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An Improved Procedure for the Synthesis of 1,5-Benzothiazepines Using Ceric Ammonium Nitrate (CAN)

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ABSTRACT. A mild and efficient procedure for the synthesis of various 1,5-benzothiazepines were developed. This method provides an easy access for preparation of 1,5-benzothiazepine derivatives in the presence of 10 mol% catalyst of CAN under ultrasonic irradiation. This method provided clean conversion, mild reaction condition, no use of toxic solvent and shorter reaction time compared to other reported method.

Key words: 1,5-Benzothiazepine, CAN, Chalcone, Catalysis, Ultrasound irradiation

INTRODUCTION

The 1,5-benzothiazepines scaffold is extremely versatile and features in a great number of famous drugs. Currently 1,5-benzothiazepines are being used as coronary vasodilators, as calcium antagonists and as antidepressants. The 1,5-benzothiazepine moiety is a privileged class of pharamacophore, as compounds bearing this structural unit possess a broad spectrum of biological activities such as anti-convulsant,[1] Ca^{+2} channel antagonist,[2] anti-anginal,[3] anti HIV,[4] squalene synthetase inhibitor,[5] V_2 arginine vasopressin receptor antagonist,[6] HIV-1 reverse transcriptase inhibitor,[7] etc. These have stimulated interest to develop new methodologies for the synthesis of 1,5-benzothiazepines.

The common strategy for the construction of the 1,5-benzothiazepine moiety is the reaction of 1,3-diarylprop-2-enones **1** with *o*-aminothiophenol **2**.[8] The various reported methodologies involve the use of inorganic solid supports such as alumina, silica gel and clay under microwave irradiation,[9-12] acetic acid or TFA,[13,14] HCl,[15] piperidine.[16] The alternate tandem reductive cleavage–condensation protocol involving the in situ generation of **2** by reduction of the corresponding disulfide followed by condensation with **1** requires additional reagents such as stoichiometric amount of triphenylphosphine, and in most of the cases affords the uncyclized thia-Michael adduct as the final product and the 1,5-benzothiazepines are formed only in the case of activated (methoxy or methyl substituted) bis-2-aminophenyldisulfides. Many of these processes suffer from limitations such as requiring harsh conditions, expensive reagents, high catalyst loading, corrosive reagents, or toxic ions; low yields and occurrence of several side reactions. It is also necessary to find a milder, selective, nonhazardous and inexpensive reagent and there is necessity to develop a more effective synthetic procedure for the synthesis of 1,5-benzothiazepines.

Ultrasound accelerated chemical reactions are well known and proceed *via* the formation and adiabatic collapse of transient cavitation bubbles. Ultrasound irradiation has been demonstrated as an alternative energy source for organic reactions ordinarily accomplished by heating. Many homogeneous and heterogeneous reactions can be conducted smoothly by sonication to provide improved yields and increased selectivities.[17] Therefore ultrasound irradiation has been established as an important technique in organic synthesis. So one of the thrust areas for achieving this target is the environmentally friendly i.e. reaction under ultrasound irradiation.

The art of performing efficient chemical transformation coupling two or more components in a single operation by a catalytic process avoiding stiochiometric toxic reagents, large amount of solvents and expensive purification techniques is the fundamental target of modern organic synthesis. Ceric (IV) ammonium nitrate (CAN) is a convenient and widely used reagent for affecting a wide array of synthetic transformations due to its many advantages such as solubility in organic solvents, low toxicity, high reactivity, and ease of handling. Although Ce (IV) derivatives are generally employed as one electron oxidants, the use of CAN as Lewis acid in C-C bond forming reaction has attracted great deal of attention.[18]

