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One-Pot Synthesis under Ultrasonic Irradiation of N-(Substituted phenyl)-N'-(5-methylisoxazoyl)-Thiourea Derivatives

XIAO-DONG YANG
Schoole of Medicine, Jinhua College of Profession and Technology
Jinhua, Zhejiang-321007, P.R. China
E-mail: jhyangxd@gmail.com

Reaction of substituted aniline with 5-methylisoxazoyl chloride and ammonium thiocyanate under the condition of solid-liquid phase-transfer catalysis using polyethylene glycol-600 (PEG-600) as the catalyst under ultrasonic irradiation yielded N-(substituted phenyl)-N'-(5-methylisoxazoyl)-thiourea derivatives **3a-3j** in good-to-excellent yield. The chemical structure of all compounds was established by ^{1}H NMR, FTIR, MS and elemental analysis studies.

Key Words: Thiourea, 5-Methylisoxazole derivatives, One-pot synthesis, Phase transfer catalysis, Ultrasonic irradiation.

INTRODUCTION

Research on the synthesis and biological activity of heterocyclic compounds is an important development in pesticide and medicine chemistry[1-4]. 5-Methylisoxazole-4-carboxylic acid is an intermediate of leflunomide which is a drug used for the treatment of rheumatoid arthritis[5]. It was shown that 2-amino-5-substitute-1,3,4-thiadiazoles are useful starting materials for the synthesis of various bioactive molecules[6,7].

Phase transfer catalysis (PTC) is a powerful technique accomplishing a variety of reactions under mild conditions and efficient way. A logical combination is when phase transfer catalyzed reactions are further promoted by ultrasound irradiation. This technique has been widely recognized as an efficient synthetic tool and attracted much attention[8,9].

In view of these facts, herein we report a one-pot facile, efficient and high-yield method for the synthesis of N-(substituted aniline)-N'-(5-methylisoxazoyl)thiourea under the condition of solid-liquid phase transfer catalysis using polyethylene glycol-600 (PEG-600).

EXPERIMENTAL

Melting points were determined using a Yanaco MP-241 apparatus and are uncorrected. Infrared spectra were recorded on a Bruker Equinox55 spectrophotometer as KBr tablets. ^{1}H NMR spectra were measured on a Bruker AC-P500 instrument (300 MHz) using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analyses were performed on a Yanaco MT-3CHN elemental analyzer.

All starting materials are commercial products of AR grade purity. Sulfuric acid was distilled and ammonium thiocyanate was baked before use. Analytical TLC was performed on silica gel GF_{254}.

Genernal process

N-(Substituted phenyl)-N'-(5-methylisoxazoyl)thiourea: Powdered ammonium thiocyanate (1.14 g, 15 mmol), 5-methylisoxazole-4-carbonyl chloride (1.41 g, 10 mmol), PEG-600 (0.18 g, 3 % with respect to ammonium thiocyanate) and methylene dichloride (25 mL) were placed in a dried round-bottomed flask containing a magnetic stirrer bar and stirred under ultrasonic irradiation at room temperature for 20 min. Then substituted aniline (4.5 mmol) in methylene dichloride (10 mL) was added dropwise over 0.5 h and the mixture was stirred under ultrasonic irradiation. The corresponding N-(substituted-phenyl)-N'-(5-methylisoxazoyl)thiourea precipitated immediately. The product was filtered, washed with water to remove inorganic salts, dried and recrystallized from DMF-EtOH-H_2O to give **3a-3j**.

N-(Phenyl)-N'-(5-methylisoxazoyl)thiourea (3a): Yield: 86.5 %; m.p.: 153-154 ºC; ^{1}H NMR: 12.09 (s, 1H, NH), 11.87 (s, 1H, NH), 7.11-7.24 (m, 4H, C_6H_4), 9.32 (s, 1H, H-isoxazole), 2.85 (s, 3H, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3168 (N-H), 1688 (C=O), 1302 (C=S); ESI-MS: 260 (M-1); Anal. (%): Calcd. for $C_{12}H_{11}N_3O_2S$: C, 55.16; H, 4.24; N, 16.08; found: C 55.36, H 4.35, N 16.23.

