Research Article

# Ultrasound accelerated one-pot five component reaction: A Facile Access to Functionalized Piperidines

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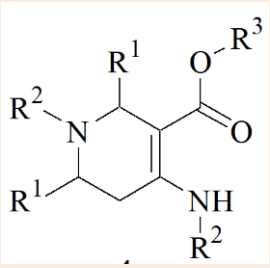
**Abstract**
A one-pot five-component coupling reaction between aromatic aldehydes, aromatic amines and a β-keto ester yielding functionalized piperidines is studied under sonic condition at 35 kHz. Cerium trichloride acts as a good catalyst and ultrasound acts as an excellent rate accelerator for this reaction resulting in good yield of the products.



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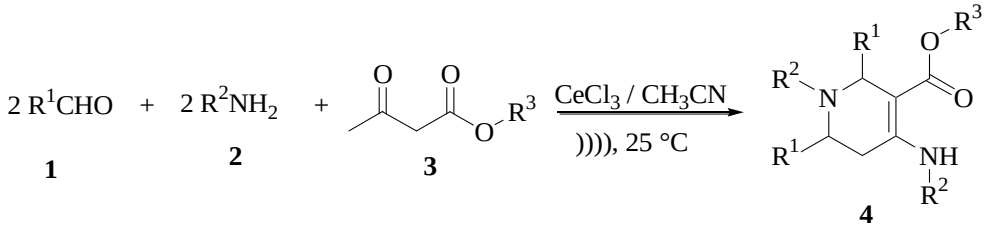
**Keywords:** aromatic aldehydes, aromatic amines, β-keto ester, coupling reaction, cerium trichloride, ultrasound.

## Introduction

Piperidine and poly-substituted piperidine rings are present in many natural products; they act as anti-hypertensive, anti-bacterial, anti-convulsant, anti-inflammatory, anti-HIV and anticancer drugs [1]. Apart from this, the 1,4-piperidine derivatives/analogous are found to posses enzyme inhibitory activity against farnesyl transferase, and are found to be useful in the treatment of Parkinson's disease and schizophrenia [2].

There are some reports on the preparation of poly-substituted piperidines *via* imino-Diels-Alder reactions [3], aza-Prins-cyclizations [4], intra-molecular Michael reactions [5], intra-molecular Mannich reaction onto iminium ions [6], tandem cyclopropane ring-opening/Conia-ene cyclization, [7] and methods involving multi-component strategies are available in the literature [8]. The limitations of the existing methods are; longer reaction durations and use of expensive and excess amounts of catalysts with lesser yields. Hence, a method which uses optimal catalyst load with lesser reaction time for this synthesis is always in demand.




**Scheme 1** Synthesis of highly functionalized pipridines

Sonochemistry is a branch of chemistry dealing with the chemical effects and applications of ultrasonic waves on chemical reactions. Sonochemical reactions contribute to sustainable chemistry as it is known to avoid/minimize the use of hazardous chemicals and solvents. Ultrasound accelerates the reactions, reduces the energy consumption and gives increased yields [9]. Based on our experience in the study of organic reactions under sonic condition [10], we have studied the present reaction in a sonic bath at 35 kHz (**Scheme 1**).

## Experimental

### *Materials and Instrument*

All starting materials were procured from commercial sources and were used without further purification, except aldehydes and amines which were distilled before use. All the reactions were carried out using SIDILU, Indian make sonic bath working at 35 kHz (constant frequency, 120 W) maintained at 25 °C by continuously circulating water. All the reactions were carried out in open vessels without mechanical stirring. Yields refer to yield of the isolated products. Melting points were measured on a Raaga, Indian make melting point apparatus. All the products are known and were compared on TLC with the authentic samples prepared by known methods [8].

### *General Procedure*

A mixture of aldehyde (2 mmol), aniline (2 mmol) and β-keto ester (1 mmol) was taken in acetonitrile (3 mL), mixed well, and to this, cerium chloride (20 mol %) was added. The contents were subjected to sonication for about 180 min (35 kHz, 25 °C). The reaction was monitored on TLC, after the completion of the reaction, the solid obtained was diluted with ethyl acetate (5 mL), washed with 10% HCl (5 mL), followed by saturated $NaHCO_3$ (2 × 5 mL) and water (2 × 5 mL). The organic layer was dried over sodium sulphate and evaporated to get the crude product, which was subjected to silica gel column chromatography for purification. In some cases the pure product was obtained directly after the evaporation of the solvent.

