), 2.37, 2.40 (6H, 2s, 2ArCH_3), 2.68 (1H, d, *J*= 15.2, 2.4 Hz, H'-5), 2.88 (1H, dd, *J*= 15.2, 5.6 Hz, H"-5), 4.34-4.41 (1H, m, OCH_aH_b), 4.47-4.55 (1H, m, OCHaHb), 5.10 (1H, d, *J*= 3.6 Hz, H-6), 6.28 (2H, dd, *J*= 8.4, 4.8 Hz, ArH), 6.37 (1H, s, H-2), 6.48 (2H, dd, *J*= 8.8, 4.0 Hz, ArH), 6.79-7.25 (12H, m, ArH), 10.25 (1H, s, NH).

Results and discussion

In our investigation we found that trichloroacetic acid (TCA) is an efficient catalyst which has been successfully utilized for the synthesis of highly functionalized piperidines via a one-pot reaction of aromatic amines, aromatic aldehydes and *β*-keto esters in MeOH at room temperature (scheme 1).



R^1, R^2: Me, OMe, NO_2, F, Cl, Br

R^3: Me, Et

Scheme 1. Synthesis of poly substituted piperidines in the presence of trichloroacetic acid as an effective catalyst.

To optimize the reaction conditions, various trial reactions were investigated with a combination of 4-methylbenzaldehyde, aniline and ethyl acetoacetate to obtain the best yield of product. We have noted that methanol is the best solvents for the present reaction among various other solvents, such as acetonitrile, ethanol and ethyl acetate. For this transformation, ethanol can be a second choice of solvent. Under solvent-free conditions, the product was obtained in a low yield (35%) that may be due to lack of effective interaction of reactants with the catalyst in the absence of solvent (Table 1).

Table 1. The solvent effect on catalytic function of (0.03 g) Trichloroacetic acid in the synthesis of piperidine [a].

Entry	Solvent	Yield (%)[b]
1	Ethanol	62
2	**Methanol**	**78**
4	Acetonitril	40
5	Ethyl acetate	38
6	No solvent	35

[a] Experimental conditions: 4-methyl benzaldehyde (2 mmol),aniline (2 mmol), and ethyl acetoacetate (1 mmol), rt. [b] Isolated yield.

For optimization of the amount of catalyst, it has also been observed that 0.10 g of Trichloroacetic acid gives the best result for the formation of product (Table 2).

Table 2. Investigation of the Amounts of trichloroacetic acid as catalyst for the synthesis of functionalized piperidine [a].

Entry	Catalyst (g)	Yield (%)[b]
1	0.01	66
2	0.03	78
3	0.05	81
4	0.07	84
5	0.09	88
6	**0.10**	**91**
7	0.12	91

[a] Experimental conditions: 4-methyl benzaldehyde (2 mmol), aniline (2 mmol), and ethyl acetoacetate (1 mmol) in 5 ml methanol as solvent , rt. [b] Isolated yield.

To explore the scope and generality of this five-component reaction under optimized conditions, a variety of aromatic aldehydes containing electron donating or electron withdrawing substituents in the aromatic ring such as -Me, -OMe, -F, -Cl, and -NO_2, were reacted with varying β-keto esters and a number of substituted amines (Table 3).

Table 3. Synthesis of functionalized piperidines using trichloroacetic acid.

Entry	R^1	R^2	R^3	Product	Time(h)	Yield(%)[a]	m.p. (lit. reported)[Ref.,[b]]
1	4-Me	H	Me	4a	4	94	212-213 (215-217)[26]
2	4-Me	H	Et	4b	5	91	227-230 (228-231)[26]
3	4-Me	4-Br	Me	4c	3	89	228-230 (230-232)[26]
4	4-Me	4-OMe	Me	4d	4	88	223-225 (225-226)[23]
5	4-Me	4-OMe	Et	4e	3	80	220-223 (221-224)[27]
6	4-Me	4-Me	Me	4f	6	85	204-205 (206-208)[26]
7	4-Me	4-F	Et	4g	11	78	186-187 (183-185)[34]
8	4-Me	3,4-di-Cl	Et	4h	3	84	172-174 (173-175)[34]
9	4-OMe	H	Me	4i	4	89	183-186 (187-188)[23]
10	4-F	H	Me	4j	8	89	177-179 (180)[10]
11	H	H	Me	4k	10	90	172-173 (169-171)[23]
12	H	H	Et	4l	8	78	172-174 (174-175)[23]
13	H	4-Br	Et	4m	3	86	198-201 (196-198)[35]
14	H	4-OMe	Et	4n	4	90	171-172 (179-181)[34]
15	3-Cl	H	Me	4o	6	85	219-220 (220-221)[27]
16	4-Cl	H	Me	4p	8	91	185-188 (189-191)[23]
17	4-NO_2	H	Me	4q	11	56	234-236 (239-241)[26]
18	3-NO_2	H	Me	4r	10	60	179-181 (178-181)[34]
19	H	4-Cl	Et	4s	2	94	195-198 (198-201)[34]
20	4-NO_2	H	Et	4t	4	89	253-255 (247-250)[27]
21	4-Cl	4-OMe	Et	4u	4	73	183-185 (184)[36]

