Research Article

Green Efficient Synthesis of Aryl Thioamides Using Ultrasound: A Comparative Study

BHAVIN R. PATEL*, DIPEN H. DESAI, JIGNESH P. RAVAL
Department of Chemistry, Uka Tarsadia University, Maliba Campus, Bardoli-Mahuva Road, Bardoli, Surat-394601, Gujarat, (INDIA).

ABSTRACT

Expeditious greener approach for the synthesis of aryl thioamide derivatives is reported. The synthetic strategy involves the reaction of aromatic carboxylic acids and thiourea in presence of Ammonium cerric nitrate as a catalyst with or without the help of ultrasound. A comparative study was done between both the synthetic methodologies. It was found that the high yield of the product in shorter reaction time was achieved in ultrasound technique.

Keywords: Sonication, arylthioamide, Ammonium cerric nitrate**.**

1. INTRODUCTION

The general structure of thioamide is R_1-CS-NR_2R_3, where R_1, R_2, and R_3 are aryl organic functionalities. They are analogous to amides with larger rotational barrier due to multiple bond character along the C-N bond [1]. The thioamide and thioureido group is a versatile building block in the synthesis of heterocycles. They are used as raw material to synthesise arylthiazoles, substituted amidenes, benzothiazines, benzodiazocines, benzotriazocines, benzothiadiazocines, quinazolines etc. They are also used in rubber vulcanization as accelerators, as inhibitors of metal corrosion, and in electroplating industries as polyolefin stabilizers [2-5]. Similarly they are important biological active pharmacophore in antitubercular drug, antitumor agent, anthelmintics, central nervous system depressant etc [6]. Synthetic methodology [7-10] for thioamide derivatives are involves the reaction of nitriles with thioacetic acid, phosphorus pentasulfide, ammonium phosphorodithioate etc.

Ammonium cerric nitrate has been found to be a versatile reagent for the construction of carbon-carbon and carbon-heteroatom bonds via radical intermediates [11]. Various organic transformation catalysed by ammonium cerric nitrate is not only based on its electron transfer capacity, but also with its Lewis acidic property [12]. It is reagent of choice as it has several advantages *viz.*, excellent solubility in water, inexpensiveness ecofriendly nature, uncomplicated handling, high reactivity, fast conversions and convenient work up procedures. Different reactions such as oxidation, 1,4 addition, protection, nitration, 1,3-dipolar cycloaddition, thiocyanation, esterification, Hantsch reaction were found to be catalysed by ammonium cerric nitrate [13-17]. Similarly, its use as an active catalyst for the synthesis of substituted pyridines by a four-component reaction between primary aliphatic amines, β-keto esters or β-

∗ **Corresponding author: Bhavin R. Patel**, Department of Chemistry, Uka Tarsadia University, Maliba Campus, Bardoli-Mahuva Road, Bardoli-394601, Surat, Gujarat, (INDIA).
E-mail: bhavin.patel@utu.ac.in
Received: 21/07/2014, Accepted: 07/11/2014

ketothioesters, α,β-unsaturated aldehydes and alcohols.

According to recent review by Timothy [18], sound of a frequency beyond that to which the human ear can respond is known as ultrasound. The normal range of hearing is between 16 Hz and about 18 kHz and ultrasound is generally considered to lie between 20 kHz to beyond 100 MHz. Sonochemistry generally uses frequencies between 20 and 40 kHz because this is the range employed in common laboratory equipment. The ultrasound provides a synthetic method of chemical activation which has broad application in synthetic organic chemistry. The use of ultrasound in chemistry (sonochemistry) offers the synthetic chemist a method of chemical activation which has broad applications and uses equipment which is relatively inexpensive. The driving force for sonochemistry is cavitation and so a general requirement is that at least one of the phases of the reaction mixture should be a liquid. Ultrasound irradiation is a powerful technique, which is being used frequently to accelerate organic transformations [19–21]. The advantages of ultrasound lies in the reduction of reaction time, high efficiency and waste minimization compared to conventional methods [22].

Here we describe the role of ultrasound at room temperature to afford aryl thioamide derivatives in presence of catalytic amount of ammonium cerric nitrate.

