Polymer-supported dichlorophosphate: a recoverable new reagent for synthesis of 2-amino-1,3,4-thiadiazoles

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Poly(ethylene glycol) (PEG) supported dichlorophosphate was efficiently used as a recoverable new dehydration reagent for rapid synthesis of 2-amino-5-substituted-1,3,4-thiadiazoles under microwave irradiation and solvent-free condition by reactions of thiosemicarbazide with aliphatic acids, benzoic acid, aryloxyacetic acids or furan-2-carboxylic acids.

Keywords: 2-amino-1,3,4-thiadiazole, polymer supported reagent

Substituted 1,3,4-thiadiazole derivatives have attracted much attention due to their diverse biological activites, such as antituberculosis,[1] antibacterial,[2] anesthetic,[3] anticonvulsant,[4] cardiotonic,[5] antidepressant,[6] antiflammatory[7] and antiulcer[8] activities. 2-Amino-5-substituted-1,3,4-thiadiazoles were generally synthesised by reactions of thiosemicarbazide with a variety of acids using excess harsh reagents, *e.g.*, concentrated sulfuric acid,[1] phosphorous oxychloride,[9] concentrated hydrochloric acid[10] and polyphosphoric acid.[10] All of these reagents not only make the reaction systems corrosive, but also cause the severely environmental problems because of difficult separation and recovery. Recently, we have successfully synthesised a polymer supported reagent, poly(ethylene glycol) (PEG) supported dichlorophosphate (PEG-$OP(O)Cl_2$), which has been utilised in the cyclisation of diacylhydrazines to form oxadiazoles as a condensation reagent.[11] In continuation of the interest in green chemistry theme with growing emphasis on pollution prevention and extending applications of this polymer supported reagent, we now report a microwave-assisted solvent-free synthesis of 2-amino-5-substituted-1,3,4-thiadiazoles using PEG-$OP(O)Cl_2$ as dehydration reagent.

The mixture of thiosemicarbazide with equivalent of various acids and 2 equivalents of PEG supported dichlorophosphate was irradiated in microwave oven to readily afford 2-amino-5-substituted-1,3,4-thiadiazoles (**1a–o**) in high yield (Scheme 1). Reactions could be monitored by TLC and completed within 4–10 min at 490 W microwave power. Aliphatic acids could be rapidly reacted with thiosemicarbazide to give desired products (entries **1a–e**). The reaction of benzoic acid with thiosemicarbazide proceeded smoothly to give **1f** as product, but a bit longer time was required. Meanwhile, the reactions of various aryloxyacetic acids with thiosemicarbazide (entries **1i–o**) were also performed efficiently without significant substituent effect. In addition, the similar reactions could also be carried out between heterocyclic acids, for example, 5-aryl-furan-2-carboxylic acid and benzofuran-2-carboxylic acid, and thiosemicarbazide (entries **1g–h**). All desired products were isolated only by washing away the polymer reagent with water. Subsequently, the PEG supported reagent was easily recovered from the aqueous solution by extraction. The results are outlined in Table 1.

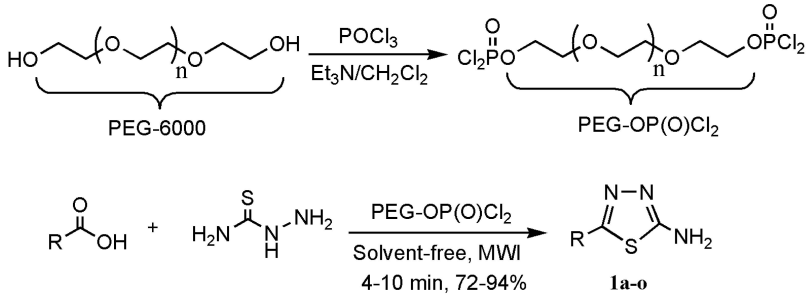
In conclusion, we have devised an efficient solvent-free MW-assisted protocol for the preparation of 2-amino-5-substituted-1,3,4-thiadiazoles by using PEG-$OP(O)Cl_2$ as dehydration reagent. The features of no corrosion, no environmental pollution, simple work-up procedure, utilisation of easily preparative and recoverable polymer supported reagent make this method more suitable to high throughput and combinatorial synthesis of 2-amino-1,3,4-thiadiazoles over previous methods.

Experimental

IR were recorded using KBr pellets on an Alpha Centauri FT-IR spectrophotometer and ^1H NMR spectra on an Avanci-D2X-200 instrument using $(CD_3)_2SO$ as solvent and Me_4Si as 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 uncorrected. PEG supported dichlorophosphate was prepared according to literature procedure.[11]

General procedure for preparation of compounds **1a–o**

Thiosemicarbazide (1 mmol), various 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 total 4–10 min at 490 W power by means of 1 min irradiation then 30 s interval in order to keep temperature at *ca* 120 °C. The completion of 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 recrystallised from DMF–EtOH to afford products. The aqueous solution was extracted by chloroform to recover PEG-supported reagent. All the



