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Solvent-Free Synthesis of 2-Amino-5-Aryloxymenthyl-1,3,4-Thiadiazoles and Their Coumarin or Benzofuran Bis-Heterocyclic Derivatives

Zheng Li
Jin-Lan Yu
Jing-Ya Yang
Wei Zhu
Yan-Long Zhao
Yu-Lin Xing
Xi-Cun Wang
Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu, People's Republic of China

2-amino-5-aryloxymethyl-1,3,4-thiadiazoles were synthesized rapidly by a microwave-accelerated solvent-free procedure in high yield via the condensation of thiosemicarbazide with aryloxyacetic acids using poly(ethylene glycol)-supported dichlorophosphate as a dehydration reagent. The solvent-free N-acylation of 2-amino-5-aryloxymethyl-1,3,4-thiadiazoles with coumarin-3-carboxylic acid chloride or benzofuran-2-carboxylic acid chloride efficiently afforded corresponding bis-heterocyclic derivatives, 2-(coumarin-3-carboxamido)-5-aryloxymethyl-1,3,4-thiadiazoles, and 2-(benzofuran-2-carboxamido)-5-aryloxymethyl-1,3,4-thiadiazoles. The strategy has advantages of no organic solvent pollution, an elevated reaction rate, an improved yield, and a simple work-up procedure.

Keywords 1,3,4-Thiadiazoles; microwave irradiation; polymer-supported reagent; room temperature grinding; solvent-free

INTRODUCTION

Heterocyclic compounds are important for their wide range of biological activities. Heterocycles containing 1,3,4-thiadiazole possess

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Address correspondence to Zheng Li, Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu, 730070 people's Republic of China. E-mail: lizheng@nwnu.edu.cn

antimicrobial, antidepressant, and antiinflammatory activities.[1] Meanwhile, heterocycles bearing coumarin exhibit anti-HIV, antitumor, antibacterial, anticoagulant, and vasorelaxant activities.[2] In addition, heterocycles including benzofuran also show insect antifeedant, cannabimimetic, reductase inhibitory, and metallothioneinogenic activities.[3] Based on these facts, bis-heterocyclic compounds involving both 1,3,4-thiadiazole and either coumarin or benzofuran might be good candidates for biologically active compounds.

The development of a solvent-free organic synthesis is of current interest because of the many advantages, such as reduced pollution, low cost, simplicity in process and handling, and potential applications in combinatorial chemistry and chemical industry.[4]

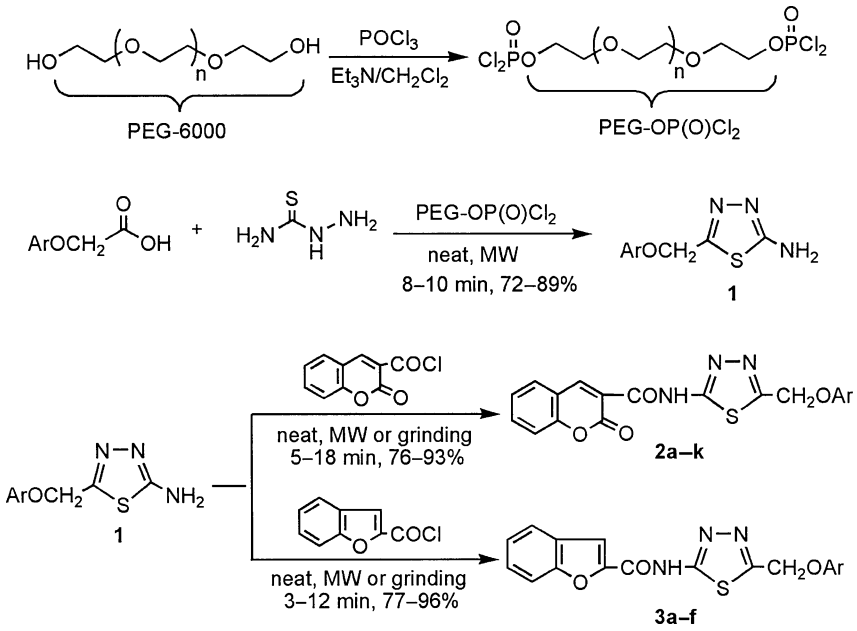
In continuation of our program to synthesize biologically active compounds and develop a benign and rapid strategy for organic synthesis under solvent-free conditions and the interest in green chemistry theme with a growing emphasis on pollution prevention, we have explored an expeditious solvent-free route to prepare 2-amino-5-aryloxymethyl-1,3,4-thiadiazoles and their bis-heterocyclic derivatives involving coumarin or benzofuran under either microwave irradiation or r.t.-grinding conditions.

