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Microwave-Enhanced Reactions of 4-Amino-5-merecapto-1,2,4-triazoles with Benzoyl Chloride and Aromatic Aldehydes

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Abstract: The microwave-enhanced reactions of 4-amino-5-mercapto-3-substituent-1,2,4-triazoles with benzoyl chloride or arylaldehydes under solvent-free conditions without catalyst were studied. 3-Substituded-6-phenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles were easily prepared by the reactions of 4-amino-5-merecapto-3-substituded-1,2,4-triazoles with benzoyl chloride. 4-Arylideneamino-5-mercapto-3-substituted-1,2,4-triazoles were obtained by the condensation of 4-amino-5-mercapto-3-substituent-1,2,4-triazoles with aryl-aldehydes. This method possessed such advantages as short reaction time, environmentally benign procedures, easy purification, and high yield.

Keywords: 4-Arylideneamino-5-mercapto-3-substituted-4H-1,2,4-triazoles, microwave irradiation, solvent free, 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles, uncatalyzed

INTRODUCTION

1,2,4-Triazole derivatives are among the most biologically active classes of compounds, processing diverse types of biological properties such as antimicrobial,[1] antibacterial,[2] anti-inflammatory,[3] antihypertensive,[4] antitubercular,[5] and antiviral[6] activities. Since 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles were first made by Kanaoka[7] in 1956, a large number of compounds with this kind of carbon skeleton have been prepared. They combine the properties of triazoles and thiadiazoles and possess a

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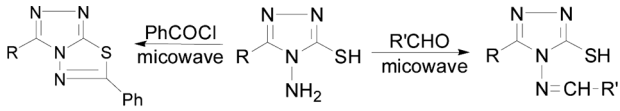

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Scheme 1. Reactions of 4-amino-5-merecapto-1,2,4- triazoles with benzoyl chloride and aromatic aldehydes: **2a–g**: R = CH_3 (**2a**); CH_3CH_2 (**2b**); $CH_3CH_2CH_2$ (**2c**); $PhCH_2$ (**2d**); Ph (**2e**); 4-ClPh (**2f**); 3,4,5-triMeO (**2g**); **3a–i**: R′ = 4-$N(CH_3)_2$-Ph: R: H (**3a**), CH_3 (**3b**), CH_3CH_2 (**3c**), $CH_3CH_2CH_2$ (**3d**), R = CH_3CH_2: R′: 2-Cl-Ph (**3e**), Ph (**3f**), 4-NO_2-Ph (**3g**), 2-OH-Ph (**3h**), 4-Cl-Ph (**3i**).

wide spectrum of biological properties.[8] Many Schiff bases carrying a 1,2,4-triazole group not only have kept the original biological activities but also are good ligands[9,10] and organic synthetic intermediates.[11,12] Both of these kinds of compounds can be synthesized from 4-amino-5-mercapto-1,2,4-triazoles **1**. Condensation of the triazoles **1** with aromatic acids or aromatic acyl chloride produces a series of 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles **2**,[13] whereas condensation with aromatic aldehydes affords a series of Schiff bases, 3-subsituted-5-mercapto-4-arylmethylene-1,2,4-triazoles **3**, or 5,6-dihydro analogs of 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles.[14] By the conventional heating method, the condensation reaction of 4-amino-5-mercapto-1,2,4-triazoles **1** with benzoyl chloride and aromatic aldehydes needs a large volume of organic solvents, acid catalysts, and a long reaction time.

Microwave-assisted reactions without solvents have attracted much interest because of the simplicity in operation, greater selectivity, and rapid synthesis of a variety of heterocyclic compounds.[15,16] This gave a great impetus to the search for a new technique of preparing 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles and 3-subsituted-5-mercapto-4-arylmethylene-1,2,4-triazoles. Here, we present the results of 4-amino-5-mercapto-1,2,4-triazoles reacted with benzoyl chloride and aromatic aldehydes, giving corresponding 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole and 3-subsituted-5-mercapto-4-arylmethylene-1,2,4-triazoles under microwave-enhanced conditions without solvents and catalysts. The synthetic route is shown in Scheme 1.

