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Aluminum Nitrate-catalyzed multi component, one-pot synthesis of 1, 5-benzothiazepines under mild conditions

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2,3- dihydro1,5-benzothiazepine derivatives have been synthesized by the reaction of 2-aminothiophenol, aromatic aldehydes and 1,3- dicarbonyl compounds in the presence of aluminum nitrate as an efficient catalyst via one-pot multi-component reaction conditions. The presented protocol afforded the 1,5-benzothiazepine derivatives 4(a-h) in good yield at the cost of shorter reaction time.

Keyword: Aluminum Nitrate, 1, 5-benzothiazepines, 2-aminothiophenol, aromatic aldehydes, 1, 3-dicarbonyl compounds.

1. Introduction

Heterocyclic compounds containing nitrogen and sulphur such as benzodiazepines and benzothiazepines have received considerable attention in recent years. A broad spectrum of biological and pharmacological properties associated with benzothiazepines attracted the attention of the chemists involved in the business to develop potent drugs against various threatening diseases. The pharmacological properties include antimicrobial [1-4], antihypertensive activities [5], anticancer activity [6, 7] hemodynamic effects [8], antiulcer activity [9, 10] and spasmolytic activities [11-15] have also been reported.

The benzothiazepine nucleus justified its importance in the discovery of potent drugs. Now days, 1,5-benzothiazepin-2-ones are being used as a coronary vasodilators (e.g. Diltiazem), as calcium antagonists (e.g. Clentiazem) and as anti-depressant (e.g. Thiazesim**,** Quetiapine fumarate) [16].

One of the most widely employed methods for the preparation of 1,5-benzothiazepines involves the reaction of *o*-aminothiophenol with chalcones under acidic or basic conditions.

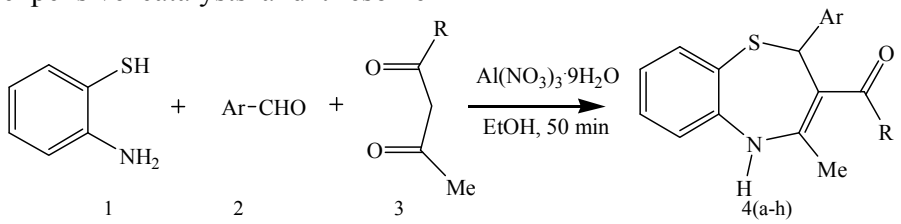
In addition to this, various reports are available for the synthesis of 1,5-benzothiazepines by the reaction of *o*-aminothiophenol, aromatic aldehydes and 1,3-dicarbonyl compounds utilizing different catalytic systems and reaction conditions in multistep process [17-23].

To contribute our efforts for the synthesis of such biological hits and environmentally benign protocols [24-25], we investigated the synthesis of 2, 3-dihyro-1,5-benzothiazepines by the reaction of *o*-aminothiophenol, aromatic aldehydes and 1, 3-dicarbonyl compounds via one-pot multi-component reaction conditions catalyzed by aluminum nitrate.

2. Results and Discussions

Literature data acknowledged us the most studied method for the synthesis of 1,5-benzothiazepines

that is via reaction of 2-aminothiophenol, aromatic aldehydes and 1,3-dicarbonyl compounds using various catalytic systems and reaction conditions in three steps. The use of hazardous and expensive catalysts and tiresome reaction conditions prompted us to develop an efficient method for the synthesis of 1, 5-benzothiazepines.



Scheme 1: Synthesis of 1,5-benzothiazepines catalyzed by Aluminum nitrate

A model reaction was carried out to evaluate the methodology using aluminum nitrate as catalyst with equimolar mixture of 2-aminotiophenol, benzaldehydes and 2,4-pentanedione. The reaction was carried out at reflux temperature using hot plate magnetic stirrer in 95 % ethanol as a solvent medium for 50 min. The reaction mixture was stirred for an hour at room temperature. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the reaction mixture was poured onto crushed ice, the solid get separated, which was washed with plenty of water and acetic acid, then filtered.

The crude product obtained was dried and recrystallized with suitable solvent affording 2,5-dihydro-4-methyl-2-phenyl-3-acetyl-1,5-benzothiazepine (4a) in good yield (60%). We did not observed any remarkable change in regard with reaction time and percentage yield on increasing the amount of catalyst only 10 mol % of the aluminum nitrate is sufficient for the successful completion of the reaction. The same experimental procedure is employed for the preparation of remaining derivatives. We observed the methodology suitable for various aromatic aldehydes, the results are summarized in (Table I). The structures of the synthesized compounds 4(a-h) were established on the basis of spectral analysis data (IR, ^{1}H NMR and Mass).

