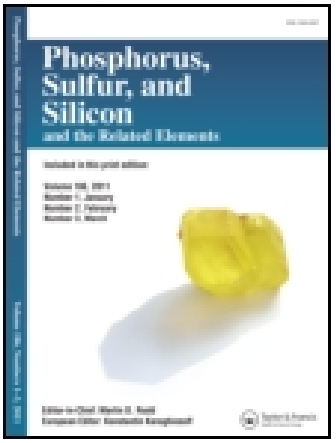

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A Facile and Rapid Method for Preparation of Thiazine and Thiadiazine Derivatives by Sonication Technique

Vijay V. Dabholkar [a] & Faisal Y. Ansari [a]
[a] Organic Research Laboratory, Department of Chemistry , K.C. College , Churchgate, Mumbai, India
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A FACILE AND RAPID METHOD FOR PREPARATION OF THIAZINE AND THIADIAZINE DERIVATIVES BY SONICATION TECHNIQUE

Vijay V. Dabholkar and Faisal Y. Ansari
Organic Research Laboratory, Department of Chemistry, K.C. College, Churchgate, Mumbai, India

Ultrasound accelerated synthesis of 2,3-(substituted)benzo-1,4-thiazino[5,6-b]-4H-9H-7-methyl-10-oxoquinolines (4), 7-substituted-2,2-dimethyl-2,3-dihydro-1H,10H-phenothiazin-4-one (5), 4-substituted-3,9, 10-trihydro-11-oxo-quinolino[2,3-b]-1,3,4-thiadiazino[2,3-d]-1,2,4-triazole (6), and 7,7-dimethyl-7,8-dihydro-3H,5H,6H-1,2,4-triazolo[3,4-b][1,3,4] benzothiadiazin-9-one (7) from carbostyril and dimedone using sulfur powder and iodine as a catalyst in THF is reported. The structures of the compounds have been elucidated on the basis of spectral and elemental analysis.

Keywords Amino-triazole; aromatic amine; carbostyril; dimedone; sonication; thiadiazine; thiazine

INTRODUCTION

During the last 10 years, a number of publications and reviews have advocated the use of ultrasound technology in organic synthesis. Ultrasound in organic synthesis is an attractive, constantly growing field of organic chemistry. The advantages of ultrasound-assisted chemical reactions include higher yields, shorter reaction times, and milder reaction conditions when compared with classical methods.[1–5] The use of ultrasound irradiation technique for activating various reactions is well documented in the literature, such as synthesis of azoles and diazenes,[6] Reformatsky reaction,[7] oxidation of substrates such as hydroquinones,[8] conversion of nitro compounds to carbamates,[9] pinacol coupling,[10] and Ullmann condensation.[11] Carbostyril[12] and dimedone[13] constitute a unique group of compounds due to the simultaneous presence of characteristic features such as a β-diketone group as a starting material. Thazines are known to exhibit various types of biological activities such as Ca^{2+} antagonist; blood platelet aggregation inhibitors;[14] and antipsychotic,[15] antiviral,[16] antimicrobial,[17] and antihypertensive[18] agents. Similarly, the thiadiazine nucleus is a versatile pharmacophore, which exhibits a wide variety of biological activity. Many

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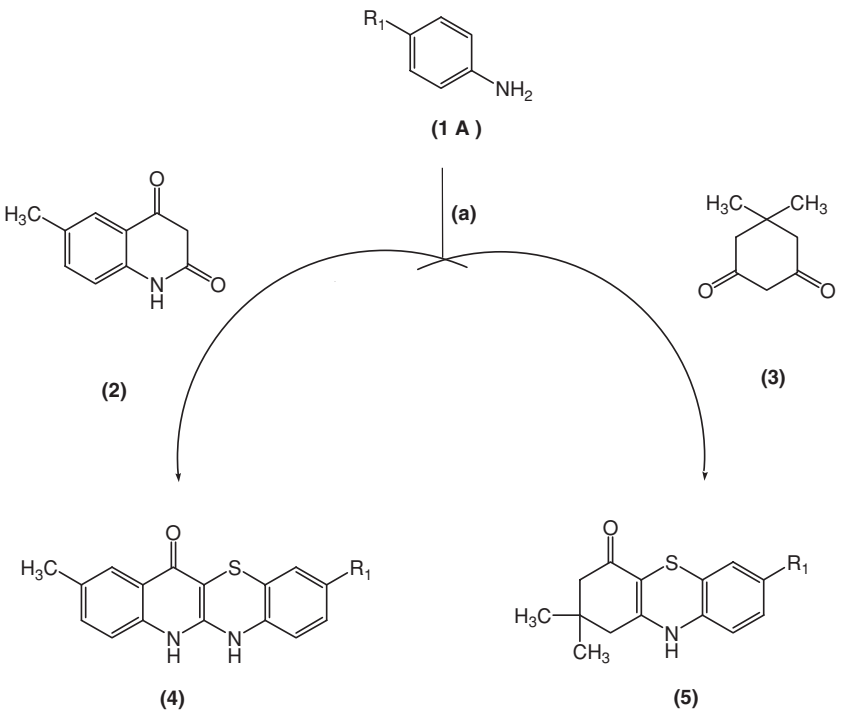
Address correspondence to Vijay V. Dabholkar, Organic Research Laboratory, Department of Chemistry, K.C. College, Churchgate, Mumbai 400 020, India. E-mail: vijaydabholkar@gmail.com