EXPERIMENTAL

Melting points were measured on an X-4 digital melting-point apparatus and are uncorrected. A Midea Microwave oven PJ17F-F(Q) was used. IR spectra were obtained in KBr discs on a Brucker Equinox-55

spectrophotometer. ^{1}H NMR spectra were recorded on a Varian spectrophotometer (400 MHz) in $CDCl_3$ using TMS as an internal standard. Mass spectra (MS) were recorded on a HP5973 GC-MS mass spectrophotometer. 4-Amino-5-merecapto-3-substituted-1,2,4-triazoles was prepared according to the literature;[17] other chemicals were purchased and used without any further purification.

Synthesis of 3-Substituded-6-phenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles

Benzoyl chloride (2.5 mmol) and 4-amino-5-mercapto-3-substituent-1,2,4-triazoles **1** (2 mmol) were mixed in a beaker covered with a watch glass. The beaker was placed in a microwave oven and irradiated at 385 W for 7 min. When it was cold, 10% $NaHCO_3$ was added until pH was 8. The precipitate was filtered, washed with water, and dried. The impure products were obtained and recrystallized from ethanol. The results are shown in Table 1.

Synthesis of 4-Arylideneamino-5-mercapto-3-substituted-1,2,4-triazoles

Arylaldehyde (2 mmol) and 4-amino-5-mercapto-3-substituent-1,2,4-triazoles **1** (2 mmol) were mixed in a beaker covered with a watch glass.

Table 1. Reaction time and yields of the products

Compound	Power (W)	Time (min)	Appearance	Yield (%)	Mp
2a	385	7	White solid	67	178–179 (176–177)[18]
2b	385	7	White solid	75	122–123 (121–122)[18]
2c	385	7	White solid	82	135–136
2d	385	7	White solid	89	159–160 (157–159)[19]
2e	385	7	White solid	85	206–208 (204–205)[13]
2f	385	7	White solid	86	205–206 (205)[20]
2g	385	7	White solid	84	224–226
3a	231	6	Light yellow solid	92	220–222 (222–223)[21]
3b	385	3	Light yellow solid	83	216–217 (214–215)[22]
3c	385	5	Light yellow solid	86	218–219 (215–217)[22]
3d	385	8	Light yellow solid	83	204–206 (202–203)[23]
3e	385	8	White solid	84	228–230 (225–227)[22]
3f	385	9	White solid	81	163–165 (160–163)[22]
3g	385	10	Yellow solid	90	223–224 (220–222)[22]
3h	385	10	White solid	86	181–183 (179–180)[22]
3i	385	8	White solid	84	175–176 (172–174)[22]

The beaker was placed in the microwave oven and irradiated for an appropriate time at an appropriate power (Table 1) until the reaction were complete as determined by thin-layer chromatography (TLC) examination. When it was cold, water was added, and the precipitates were separated by suction. The solid was washed with water, dried, and recrystallized from ethanol. The results are shown in Table 1.

3-Methyl-6-phenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole **2a**: ^{1}H NMR δ: 7.89 (d, $J = 8.0$ Hz, 2H), 7.61–7.53 (m, 3H), 2.80 (s, 3H); IR ν: 3058, 2952, 1596, 1536, 1478, 1315, 1267, 1229, 763, 688 cm^{-1}.

3-Ethyl-6-phenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole **2b**: ^{1}H NMR δ: 8.03 (d, $J = 8.0$ Hz, 2H), 7.69–7.63 (m, 3H), 3.11 (q, $J = 8.4$ Hz, 2H), 1.45 (t, $J = 8.4$ Hz, 3H); IR ν: 3066, 2979, 2937, 1599, 1520, 1479, 1313, 1251, 1212, 764, 685 cm^{-1}.

