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# Ultrasound Assisted Convenient and Efficient Protocol for Synthesis of Dihydropyrimidine-2-thiones

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## ABSTRACT

Chalcones were prepared by condensation of various substituted aromatic aldehydes or heterocyclic aldehydes and acetophenone in alkaline ethanol, while pyrimidine-2-thione derivatives were prepared by condensation of chalcones and thiourea under ultrasonic irradiation at room temperature. The most important advantage of ultrasound irradiation was observed and high yields of the products were obtained after 10-15 min. sonication.
**Keywords:** Chalcones, Dihydropyrimidine-2-thione, Cu (I) catalyst, Sodamide, Ultrasound irradiation.

## I. INTRODUCTION

Ultrasound technique has increasingly been used in organic synthesis in the recent years. Ultrasonic irradiation enhances the chemical reaction via the process of acoustic cavitation. The assistance of ultrasonic irradiation efficiently shortens the reaction time. Simple experimental procedure, very high yields, increased selectivity, and clean reaction of many ultrasound induced organic transformations offer additional convenience in the field of organic chemistry.[1-4] The chemical effects resulting from the irradiation of aqueous solutions with ultrasound were first time introduced by Loomis et al.[5] There has been report of Zinc-Cu (I) ultrasound-mediated conjugate addition reactions developed by Luche & co-workers which involves reactions carried out under aqueous conditions.[6-7] A number of the alkyl pyrimidine-2-thiones, particularly those substituted in the 6 position showed considerably greater antithyroid activity in rats than pyrimidine-2-thones itself.[8] Pyrrimidine-2-thione derivative exhibit biological activities[9] such as antiviral, antitumor, antibacterial, anti-inflammatory, antihypertension etc. Antiviral properties of certain thiourea and urea derivatives have been reported in the presence of an intact NH-C(=S)-NH and NH-C(=O)-NH grouping.[10] The Bigineli condensation involving the reaction of aldehydes, urea or thiourea and ethylacetoacetate under strongly acidic conditions to give 3,4 dihydropyrimidin-2-ones. In recent years, several methods for the synthesis of dihydropyrimidines have been developed to improve and modify this reaction by means of ultrasound irradiation, microwave irradiation[11] and ionic liquids.[12] One method involves the reaction of aldehydes, β-dicarbonyl compounds and thiourea/urea in the presence of tetrachlorosilane in DMF at ambient temperature.[13]

In reported method pyrimidine derivatives were synthesized using sodium ethoxide, $K_2CO_3$ in ethanol,[14] $CrCl_3$ $6H_2O$, KOH, $CH_3CN$-$H_2O$,[15] MeOH, HCl,[16] $P_2O_5$/EtOH,[17] acidic ionic liquid,[18] alcoholic KOH,[19] hydroxy tosyloxy iodobenzene (HTIB),[20] under conventional heating, $H_2SO_4$/EtOH-mediated microwave irradiation[21] and dihydropyrimidine-2-thiones were reported in alcoholic KOH under conventional and ultrasound conditions using only activated aldehydes.[22]

Most of the reported methods suffer from the serious drawbacks such as involvement of expensive reagents, acidic conditions, longer reaction time, environmental pollution and moderate yields. Moreover, some of the methods are only practical for aromatic aldehydes. Thus, there is still a need for a simple and general procedure for the synthesis of dihydropyrimidine-2-thione using sodamide in EtOH and Nitratobis (Triphenyl phosphine) Copper (I) as a catalyst (Scheme I). To the best of our knowledge, the use of Nitratobis (Triphenyl phosphine) Copper (I) catalyst for the synthesis of dihydropyrimidine-2-thione is not reported in the

literature keeping in the view of these observations it was planned to synthesize a novel series of dihydropyrimidine-2-thione using chalcones prepared from variety of aromatic aldehydes, heterocyclic aldehydes and thiourea.

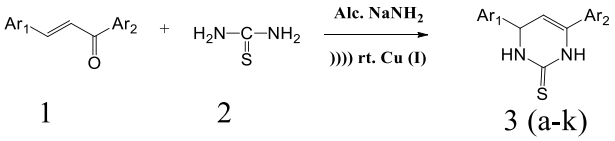
## II. METHODS AND MATERIAL

The melting points of all compounds are uncorrected are determined by in a open capillary tube. The IR spectra were recorded on a Shimadzu Miracle 10 ATR. The $^1$HNMR spectra were obtained on a Bruker Avance III HD NMR 400 MHz with $CDCl_3$ as the solvent using TMS as the internal standard. Sonication was performed in an Ultrasonic Cleaner with frequency 33 KHz and a normal power of 250 W. The progress of reactions are checked by TLC using pet. Ether/ethyl acetate (8:2) as the mobile phase. The spots were visualized using UV cabinet. Crude products were purified by recrystallization using ethanol and column chromatography using pet. Ether/ethyl acetate as a solvent.