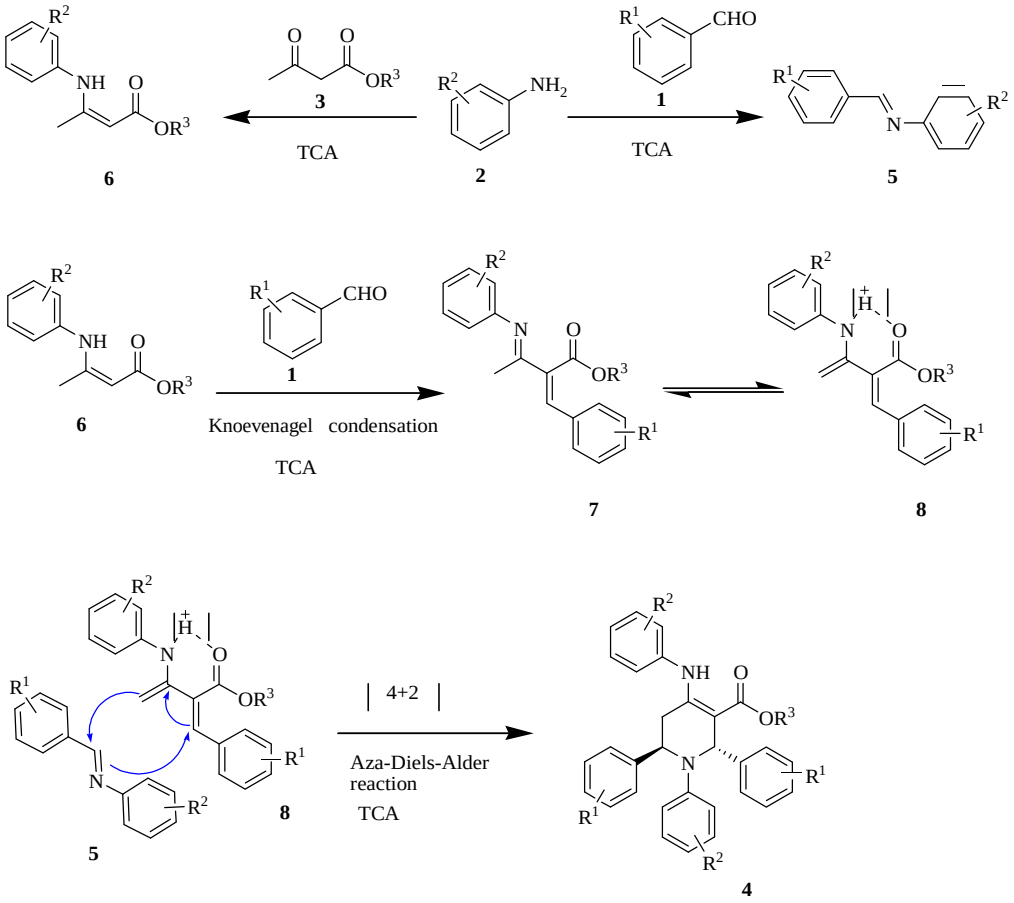
[a] Isolated yield. [b] The references of known products in the literature.

In general, aromatic aldehydes bearing electron-donating or electron-withdrawing functional groups at different positions reacted with trichloroacetic acid smoothly in the presence of substituted anilines to generate the corresponding products in moderate to good yields (Table 3).

Several aromatic amines were examined to study the generality and scope of the present protocol too. Various anilines with substituents such as -Me, -OMe, -F, -Cl, and -Br were treated with varying aromatic aldehydes and β-keto esters in presence of Trichloroacetic Acid as a catalyst. All these reactions underwent smoothly to provide the corresponding piperidine derivatives in good to exelent yields (Table 3). The present protocol was also examined for various 1,3-dicarbonyl compounds such as ethyl acetoacetate and methyl acetocetate with varying aromatic

aldehydes and anilines, where the desired piperidine derivatives were obtained in good yields as shown in Table 3.

The structures of all compounds were characterized by comparison of their IR and NMR spectra with authentic samples. Also, the relative stereochemistry of these piperidines has been confirmed by single X-ray crystallography analysis in previously reported literature [23-27], and the relative stereochemistry of the products in the present work was proved by comparison of spectroscopic data of some products with those authentic samples.



Scheme 2. Mechanistic pathway for five-component one-pot reaction leading to highly functionalized piperdine.

In the end, we turned our attention towards mechanistic studies for this transformation. On the basis of the proposed mechanism in the literature [23, 28- 31], possible mechanism for this five-component reaction is shown in Scheme 2. TCA can serve as a Brønsted acidic catalyst for the reaction of amine and acetoacetic ester or aldehyde to give enamine **6** or imine **5** respectively. The produced enamine in previous step reacts more with one equivalent of aldehyde under Knoevenagel condensation to form an intermediate **7** and reactive form 8. Finally, due to the diene core present in intermediate 8, the form **8** proceeds

towards an inter-molecular aza-Diels-Alder reaction with imine **5** (serves as dienophile) to generate a poly substituted piperidine.

Conclusion

In conclusion, we described a mild and efficient method for the synthesis of highly functionalized piperidines via a one-pot Multicomponent Reaction using Trichloroacetic Acid as a catalyst. The simple work-up, lack of need for column chromatography, short reaction times and very good yields make this method a valid contribution to the existing methodologies.

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