3. Experimental Section:

The required chemicals were purchased from S.D. fine chemicals (India). Melting points were determined by an open capillary method and are uncorrected. The IR spectra were recorded on Shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra were recorded using $CDCl_3$ or DMSO-d_6 as solvent and TMS as an internal standard either on Brucker 300 MHz or 400 MHz NMR spectrophotometer. The chemical shift values are expressed in part per million (ppm). The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) technique on silica gel plate using petroleum ether and ethyl acetate (7:3 v/v) as an eluent.

3.1 Methods:

General Procedure for the Synthesis of 2,5-dihydro-4 methyl-2aryl-3acetyl- 1,5-benzothiazepines 4(a-h) from 1,3-dicarbonyl Compounds:

An equimolar mixture of 2-aminothiophenol , substituted benzaldehydes and 1,3- dicarbonyl compounds, Aluminum Nitrate (10 mol%) in 20 ml ethyl alcohol was refluxed on hotplate magnetic stirrer for 50 min which was further stirred for next 1 h. Completion of the reaction was monitored by TLC [eluent ; ethyl acetate : pet. ether (3:7)]. After completion of the reaction, the reaction mixture was poured onto crushed ice, the solid crude product was washed with water and aqueous AcOH. The crude product was purified by recrystallisation with suitable solvent. The corresponding 1, 5-benzothiazepines 4(a-h)

were obtained in good yield (60-65%) (Scheme-I). The results are summarized in Table-I.

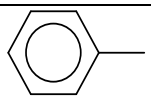
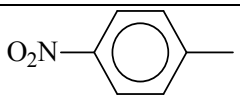
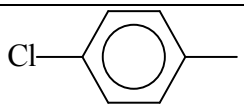
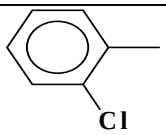
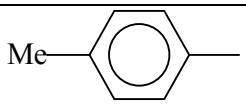
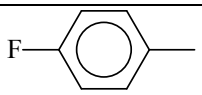
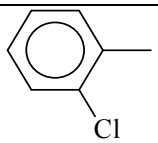
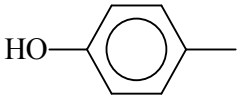
3.2 Spectral data for selected compounds:

2,5-Dihydro-4-methyl-2-phenyl-3-acetyl-1,5-benzothiazepine (4a)
Yield: 60 %; m.p=167^{0}C;
IR KBr (cm^{-1}): 1708 (CO), 1614 (C=C);
^{1}H NMR (DMSO-d$_6$), ð (ppm): 7.0-8.0(9H, m), 2.61 (1H, s), 4.4 (1H, s), 2.29 (3H, s), 1.3 (3H, s); MS (m/z): 295 (M$^+$)

2,5-Dihydro-4-methyl-2(4-nitrophenyl) -3-acetyl-1,5-benzothiazepine (4b)
Yield: 65 %; m.p=161^{0}C;
IR KBr (cm^{-1}): 1720 (CO), 1610 (C=C);
^{1}H NMR (DMSO-d$_6$), ð (ppm): 8.4-9.4(8H, m), 5.7 (1H, s), 4.8 (1H, s), 3.0 (3H, s), 1.7 (3H, s).
MS (m/z): 340 (M$^+$)

2,5-Dihydro-4-methyl-2(4-chlorophenyl) -3-acetyl-1,5-benzothiazepine (4c)
Yield: 62 %; m.p.: 117^{0}C;
IR KBr (cm^{-1}): 1715 (CO), 1600 (C=C);
^{1}H NMR (DMSO-d$_6$), ð (ppm): 7.8-8.4(8H, m), 3.7 (1H, s), 4.0 (1H, s), 2.20 (3H, s), 1.7 (3H, s).

Table 1: One-pot synthesis of 2,5-dihydro-4-methyl-2-aryl-3-acetyl-1, 5-benzothiazepine Catalyzed by Aluminum nitrate:

Sr. No	Ar	R	M.P (ºC)	Yield (%)
4a		Me	167	60
4b		Me	161	65
4c		Me	117	62
4d		Me	149	62
4e		OEt	155	64
4f		OEt	136	65
4g		OEt	135	65
4h		OEt	161	62

4. Conclusion

In summary, we have demonstrated here an efficient one-pot, multi-component synthesis of 2,3-dihydro-1,5-benzothiazepines 4(a-h) catalyzed by aluminum nitrate under mild conditions. The methodology can produce fruitful results for the synthesis of a wide variety of 1,5-benzothiazepine derivatives in good yields.

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