3-Propyl-6-phenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole **2c**: ^{1}H NMR δ: 7.90 (d, $J = 7.6$ Hz, 2H), 7.61–7.53 (m, 3H), 3.14 (t, $J = 7.2$ Hz, 2H), 2.01–1.95 (m, 2H), 1.09 (t, $J = 7.2$ Hz, 3H); IR ν: 3065, 2964, 2935, 1599, 1515, 1470, 1316, 1246, 1199, 766, 687 cm^{-1}; MS (70 eV) m/z (%): 244 (M^+, 5), 229 (15), 216 (100), 121 (16), 103 (4), 84 (3.8).

3-Benzyl-6-phenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole **2d**: ^{1}H NMR δ: 7.87 (d, $J = 7.6$ Hz, 2H), 7.64 (t, $J = 7.2$ Hz, 1H), 7.57 (t, $J = 8.0$ Hz, 2H), 7.51 (d, $J = 7.6$ Hz, 2H,), 7.36 (t, $J = 8.0$ Hz, 2H), 7.29 (t, $J = 7.6$ Hz, 1H), 4.60 (s, 2H); IR ν: 3037, 2915, 2848, 1598, 1517, 1492, 1469, 1267, 1163, 760, 681 cm^{-1}.

3,6-Diphenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole **2e**: ^{1}H NMR δ: 8.42 (d, $J = 8.0$ Hz, 2H), 7.97 (d, $J = 7.6$ Hz, 2H), 7.63–7.53 (m, 6H); IR ν: 3060, 1600, 1514, 1467, 1312, 1288, 768, 686 cm^{-1}.

3-(4-Chlorophenyl)-6-phenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole **2f**: ^{1}H NMR δ: 8.39 (d, $J = 8.0$ Hz, 2H), 7.96 (d, $J = 7.8$ Hz, 2H), 7.67–7.55 (m, 5H); IR ν: 3054, 1599, 1525, 1467, 1316, 1280, 1238, 828, 766, 686 cm^{-1}.

3-(3,4,5-Trimethoxylphenyl)-6-phenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole **2g**: ^{1}H NMR δ: 7.92 (d, $J = 7.2$ Hz, 2H), 7.72 (s, 2H), 7.64–7.57 (m, 3H), 4.01 (s, 6H), 3.95 (s, 3H); IR ν: 3067, 2937, 2835, 1591, 1528, 1477, 1306, 1127, 764, 685 cm^{-1}. MS (70 eV) m/z (%): 368 (M^+, 100), 353 (64), 325 (12), 193 (18), 178 (32), 150 (30), 135 (24), 121 (46), 103 (18), 77 (23).

4-(N,N-Dimethylbenzylideneamino)-5-mercapto-4H-1,2,4-triazole **3a**: ^{1}H NMR δ: 10.85 (s, 1H), 9.77 (s, 1H), 8.02 (s, 1H), 7.73 (d, $J = 8.4$ Hz, 2H), 6.74 (d, $J = 8.4$ Hz, 2H), 3.08 (s, 6H); IR ν: 3454, 3100, 3047, 2823, 2766, 1613, 1591, 1534, 1300, 1184, 811 cm^{-1}.

4-(N,N-Dimethylbenzylideneamino)-5-mercapto-3-methyl-4H-1,2,4-triazole **3b**: ^{1}H NMR δ: 10.75 (s, 1H), 9.80 (s, 1H), 7.75 (d, $J = 8.0$ Hz, 2H), 6.75 (d, $J = 8.0$ Hz, 2H), 3.08 (s, 6H), 2.43 (s, 3H); IR ν: 3450, 3100, 3057, 2924, 2751, 1591, 1531, 1498, 1311, 1162, 815 cm^{-1}.

4-(N,N-Dimethylbenzylideneamino)-5-mercapto-3-ethyl-4H-1,2,4-triazole **3c**: ^{1}H NMR δ: 10.84 (s, 1H), 9.79 (s, 1H), 7.75 (d, $J = 8.8$ Hz, 2H), 6.75 (d, $J = 8.8$ Hz, 2H), 3.08 (s, 6H), 2.83 (q, $J = 7.2$ Hz, 2H), 1.32 (t, $J = 7.2$ Hz, 3H); IR ν: 3449, 3103, 3064, 2937, 2750, 1589, 1529, 1498, 1316, 1159, 813 cm^{-1}.

