# Solvent-free Synthesis of Heterocyclic Thioureas Using Microwave Technology

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A new and rapid solvent-free synthesis of heterocyclic thioureas in a microwave oven has been reported for the first time. Nine heterocyclic thioureas that possess biological activity have been synthesized. The reaction time is short (2-4.5 min) and gives excellent yields (82.9-95.5%).

## INTRODUCTION

In recent years, the use of microwave technology in organic synthesis has received considerable attention,[1-4] the reason is that this technology can increase the purity of the resulting products, enhance the chemical yield and shorten the reaction time.[5-7] But most of them use solvents,[8-9] but with the high vapour pressure of solvents, it sometimes leading to explosions.

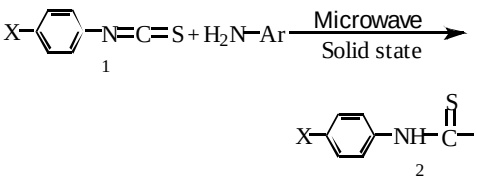
More over, as we know, solvent-free organic synthesis has great applied value and expansive prospects. It has many advantages such as high efficiency and selectivity, easy separation and purification and environmental acceptability.[10] All these merits are in accord with the green production's requests of energy-saving and high efficiency. It is one of the few clean-productions that can be used by chemists. Today, it has been widely used in a variety of organic reactions.[11-15] However, the solid-state synthesis of heterocyclic thioureas has not been reported so far.

## RESULTS AND DISCUSSION

Heterocyclic thioureas compounds are known to exhibit antiviral,[16] antituberculous,[17] fungicidal,[18] and herbicidal activities.[19] Meanwhile, some N-heterocyclic compounds (such as antipyrine) have been found to exhibit wide physiological activity,[20] too. Therefore, particularly intense interest has been directed toward the synthesis of them. Generally, the preparation of these compounds has been carried out in solution. All the existing methods have their merits. But they also have drawbacks such as using large amounts of volatile and poisonous solvents and need a long reaction time.

In order to overcome the disadvantages discussed above, avoid the use of a solvent and synthesize these valuable compounds rapidly and with a high efficiently, we investigated a new way—solvent-free synthesis using a microwave oven.

**Scheme**




*a*) X=Cl, Ar= 2-Pyridyl *b*) X=Cl, Ar =2-Benzothiazolyl
*c*) X=Cl, Ar = 4-Antipyrinyl *d*) X=Br, Ar = 2-Pyridyl
*e*) X=Br,Ar=2-Benzothiazolyl *f*) X=Br, Ar = 4-Antipyrinyl
*g*) X=EtO, Ar = 2-Pyridyl *h*) X=EtO, Ar=2-Benzothiazolyl
*i*) X=EtO, Ar= 4-Antipyrinyl

In this paper, a new solvent-free addition reaction of isothiocyanates and heterocyclic primary amine was studied. By this new method, nine heterocyclic thioureas have been synthesized in excellent yields (82.9-95.5%). This method needs only a short reaction time (2-4.5 min). The structures of the products were confirmed by Elemental analysis IR and $^1$H NMR spectroscopy. The references in the literatures of these compounds were given.[21]

## EXPERIMENTAL SECTION

Melting points were determined with a Kofler micro melting point apparatus and were uncorrected. IR spectra were recorded on a SP3-300 spectrophotometer in KBr. $^1$H NMR spectra were measured on a Bruker DPX-400M spectrometer using TMS as internal standard and $CDCl_3$ as solvent. Elemental analyses were performed on a PE-2400 CHN elemental analyser. Mass spectra were recorded on a KRATOS-AEI-MS50 (U.K.).

### General Procedure for the Preparation of N-Aryl-N′-heterocyclyl Thiourea (2a-2i)

Aryl isothiocyanate (1 mmol) and heterocyclic primary amine (1 mmol) were mixed thoroughly in an agate mortar. Then the mixture was put into a household microwave oven (the power output is 750W). The adjustor of the microwave oven was set to the proper temperature (about 50 °C). The reactants were irradiated for a period of 2-4.5 min. The reaction was traced with thin-layer chromatography. After the reaction was completed, the crude products were recrystallized with ethanol and dried under vacuum to yield the pure products.

### N-(4-chlorophenyl)-N′-(2-pyridyl) thiourea (2a)

White tabular; Yield 88.5%; mp 198-200 °C; IR $\nu_{max}$ (KBr): 3217, 3170 (m, N-H), 3080 (w, ArH), 1600, 1540 (m, Ar), 1260 (m, C=S), 1186 (m, C-N), 825, 776, 725 cm$^{-1}$; $^1$H NMR δ: 6.69-8.26 (m, 8H, ArH), 9.38 (s, 1H, NH), 13.74 (s, 1H, NH); Anal. Calcd. for $C_{12}H_{10}ClN_3S$: C, 54.65; H, 3.80; N, 15.94. Found: C, 54.51; H, 3.55; N, 15.96.

