Synthesis of 1,3,4-Oxadiazoles Having Phenol or Thiophenol Group

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Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical and material interest, which is documented by a steadily increasing number of publications and patents. For instance, 2-amino-1,3,4-oxadiazoles act as muscle relaxants[1] and show antimitotic activity.[2] Analgesic, antiinflammatory, anticonvulsive, diuretic and antiemetic properties are exhibited by 5-aryl-2-hydroxymethyl-1,3,4-oxadiazole derivatives,[3] and 2-hydroxyphenyl-1,3,4-oxadiazole acts as a hypnotic and as a sedative.[4] Some material applications of 1,3,4-oxadiazole derivatives lie in the fields of photosensitizers[5] and liquid crystals.[6]

The common synthetic approaches to oxadiazoles[7] involve cyclization of diacylhydrazines. A variety of reaction conditions influence the cyclization reaction. Typically, the reaction is promoted by heat and anhydrous reagents including thionyl chloride,[8] phosphorous oxychloride,[9] phosphorous pentoxide,[10] triphenylphosphine,[11] and triflic anhydride.[12] Alternative synthetic methods comprise reaction of carboxylic hydrazides with keteneylidene triphenylphosphorane[13] or base-promoted cyclization reaction of trichloroacetic acid hydrazones.[14] Herein we report a simple method for the synthesis of 1,3,4-oxadiazoles having phenol[15] or thiophenol group.

Treatment of a suspension of salicylic hydrazide (**1**) in toluene with acetic anhydride or an acid chloride in the presence of an equimolecular amount of methanesulfonic acid at room temperature, and then heating to reflux temperature gave 1,3,4-oxadiazoles **3a**, **3c**, **3e** and **3g** in yields ranging from 43 to 68%. Similarly, thiosalicylic hydrazide afforded the corresponding 1,3,4-oxadiazoles **3b**, **3d**, **3f**, and **3h** (31-36%) (Scheme 1, Table 1).

Also, the preparation of 2-substituted amino-1,3,4-oxadiazoles[16] from salicylic semicarbazide **2** was conducted. Thus, treatment of salicylic semicarbazides **2**, which were readily obtainable by the reaction of **1** with isocyanates, under Appel's dehydration condition ($Ph_3P/CCl_4/Et_3N$)[17] smoothly afforded 1,3,4-oxadiazoles **3i-3n** (47-85%) *via* carbodiimide intermediates followed by intramolecular cyclization reaction and hydride shift.

The advantage of the present method is cheap, nontoxic, stable, and easy to handle. There are some limitations as regards to the low yields of 1,3,4-oxadiazoles having thiophenol group.

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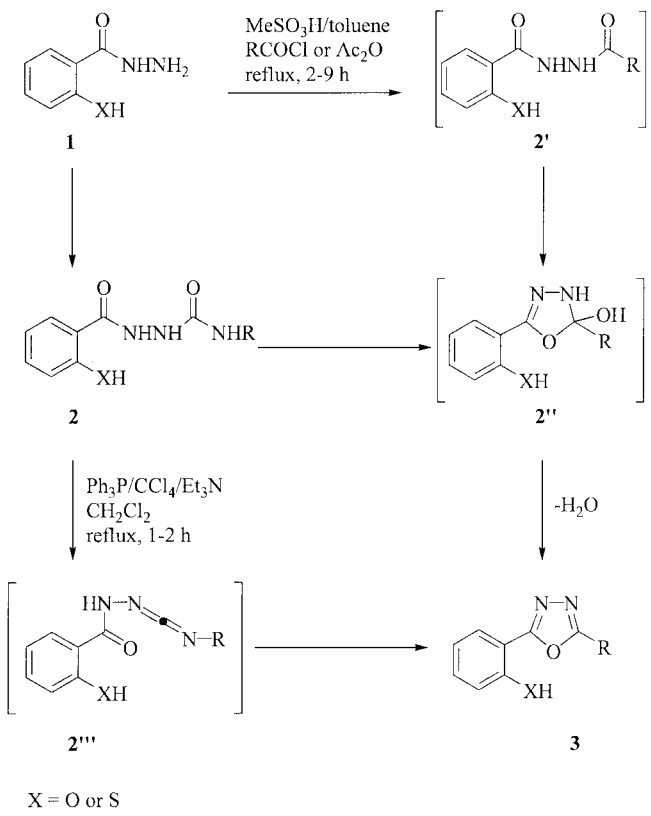