2. EXPERIMENTAL

2.1. Materials and Instruments

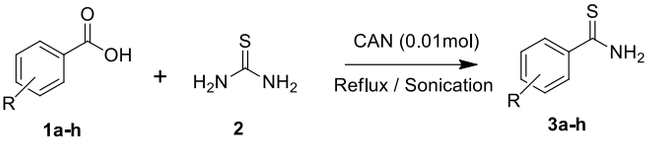
Melting points were determined using an open capillary tube method. NMR spectra were taken on Bruker DRX - 400 MHz NMR spectrometer using TMS as internal standard in $CDCl_3$-DMSO-d_6 solvent at SICART, Vallabh Vidyanagar. IR spectra were obtained using FTIR (Bruker optics) ALPHA-T instrument. All chemicals were purchased from S.D. Fine Chemical Limited and were of laboratory grade.

2.2. Conventional method for the synthesis of Aryl thioamide derivatives

A mixture of aromatic carboxylic acid (0.1 mol) and thiourea (0.1 mol) was ground well and mixed with ammonium cerric nitrate (0.01 mol). The mixture was dissolve in methanol (10 ml) in 250 ml RBF and refluxed in water condenser for 3 to 4 hours, on completion of reaction monitored by TLC, Hexane: ethyl acetate (4:1 V/V). The reaction mixture was cooled to room temperature and extracted with ethyl acetate. The extract was washed with water successively, dried and recrystallized using alcohol. (Table 1)

2.3. Ultrasound assisted synthesis of Aryl thioamide derivatives

A mixture of acid (0.1 mol) and thiourea (0.1 mol) was ground well in motar-pestle and mixed with ammonium cerric nitrate (0.01 mol). The mixture was dissolve in methanol (10 ml) and was sonicated at 33 KHz for 90 min. The reaction mixture was extracted with ethylacetate. The extract was washed with water, dried and recrystallized using alcohol.



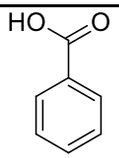
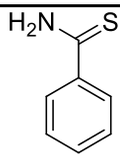
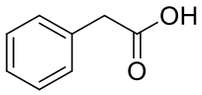
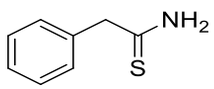
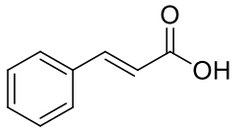
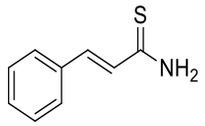
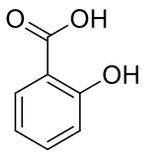
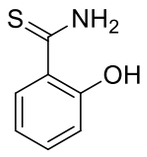
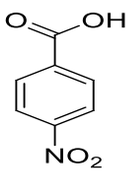
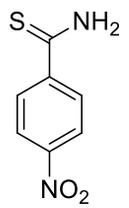
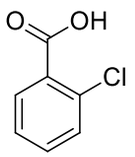
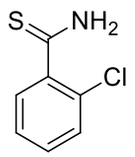
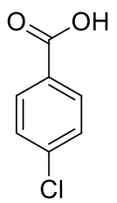
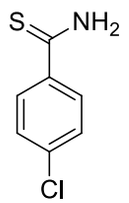
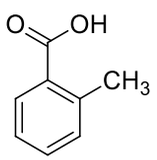
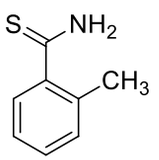
Scheme 1: Synthetic route for aryl thioamide derivatives.

3. RESULTS AND DISCUSSION

Expeditious synthesis for thioamide derivatives was developed. The reaction was performed with and without ultrasound. From Table – 1, it is found that ultrasonication is useful for the conversion of acid into thioamide in presence of thiourea and catalytic amount of ammonium cerric nitrate. No reaction is observed in the absence of catalyst. The reaction without ultrasound requires longer reaction time (3 – 4 hours with 67 to 79% yield) under ambient condition. It was noted that the shortest reaction time (70 to 90 min) and best yield (83 to 89%) were obtained under sonic conditions. It is apparent that the ultrasound can accelerate the reaction significantly [21,22]. The experiment was performed at 33 kHz. The result

with variety of substrates is summarized in Table- 1.