### *Spectral data*

**4a** [8]: White solid, mp 194–196 °C.
IR (KBr) $cm^{-1}$: ν 3859, 3427, 3020, 2360, 1653, 1592, 1498, 1257.
$^1$H NMR (300 MHz, $CDCl_3$ + $CCl_4$) δ: 2.73 (dd, *J* = 15.0 and 2.2 Hz, 1H, H-5a), 2.85 (dd, *J* = 15.0 and 5.4 Hz, 1H), 3.91 (s, 3H), 5.1 (brs, 1H, H-6), 6.25–6.28 (m, 2H), 6.42–6.50 (m, 2H), 6.54–6.59 (t, *J* = 7.2 Hz, 1H), 6.99– 7.09 (m, 5H), 7.13–7.29 (m, 10H), 10.29 (brs, 1H).
$^{13}$C NMR (50 Hz, $CDCl_3$ + $CCl_4$) δ: 34.0, 51.4, 55.5, 58.7, 98.5, 113.4, 116.7, 126.1, 126.2, 126.8, 127.0, 127.6, 128.7, 129.0, 129.2, 129.3, 129.7, 138.3, 143.2, 144.3, 147.3, 156.5, 168.9.
$C_{31}H_{28}N_2O_2$: calcd C, 80.84; H, 6.13; N, 6.08; found: C, 80.82; H, 6.15; N, 6.06.
ESMS (m/z): $[M+H]^+$ 460.

**4b** [8]: Light yellow solid, mp 153–156 °C.
IR (KBr) $cm^{-1}$: ν 3241, 2996, 2938, 2835, 1656, 1592, 1502, 1461, 1416, 1323, 1256, 1126, 1006.
$^1$H NMR (400 MHz, $CDCl_3$) δ: 2.74 (dd, *J* = 2.4 Hz, *J* = 14.8 Hz, 1H), 2.93 (dd, *J* = 5.6 Hz, *J* = 14.8 Hz, 1H), 3.67 (s, 6H), 3.71 (s, 6H), 3.81 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 5.01-5.02 (m, 1H), 6.33 (s, 3H), 6.37 (d, *J* = 6.8 Hz, 2H), 6.51 (s, 2H), 6.55 (d, *J* = 8.4 Hz, 2H), 6.62 (t, *J* = 7.2 Hz, 1H), 7.06 –7.16 (m, 5H), 10.24 (brs, 1H).
$^{13}$C NMR (100 MHz, $CDCl_3$) δ: 33.8, 51.0, 55.6, 56.0, 58.3, 60.9, 97.3, 103.2, 103.9, 113.1, 116.6, 126.1, 126.3, 128.9, 137.8, 138.5, 139.7, 146.9, 153.1, 153.4, 157.0, 168.5.
$C_{37}H_{40}N_2O_8$ : calcd C, 69.36; H, 6.29; N, 4.37.; found C, 69.21; H, 6.34; N, 4.51.
HRMS: calcd 641.2863; found: 641.2800.

**4c** [8]: White solid, mp 193–195 °C.
IR (KBr) $cm^{-1}$: ν 3442, 1659, 1591, 1498, 1447, 1384, 1251, 1186, 1070, 1013, 976, 826, 754, 698.
$^1$H NMR (400 MHz, $CDCl_3$) δ: 2.74 (d, *J* = 15.5 Hz, 1H), 2.82 (dd, *J* = 15 Hz, 3.0 Hz, 1H), 3.91 (s, 3H), 5.09 (s, 1H), 6.35 (s, 1H), 6.40 (d, *J* = 7.5 Hz, 2H), 6.45 (d, *J* = 7.5 Hz, 2H), 6.64 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.07 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.0 Hz, 2H), 7.24–7.36 (m, 5H), 10.25 (brs, 1H)
$^{13}$C NMR (100 MHz, $CDCl_3$) δ: 33.7, 51.2, 54.8, 57.4, 97.6, 112.9, 116.8, 125.8, 126.1, 127.8, 128.1, 128.4, 128.8, 129.0, 129.1, 132.2, 132.9, 137.6, 140.9, 142.4, 146.5, 156.0, 168.3.