Scheme 1

Experimental Section

Toluene was dried and distilled from CaH_2. Silica gel EM 7747 for column chromatogrophy was used throughout for product separation. Melting points were taken using an Electrothermal melting point apparatus and were uncorrected. Mass spectra were obtained using either Hewlett Packard model 5985 B or ThermoQuest Polaris Q mass spectrometer operating at 70 eV. ^1H NMR spectra were measured on a Varian Gemini 300 spectrometer. Thiosalicylic hydrazide[18] was prepared following the literature procedure.

General procedure for the preparation of 1,3,4-oxadiazoles 3a-3h. To a stirred suspension of salicylic hydrazide (**1**, 10 mmol) in 50 mL of toluene was added $MeSO_3H$ (0.96 g, 10 mmol) at r.t. The mixture was stirred for 10 min at ambient temperature, then either acetic anhydride (10 mmol) or acid chloride (10 mmol) was added, and the stirring was continued for the time indicated in Table 1 at reflux temper-

Table 1. 1,3,4-Oxadiazoles **3** Prepared

Product	X	R	Reaction Time (h)	Yield (%)	Mp (°C)	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
3a	O	Me	3	68	72-73	2.63 (s, 3H, CH_3),6.90-7.80 (m, 4H, Ar), 10.09 (s, 1H, OH)	176 (M^+, 100), 121 (67), 105 (23), 92 (17)
3b	S	Me	2	35	78-80	2.64 (s, 3H, CH_3),6.85 (s, 1H, SH), 7.22-7.46 (m, 3H, Ar), 7.88-7.91 (m, 1H, Ar)	192 (M^+, 100), 163 (21), 151 (68)
3c	O	CH_2Cl	6	59	130	4.81 (s, 2H, CH_2), 7.03-7.81 (m, 4H, Ar), 9.95 (s, 1H, OH)	212 (M^+, 13), 210 (M^-, 42), 121 (100)
3d	S	CH_2Cl	2	36	104-105	4.80 (s, 2H, CH_2), 6.57 (s, 1H, SH), 7.22-7.4 (m, 3H, Ar), 7.93-7.97 (m, 1H, Ar)	228 (M^+, 31), 226 (M^-, 85), 151 (100)
3e	O	CO_2Et	9	44	68-69	1.50 (t, 3H, J = 7.1, CH_3), 4.58 (q, 2H, J = 7.1, CH_2), 7.05-7.91 (m, 4H, Ar), 9.94 (s, 1H, OH)	234 (M^+, 11), 206 (29), 161 (55), 133 (17), 121 (100)
3f	S	CO_2Et	2	36	107-108	1.49 (t, 3H, J = 7.1, CH_3), 4.57 (q, 2H, J = 7.1, CH_2), 6.53 (s, 1H, SH), 7.27-7.49 (m, 3H, Ar), 8.04-8.07 (m, 1H, Ar)	250 (M^+, 36), 151 (100), 136 (11)
3g	O	Ph	4	43	164-165	7.05-8.18 (m, 9H, Ar), 10.19 (s, 1H, OH)	238 (M^+, 22), 181 (86), 121 (100), 105 (82)
3h	S	Ph	2	31	114-115	6.83 (s, 1H, SH), 7.26-7.57 (m, 6H, Ar), 8.04-8.18 (m, 3H, Ar)	254 (M^+, 100), 225 (21), 197 (29), 151 (61)
3i	O	PhNH	1	75	222	6.97-7.17 (m, 3H, Ar), 7.32 (s, 1H, NH), 7.38-7.66 (m, 6H, Ar), 10.02 (s, 1H, OH)	253 (M^+, 100), 252 (29), 196 (15), 161 (20), 93 (39)
3j	S	PhNH	2	57	192-193	6.87 (s, 1H, SH), 7.10-7.82 (m, 10H, Ar + NH)	269 (M^+, 70), 268 (41), 177 (52), 151 (100), 135 (52), 91 (37)
3k	O	4-ClC_6H_4NH	1	82	245-247	6.96-7.13 (m, 2H, Ar), 7.36-7.63 (m, 9H, Ar + NH), 9.95 (s, 1H, NH)	289 (M^+, 34), 287 (M^-, 100), 286 (39), 16 (55), 129 (18), 127 (46)
3l	S	4-ClC_6H_4NH	2	47	228-229	6.75 (s, 1H, SH), 7.26-7.78 (m, 9H, Ar + NH)	305 (M^+, 1), 303 (M^-, 2), 153 (93), 151 (100), 127 (78)
3m	O	4-$MeOC_6H_4NH$	1	85	202-204	3.83 (s, 3H, CH_3O), 6.93-7.62 (m, 9H, Ar + NH), 10.02 (s, 1H, OH)	283 (M^+, 100), 282 (36), 268 (19), 226 (17), 151 (23), 123 (42)
3n	S	4-$MeOC_6H_4NH$	2	41	161-163	3.82 (s, 3H, CH_3O), 6.87 (s, 1H, SH), 6.93-7.79 (m, 9H, Ar+NH)	299 (M^+, 19), 298 (9), 149 (100), 123 (79)