Table 1: Comparative data regarding reaction time, yield of conventional and ultrasound process for 3a-h.

Entry	Acid	Structure of product	Time		Yield (%)		M.P**
			Conv. Process (hours)	Sono chemical Process* (min)	Conv. Process	Sono chemical Process	
3a			3-4	90	79	89%	100-102 °C
3b			3-4	90	76	86%	109-110°C
3c			3-4	90	75	87%	121-122°C
3d			3-4	90	78	86%	154-156°C
3e			3-4	90	69	84%	118-121°C
3f			3-4	90	72	85%	120-121°C
3g			3-4	90	67	83%	110-112°C
3h			3-4	90	77	87%	132-135°C

** Reaction under sonication at 33kHz, ** Melting points are taken in open capillaries and are uncorrected.*

The isolated products were identified with spectral data. The IR spectrum of the products shows strong band in the region of 3333-3207cm^{1-} which is due to –NH stretching and 1100-1300 cm^{1-} which is due to presence of –C=S stretching.

3.1.1. Spectral data of some selected compounds

3d: IR (cm^{1-}): 3338 – 3117, 1308, 1614; ^{1}H NMR ($CDCl_3$-DMSO-d_6): δ 5.38 (s, 1H, -O**H**), δ 7.11, 7.25, 7.43, 7.69 (m, 4H, Ar-**H**), δ 8.29 (s, 2H, -N**H$_2$**); **3g :**IR (cm^{1-}): 3317, 1303, 1614, 707; ^{1}H NMR ($CDCl_3$-DMSO-d_6): δ 6.92, 6.94, 7.27, 7.29 (m, 4H, Ar-**H**), δ 8.92 (s, 2H, -N**H$_2$**); **3h:**IR (cm^{1-}): 3167, 1297; ^{1}H NMR ($CDCl_3$-DMSO-d_6): δ 2.29 (s, 3H, -C**H$_3$**), δ 6.94, 7.19, 7.27, 7.29 (m, 4H, Ar-**H**), δ 8.27 (s, 2H, -N**H$_2$**); **3c:** IR (cm^{1-}): 3180, 1289, 1435; ^{1}H NMR ($CDCl_3$-DMSO-d_6): δ 5.92, 6.22 (d, 2H+2H, -C**H**=C**H**-), δ 7.01 7.11, 7.69, 7.77 (m, 4H, Ar-**H**), δ 10.14 (s, 2H, -N**H$_2$**).

4. CONCLUSION

The utility of ultrasonication in expedition the metal catalyzed reaction was demonstrated. This methodology may be useful for other transformations also which has produced the targeted moiety in good to moderate yield at room temperature under ultrasonic irradiation.

5. ACKNOWLEDGEMENT

Authors would like to thank Department of Chemistry, Uka Tarsadia University, Maliba campus, Bardoli, Gujarat, India, for providing all the necessary research facilities