### N-(4-chlorophenyl)-N′-(2-benzothiazolyl) thiourea (2b)

White stick; Yield 83.7%; mp 219.5-221.5 °C; IR $\nu_{max}$ (KBr): 3174 (m, N-H), 3030 (w, ArH), 1605, 1590 (m, Ar), 1262 (m, C=S), 1189 (m, C-N), 836, 757 cm$^{-1}$; $^1$H NMR δ: 7.28-7.75 (m, 8H, ArH), 9.15 (s, 1H, NH), 12.98 (s, 1H, NH); Anal. Calcd. for $C_{14}H_{10}ClN_3S_2$: C, 52.58; H, 3.13; N, 13.15. Found: C, 52.39; H, 3.25; N, 13.10.

### N-(4-chlorophenyl)-N′-(4-antipyrinyl) thiourea (2c)

White needle; Yield 95.5%; mp 210-212 °C; IR $\nu_{max}$ (KBr): 3262, 3110 (m, N-H), 3066 (w, ArH), 2929 (w, $CH_3$), 1636 (m, C=O), 1617, 1574 (m, Ar), 1293 (m, C=S), 833, 726, 721 cm$^{-1}$; $^1$H NMR δ: 2.30 (s, 3H, $CH_3$), 3.17 (s, 3H, $CH_3$), 7.17-7.59 (m, 9H, ArH), 8.88-8.07 (s, 1H, NH), 10.10 (s, 1H, NH); Anal. Calcd. for $C_{18}H_{17}ClN_4OS$: C, 57.99; H, 4.56; N, 15.03. Found: C, 57.72; H, 4.39; N, 14.89.

### N-(4-bromophenyl)-N′-(2-pyridyl) thiourea (2d)

White needle; Yield 87.2%; mp 207.5-208.5 °C; IR $\nu_{max}$ (KBr): 3215, 3170 (m, N-H), 3082 (w, ArH), 1599, 1535 (m, Ar), 1264 (m, C=S), 1187 (m, C-N), 826, 776, 720 cm$^{-1}$; $^1$H NMR δ: 6.67-8.26 (m, 8H, ArH), 9.20 (s, 1H, NH), 13.75 (s, 1H, NH); Anal. Calcd. for $C_{12}H_{10}BrN_3S$: C, 46.75; H, 3.25; N, 13.64. Found: C, 46.45; H, 3.02; N, 13.79.

### N-(4-bromophenyl)-N′-(2-benzothiazolyl) thiourea (2e)

White needle; Yield 84.0%; mp221-223 °C; IR $\nu_{max}$ (KBr): 3175 (m, N-H), 3035 (w, ArH), 1600, 1590 (m, Ar), 1260 (m, C=S), 1188 (m, C-N), 837, 756 cm$^{-1}$; $^1$H NMR δ: 7.18-7.77 (m, 8H, ArH), 9.30 (s, 1H, NH), 12.05 (s, 1H, NH); Anal. Calcd. for $C_{14}H_{10}BrN_3S_2$: C, 46.15; H, 2.75; N, 11.54. Found: C, 46.50; H, 2.72; N, 11.33.

### N-(4-bromophenyl)-N′-(4-antipyrinyl) thiourea (2f)

White needle; Yield 93.9%; mp 210-212 °C; IR $\nu_{max}$ (KBr): 3261, 3111 (m, N-H), 3066 (w, ArH), 2930 (w, $CH_3$), 1635 (m, C=O), 1617, 1576 (m, Ar), 1294 (m, C=S), 829, 761, 721 cm$^{-1}$; $^1$H NMR δ: 2.32 (s, 3H, $CH_3$), 3.17 (s, 3H, $CH_3$), 7.41-7.69 (m, 8H, ArH), 8.61 (s, 1H, NH), 10.23 (s, 1H, NH); Anal. Calcd. for $C_{18}H_{17}BrN_4OS$: C, 51.80; H, 4.08; N, 13.43. Found: C, 51.61; H, 4.33; N, 13.15.

### N-(4-ethoxyphenyl)-N′-(2-pyridyl) thiourea (2g)

White needle; Yield 88.2%; mp 200-202 °C; IR $\nu_{max}$ (KBr): 3219, 3169 (m, N-H), 3084 (w, ArH), 2980, 2935 (w, Et), 1596, 1536 (m, Ar), 1244 (m, C=S), 1188 (m, C-N), 820, 776, 746 cm$^{-1}$; $^1$H NMR δ: 1.44 (t, 3H, $CH_3$), 4.07 (q, 2H, $CH_2$), 6.65-8.27 (m, 8H, ArH), 9.46 (s, 1H, NH), 13.48 (s, 1H, NH); MS (*m/z*): 273 ($M^+$) 179, 137, 108, 94 (B), 78; Anal. Calcd. for $C_{14}H_{15}N_3OS$: C, 61.54; H, 5.49; N, 15.38. Found: C, 61.14; H, 5.76; N, 15.21.