RESULTS AND DISCUSSION

The mixture of thiosemicarbazide with an equivalent of aryloxyacetic acids and 2 equivalents of poly(ethylene glycol)(PEG)-supported dichlorophosphate (PEG-O-P(O)Cl_2) was irradiated in a microwave oven to afford readily 2-amino-5-aryloxymethyl-1,3,4-thiadiazoles (**1**) in a 72–89% yield (Scheme 1). Reactions could be monitored by TLC and completed within 8–10 min at 490 W microwave power. This protocol using a recoverable polymer supported the dichlorophosphate as a dehydration reagent and efficiently avoided the corrosion and environmental pollution caused by using traditional harsh reagents, e.g., concentrated sulfuric acid,[5] phosphorus oxychloride,[6] and concentrated hydrochloric acid.[7]

The homogeneous mixture of compound **1** and an equivalent of coumarin-3-carboxylic acid chloride was ground in a mortar with a pestle for 15–18 min to efficiently afford 2-(coumarin-3-carboxamido)-5-aryloxymethyl-1,3,4-thiadiazoles (**2a–k**) in a 76–90% yield (Scheme 1). The progress of the reaction was readily monitored by TLC. The different substituents on the thiadiazole ring appeared to have no significant effect on the reaction rate and the yield of the products. The same reaction also could be subjected to microwave irradiation for 5–8 min to give

the products in a 87–93% yield with an exception of **2k**, which needed 12 min to complete its reaction.



SCHEME 1

Similarly, the mixture of 2-amino-5-aryloxymethyl-1,3,4-thiadiazoles with an equivalent of benzofuran-2-carboxylic acid chloride was ground in a mortar with a pestle for 12 min to afford 2-(benzofuran-2-carboxamido)-5-aryloxymethyl-1,3,4-thiadiazoles (**3a–f**) in a 68–89% yield. The same reactions also could efficiently be effected under microwave irradiation within 3 min with no significant difference over various substituents in a very high yield (90–96%), (Scheme 1). The related data are summarized in the Table I.

As a comparison, these reactions also were tested using the solution method. Therefore, the selected compounds **2a**, **2g**, and **2j** were attempted to be obtained by refluxing the corresponding reactants in the solution of chloroform and DMSO in the presence of triethylamine for 12 h. However, only moderate yields (58%, 49%, and 40%, respectively) were obtained. The possible reason for lower yields is that the large steric hindrance caused by two heterocyclic rings make the nucleophilic substitutions more difficult in the solution condition than those in the solvent-free condition.

TABLE I The Solvent-Free Preparation of Bis-Heterocyclic Compounds 2a–k and 3a–f

		Microwave irradiation			Room-temperature grinding		
Product	Ar	Power (W)	Time (min)	Yield (%)[a]	Time (min)	Yield (%)[a]	m.p. (°C)
2a	C_6H_5	490	7	90	15	88	287–288
2b	2-$CH_3C_6H_4$	490	8	91	15	90	254–255
2c	3-$CH_3C_6H_4$	490	8	88	15	86	248–250
2d	4-$CH_3C_6H_4$	700	5	91	15	87	260–261
2e	4-$CH_3OC_6H_4$	490	8	93	15	90	246–247
2f	4-ClC_6H_4	700	5	92	15	84	297–299
2g	2,4-$Cl_2C_6H_3$	700	5	88	15	76	282–284
2h	3-$O_2NC_6H_4$	490	8	87	18	79	260–262
2i	4-$O_2NC_6H_4$	700	5	88	18	84	290–292
2j	1-Naphthyl	700	5	89	18	90	274–276
2k	2-Naphthyl	490	12	93	18	79	293–295
3a	C_6H_5	210	3	96	12	82	245–246
3b	2-$CH_3C_6H_4$	210	3	94	12	84	240–241
3c	4-$CH_3C_6H_4$	210	3	95	12	79	256–258
3d	4-$CH_3OC_6H_4$	210	3	96	12	89	231–233
3e	4-$O_2NC_6H_4$	210	3	93	12	68	296–298
3f	1-Naphthyl	210	3	90	12	77	225–226

[a]Yields refer to the isolated products.

