Samarium triflet: Sm(OTf)₃ a simple and efficient catalyst for the synthesis of 1,4-dihydropyridine (Hantzsch pyridines)

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A B S T R A C T
1,4-Dihydropyridine synthesis has been carried out using Samarium triflet, as a catalyst. This protocol is applicable to a variety of aldehydes with β-ketoester and ammonium acetate to afford the corresponding Hantzsch pyridines in excellent yields. This multi component condensation took place very smoothly in acetonitrile reflux.

Keywords: Aldehydes, Di ketones, NH₄OAc, Samarium triflet, (Sm (OTf)₃), 1,4-dihydropyridine

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1. Introduction
Multicomponent condensation strategies offer significant advantages over conventional linear-type synthesis in providing products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry (1-6). In 1882, Arthur Rudolf Hantzsch, a German chemist, reported a cyclo condensation between ethyl acetoacetate, aldehyde and aqueous ammonium hydroxide to afford a heterocyclic system of 1,4-dihydropyridine; since then, it became familiar as the Hantzsch reaction [7,8]. The dihydro pyridine derivatives exhibit a large range of biological activities such as anticonvulsant, antitumor, antianxiety, vasodilator, bronchodilator, antidepressant, analgesic, hypnotic, anti-inflammatory and neuro protectants as well as platelet anti aggregatory agents [9-12]. Dihydropyridines are commercially used as calcium channel blockers...
Encouraged by the result obtained in a model reaction, benzaldehyde, β-(OTf) [20], ionic liquid [21], organo 3,5-sodium pentyl 155°C to 156°C. IR (KBr): υ = 3,342, 2,978, 2,931, 1,690, 1,651, 1,489, 1,453, 1,375, 1,300, 1,248, 1,212, 1,121, 1,091, 1,024, 825, 767 and 701 cm⁻¹ : 1H NMR (300 MHz, CDCl3): δ 1.25 (t, 6 H, J = 6.0 Hz), 2.35 (s, 6 H), 4.10 (q, 4 H, J = 6.0 Hz), 4.90 (s, 1 H), 5.52 (brs, 1 H, NH) and 7.08 to 7.25 (m, 5 H); 13C NMR (75 MHz, CDCl3): δ 168.3, 146.1, 143.9, 136.1, 118.8, 115.2, 109.2, 106.0, 101.2, 101.0, 83.8, 83.5, 43.5, 43.4, 34.9, 34.8, 28.3, 28.2, 24.9, 24.8, 21.9, 21.8 and 12.2 ppm.

Figure 1: Some biologically active compounds of 1,4-dihydropyridines

The tremendous biological activity of Hantzsch pyridines attracted many researchers and academicians. Hence, several attempts have been made to synthesize 1,4-dihydropyridine derivatives using various catalysts and reaction conditions such as triphenyl phosphine [13], CAN [14], hetero polyacids [15], Zn complex [16], phenyl boronic acid [17], magnesium perchlorate [18], cyanuric chloride [19], Yb(OTf) [20], ionic liquid [21], organo catalyst [22], L-proline [23], molecular iodine [24], tetra butyl ammonium hydrogen sulfate [25] and glycine-CeClO2.7H2O. But many of the methods are suffering from some drawbacks such as long reaction time, low yields, tedious workup procedures and the use of expensive catalysts. Therefore, the development of efficient protocol is still in demand. As part of our research program in developing new methodologies [28-31], we report here in a simple and efficient procedure for the synthesis of 1,4-dihydropyridine derivatives using samarium triflate as a catalyst. Samarium triflate is a non hygroscopic white solid that is highly soluble in water, a mild Lewis acid and a catalyst known for various organic transformations in the literature.

2. Materials and Methods
All the reaction mixtures were stirred megetically and were monitored by TLC using 0.25mm. E-Mercur Silica gel 60f254 percolated glass plates, which were visualized with UV light Melting points were recorded on a Bucher-R-535 apparatus (BUCHI india private Ltd., Mumbai, India) and were uncorrected. IR spectro were recorded on a perkin-Elmer FT-IR 240-c spectrophotometer (perkin Elmer Inc., Walthams, MA, USA) (IdORZBA) India private Ltd., New Delhi, india) in coely using TMS as internal standard Mass Specetro were recorded on a Finnigan MAT 1020 mass Spectrometer Thermo Scientific, Walthon, MA, USA) operating at 70er.