of its compounds are antimicrobial,[19] anti-irradiation,[20] and antiparasitic agents.[21] Fused *s*-triazoles and their derivatives have been investigated for their potential pharmacological properties such as antifungal,[22] antidepressant,[23] and plant growth regulators.[24]

Our research group has a longstanding interest in the synthesis of heterocyclic compounds by newer methods such as microwave[25–28] and sonication[29–31] aiming to develop more rapid and advantageous construction of libraries of small heterocyclic compounds. As a result we have recently reported the synthesis of benzothiazipine, thiophene, triazole, thiadiazole, and spiro oxadiazole, and also their biological studies.[29–31] In view of these observations, and as an extension of our earlier work, thiazine and thiadiazine derivatives have been prepared by sonication methods as well as by conventional synthetic methodologies. The synthesis of novel thiazines and thiadiazine[32,33] have been reported by us using 2-bromo dimedone/3-bromo carbostyril with aminothiophenols, and in this article we describe the synthesis of thiazine/thiadiazine using an alternative route by reacting substituted amines/amino-triazole using sulfur powder and iodine as a catalyst in the presence of THF as a solvent.[34]

However, in the earlier reported processes, expensive chemicals were used and the method was time consuming. In order to overcome these limitations and in vision of the requirement of green chemistry for energy saving, high efficiency, and environmental benevolence, we carried out this series of reactions under sonication, in addition to

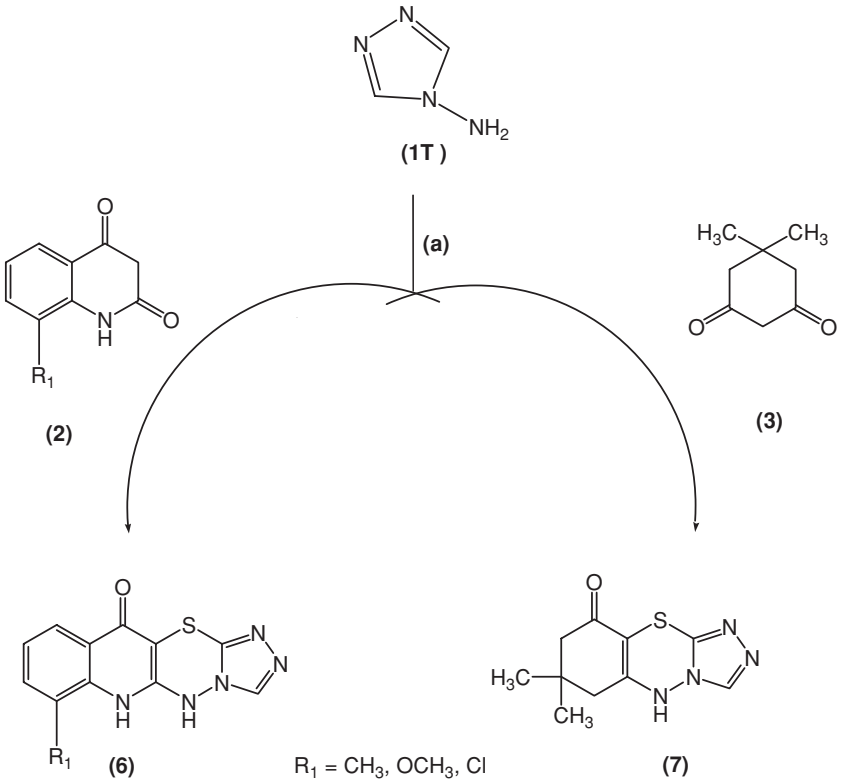


Scheme 1

conventional methods. It was found that the sonication method is environmentally beneficial and superior to the conventional method. It is also a very rapid method for the preparation of thiazine and thiadiazine derivatives (Scheme 1).