In conclusion, we have developed an efficient, expeditious, and solvent-free method for the synthesis of 2-amino-5-aryloxymethyl-1,3,4-thiadiazoles using a polymer-supported dehydration reagent and their bis-heterocyclic compounds bearing coumarin or benzofuran via N-acylation reactions, in which the steric hindered compounds readily can be prepared within a shorter time in a much higher yield than in the traditional solution method. Furthermore, the solvent-free strategy exhibits advantages of no organic solvent pollution, an elevated reaction rate, and a simple work-up procedure.

EXPERIMENTAL

IR were recorded using KBr pellets on an Alpha Centauri FTIR spectrophotometer and ^{1}H NMR spectra on an Avanci-D2X-200 instrument using $(CD_3)_2SO$ as a solvent and Me_4Si as an internal standard. Elemental analyses were performed on a Vario E1 Elemental Analysis instrument. Mass spectra were recorded on a QP-1000A GC-MS using the impact mode (70 eV). Melting points were observed in an electrothermal melting point apparatus and were uncorrected. Polymer-supported dichlorophosphate was prepared according to a literature procedure.[8]

Coumarin-3-carboxylic acid chloride and benzofuran-2-carboxylic acid chloride were prepared by the reactions of the corresponding acids with thionyl chloride.

General Procedure for the Preparation of 2-amino-5-aryloxymethyl-1,3,4-thiadiazoles

Thiosemicarbazide (1 mmol), aryloxyacetic acids (1 mmol) and PEG-supported dichlorophosphate (2 mmol) was mixed in a mortar using a pestle until a fine and homogeneous mixture was obtained. Then the mixture was placed in a microwave oven and irradiated for 8–10 min at 490 W power by means of 1 min of irradiation and then at a 30 s interval in order to keep the temperature at *ca.* 120°C. The completion of the reactions was monitored by TLC using ethyl acetate, acetone, and petroleum ether (3:2:4) as eluent. Then distilled water was added to the resulting mixture, and the precipitate was collected by filtration and recrystallized from DMF-EtOH to afford the products. The physical and spectral data of representative compounds **1a** and **1e** are shown below:

2-amino-5-phenoxymethyl-1,3,4-thiadiazole (**1a**): Yield: 84%; m.p.: 201–202°C; ^{1}H NMR: (DMSO-d_6, 200 MHz): δ 6.28 (2H, s, NH_2, exchangeable with D_2O), 6.84–7.28 (5H, m, Ar-H), 5.27 (2H, s, OCH_2); IR (KBr, ν, cm^{-1}): 3264, 3097 (N—H), 1637 (C=N), 1509, 1362, 1246, 1040 (1,3,4-thiadiazole nucleus). MS: *m/z*, 207 (M^+). Anal. calcd. for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.27. Found: C, 52.04; H, 4.44; N, 20.19.

2-amino-5-(4-methoxylphenoxymethyl)-1,3,4-thiadiazole (**1e**): Yield: 74%; m.p.: 210–212°C; ^{1}H NMR: (DMSO-d_6, 200 MHz): δ 6.29 (2H, s, NH_2, exchangeable with D_2O), 6.90–7.24 (4H, m, Ar-H), 5.28 (2H, s, OCH_2), 3.82 (3H, s, OCH_3); IR (KBr, ν, cm^{-1}): 3265, 3094 (N—H), 1639 (C=N), 1507, 1363, 1246, 1036 (1,3,4-thiadiazole nucleus). MS: *m/z*, 237 (M^+). Anal. calcd. for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71. Found: C, 50.57; H, 4.74; N, 17.85.

General Procedure for the Preparation of Compounds 2a–k and 3a–f

The mixture of 2-amino-5-aryloxymethyl-1,3,4-thiadiazole (0.5 mmol) and coumarin-3-carboxylic acid chloride or benzofuran-2-carboxylic acid chloride (0.5 mmol) was ground in a mortar with a pestle until the mixture was homogeneous. Then the resulting mixture was either irradiated in a microwave oven at an appropriate power for a certain time or was ground for a certain time at r.t. The progress of the reactions was monitored by TLC using acetone/ethyl acetate/petroleum

ether (1:1:2) as an eluent. The resulting solid was crystallized from AcOH or AcOH-DMF to afford the products. The analytic data for compounds **2a–k** and **3a–f** are as follows:

2a: White crystal. ^{1}H NMR (DMSO-d_6): δ 12.35 (1H, s, NH), 8.97 (1H, s, =CH), 6.90–7.94 (9H, m, Ar-H), 5.50 (2H, s, CH_2). IR (KBr,ν, cm^{-1}): 3189 (N–H), 1713 (C=O), 1666 (C=O). MS: *m/z*, 379 (M^+). Anal. calcd. for $C_{19}H_{13}N_3O_4S$: C, 60.15; H, 3.45; N, 11.08. Found: C, 60.21; H, 3.38; N, 11.01.