$C_{31}H_{26}N_2O_2F_2$: calcd C, 74.98; H, 5.28; N, 5.64.; found C, 74.91; H, 5.11; N, 5.84.
HRMS (ESI): calcd 497.2241; found 497.2245

**4d** [8]: White crystal; mp 220–222 °C.
IR (KBr) cm $^{-1}$: ν 3259, 3206, 2947, 2862, 2361, 1653, 1592, 1517, 1452, 1318, 1257, 1077.
$^1$H NMR (400 MHz, $CDCl_3$) δ: 2.18 (s, 3H) 2.28 (s, 3H), 2.73–2.89 (m, 2H), 3.94 (s, 3H), 5.14 (s, 1H), 6.18 (d, *J* = 7.5 Hz, 2H), 6.45 (d, *J* = 8.3 Hz, 3H), 6.90–6.91 (m, 4H), 7.20–7.33 (m, 10H), 10.20 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 20.1, 20.9, 31.0, 51.8, 58.2, 59.6, 97.5, 112.9, 125.1, 126.0, 126.2, 126.5, 126.7, 127.1, 127.9, 128.2, 128.6, 129.5, 135.2, 135.7, 143.0, 144.3, 144.8, 156.7, 168.6.
$C_{33}H_{32}N_2O_2$: calcd C, 81.15; H, 6.64; N, 5.70 found C, 81.12; H, 6.60; N, 5.73.
ESI-HRMS: calcd 488.2463; found 511.2365[M+Na] $^+$.

**4e** [8]: White solid mp 174–175 °C.
IR (KBr) cm $^{-1}$: ν 3242, 3059, 2979, 1651, 1594, 1500, 1251, 1068.
$^1$H NMR (400 MHz, $CDCl_3$) δ: 1.47 (t, *J* = 7.2 Hz, 3H), 2.30 (s, 3H), 2.32 (s, 3H), 2.77 (dd, *J* = 2.4 Hz, *J* = 15.2 Hz, 1H), 2.87 (dd, *J* = 5.6 Hz, *J* = 15.2 Hz, 1H), 4.29–4.37 (m, 1H), 4.42–4.50 (m, 1H), 5.14–5.15 (m, 1H), 6.27–6.29 (m, 2H), 6.46 (s, 1H), 6.52 (d, *J* = 8.0 Hz, 2H), 6.61 (t, *J* = 7.2 Hz, 1H), 7.05–7.11 (m, 5H), 7.16-7.19 (m, 2H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.25–7.30 (m, 5H), 7.34 (d, *J* = 7.6 Hz, 2H ), 10.29 (brs, 1H).
$^{13}$C NMR (100 MHz, CDCl3) δ: 15.0, 21.2, 21.3, 33.8, 55.3, 58.4, 59.9, 98.4, 113.1, 116.3, 125.9, 126.0, 126.5, 126.6, 126.8, 127.3, 128.4, 128.8, 129.0, 129.1, 138.1, 143.0, 144.2, 147.2, 156.3, 168.4.
$C_{34}H_{34}N_2O_2$: calcd C, 81.24; H, 6.82; N, 5.57; found C, 81.23; H, 6.87; N, 5.54
HRMS: calcd 502.2620; found 502.2619.

## Results and Discussion

In order to optimize the reaction condition, the reaction of 4-fluorobenzaldehyde (2 mmol), aniline (2 mmol) and methyl acetoacetate (1 mmol) was treated with various Lewis acids under sonication without any solvent for about 5 h, since all the reactants are liquids we expected the reaction to proceed to completion and give better yields, however this did not happen, we obtained the product in 40% yield with cerium chloride (**Table 1**, entry 5). We then worked on a suitable solvent for this reaction and it was observed that, the reaction works well in acetonitrile as a solvent (**Table 2**, entry 4). To have a meaning full comparison we also carried out the reaction under silent condition with different catalysts and found that there was no product formation either under solvent-free condition or in a solvent.

**Table 1** Optimization of the catalyst for the one-pot five-component reaction.

| S.No | Catalyst (20mol %) | Time (h) | Silent condition[a] Yield (%) | Sonic condition[b] Yield (%) |
|---|---|---|---|---|
| 1 | Aluminium chloride | 5 | No product | No product |
| 2 | Ferric chloride | 5 | 10 | 10 |
| 3 | Zinc bromide | 5 | No product | 10 |
| 4 | Cuprous chloride | 5 | No product | No product |
| 5 | Cerium chloride | 5 | 10 | 40[¥] |

[a] Silent condition: stirring all the starting material without solvent and with the respective catalyst at 25 °C.
[b] Sonic Condition: mixing the starting materials without solvent and subjecting for sonication at 25 °C.
[¥] Isolated yield of the product