RESULT AND DISCUSSION

The series of heterocyclic compounds **4**, **5**, **6**, and **7** have been synthesized as depicted in Schemes 1 and 2. The starting materials carbostyril **(2)** and dimedone **(3)** were synthesized as reported earlier.[20] The reaction of **2** and **3** with substituted aromatic amines, sulfur, and iodine in THF gave the 2,3-(substituted)benzo-1,4-thiazino [5, 6-b]-4H-9H-7-methyl-10-oxo quinolines **4** and 7-substituted-2, 2-dimethyl-2,3-dihydro-1H,10H-Phenothiazin-4-one **5** (Scheme 1). In the IR spectra of compounds **4**, the following characteristic absorption



(a) = Sulphur powder,Iodine/THF

Scheme 2

bands were observed: 1687 υ_{max}/cm^{-1} (C=O) and 3425 υ_{max}/cm^{-1} (NH). In its ^1H NMR spectra, two signals of NH group at 10.25 and 12.50 ppm were observed. Similarly, the compounds **5** were confirmed by IR spectra, which showed NH bands in the region of 3285 υ_{max}/cm^{-1} and C=O absorption bands at 1240 υ_{max}/cm^{-1}. Also, in its ^1H NMR spectra, the NH group shows a chemical shift that is a characteristic of thiazine. This is observed in the downfield region at 8.9–9.4 ppm and also supports the proposed structure.

Similarly, the compound 4-substituted-3,9,10-trihydro-11-oxo-quinolino[2,3-*b*]-1,3,4-thiadiazino[2,3-d]-1,2,4-triazole **(6)** and 7,7-dimethyl-7,8-dihydro-3*H*,5*H*,6*H*-1,2,4-triazolo[3,4-b][1,3,4]benzothiadiazin-9-one **(7)** have been prepared by the same procedure using amino-triazole (Scheme 2). Evidence of the formation of compound **6** was shown by the appearance of a signal at 1632 υ_{max}/cm^{-1} and 3137 υ_{max}/cm^{-1} for (C=O) and (NH). In its ^1H NMR spectra, two signals of NH group at 12.43 and 12.72 ppm were observed. Similarly, the compound **7** was confirmed by IR spectra, which showed NH bands in the region of 3267 υ_{max}/cm^{-1} and C=O absorption bands at 1623 υ_{max}/cm^{-1}. Also, in its ^1H NMR spectrum, the NH group shows a chemical shift that is characteristic of thiadazine. This was observed in the downfield region at 11.43 ppm, and the CH in the triazole ring was shown at 7.45 ppm. This also supports the proposed structure.

CONCLUSION

The process of ultrasound irradiation for synthesis of the title compound undergoes a significant reduction in the reaction time. There is simplicity in the operation, the reaction is cleaner, the process is easier, and the yield is enhanced. The procedure clearly highlights the advantages of ultrasound technique. Both synthones (carbostyril and dimedone) have been successfully utilized in the preparation of 2,3-(substituted)benzo-1,4-thiazino [5,6-b]-4H-9H-7-methyl-10-oxoquinolines **(4)**, 7-substituted-2,2-dimethyl-2,3-dihydro-1H,10H-phenothiazin-4-one **(5)**, 4-substituted-3,9,10-trihydro-11-oxo-quinolino[2,3-*b*]-1,3,4-thiadiazino[2,3-*d*]-1,2,4-triazole **(6)**, and 7,7-dimethyl-7,8-dihydro-3*H*,5*H*,6*H*-1,2,4-triazolo[3,4-b][1,3,4] benzothiadiazin-9-one **(7)**, and their structures were elucidated with the help of elementary and spectral analysis.