4-(N,N-Dimethylbenzylideneamino)-5-mercapto-3-propyl-4H-1,2,4-triazole **3d**: ^{1}H NMR δ: 10.48 (s, 1H), 9.83 (s, 1H), 7.76 (d, $J = 8.2$ Hz, 2H), 6.80 (d, $J = 8.2$ Hz, 2H), 3.08 (s, 6H), 2.76 (t, $J = 7.6$ Hz, 2H), 1.79 (m, 2H), 1.01 (t, $J = 7.4$ Hz, 3H); IR ν: 3446, 3100, 3062, 2956, 2765, 1592, 1530, 1500, 1319, 1163, 815 cm^{-1}.

4-(2-Chlorobenzylideneamino)-5-mercapto-3-ethyl-4H-1,2,4-triazole **3e**: ^{1}H NMR δ: 11.01 (s, 1H), 10.23 (s, 1H), 8.13 (d, $J = 8.0$ Hz, 1H), 7.48–7.35 (m, 3H), 2.87 (q, $J = 6.8$ Hz, 2H), 1.36 (t, $J = 6.8$ Hz, 3H); IR ν: 3453, 3101, 3065, 2936, 2774, 1585, 1502, 1463, 1282, 1102, 768 cm^{-1}.

4-Benzylideneamino-5-mercapto-3-ethyl-4H-1,2,4-triazole **3f**: ^{1}H NMR δ: 10.42 (s, 1H), 10.33 (s, 1H), 7.87 (d, $J = 8.0$ Hz, 2H), 7.56–7.46 (m, 3H), 2.86 (q, $J = 7.2$ Hz, 2H), 1.34 (t, $J = 7.2$ Hz, 3H); IR ν: 3483, 3097, 3058, 2938, 2783, 1604, 1575, 1498, 1290, 1102, 762 cm^{-1}.

4-(4-Nitrobenzylideneamino)-5-mercapto-3-ethyl-4H-1,2,4-triazole **3g**: ^{1}H NMR δ: 10.93 (s, 1H), 10.47 (s, 1H), 8.34 (d, $J = 8.8$ Hz, 2H), 8.03 (d, $J = 8.8$ Hz, 2H), 2.88 (q, $J = 7.6$ Hz, 2H), 1.38 (t, $J = 7.6$ Hz, 3H); IR ν: 3500, 3325, 2975, 2938, 1583, 1524, 1460 , 1345, 1278, 1103 , 849 cm^{-1}.

4-(2-Hydroxybenzylideneamino)-5-mercapto-3-ethyl-4H-1,2,4-triazole **3h**: ^{1}H NMR δ: 10.49 (s, 1H), 10.30 (s, 1H), 10.23 (s, 1H), 7.49–7.43 (m, 2H), 7.10–7.00 (m, 2H), 2.82 (q, $J = 7.2$ Hz, 2H), 1.36 (t, $J = 7.2$ Hz, 3H); IR ν: 3448, 3106, 3067, 2942, 2789, 1619, 1587, 1462, 1297, 1109, 757 cm^{-1}.

4-(4-Chlorobenzylideneamino)-5-mercapto-3-ethyl-4H-1,2,4-triazole **3i**: ^{1}H NMR δ: 10.66 (s, 1H), 10.51 (s, 1H), 7.81 (d, $J = 8.2$ Hz, 2H), 7.47 (d, $J = 8.2$ Hz, 2H), 2.86 (q, $J = 7.4$ Hz, 2H), 1.36 (t, $J = 7.4$ Hz, 3H); IR ν: 3482, 3104, 3067, 2939, 2762, 1589, 1496, 1414, 1284, 1091, 819 cm^{-1}.