N-(3-Methyl-phenyl)-N'-(5-methylisoxazoyl)thiourea (3b): Yield: 86.4 %; m.p.: 106-107 ºC; ^{1}H NMR: 12.19 (s, 1H, NH), 11.68 (s, 1H, NH), 9.43 (s, 1H, H-isoxazole), 7.11-7.24 (m, 4H, C_6H_4), 2.67 (s, 3H, CH_3), 2.28 (s, 3H, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3161 (N-H), 1687 (C=O), 1298 (C=S); ESI-MS: 274 (M-1) ; Anal. (%): Calcd. for $C_{13}H_{13}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26; found: C 56.78, H 4.51, N 15.38.

N-(2-Chlorophenyl)-N'-(5-methylisoxazoyl)thiourea (3c): Yield: 88.8 %; m.p.: 210-211 ºC; ^{1}H NMR: 12.25 (s, 1H, NH), 11.88 (s, 1H, NH), 8.72 (s, 1H, H-isoxazole), 7.20-7.86 (m, 4H, C_6H_4), 2.83 (s, 3H, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3165 (N-H), 1680 (C=O), 1304 (C=S); ESI-MS: 294 (M-1); Anal. (%): Calcd. for $C_{12}H_{10}N_3O_2SCl$: C, 48.73; H, 3.41; N, 14.21; found: C 48.70, H 3.65, N 14.24.

N-(3-Chlorophenyl)-N'-(5-methylisoxazoyl)thiourea (3d): Yield: 86.7 %; m.p.: 232-234 ºC; ^{1}H NMR: 12.19 (s, 1H, NH), 11.84 (s, 1H, NH), 9.49 (s, 1H, H-isoxazole), 7.20-7.86 (m, 4H, C_6H_4), 2.66 (s, 3H, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3170 (N-H), 1687 (C=O), 1310 (C=S); ESI-MS: 294 (M-1); Anal. (%): Calcd. for $C_{12}H_{10}N_3O_2SCl$: C, 48.73; H, 3.41; N, 14.21; found: C 48.65, H 3.68, N 14.02.

N-(2,5-Dichlorophenyl) -N'-(5-methylisoxazoyl)thiourea (3e): Yield: 82.6 %; m.p.: 206-207 ºC; ^{1}H NMR: 12.23 (s, 1H, NH), 11.85 (s, 1H, NH), 9.62 (s, 1H, H-isoxazole), 7.09-7.52 (m, 3H, C_6H_5), 2.67 (s, 3H, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3165 (N-H), 1680 (C=O), 1303 (C=S); ESI-MS: 328 (M-1); Anal. (%): Calcd. for $C_{12}H_9N_3O_2SCl_2$: C, 43.65; H, 2.75; N, 12.73; found: C 43.91, H 2.56, N 12.44.

N-(2,4,5-Trichlorophenyl)-N'-(5-methylisoxazoyl)thiourea (3f): Yield: 80.2 %; m.p.: 199-200 ºC; ^{1}H NMR: 12.44 (s, 1H, NH), 11.90 (s, 1H, NH), 9.25 (s, 1H, H-isoxazole), 8.05, 8.26 (d, 1H, Ar-H), 2.68 (s, 3H, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3161 (N-H), 1686 (C=O), 1289 (C=S); ESI-MS: 362 (M-1); Anal. (%): Calcd. for $C_{12}H_8N_3O_2SCl_3$: C, 39.53; H, 2.21; N, 11.52; found: C 39.23, H 2.55, N 11.65.

N-(2-Iodophenyl)-N'-(5-methylisoxazoyl)thiourea (3g): Yield: 81.4 %; m.p.: 238-240 ºC; ^{1}H NMR: 12.44 (s, 1H, NH), 12.01 (s, 1H, NH), 9.36 (s, 1H, H-isoxazole), 7.16-7.59 (m, 4H, C_6H_4), 2.64 (s, 3H, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3154 (N-H), 16801 (C=O), 1315 (C=S); ESI-MS: 386 (M-1); Anal. (%): Calcd. for $C_{12}H_{10}N_3O_2SI$: C, 37.22; H, 2.60; N, 10.85; found: C 37.02, H 2.56, N 10.66.