EXPERIMENTAL

The chemicals were supplied by E. Merck (Germany) and S.D. Fine Chemicals (India). The melting points of synthesized compounds were determined in open capillary tubes using a Veego VMP-1 melting point apparatus, expressed in °C, and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as an adsorbent and UV light as a visualizing agent. IR spectra (KBr in υ_{max}/cm^{-1}) were recorded on a Perkin-Elmer spectrophotometer in the range of 400–4000 υ_{max}/cm^{-1}. ^1H NMR spectra were recorded on Brucker Avance 500 MHz NMR spectrophotometer from International Equipment Trading LTD, using $CDCl_3$/DMSO-d_6 as a solvent and TMS as an internal standard (chemical shifts in δ, given in ppm). C, H, N estimations were done on Carlo Erba 1108 (C H N) Elemental Analyser. The experiment under ultrasound irradiation was carried out in probe ultrasound manufactured by Dakshin pvt Ltd, Mumbai (Electrical Supply 230V A.C., 50 Hz).

2,3-(Substituted)benzo-1,4-thiazino[5,6-b]-4H-9H-7-methyl-10-oxoquinolines (4)

Method A (ultrasound method): General procedure. The mixture of carbostyrils **(CAB) (2)** (50 mmol), substituted amines **(1A)** (50 mmol), and sulfur powder (15.6 mmol) in THF (5 mL) was irradiated on a sonicator in the presence of iodine (1 mmol) as catalyst for 25 min. After completion of the reaction (monitored on TLC) and the contents were cooled, the solid formed was filtered, washed with dil. HCl and warm water followed by CS_2, and recrystallized from glacial acetic acid.

Method B (conventional method): General procedure. An equimolar mixture of carbostyrils (CAB) **(2)** (50 mmol), substituted amines **(1A)** (50 mmol), and sulfur powder (15.6 mmol) in THF 5 mL was refluxed in the presence of iodine (1 mmol) as catalyst for 3 h at 180°C. Upon completion of the reaction (monitored by TLC), the mixture was brought to room temperature, the solid formed was filtered washed with dil. HCl with followed by CS_2, and then recrystallized from glacial acetic acid.

2,3-Benzo-1,4-thiazino[5,6-b]-4H-9H-7-methyl-10-oxoquinolines (4a). This compound was obtained in 69% yield (Soni 84%), mp 205°C; [found: C, 68.45; H, 4.21; N, 9.92. $C_{16}H_{12}ON_2S$ requires C, 68.5; H, 4.28; N, 10.00%]; υ_{max}/cm^{-1}: 1620 (C=O), 3248 (NH); δ_H: 2.4 (s, 3H, CH_3), 6.91–8.22 (m, 7H, ArH), 10.98 (s, 1H, ring NH), 12.48 (s, 1H, ring NH).

2,3-(4′-Methyl)benzo-1,4-thiazino[5,6-b]-4H-9H-7-methyl-10-oxoquinolines (4b). This compound was obtained in 60% yield (Soni 83%), mp 202°C; [found: C, 69.32; H, 4.72; N, 9.46. $C_{17}H_{14}ON_2S$ requires C, 69.38; H, 4.76; N, 9.52%]; υ_{max}/cm^{-1}: 1657 (C=O), 3264 (NH); δ_H: 2.27 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.7–8.2 (m, 6H, ArH), 10.85 (s, 1H, ring NH), 12.04 (s, 1H, ring NH).

2,3-(4′-Methoxy)benzo-1,4-thiazino[5,6-b]-4H-9H-7-methyl-10-oxoquinolines (4c). This compound was obtained in 64% yield (Soni 80%), mp 204°C; [found: C, 65.67; H, 4.38; N, 8.92. $C_{17}H_{14}O_2N_2S$ requires C, 65.80; H, 4.51; N, 9.03%]; υ_{max}/cm^{-1}: 1657 (C=O), 3264 (NH); δ_H: 2.27 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.70–8.20 (m, 6H, ArH), 10.85 (s, 1H, ring NH), 12.04 (s, 1H, ring NH).

2,3-(4′-Chloro)benzo-1,4-thiazino[5,6-b]-4H-9H-7-methyl-10-oxoquinolines (4d). This compound was obtained in 65% yield (Soni 84%), mp 148°C; [found: C, 60.87; H, 3.42; N, 8.82. $C_{16}H_{11}ON_2SCl$ requires C, 60.95; H, 3.49; N, 8.88%]; υ_{max}/cm^{-1}: 1653 (C=O), 3300 (NH); δ_H: 2.3 (s, 3H, CH_3), 7.14–7.72 (m, 6H, ArH), 11.5 (s, 1H, ring NH), 12.15 (s, 1H, ring NH).