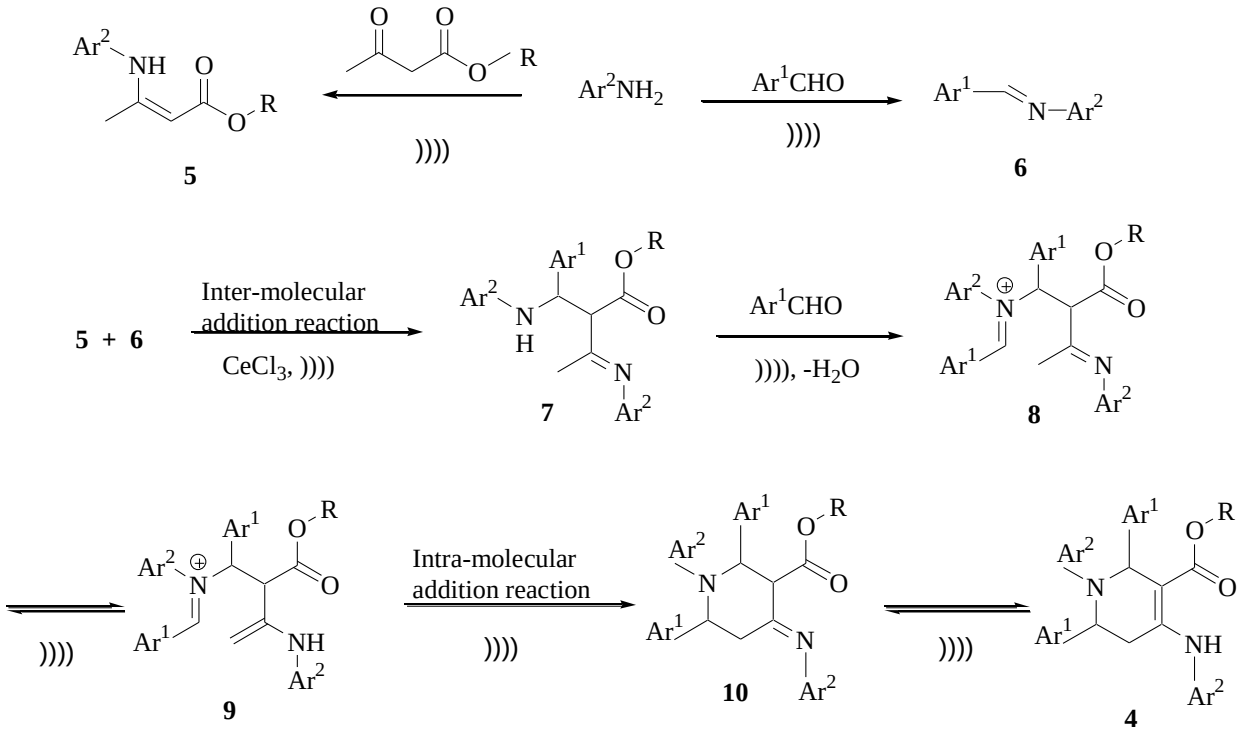
To study the scope and limitations of this one-pot five-component sonic reaction, a variety of aromatic aldehydes, aromatic amines and β-keto esters were studied and the results are given in **Table-3**. It is clear from this table that, both electron-donating and electron-withdrawing aldehydes the substrates did not have much effect of the yield of the products. Both aromatic aldehydes and aryl amines gave the respective products in very good yield.

In the present reaction, aniline is expected to react with a molecule of aromatic aldehyde and a molecule of β-keto ester to form the corresponding intermediates **5** (a β-enaminone) and **6** (an imine) respectively. The intermediates **5** and **6** are expected to get activated by cerium chloride on sonication and give the intermediate **7** by an inter-molecular addition reaction. The reaction between the intermediate **7** with a molecule of the aromatic aldehyde is expected to give **8**. The intermediate **8** may then tautomerize to **9** and undergo an intra-molecular addition to give **10** which may get tautomerized to **4** as shown in the **Scheme 2**.

**Table 2** Optimization of the solvent for the cerium chloride catalysed reaction.

| S.No | Solvent | Time (h) | Silent condition[a] Yield (%) | Sonic condition[b] Yield (%) |
|---|---|---|---|---|
| 1 | DCM | 5 | No product | No product |
| 2 | Water | 5 | No product | No product |
| 3 | Water: acetonitrile (1:1) | 4 | 20 | 40 |
| 4 | Acetonitrile | 2–3 | 50%[c] | 75[¥] % [product only] |

[a] Silent condition: stirring all the starting materials + 20 mol% $CeCl_3$ with solvent at 25 °C.
[b] Sonic Condition: mixing the starting materials with 20 mol% $CeCl_3$ and subjecting for sonication at 25 °C.
[c] intermediate **5** was obtained and increase in time did not make much difference.
[¥] Isolated yield of the desired product




**Scheme 2** A plausible mechanism

## Conclusions

To summarize, cerium chloride catalysed, atom-economic, one-pot five-component synthesis of highly functionalized piperidines under sonic condition is developed. Shorter reaction durations and reduced by-product formation, use of an energy efficient technique are the added advantages of this protocol.