### N-(4-ethoxyphenyl)-N′-(2-benzothiazolyl) thiourea (2h)

White stick; Yield 82.9%; mp 212-214 °C; IR $\nu_{max}$ (KBr): 3174 (m, N-H), 3025 (w, ArH), 2983, 2920 (w, Et), 1594, 1573 (m, C=O), 1242 (m, C=S), 1188 (m, C-N), 839, 756 cm$^{-1}$; $^1$H NMR δ: 1.44 (t, 3H, $CH_3$), 4.08 (q, 2H, $CH_2$), 6.91-7.79 (m, 8H, ArH), 9.31 (s, 1H, NH), 12.55 (s, 1H, NH); Anal. Calcd. for $C_{16}H_{15}N_3OS_2$: C, 58.36; H, 4.56; N, 12.77. Found: C, 58.22; H, 4.57; N, 12.42.

### N-(4-ethoxyphenyl)-N′-(4-antipyrinyl) thiourea (2i)

White needle; Yield 91.1%; mp 206-208 °C; IR $\nu_{max}$ (KBr): 3262, 3111 (m, N-H), 3065 (w, ArH), 2929 (w $CH_3$), 1637 (m, C=O), 1618, 1574 (m, C=O), 1293 (m, C=S), 830,

761, 720 $cm^{-1}$; $^1H$ NMR δ: 1.37 (t, 3H, $CH_3$), 2.31 (s, 3H, $CH_3$), 3.16 (s, 3H, $CH_3$), 3.98 (q, 2H, $CH_2$), 6.74-7.40 (m, 9H, ArH), 8.40 (s, 1H, NH), 9.51 (s, 1H, NH); Anal. Calcd. for $C_{20}H_{22}N_4O_2S$: C, 62.83; H, 5.76; N, 14.66. Found: C, 62.74; H, 5.47; N, 14.56.

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**Key Words**

Solvent-free synthesis; Microwave technology; Heterocyclic thioureas.

## REFERENCES

1. Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233.
2. Caddick, S. *Tetrahedron* **1995**, *51*, 10403-10432.
3. Mingos, D. M. P. *Res. Chem. Intermed.* **1994**, *20*, 85-91.
4. Sridar, V. *Curr. Sci*. **1998**, *74*, 446-450.
5. Loupy, A.; Petit, A.; Hamelin, J.; Texierboullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213-1234.
6. Loupy, A. *Top. Curr. Chem.* **1999,** *206*, 153-207.
7. Majetich, G.; Hicks, R. *Radiat. Phys. Chem*. **1995**, *45*, 567-579.
8. Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1-47.
9. Gedye, R. J.; Smith, F.; Westaway, K. C.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279.
10. Goff, D. A.; Zuckermann, R. N. *J. Org. Chem.* **1995**, *60*, 5744.
11. Toda, F.; Tanaka, K.; Hamai, K. *J. Chem. Soc., Perkin Trans. I* **1990**, 3207.
12. Morey, J.; Frontera, A. *J. Chem.* Ed. **1995**, *72*, 63.
13. Toda, F.; Shigemasa, T. *J. Chem. Soc., Perkin Trans. I* **1989,** 209.
14. Toda, F.; Takumi, H.; Akehi, M. *J. Chem. Soc. Chem. Commun.* **1990**, 1270.
15. Strauss, C. R. *Aust. J. Chem.* **1999**, *52*, 83-96.
16. Galabov, A. S.; Galabov, B. S.; Neykova, N. A. *J. Med. Chem*. **1980**, *23*, 1048.
17. (a) Doub, L.; Richardson, L. M.; Herbst, D. R.; Black, M. L.; Stevenson, D. L.; Bambas, L. L.; Youmans, G. P.; Youmans, A. S. *J. Am. Chem. Soc*. **1958**, *80*, 2205. (b) Glasser, A. C.; Doughty, R. M. *J. Pharm. Sci.* **1962**, *51*, 1031.
18. (a) Vasilev, G.; Tomaleva, Z. *Arch. Phytopathol. Pflanzenshuts* **1973**, *9*, 309. (b) Krause, G.; Franke, R.; Vasilev, G. N. *Biochem. Physiol. Pflanz.* **1979**, *174***,** 128.
19. Vasilev, G.; Iliev, L.; Vasilev, R. *Mekh Deistviya Gerbits* **1971**, *187* [*Chem. Abstr.* **1977**, *86*, 5117d].
20. Li, X.-L.; Wang, Y.-M.; Do, D.-M.; Wen, Z.; Xiong, G.-Q.; Meng, J.-B. *Science In China (Series B)* **1997**, *27*(*3*), 202.
21. (a) Buu-Hoi, N. G.; Xuong, N. D.; Nam, N. H. *J. Chem. Soc.* **1995**, 1573-81. (b) Bhargava, P. N.; Devi, K. S. *J. India. Chem. Soc.* **1963**, *40(10)*, 868-70. (c) Takahashi, T.; Kanematsu, K. *Yakugaku Zasshi 79.* **1959**, 172-7.