N-(2-Trifluoromethyl-phenyl)-N'-(5-methylisoxazoyl)thiourea (3h): Yield: 88.6 %; m.p.: 203-204 ºC; ^{1}H NMR: 12.21 (s, 1H, NH), 11.78 (s, 1H, NH), 9.34 (s, 1H, H-isoxazole), 7.31-7.58 (m, 4H, C_6H_4), 2.66 (s, 3H, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3167 (N-H), 1682 (C=O), 1296 (C=S); ESI-MS: 328 (M-1); Anal. (%): Calcd. for $C_{13}H_{10}N_3O_2SF_3$: C, 47.42; H, 3.06; N, 12.76; found: C 47.44, H 2.96, N 12.46.

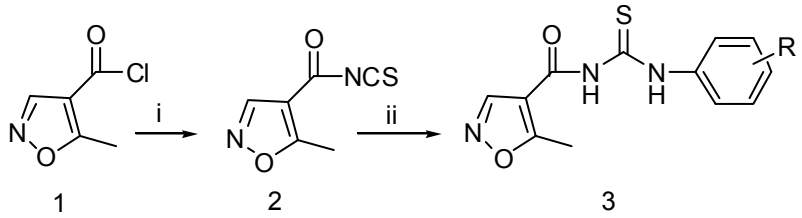
N-(3-Trifluoromethyl-phenyl)-N'-(5-methylisoxazoyl)thiourea (3i): Yield: 89.6 %; m.p.: > 250 ºC; ^{1}H NMR: 12.31 (s, 1H, NH), 11.88 (s, 1H, NH), 9.64 (s, 1H, H-isoxazole), 7.06-7.24 (m, 4H, C_6H_4), 2.65 (s, 3H, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3161 (N-H), 1697 (C=O), 1302 (C=S); ESI-MS: 328 (M-1); Anal. (%): Calcd. for $C_{13}H_{10}N_3O_2SF_3$: C, 47.42; H, 3.06; N, 12.76; found: C 47.89, H 3.28, N 12.68.

N-(4-Trifluoromethyl-phenyl)-N'-(5-methylisoxazoyl)thiourea (3j): Yield: 88.6 %; m.p. 121-123 ºC; ^{1}H NMR: 12.26 (s, 1H, NH), 11.80 (s, 1H, NH), 9.67 (s, 1H, H-isoxazole), 7.38-7.79 (m, 4H, C_6H_4), 2.83 (s, 3H, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3169 (N-H), 1684 (C=O), 1304 (C=S); ESI-MS: 328 (M-1); Anal. (%): Calcd. for $C_{13}H_{10}N_3O_2SF_3$: C, 47.42; H, 3.06; N, 12.76; found: C 47.68, H 3.28, N 12.67.

RESULTS AND DISCUSSION

The reaction under ultrasound required only 0.5 h to complete with excellent yields. Ultrasonic irradiation was carried out with KQ-218 ultrasonic cleaner 20 kHz/50 W. Compared with the conventional method, a shorter time, cleaner reaction accompained with higher yields were observed (from 76-79 to 86-88 % compared with conventional method at room temperature). Generally, the reaction proceeded quickly with excellent yield.

In present studies, we have conducted the reaction using PEG-600 as solid-liquid phase transfer catalyst under ultrasonic irradiation. This is a facile and convenient method for the synthesis of N-(substituted phenyl)-N'-(5-methylisoxazoyl)thiourea derivatives (**Scheme-I**), PEG-600 as a phase transfer catalyst is indispensable for these reactions. In addition, the ultrasonic irradiation method distinctly improves the efficiency of the synthetic process and shorten the reaction time. The catalyst PEG-600 is inexpensive, relatively non-toxic, highly stable and easily available.



Scheme-I: Reagents and conditions: (i) NH_4NCS, PEG-600, room temperature ultrasonic irradiation; (ii) $ArNH_2$, room temperature ultrasonic irradiation

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