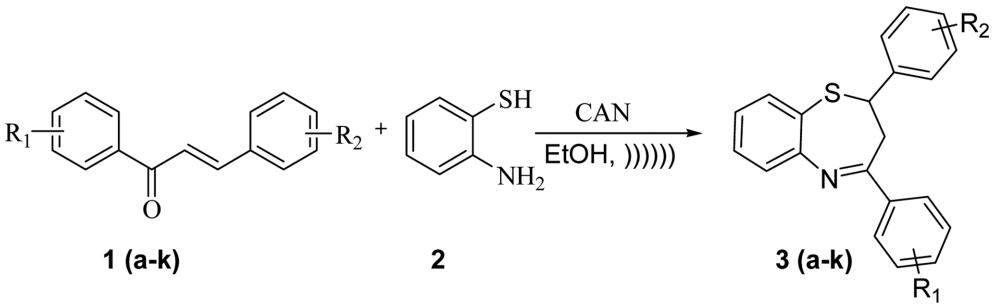
In continuation of research work to synthesized the bioactive heterocycles and synthetic methodologies.[19-20] Herein, we report a simple, mild and efficient protocol for synthesis of 1,5-benzothiazepines using CAN in ethanol under ultrasonic irradiation.

RESULT AND DISCUSSION

In the present work firstly, we have optimized the reaction condition, effect of solvent and catalyst concentration. We have developed methodologies for the synthesis of 1,5-benzothiazepines from chalcone with *o*-aminothiophenol using CAN. Which makes use of simple reaction condition over the reported methods in (*Scheme* 1). Primarily, α,β-unsaturated carbonyl compounds or chalcones were prepared by the well-known Claisen-Schmidt condensation of substituted acetophenones and substituted aldehyde by using alcoholic KOH at room temperature.[21] At the outset, the condensation of chalcone **1a** and *o*-aminothiophenol **2** was carried out in a typical general experimental procedure and the effects of various solvent and concentration of catalyst. Firstly, we optimized this reaction in various solvents such as Water, Toluene, DMSO and Ethanol were examined but, we have not get satisfactory results in reaction time and yield of products. But the reaction in EtOH gave better result as compared to other solvents. In EtOH, the reaction completed within 32 min to gave 1,5-benzodiazepines in 93% yield.

Further, we have optimized the catalyst concentration on model reaction. We initially tested the reaction of chalcone **1a** with *o*-aminothiophenol at 60-65 °C in absence of catalyst. However, in the absence of CAN, the reaction did not proceed after extensive long reaction times (8-10h) with lower yield. When the 2 mol% of CAN was used, the conversion was 70%. When the 6 mol% of CAN was used the conversion reached upto 85%. The subsequent condition optimization experiments revealed that the 10 mol% of catalyst amount was sufficient to complete the reaction. This methodology is simple with good to excellent yields (93%), higher amount of catalyst did not affect the reaction times and yields. The reaction proceeds smoothly at 60-65 °C temperatures under ultrasonic irradiation with 10 mol% of catalyst and completes within 32 min without any undesirable side-product being observed. The best result obtained at 10 mol% (CAN) in ethanol at 32 min under ultrasonic irradiation with 93% yield. After optimizing the conditions, the generality of this method was examined by the reaction of several substituted chalcones **1 (b-h)** with *o*-aminothiophenol. So we have tried this reaction of *o*-aminothiphenol with three principal heterocyclic chalcones **1 (i-k)** by applying the same experimental conditions. On these chalcones reaction was proceed smoothly as compare to the aromatic chalcones and gave the reaction products in shorter time span and yields.

The reactions were compatible with various substitutents such as F, NO_2, Cl, Me, and OMe. No competitive



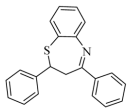
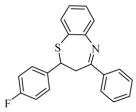
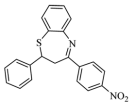
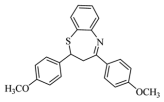
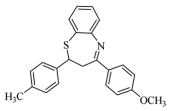
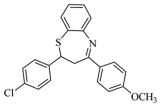
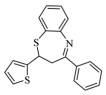
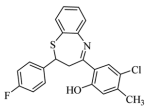
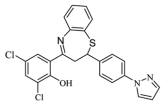
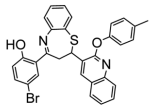
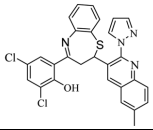
***Scheme* 1.** Synthesis of 1,5-benzothiazepines from chalcones and *o*-aminothiophenol.