6. REFERENCES

1. Wiberg KB, Rablen PR. Why Does Thioformamide Have a Larger Rotational Barrier Than Formamide? Journal of American Chemical Society, 1995 117(8): 2201.
2. Oik RM., Oik B., Dietzsch W., Kirmse R., Hoyer E., The Chemistry of 1,3-dithiole-2-thione-4,5-dithiolate (dmit). Coordination Chemistry Reviews, 1992 117: 99
3. Blower PJ., Dilworth JR., Thiolato-complexes of transition metal. Coordination Chemistry Reviews, 1987 76: 121.
4. Vannelli TA., Dykman A., Montellano P.R.O., The Antituberculosis Drug Ethionamide Is Activated by a Flavoprotein Monooxygenase. The Journal Biological Chemistry, 2002 277 (15): 12824
5. Hanoulle X., Wieruszeski JM., Rousselot-Pailley P., Landrieu I., Baulard AR., Lippens G., Monitoring of ethionamide pro drug activation in mycobacteria by ^{1}H high resolution magic angle spinning NMR. Biochemical and Biophysical Research Communication, 2005 331(2): 452.
6. Wei QL., Zhang SS., Gao J., Li WH., Xu LZ., Yu GZ., Synthesis and QSAR studies of novel triazole compounds containing thioamide as potential antifungal agents. Bioorganic and Medicinal Chemistry, 2006 14(21): 7146.
7. Mahammed KA., Jayashankara VP., Rai NP., Raju KM., Arunachalam PN., A Mild and Versatile Synthesis of Thioamides. Synlett, 2009 (14) 2338.
8. Kaboudin B., Elhamifar D., Phosphorus Pentasulfide: A Mild and Versatile Reagent for the Preparation of Thioamides from Nitriles. Synthesis, 2006 (2) 224.
9. Kaboudin B., Malekzadeh L., Ammonium Phosphorodithioate: A Mild, Easily Handled, Efficient, and Air-Stable Reagent for the Conversion of Amides into Thioamides. Synlett, 2011 (19) 2807.
10. Zubruyev OI., Stiasni N., Kappe CO., Preparation of Thioamide Building Blocks via Microwave-Promoted Three-Component Kindler Reactions. Journal of Combinatorial Chemistry, 2003 5(2) 145.
11. Itoh K.; Akira Horiuchi C. Formation of isoxazole derivatives via nitrile oxide using ammonium cerium nitrate (CAN): a novel one-pot synthesis of 3-acetyl- and 3-benzoylisoxazole derivatives. Tetrahedron, 2004, 60 (7) 1671.
12. Zhou Y-L., Yang L.; Liu Z., Yu W, Han B.,Jia X-D, Jin L-X A CAN-initiated aza-Diels–Alder reaction for a facile synthesis of 4-amido-N-yl tetrahydroquinolines. Tetrahedron Letters, 2006 47(21) 3545.
13. Vargas A.J.M., Robina I., Bolanos J.G.F., Fuentes J., Oxidation of polyhydroxyalkyl - heterocycles

by cerium (IV). A convenient route to pyrrole-2,5-dicarbaldehydes Tetrahedron Letters, 1998 39(50) 9271.

14. Chu C-M., Gao S., Sastry M.N.V., . Kuo C.W, Lu C., Liu J-T., Yao C-F., Ceric ammonium nitrate (CAN) as a green and highly efficient promoter for the 1,4-addition of thiols and benzeneselenol to α,β-unsaturated ketones. Tetrahedron, 2007 63(8) 1863.
15. Comin MJ., Elhalem E., Rodriguez JB., Cerium ammonium nitrate: a new catalyst for regioselective protection of glycols. Tetrahedron, 2004 60(51) 11851.
16. Ganguly NC., Datta M., De P., Chakravarty R., Studies on Regioselectivity of Nitration of Coumarins with Cerium(IV) Ammonium Nitrate: Solid-State Nitration of 6-Hydroxy-Coumarins on Montmorillonite K-10 Clay Support Under Microwave Irradiation. Synthetic Communications, 2003 33(4) 647.
17. Ko S., Yao C-F., Ceric Ammonium Nitrate (CAN) catalyzes the one-pot synthesis of polyhydroquinoline via the Hantzsch reaction. Tetrahedron, 2006 62(31) 7293.
18. Mason Tj., Ultrasound in synthetic organic chemistry. Chemical Society Reviews, 1997 26 443
19. Ghahremanzadeh R., Fereshtehnejad F., Mirzaei P., Bazgir A., Ultrasound-assisted synthesis of 2,2′-(2-oxoindoline-3,3-diyl)bis(1H-indene-1,3(2H)-dione) derivatives. Ultrasound Sonochemistry, 2011 18(1) 415.
20. He J-Y., Xin H-X., Yan H., Song X-Q., Zhong R.G., Convenient ultrasound-mediated synthesis of 1,4-diazabutadienes under solvent-free conditions. Ultrasound Sonochemistry, 2011 18(1) 466.
21. Li J.T., Li Y.W., Song Y-L., Chen G.F., Improved synthesis of 2,2′-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives catalyzed by urea under ultrasound. Ultrasound Sonochemistry, 2012 19(1) 1.
22. Bazgir A., Ahadi S., Ghahremanzadeh R., Khavasi H.R., Mirzaei P., Ultrasound-assisted one-pot, three-component synthesis of spiro[indoline-3,4′-pyrazolo[3,4-b]pyridine]-2,6′(1′H)-diones in water. Ultrasound Sonochemistry, 2010 17(2) 447.