General procedure: A stirred mixture of aldehyde (1mmol), ethyl acetooacetate (2.2mmol) and ammonium acetate (1.1mmol) were stirred in acetonitrile (5 mL) in the presence of Sm (OTf)₃, for a period of appropriate time (3-5 hours) mentioned in the Table 1. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of reaction, as indicated by TLC, the solvent was removed under reduced pressure and the residue was extracted with ethyl acetate(2x10mL). The combined organic layer were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to obtain the crude products, which were purified by column chromatography using silica-gel (60-120mesh) by eluting with ethyl acetate-hexane (3:7) mixture. All the pure products were confirmed by their spectral data.

3. Results and Discussion
In a model reaction, benzaldehyde, β-ketoester and ammonium acetate were reacted in the presence of a catalytic amount (10 mol%) of Sm(OTf)₃ at acetoriterate reflux. The reaction was completed within 3h to afford the corresponding product, diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (3a), in excellent yields as shown in Scheme 1. Encouraged by the result obtained with benzaldehyde, we had applied this methodology to a variety of aldehydes such as aromatic, hetero aromatic and aliphatic aldehydes successfully. at acetoriterate reflux to give the corresponding 1,4-dihydropyridine derivatives in very good yields in 75% to 93%. All the products were confirmed by their Proton NMR (1H NMR), Infrared (IR) and Mass spectroscopy data.

Spectral data for all the compounds Diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (3a):
Solid, Melting point (Mp) 155°C to 156°C. IR (KBr): ν = 3,342, 3,061, 2,978, 2,931, 1,690, 1,651, 1,489, 1,453, 1,375, 1,300, 1,248, 1,212, 1,121, 1,091, 1,024, 825, 767 and 701 cm⁻¹ ; 1H NMR (300 MHz, CDCl3): δ 1.25 (t, 6 H, J = 6.0 Hz), 2.35 (s, 6 H), 4.10 (q, 4 H, J = 6.0 Hz), 4.90 (s, 1 H), 5.52 (brs, 1 H, NH) and 7.08 to 7.25 (m, 5 H); 13C NMR (75 MHz, CDCl3): δ 168.3, 146.1, 143.9, 136.1, 128.9, 118.8, 115.2, 109.2, 106.0, 101.2, 101.0, 83.8, 83.5, 43.5, 43.4, 34.9, 34.8, 28.3, 28.2, 24.9, 24.8, 21.9, 21.8 and 12.2 ppm.
129.2, 126.8, 103.9, 60.1, 40.0, 20.5 and 14.3; EIMS m/z (%): 328 (m+ 95), 284 (100), 256 (25), 252 (35), 225 (15), 219 (10), 195 (10), 181 (12), 173 (25), 131 (15) and 107 (20).

Table 1: Sm(OTf)_3-Catalyzed Synthesis of Hantzsch Pyridines (3a-j)

<table>
<thead>
<tr>
<th>S.No</th>
<th>Aldehyde (R)</th>
<th>Products</th>
<th>Time(min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td></td>
<td></td>
<td>20</td>
<td>86</td>
</tr>
<tr>
<td>b.</td>
<td></td>
<td></td>
<td>25</td>
<td>83</td>
</tr>
<tr>
<td>c.</td>
<td></td>
<td></td>
<td>25</td>
<td>82</td>
</tr>
<tr>
<td>d.</td>
<td></td>
<td></td>
<td>20</td>
<td>84</td>
</tr>
<tr>
<td>e.</td>
<td></td>
<td></td>
<td>30</td>
<td>75</td>
</tr>
<tr>
<td>f.</td>
<td></td>
<td></td>
<td>3.0</td>
<td>93</td>
</tr>
<tr>
<td>g.</td>
<td></td>
<td></td>
<td>4.0</td>
<td>89</td>
</tr>
</tbody>
</table>
4. Conclusions
In conclusion, we have demonstrated a simple and efficient three-component process for the synthesis of 1, 4-dihydropyridines by condensation of aldehyde, β-ketoester and ammonium acetate using samarium triflate as the catalyst. The notable features of this protocol are mild reaction conditions, simplicity in operation, improved yields, and cleaner reaction profiles.

5. References