***Table* 1.** Optimization of solvent effect on the model reaction[a]

Entry	Solvent	With US[a]		Without US[b]	
		Time (min)	Yield[c] (%)	Time (min)	Yield[c] (%)
1	Water	32	25	150	20
2	Toulene	32	34	150	28
3	DMSO	32	72	150	65
4	Ethanol	32	93	150	68

[a]Reaction of chalcone with *o*-aminothiophenol in presence of CAN (10 mol%) under ultrasonic waves; [b]Reaction of chalcone **1a** with *o*-amonothiophenol **2** in presence of CAN (10 mol%) under reflux condition; [c]Isolated yield

***Table* 2.** Synthesis of 1,5-benzothiazapines using CAN as a catalysts under ultrasonic irradiation

Compound	Structure	Time		Yield[a] (%)		Melting point(°C)
		With US (min)	Without US (hr)	With US	Without US	
3a		32	8-9	93	71	113-117[22]
3b		30	6-8	89	64	102-103[22]
3c		32	8-9	86	72	115-117[22]
3d		37	8-10	79	64	106-108[22]
3e		34	6-7	81	62	109-111[22]
3f		30	7-9	87	68	132-134[22]
3g		38	9-10	91	70	123-126[22]
3h		28	5-6	89	71	174-177[b]
3i		34	1-3	87	75	188-189[b]
3j		31	2-4	85	71	146-147[b]
3k		30	2-4	87	68	252-253[b]

Compounds **3 (a-g)** characterized by their spectroscopy method IR, ^{1}H NMR, Mass and melting point from authentic sample. [a]Isolated Yield. [b]Newly synthesized compound **3 (h-k)**.

nucleophilic either cleavage were observed for the substrate having an aryl, Me or OMe groups. In case of electron donating substitutents resulted in longer reaction times whereas electron withdrawing substitutents requires shorter time for the complete reaction (*Table* 2). However, no significant substituent effect was found in case of heteroaryl aldehydes.

The yield of isolated products, after recrystallization were found to be excellent. The results showed that the efficiency and yield of the reaction was good as compared with other conventional methods. This method reduces both the cost of product and environmental pollution; thus, considered as a green chemistry. This method offers significant advantages over the reported method include the fact that (i) the reaction is simple to execute; (ii) the product are isolated in good to excellent yields; (iii) the

work-up is simple; (iv) the reaction time is short (32-38 min); (v) the products are obtained in excellent purity.

The newly synthesized compounds were characterized by (IR, ^{1}H NMR and MS) which shows the desired characteristic peak to conformation of the structure of compound. This comparison revealed that the compounds synthesized by this newly developed method were exactly identical in all aspects to the reference compounds.[22]

CONCLUSION

In summary, we have developed a new methodologies for the synthesis of 1,5-benzothiazepines by ultrasound irradiation. Our method has many advantages over existing methods, including high yield, simple work-up, shorter reaction span, no side reactions no critical purification method. This procedure represents a convenient, economic and environmentally friendly process for the synthesis of 1,5-benzothiazepines.