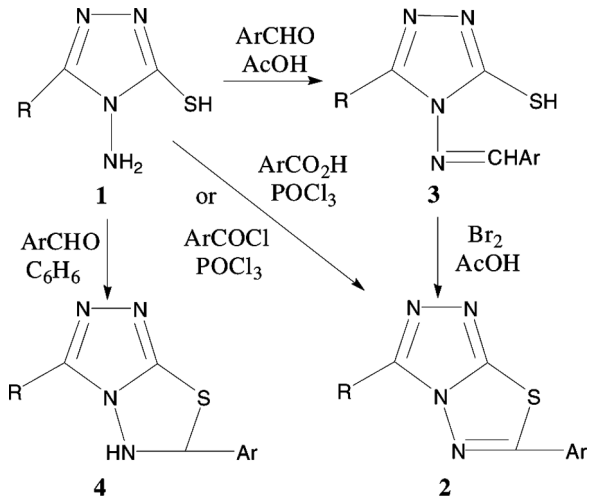
RESULTS AND DISCUSSION

The reported synthetic methods for 3,6-disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles required 5–8 h of reaction time under refluxing in phosphoryl chloride conditions. The reaction mixture needed to use crushed ice and solid potassium carbonate or potassium hydroxide to neutralize the excess of phosphoryl chloride, or the excess of phosphoryl chloride was remove under reduced pressure.[23,24] The reaction time for preparing 4-benzylideneamino-5-mercapto-3-alkyl-4H-1,2,4-triazoles under refluxing condition was 1–4 h in ethanol, and acidic catalyst also

was needed.[25,26] Under refluxing conditions in acetic acid, the reaction time can be reduced.[22] The products can be precipitated from acetic acid. However, the wasted acid needs to be treated. While under microwave irradiation, the reaction required shorter times, no solvents, and no catalysts. Purification was simple, and higher product yields make it an environmentally friendly method.

4-Amino-5-mercapto-1,2,4-triazoles **1** are important kinds of heterocyclic compounds. Triazole cycle has been incorporated into a wide variety of molecules by 4-amino-5-mercapto-1,2,4-triazoles. 1,2,4-Triazolo[3,4-b]-1,3,4-thiadiazoles generally be prepared from condensation with carboxylic acid or acyl chloride, using phosphoryl chloride as catalyst and dehydrating agent (Scheme 2). Under microwave irradiation, the condensation with benzoic acid was more difficult than with benzoyl chloride, even when phosphoryl chloride was added. Sublimation of benzoic acid and volatilization of phosphoryl chloride occurred badly.

The condensation of compound **1** with aromatic aldehydes afforded a series of Schiff bases or 5,6-dihydro triazolothiadiazoles according to different reaction conditions (Scheme 2). It was reported that compound **1** reacted with aromatic aldehydes, catalyzed by acid such as acetic acid and H_2SO_4 in ethanol or refluxed in acetic acid, to give Schiff bases. However, when it was refluxed in an aprotic solvent such as benzene, 5,6-dihydrotriazolothiadiazoles (**4**) were obtained.[14] These Schiff bases



Scheme 2. Conventional reactions of 4-amino-5-merecapto-1,2,4-triazoles with aromatic carboxylic acids or acyl chloride and aromatic aldehydes.

also could be converted to **2** if stirred with bromine in acetic acid.[27] It was found that by refluxing **1** and aldehyde in ethanol, catalyzed by hydrogen chloride, the amino group of **1** combined with the carbonyl group of aldehydes first. The products precipitated from the solution, and the precipitates were confirmed to be Schiff bases. With the reaction development, the precipitates were dissolved in the solvent gradually again. Finally, precipitates of **4** were generated, and the total reaction time was about 8–10 h.[28] Under microwave irradiation without catalyst and solvent, the reaction is very simple. The mercapto group does not react with the imine group, so the products with two heterocycles are not be obtained. There is only one kind of compound produced, the Schiff base, 4-arylmethylene-5-mercapto-1,2,4-triazoles.

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