### Typical procedure for synthesis of dihydropyrimidine-2-thione

The chalcones were prepared from substituted aromatic aldehydes or heterocyclic aldehydes and acetophenone by reported method. Dihydropyrimidine-2-thiones were prepared by dissolving chalcones (10 mmol) and thiourea (10 mmol) in alcoholic $NaNH_2$ (1 gm $NaNH_2$ in 40 ml ethanol ) in a 100 ml round bottom flask. Then $Cu(PPh_3)_2NO_3$ catalyst (10 mol % i.e.62 mg) was added in the reaction mixture. The reaction mixture was irradiated in the water bath of an ultrasonic cleaner for the period as indicated in Table:2. The reaction mixture was left over night and the reaction mixture was extracted in diethyl ether, washed by water and organic phase was dried. The product was purified using column chromatography and yield was reported.

## III. RESULTS AND DISCUSSION




1 2 3 (a-k)

Scheme: 1 General scheme of reaction

The effect of reaction conditions on the formation of dihydropyrimidine-2-thione under ultrasound irradiation was summarized in Table:1.

Table: 1 Effect of reaction condition on synthesis of dihydropyrimidine-2-thione under ultrasound irradiation.

| Entry | Base | Catalyst | Isolated Yield % |
|---|---|---|---|
| 3a | LiOH | $Cu(PPh_3)_2NO_3$ | trace |
| 3a | $K_2CO_3$ | $Cu(PPh_3)_2NO_3$ | trace |
| 3b | $NaNH_2$ | Without catalyst | 40% |
| 3c | $NaNH_2$ | $Cu(MeCN)_4PF_6$ | 45% |
| 3d | $NaNH_2$ | $Cu(MeCN)_4BF_4$ | 70% |
| 3e | $NaNH_2$ | $Cu(PPh_3)_2NO_3$ | 96% |

When we performed the reaction in other bases such as LiOH, $K_2CO_3$ trace amount of product was obtained. It is also important to mention that when reaction was performed in water no product was obtained because chalcones are insoluble in water at room temperature. It is apparent that the reaction can be finished in shorter time to give excellent yield under ultrasound. The yield of product was not affected using chalcones obtained from electron donating or electron withdrawing aromatic aldehydes. For the synthesis of chalcones different varieties of aldehydes were used. The sodamide is the base, ethanol as a reaction solvent and $Cu(PPh_3)_2NO_3$ is the catalyst. In Nitratobis (Triphenyl phosphine) Copper (I) reaction proceeded smoothly under ultrasound irradiation.

Table 2. Synthesis of dihydropyrimidine-2-thiones in alcoholic NaNH2 under ultrasound irradiation at room temperature.

| Entry | $Ar_1$ | $Ar_2$ | Time, min. | Yield % | M.P. Found $^0$c[Ref.] |
|---|---|---|---|---|---|
| 3a | $C_6H_5$ | $C_6H_5$ | 14 | 80 | 180 (182-184)[22] |
| 3b | 4-$CH_3C_6H_4$ | $C_6H_5$ | 11 | 91 | 200 (198-200)[22] |
| 3c | 4-$CH_3OC_6H_4$ | $C_6H_5$ | 10 | 93 | 123 (123-125)[22] |
| 3d | 2-$ClC_6H_4$ | $C_6H_5$ | 12 | 85 | 108 |
| 3e | 3-$ClC_6H_4$ | $C_6H_5$ | 15 | 89 | 104 |
| 3f | 3-$NO_2C6H4$ | $C_6H_5$ | 15 | 90 | 114 |
| 3g | 4-$NO_2C_6H_4$ | $C_6H_5$ | 10 | 92 | 98 |
| 3h | $C_4H_4N$ | $C_6H_5$ | 14 | 82 | 118 |
| 3i | $C_4H_3O$ | $C_6H_5$ | 12 | 85 | 68 |
| 3j | $C_4H_3S$ | $C_6H_5$ | 12 | 87 | 88 |
| 3k | $C_8H_5O$ | $C_6H_5$ | 14 | 80 | 114 |

From the Table 2 we have found that using Cu(PPh3)2NO3 as a catalyst the reaction time was shortened for the preparation of dihydropyrimidine-2-thiones from 30 to 15 min. In addition the yields of products were improved by 10-20% in comparison with those obtained by the previous method.

## IV. CONCLUSION

In conclusion, we have developed a simple, efficient and general method for the synthesis of dihydropyrimidine-2-thione using Cu (I) catalyst. Moreover, the present method offered several advantages including high yields, shorter reaction time, and simple workup procedure makes this catalyst a more convenient alternative to the reported catalysts.

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