7-Substituted-2,2-dimethyl-2,3-dihydro-1H,10H-Phenothiazin-4-one (5)

Method A (ultrasound method): General procedure. A mixture of dimedone (DIM) **(3)** (50 mmol), substituted amines **(1A)** (50 mmol), sulfur powder (15.6 mmol), iodine (1 mmol), and THF (5 mL) as a solvent was taken in a 100 mL round bottom flask and subjected to ultrasound for 15 min. After monitoring the reaction on TLC, the reaction mixture was cooled at room temperature to obtain **5**, which was filtered and washed with dil. HCl, warm water, and then with CS_2. It was recrystallized from ethanol.

Method B (conventional method): General procedure. Mixture of dimedone (DIM) **(3)** (50 mmol), substituted amines **(1A)** (50 mmol), sulfur powder (15.6 mmol), iodine (1 mmol), and THF (5 mL) as a solvent was taken in 100 mL round bottom flask, and the mixture was heated at 80°C for 3 h. After monitoring the reaction on TLC, the reaction mixture was worked up in the same manner as discussed above.

2,2-Dimethyl-2,3-dihydro-1H,10H-phenothiazin-4-one (5a). This compound was obtained in 64% yield (Soni 86%), mp 264°C; [found: C, 68.23; H, 6.32; N, 5.45. $C_{14}H_{15}ONS$ requires C, 68.57; H, 6.12; N, 5.71%]; υ_{max}/cm^{-1}: 1618 (C=O), 3276 (NH); δ_H: 1.10 (s, 6H, $2CH_3$), 2.17 (s, 2H, CH_3), 2.29 (s, 2H, CH_2), 6.22–7.24 (m, 4H, ArH), 8.96 (s, 1H, ring NH).

7-Methyl-2,2-dimethyl-2,3-dihydro-1H,10H-phenothiazin-4-one (5b). This compound was obtained in 59% yield (Soni 88%), mp 194°C; [found: C, 69.21; H, 6.68; N, 5.21. $C_{15}H_{17}ONS$ requires C, 69.49; H, 6.56; N, 5.40%]; υ_{max}/cm^{-1}: 1608 (C=O), 3262 (NH); δ_H: 1.08 (s, 6H, $2CH_3$), 2.2 (s, 2H, CH_3), 2.30 (s, 2H, CH_2), 2.42 (s, 2H, CH_3), 7.05–7.35 (m, 3H, ArH), 9.42 (s, 1H, ring NH).

7-Methoxy-2,2-dimethyl-2,3-dihydro-1H,10H-phenothiazin-4-one (5c). This compound was obtained in 67% yield (Soni 80%), mp 242°C; [found: C, 69.23; H, 6.74; N, 5.21. $C_{15}H_{17}O_2NS$ requires C, 69.49; H, 6.59; N, 5.40%]; υ_{max}/cm^{-1}: 1610 (C=O), 3312 (NH); δ_H: 1.08 (s, 6H, $2CH_3$), 2.08 (s, 2H, CH_3), 2.15 (s, 2H, CH_2), 3.9 (s, 3H, OCH_3), 7.05–7.35 (m, 3H, ArH), 9.34 (s, 1H, ring NH).

7-Chloro-2,2-dimethyl-2,3-dihydro-1H,10H-phenothiazin-4-one (5d). This compound was obtained in 62% yield (Soni 84%), mp 215°C; [found: C, 69.45; H, 6.48; N, 5.32. $C_{14}H_{14}ONSCl$ requires C, 69.49; H, 6.59; N, 5.40%]; υ_{max}/cm^{-1}: 629 (C—Cl), 1610 (C=O), 3312 (NH); δ_H: 1.11 (s, 6H, $2CH_3$), 2.12 (s, 2H, CH_3), 2.24 (s, 2H, CH_2), 7.15–7.65 (m, 3H, ArH), 9.21 (s, 1H, ring NH).

4-Substituted-3,9,10-trihydro-11-oxo-quinolino[2,3-*b*]-1,3,4-thiadiazino [2,3-*d*]–1,2,4-triazole (6a–c)

Method A (ultrasound method): General procedure. An equimolar solution of carbostyril (CAB) (**2**) (50 mmol) and triazole (1T) (50 mmol), sulfur powder (15.6 mmol), iodine (1 mmol), and THF (5 mL) as a solvent was taken in 100 mL round bottom flask and subjected to ultrasound irradiation for 28 min. After monitoring the reaction on TLC, the reaction mixture was cooled at room temperature to obtain **6**, which was filtered and washed with dil. HCl, warm water, and then with CS_2. It was recrystallised from ethanol.