2b: White crystal. ^{1}H NMR (DMSO-d_6): δ 12.36 (1H, s, NH), 9.00 (1H, s, =CH), 6.93–8.02 (8H, m, Ar-H), 5.52 (2H, s, CH_2), 2.24 (3H, s, CH_3). IR (KBr, ν, cm^{-1}): 3206 (N–H), 1718 (C=O), 1669 (C=O). MS: *m/z*, 393 (M^+). Anal. calcd. for $C_{20}H_{15}N_3O_4S$: C, 61.06; H, 3.84; N, 10.68. Found: C, 61.18; H, 3.90; N, 10.72.

2c: White crystal. ^{1}H NMR (DMSO-d_6): δ 12.39 (1H, s, NH), 9.01 (1H, s, =CH), 6.94–7.98 (8H, m, Ar-H), 5.51 (2H, s, CH_2), 2.22 (3H, s, CH_3). IR (KBr, ν, cm^{-1}): 3205 (N–H), 1715 (C=O), 1666 (C=O). MS: *m/z*, 393 (M^+). Anal. calcd. for $C_{20}H_{15}N_3O_4S$: C, 61.06; H, 3.84; N, 10.68. Found: C, 60.98; H, 3.88; N, 10.70.

2d: White crystal. ^{1}H NMR (DMSO-d_6): δ 12.38 (1H, s, NH), 9.00 (1H, s, =CH), 6.95–8.00 (8H, m, Ar-H), 5.50 (2H, s, CH_2), 2.23 (3H, s, CH_3). IR (KBr, ν, cm^{-1}): 3204 (N–H), 1716 (C=O), 1667 (C=O). MS: *m/z*, 393 (M^+). Anal. calcd. for $C_{20}H_{15}N_3O_4S$: C, 61.06; H, 3.84; N, 10.68. Found: C, 61.11; H, 3.78; N, 10.57.

2e: Yellow crystal. ^{1}H NMR (DMSO-d_6): δ12.40 (1H, s, NH), 9.01 (1H, s, =CH), 6.97–8.02 (8H, m, Ar-H), 5.53 (2H, s, CH_2), 3.52 (3H, s, CH_3). IR (KBr, ν, cm^{-1}): 3199 (N–H), 1724 (C=O), 1670 (C=O). MS: *m/z*, 409 (M^+). Anal. calcd. for $C_{20}H_{15}N_3O_5S$: C, 58.67; H, 3.69; N, 10.26. Found: C, 58.74; H, 3.60; N, 10.19.

2f: Yellow crystal. ^{1}H NMR (DMSO-d_6): δ 12.41 (1H, s, NH), 9.02 (1H, s,=CH), 6.94–8.03 (8H, m, Ar-H), 5.54 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3202 (N–H), 1726 (C=O), 1679 (C=O). MS: *m/z*, 413 (M^+). Anal. calcd. for $C_{19}H_{12}ClN_3O_4S$: C, 55.14; H, 2.92; N, 10.15. Found: C, 55.07; H, 3.00; N, 10.10.

2g: Yellow crystal. ^{1}H NMR (DMSO-d_6): δ 12.43 (1H, s, NH), 9.04 (1H, s, =CH), 6.94–8.07 (7H, m, Ar-H), 5.54 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3212 (N–H), 1729 (C=O), 1689 (C=O). MS: *m/z*, 447 (M^+). Anal. calcd. for $C_{19}H_{11}Cl_2N_3O_4S$: C, 50.91; H, 2.47; N, 9.37. Found: C, 50.84; H, 2.53; N, 9.44.

2h: White crystal. ^{1}H NMR (DMSO-d_6): δ 12.42 (1H, s, NH), 9.04 (1H, s, =CH), 7.01–8.09 (8H, m, Ar-H), 5.53 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3207 (N–H), 1724 (C=O), 1667 (C=O). MS: *m/z*, 424 (M^+). Anal. calcd. for $C_{19}H_{12}N_4O_6S$: C, 53.77; H, 2.85; N, 13.20. Found: C, 53.86; H, 2.78; N, 13.14.