**Table 3** Ultrasound assisted synthesis of highly substituted piperidines.

| Aldehyde ($Ar^1$) | Amine ($Ar^2$) | R | Product | Yield (%) [a,b] |
|---|---|---|---|---|
| $C_6H_5$ | $C_6H_5$ | Me | **4a** | 82 |
| 3,4,5-$(OMe)_3C_6H_2$ | $C_6H_5$ | Me | **4b** | 73 |
| 4-$FC_6H_4$ | $C_6H_5$ | Me | **4c** | 81 |
| $C_6H_5$ | 4-Me $C_6H_4$ | Me | **4d** | 85 |
| $C_6H_5$ | 4-$MeC_6H_4$ | Et | **4e** | 75 |

[a] Isolated yields.
[b] Products were confirmed on TLC by comparing with authentic samples prepared by the known method [8]

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## References:

[1] N. N. Mateeva, L. L Winfield, K. K Redda, *Curr. Med. Chem*., **2005**, 12, 551–556.
[2] P. S. Watson, B. Jiang, B. Scott, *Org. Lett*., 2000, 2, 3679–3681.
[3] H. Bin, A. M. Crider, J.P. Stables, *Eur. J. Med. Chem.*, **2001**, 36, 265–286.
[4] B. Beeler, V. S. Gadepalli, S. Rama, S. Steyn, N. Castagnoli Jr, J. M. Rimoldi, *Bioorg. Med. Chem*., **2003**, 11, 5229–5234.
[5] J. Barluenga, C. Mateos, F. Aznar, F. Valdes, *Org Lett.*, **2002**, 4, 3667–3670 .
[6] R. M. Carballo, M. A. Ramírez, M. L. Rodríguez, V. S. Martín, J. I Padrón, *Org. Lett*., **2006**, 8, 3837–3840.
[7] S. Fustero, D. Jiménez, J. Moscardó, S. Catalán, P. Carlos, *Org. Lett*., **2007**, 9, 5283–5286.
[8] F. A. Davis, B. Chao, R. Ashwin, *Org. Lett*., **2001**, 3, 3169–3172.
[9] T. P. Lebold, A. B. Leduc, M.A. Kerr, *Org. Lett*., **2009**, 11, 3770–3772.
[10] T. K. Abu, P. Tasneem, H. Lokman, Choudhury, *J. Org. Chem*., **2008**, 73, 8398–8402.
[11] P. A . Clarke, P. A. Zaytzev, A. C. Whitwood, *Tetrahedron Lett*., **2007**, 48, 5209–5212.
[12] M. Misra, S.K. Pandey, V. P. Pandey, J. Pandey, R. Tripathi, R. P. Tripathi, *Bioorg. Med. Chem*., **2009**, 17, 625–633.
[13] S. Mishra, R. Ghosh, *Tetrahedron Lett*., **2011**, 52, 2861–2897.
[14] J. W. Hong, P.M. Li, H.Z. Zhan, *ACS Comb. Sci*., **2011**, 13, 181–185.
[15] T. K. Abu, M.K. Musawwer, K.R.B. Kranthi, *Tetrahedron* **2010**, 66, 7762–7772.
[16] T. J Mason, *Chem. Soc. Rev*., **1997**, 26, 443–451.
[17] J. L. Luche, *Synthetic Organic Sonochemistry*, Plenum Press, New York, **1998**.
[18] P. Cintas, G. Cravotto, *Chem. Soc. Rev*., **2006**, 35, 180–196.
[19] B. Datta, M. A. Pasha, *Ultrason. Sonochem*., **2013**, 20, 303–307.
[20] S. Nagashree, M. A. Pasha, *Ultrason. Sonochem*., **2013**, 20, 810–814.
[21] S. Sudha, M. A. Pasha, *Ultrason. Sonochem*., **2012**, 19, 994–998.
[22] B. Datta, M. A. Pasha, *Ultrason. Sonochem*., **2012**, 19, 725–728.



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