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REFERENCES

1. Sarro, G. D.; Chimirri, A.; Sarro, A. D.; Gitto, R.; Grasso, S.; Zappala, M. *Eur. J. Med. Chem.* **1995**, *30*, 925.
2. (a) Shinichi, Y.; Yoshikazu, M.; Katsuji, M.; Yoshinori, I.; Yasuhiko, O.; Ryuzo, Y.; Tadashi, N.; Hiroyasu, S. *J. Org. Chem.* **1996**, *61*, 8586. (b) Kurokawa, J.; Adachi Akahane, S.; Nagao, T. *Eur. J. Pharmacol.* **1997**, *325*, 229.
3. Miyata, O.; Tetsuro, S.; Ichiya, N.; Takeaki, N. *Tetrahedron* **1997**, *53*, 2421.
4. Grandolini, G.; Perioli, L.; Ambrogi, V. *Eur. J. Med. Chem.* **1999**, *34*, 701.
5. Yang, X.; Buzon, L.; Hamanaka, E.; Liu, K. K.-C. *Tetrahedron: Asymmetry* **2000**, *11*, 4447.
6. Urbanski, M. J.; Chen, R. H.; Demarest, K. T.; Gunnet, J.; Look, R.; Ericson, E.; Murray, W. V.; Rybczynski, P. J.; Zhang, X. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4031.
7. Di Santo, R.; Costi, R. *Farmaco* **2005**, *60*, 385.
8. Lévai, A. *J. Heterocycl. Chem.* **2000**, *37*, 199.
9. Kodomari, M.; Noguchi, T.; Aoyama, T. *Synth. Commun.* **2004**, *34*, 1783.
10. Patel, V. M.; Desai, K. R. *Indian J. Chem. Sect. B: Org. Chem. Incl. Med. Chem.* **2004**, *43*, 199.
11. Katritzky, A. R.; Rogovoy, B. V.; Chassaing, C.; Vvedensky, V.; Forood, B.; Flatt, B.; Nakai, H. *J. Heterocycl. Chem.* **2000**, *37*, 1655.
12. Dandia, A.; Sati, M.; Loupy, A. *Green Chem*. **2002**, *4*, 599.
13. (a) Lévai, A. *J. Heterocycl. Chem.* **2004**, *41*, 399. (b) Levai, A. *J. Heterocycl. Commun.* **2002**, *8*, 227. (c) Lévai, A. *J. Heterocycl. Commun.* **2002**, *8*, 375.
14. Micheli, F.; Degiorgis, F.; Feriani, A.; Paio, A.; Pozzan, A.; Zarantonello, P.; Seneci, P. *J. Comb. Chem.* **2001**, *3*, 224.
15. Pant, S.; Singhal, B.; Upreti, M.; Pant, U. *Molecules* **1998**, *3*, 159.
16. (a) Upreti, M.; Pant, S.; Dandia, A.; Pant, U. C., *Sect. B: Indian J. Chem.* **1997**, *36*, 1181 (b) Pant, S.; Sharma, A.; Sharma, S. K.; Pant, U. C.; Goel, A. K., *Sect. B: Indian J. Chem.* **1996**, *35*, 794.
17. (a) Gaplovsky, A.; Gaplovsky, M.; Toma, S.; Luche, J. L. *J. Org. Chem*. **2000**, *65,* 8444. (b) Suslick, K. S. In *ultrasound, it's Chemical, physical and biological effects*; VCH: Weinheim, 1988. (c) Rajagopal, R.; Jarikote, D. V.; Srinivasan, K .V. *Chem. Commun*. **2002**, 616. (d) Deshmukh, R. R.; Rajagopal, R.; Srinivasan, K. V.; *Chem. Commun*. **2001**, 1544.
18. (a) Hwu, J. R.; King, K. Y. *Curr. Sci*. **2001**, *81,* 1043. (b) Nair, V.; Panicker, S. B.; Nair, L. G.; George, T. G.; Augustine, A. *Synlett*. **2003**, 156. (c) Dhakshinmoorty, A. *Synlett*. 3014. (d) Varala, R.; Enugala, R.; Sreelatha, N. S. R.; Adapa, S. R. *Synlett*. **2006**, 1009. (e) Varala, R.; Sreelatha, N.; Adapa, S. R. *Synlett*. **2006**, 1549. (f) Nair, V.; Mathew, J.; Prabhakaran, J. *Chem. Soc. Rev.* **1997**, 127. (g) Nair, V.; Balagopal, L.; Rajan, R.; Mathew, J. *Acc. Chem. Res*. **2004**, *21*. (h) Nair, V.; Deepathi, A *Chem. Rev.* **2007**, 1862.
19. (a) Joshi, R. S.; Mandhane, P. G.; Diwakar, S. D.; Dabhade, S. K.; Gill, C. H. *Bioorg. Med. Chem. Lett.* **2010**, *20,* 3721. (b) Jadhav, G. R.; Shaikh, M. U.; Shingare, M. S.; Gill, C. H. *J. Het. Chem.* **2008**, *45*, 1287. (c) Jadhav, G. R.; Kale, R. P.; Shaikh, M. U.; Ghawalkar, A. R.; Nagargoje, D. R.; Shiradkar, M.; Gill, C. H. *Bioorg. & Med. Chem. Lett*. **2008**, *16,* 6244.
20. (a) Joshi, R. S.; Mandhane, P. G.; Diwakar, S. D.; Gill, C. H. *Ultrason. Sonochem*. **2010**, *17* 298. (b) Mandhane, P. G.; Joshi, R. S.; Nagargoje, D. R.; Gill, C. H. *Tett. Letts*. **2010**, *51,* 1490. (c) Mandhane, P. G.; Joshi, R. S.; Nagargoje, D. R.; Gill, C. H. *Tett. Lett*. **2010**, *51,* 3138.
21. Wattanasin, S.; Murphy, W. S. *Synthesis* **1980**, *8*, 647
22. Sharma, G.; Kumar, R.; Chakraborti, A. K. *Tetrahedron Lett.* **2008**, *49*, 4269.
23. ***General procedure for the synthesis of 1,5-Benzothiazepines:*** In a typical experiment, CAN (10 %mol) was dissolved into the mixture of chalcone (10 mmol) and *o*-aminothiophenol (10 mmol) in ethanol (5 ml) in a 25 ml round-bottom flask equipped with a stopper. The reaction mixture was irradiated under ultrasonication at 60-65 °C for the desired time as shown in (*Table* 1). The completion of reaction was monitered by TLC (20:80 Ethyl acetate: Petroleum ether as eluent). After completion, the reaction mixture was poured over crushed ice & the solid obtained was filtered, dried and recryalisation in appro-