2i Yellow crystal. ^{1}H NMR (DMSO-d_6): δ 12.41 (1H, s, NH), 9.03 (1H, s, =CH), 7.03–8.12 (8H, m, Ar-H), 5.54 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3210 (N–H), 1730 (C=O), 1669 (C=O). MS: *m/z*, 424 (M^+). Anal. calcd. for $C_{19}H_{12}N_4O_6S$: C, 53.77; H, 2.85; N, 13.20. Found: C, 53.70; H, 2.91; N, 13.13.

2j: White crystal. ^{1}H NMR (DMSO-d_6): δ 12.38 (1H, s, NH), 9.00 (1H, s, =CH), 6.93–7.99 (11H, m, Ar-H), 5.51 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3206 (N–H), 1720 (C=O), 1668 (C=O). MS: *m/z*, 429 (M^+). Anal. calcd. for $C_{23}H_{15}N_3O_4S$: C, 64.33; H, 3.52; N, 9.78. Found: C, 64.25; H, 3.48; N, 9.86.

2k: Yellow crystal. ^{1}H NMR (DMSO-d_6): δ 12.40 (1H, s, NH), 8.98 (1H, s, =CH), 6.97–8.01 (11H, m, Ar-H), 5.52 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3205 (N–H), 1723 (C=O), 1676 (C=O). MS: *m/z*, 393 (M^+). Anal. calcd. for $C_{23}H_{15}N_3O_4S$: C, 64.33; H, 3.52; N, 9.78. Found: C, 64.40; H, 3.49; N, 9.71.

3a: White crystal. ^{1}H NMR (DMSO-d_6): δ 13.44 (1H, s, NH), 6.96–8.10 (10H, m, Ar-H and Fu-H), 5.53 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3218 (N–H), 1676 (C=O). MS: *m/z*, 351 (M^+). Anal. calcd. for $C_{18}H_{13}N_3O_3S$: C, 61.53; H, 3.73; N, 11.96. Found: C, 61.46; H, 3.80; N, 12.00.

3b: White crystal. ^{1}H NMR (DMSO-d_6): δ 13.43 (1H, s, NH), 7.04–8.21 (9H, m, Ar-H and Fu-H), 5.52 (2H, s, CH_2), 2.30 (3H, s, CH_3). IR (KBr, ν, cm^{-1}): 3212 (N–H), 1675 (C=O). MS: *m/z*, 365 (M^+). Anal. calcd. for $C_{19}H_{15}N_3O_3S$: C, 62.45; H, 4.14; N, 11.50. Found: C, 62.33; H, 4.10; N, 11.58.

3c: White crystal. ^{1}H NMR (DMSO-d_6): δ 13.45 (1H, s, NH), 7.03–8.19 (9H, m, Ar-H and Fu-H), 5.53 (2H, s, CH_2), 2.28 (3H, s, CH_3). IR (KBr, ν, cm^{-1}): 3213 (N–H), 1674 (C=O). MS: *m/z*, 365 (M^+). Anal. calcd. for $C_{19}H_{15}N_3O_3S$: C, 62.45; H, 4.14; N, 11.50. Found: C, 62.51; H, 4.08; N, 11.44.

3d: White crystal. ^{1}H NMR (DMSO-d_6): δ 13.48 (1H, s, NH), 7.02–8.14 (9H, m, Ar-H and Fu–H), 5.54 (2H, s, CH_2), 3.51 (3H, s, CH_3). IR (KBr, ν, cm^{-1}): 3108 (N–H), 1677 (C=O). MS: *m/z*, 381 (M^+). Anal. calcd. for $C_{19}H_{15}N_3O_4S$: C, 59.83; H, 3.96; N, 11.02. Found: C, 59.76; H, 4.01; N, 11.12.

3e: White crystal. ^{1}H NMR (DMSO-d_6): δ 13.50 (1H, s, NH), 7.21–8.29 (9H, m, Ar-H and Fu-H), 5.55 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3105 (N–H), 1674 (C=O). MS: *m/z*, 396 (M^+). Anal. calcd. for $C_{18}H_{12}N_4O_5S$: C, 54.54; H, 3.05; N, 14.13. Found: C, 54.62; H, 3.11; N, 14.04.

3f:White crystal. ^{1}H NMR (DMSO-d_6): δ 13.45 (1H, s, NH), 7.01–8.14 (12H, m, Ar-H and Fu-H), 5.53 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3213 (N–H), 1688 (C=O). MS: *m/z*, 401 (M^+). Anal. calcd. for $C_{22}H_{15}N_3O_3S$: C, 65.82; H, 3.77; N, 10.47. Found: C, 65.75; H, 3.82; N, 10.54.

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