Method B (conventional method): General procedure. A mixture of carbostyril (CAB) (**2**) (50 mmol), triazole (1T) (50 mmol), sulfur powder (15.6 mmol), iodine (1 mmol), and THF (5 mL) as a solvent was taken in 100 mL round bottom flask, and the mixture was heated at 80°C for 4 h. After monitoring the reaction on TLC, the reaction mixture was worked up in the same manner as discussed above.

4-Methyl-3,9,10-trihydro-11-oxo-quinolino[2,3-*b*]-1,3,4-thiadiazino[2,3-*d*]-1,2,4-triazole (6a). This compound was obtained in 63% yield (Soni 78%), mp 225°C [found: C, 53.05; H, 3.24; N, 25.72 $C_{12}H_9ON_5S$ requires C, 53.13; H, 3.32; N, 25.8%]; υ_{max}/cm^{-1}: 3137 (NH), 1632 (C=O), 1585 (C=N). δ_H: 2.47 (s, H, CH_3), 7.18–7.91 (m, 4H, aromatic H& CH), 12.43 (s, ring NH), 12.72 (s, ring NH).

4-Methoxy-3,9,10-trihydro-11-oxo-quinolino[2,3-*b*]-1,3,4-thiadiazino[2,3-*d*]-1,2,4-triazole (6b). This compound was obtained in 57% yield (Soni 82%), mp 254°C [found: C, 50.17; H, 3.13; N, 24.39. $C_{12}H_9O_2N_5S$ requires C, 50.10; H, 3.04; N, 24.32%]; υ_{max}/cm^{-1}: 3121 (NH), 1611 (C=O), 1565 (C=N). δ_H: 3.82 (s, H, OCH_3), 7.23–7.87 (m, 4H, aromatic H & CH), 12.41 (s, ring NH), 12.70 (s, ring NH).

4-Chloro-3,9,10-trihydro-11-oxo-quinolino[2,3-*b*]-1,3,4-thiadiazino[2,3-*d*]-1,2,4-triazole (6c). This compound was obtained in 60% yield (Soni 84%), mp

268°C [found: C, 51.36; H, 2.72; N, 27.23. $C_{11}H_7ON_5SCl$ requires C, 51.30; H, 2.65; N, 27.15%]; υ_{max}/cm^{-1}: 3130 (NH), 1610 (C=O), 1570 (C=N), 625 (C−Cl). δ_H: 7.21–7.89 (m, 4H, aromatic H& CH), 12.34 (s, ring NH), 12.70 (s, ring NH).

7,7-Dimethyl-7,8-dihydro-3*H*,5*H*,6*H*-1,2,4-triazolo[3,4-b][1,3,4] benzothiadiazin-9-one (7)

Method A (ultrasound method): General procedure. An equimolar solution of dimedone (DIM) **(3)** (50 mmol), and triazole (1T) (50 mmol), sulfur powder (15.6 mmol), iodine (1 mmol), and THF (5 mL) as a solvent was taken in 100 mL round bottom flask and subjected to ultrasound for 22 min. After monitoring the reaction on TLC, the reaction mixture was cooled at room temperature to obtain **7**, which was filtered and washed with dil. HCl, warm water, and then with CS_2. It was recrystallized from ethanol.

Method B (conventional method): General procedure. Mixture of dimedone (DIM) **(3)** (50 mmol), triazole (1T) (50 mmol), sulfur powder (15.6 mmol), iodine (1 mmol), and THF (5 mL) as a solvent was taken in 100 mL round bottom flask and the mixture was heated at 80°C for 3.5 h. After monitoring the reaction on TLC, the reaction mixture was worked up in the same manner as discussed above.

The above compound was obtained in 69% yield (Soni 86%), mp 261°C; [found: C, 50.76; H, 5.02; N, 23.65 $C_{10}H_{12}ON_4S$ requires C, 50.84; H, 5.08; N, 23.72%];υ_{max}/cm^{-1}: 1632 (C=O), 3202 (NH); δ_H: 0.99 (s, 6H, 2×CH_3), 2.31 (s, 2H, CH_2), 2.38 (s, 2H, CH_2), 7.45 (s, H, N=CH), 11.72 (s, 1H, NH)

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