Scheme 1

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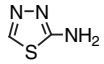
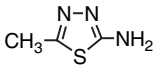
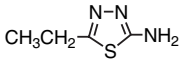
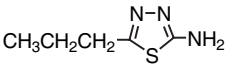
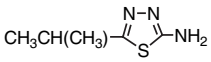
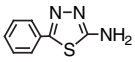
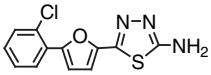
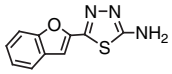
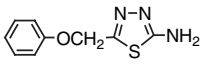
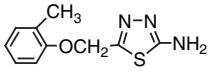
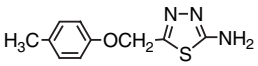
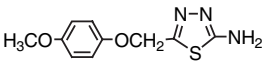
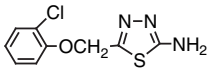
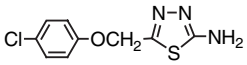
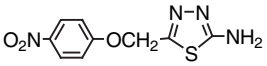
Table 1 Solvent-free synthesis of **1a–o** under MWI using PEG supported reagent

Entry	Product	Reaction time/min	M.p. (lit)/°C	Yield [a] (lit)/%
1a		4	191–192 (190–192[10])	94 (96[10])
1b		5	200–201 (202–204[10])	85 (74[10])
1c		5	198–199 (196–198[10])	84(73[10])
1d		6	194–195 (193–195[10])	88 (71[10])
1e		6	189–190 (187–189[10])	90 (68[10])
1f		8	225–227 (226–227[12])	77 (51[12])
1g		10	202–203 (203–204[13])	87 (92[13])
1h		10	278–279 (278–279[13])	89 (95[13])
1i		8	201–202	84
1j		10	206–207	82
1k		8	228–230	74
1l		8	210–212	74
1m		10	222–223	72
1n		9	228–229	84
1o		10	215–216	89

[a]Yields refer to the isolated products.

products were identified by ^{1}H NMR, IR, MS, elemental analyses and compared with authentic samples. The physical and spectral data of some unknown compounds are shown below:

1i: ^{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.

1j: ^{1}H NMR: (DMSO-d_6, 200 MHz): δ 6.27 (2H, s, NH_2, exchangeable with D_2O), 6.97–7.32 (4H, m, Ar–H), 5.26 (2H, s, OCH_2), 2.13 (3H, s, CH_3); IR (KBr, ν, cm^{-1}): 3254, 3094 (N–H), 1640 (C=N), 1508, 1363, 1248, 1035 (1,3,4-thiadiazole nucleus). MS: *m/z*, 221 (M^+). Anal. Calcd. for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.20; H, 4.94; N, 19.10.

1k: ^{1}H NMR: (DMSO-d_6, 200 MHz): δ 6.27 (2H, s, NH_2, exchangeable with D_2O), 6.97–7.34 (4H, m, Ar–H), 5.25 (2H, s, OCH_2), 2.14 (3H, s, CH_3); IR (KBr, ν, cm^{-1}): 3255, 3096 (N–H), 1641 (C=N), 1509, 1365, 1249, 1035 (1,3,4-thiadiazole nucleus). MS: *m/z*, 221 (M^+). Anal. Calcd. for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.33; H, 5.09; N, 18.92.

1l: ^{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), 5.27 (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.

1m: ^{1}H NMR: (DMSO-d_6, 200 MHz): δ 6.30 (2H, s, NH_2, exchangeable with D_2O), 7.04–7.39 (4H, m, Ar–H), 5.29 (2H, s, OCH_2); IR (KBr, ν, cm^{-1}): 3262, 3098 (N–H), 1643 (C=N), 1506, 1365, 1247, 1037 (1,3,4-thiadiazole nucleus). MS: *m/z*, 241 (M^+). Anal. Calcd. for $C_9H_8ClN_3OS$: C, 44.72; H, 3.34; N, 17.39. Found: C, 44.80; H, 3.45; N, 17.46.

1n: ^{1}H NMR: (DMSO-d_6, 200 MHz): δ 6.32 (2H, s, NH_2, exchangeable with D_2O), 7.06–7.43 (4H, m, Ar–H), 5.28 (2H, s, OCH_2); IR (KBr, ν, cm^{-1}): 3263, 3096 (N–H), 1644 (C=N), 1507, 1365, 1246, 1036 (1,3,4-thiadiazole nucleus). MS: *m/z*, 241 (M^+). Anal. Calcd. for $C_9H_8ClN_3OS$: C, 44.72; H, 3.34; N, 17.39. Found: C, 44.67; H, 3.29; N, 17.44.

1o: ^{1}H NMR: (DMSO-d_6, 200 MHz): δ 6.32 (2H, s, NH_2, exchangeable with D_2O), 7.12–7.48 (4H, m, Ar–H), 5.30 (2H, s, OCH_2); IR (KBr, ν, cm^{-1}): 3270, 3099 (N–H), 1646 (C=N), 1509, 1368, 1245, 1038 (1,3,4-thiadiazole nucleus). MS: *m/z*, 252 (M^+). Anal. Calcd. for $C_9H_8N_4O_3S$: C, 42.85; H, 3.20; N, 22.21. Found: C, 42.90; H, 3.17; N, 22.16.

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