priate solvent to afford the corresponding 1,5-benzothiazepines. Spectral data of principal compounds. **(3h)**: IR (KBr): 3417, 2864, 1600, 1539, 1504, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.38 (s, 3H, CH_3), 3.01 (apparent triplet, *J* = 12Hz, 1H, C_3-H), 3.28 (dd, *J* = 12.4 Hz & 4.4 Hz, 1H, C_3-H), 5.03 (dd, *J* = 11.5 Hz & 4.4 Hz, 1H, C_2-H), 6.90-7.04 (m, 3H, Ar-H), 7.20-7.25 (m, 1H, Ar-H), 7.28-7.31 (m, 3H, Ar-H), 7.42-7.51 (m, 2H, Ar-H), 7.61 (d, *J* = 7.4 Hz, 1H, Ar-H); MS (M+): *m/z* 396.5. **(3i):** IR (KBr): 3400, 1600, 1533, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.11 (dd, *J* = 4.0 Hz,1H), 3.36 (dd, *J* = 4 Hz, 1H), 5.13 (dd, *J* = 4 Hz, 1H), 6.42 (t, *J* = 2 Hz, 1H, Ar-H), 7.28-7.35 (m, 10H, Ar-H), 7.52 (d, *J* = 2.2 Hz, 1H, Ar-H),7.91 (d, *J* = 2.2 Hz, 1H, Ar-H), 15.67 (s, 1H, D_2O exchangeable); MS (M+): *m/z* = 466 (M+1), 468 (M+3). **(3j):** IR (KBr): 3404, 1623, 1600, 1253 cm^{-1}; ^1H NMR (DMSO, 400 MHz): δ 2.33 (s, 3H, -CH_3), 3.29 (t, *J* = 11.6 Hz, 1H), 3.42 (dd, *J* = 12.4 Hz & 3.91 Hz, 1H), 4.99 (dd, *J* = 10.2 Hz, 1H), 8.16 (m, 16H, Ar-H), 8.74 (s, 1H, Ar-H); (M+): *m/z* = 565.0 (M+1), 533 (M+3). **(3k)** IR (KBr): 3142, 1653, 1604, 1592, 1035; cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.36 (s, 3H, CH_3), 3.01 (apparent triplet, *J* = 12Hz, 1H), 3.26 (dd, *J* = 12.2 Hz & 4.2 Hz, 1H), 5.01 (dd, *J* = 11.5 Hz & 4.3 Hz, 1H), 6.31 (t, *J* = 2.2 Hz, 1H, Ar-H), 7.00-8.01 (m, 12H, Ar-H), 12.19 (s, 1H, -OH, D_2O exchangeable); MS (M+): *m/z* = 532 (M+1), 534 (M+3).