ature. After cooling, the mixture was neutralized with sat. $NaHCO_3$ solution (pH = 8-9), and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), combined, and dried over $MgSO_4$. The solvent was evaporated and residual material was chromatographed on a silica gel column eluted with CH_2Cl_2 to give **3a-3h**. The physical and spectral data are listed in Table 1.

General procedure for the preparation of salicylic semicarbazides 2i-2n. To a stirred suspension of salicylic hydrazide (**1**, 10 mmol) in 20 mL of CH_2Cl_2 was added isocyanate (10 mmol) at r.t. The white solid was precipitated as soon as addition was completed. After stirring for 30 min. at ambient temperature, the precipitated solid was separated by filtration, washed with ether to give **2i-2n**.

The spectral and analytical data of products are as follows:

2i (X = O, R = C_6H_5NH): yield 99%, mp 219-220 °C. ^{1}H NMR (DMSO-d_6) δ 6.92-7.92 (m, 9H, Ar), 8.35 (s, 1H, NH), 8.94 (s, 1H, NH), 10.46 (s, 1H, OH), 11.98 (s, 1H, NH).

2j (X = S, R = C_6H_5NH): yield 94%, mp 202-203 °C. ^{1}H NMR (DMSO-d_6) δ 5.43 (s, 1H, SH), 6.94-7.67 (m, 9H, Ar), 8.25 (s, 1H, NH), 8.87 (s, 1H, NH), 10.25 (s, 1H, NH).

2k (X = O, R = 4-ClC_6H_4NH): yield 95%, mp 238-240 °C. ^{1}H NMR (DMSO-d_6) δ 6.92-7.91 (m, 8H, Ar), 8.43 (s, 1H, NH), 9.09 (s, 1H, NH), 10.45 (s, 1H, OH), 11.96 (s, 1H, NH).

2l (X = S, R = 4-ClC_6H_4NH): yield 93%, mp 166-168 °C. ^{1}H NMR (DMSO-d_6) δ 5.32 (s, 1H, SH), 7.20-7.67 (m, 8H, Ar), 8.33 (s, 1H, NH), 9.05 (s, 1H, NH), 10.26 (s, 1H, NH).

2m (X = O, R = 4-$CH_3OC_6H_4NH$): yield 99%, mp 213-215 °C. ^{1}H NMR (DMSO-d_6) δ 3.71 (s, 3H, OCH_3), 6.84-7.92 (m, 8H, Ar), 8.25 (s, 1H, NH), 8.76 (s, 1H, NH), 10.43 (s, 1H, OH), 11.99 (s, 1H, NH).

2n (X = S, R = 4-$CH_3OC_6H_4NH$): yield 95%, mp 159-161 °C. ^{1}H NMR (DMSO-d_6) δ 3.71 (s, 3H, OCH_3), 6.84-7.67 (m, 8H, Ar), 8.14 (s, 1H, NH), 8.66 (s, 1H, NH), 10.18 (s, 1H, NH).

General procedure for the preparation of 1,3,4-oxadiazoles 3i-3n. To a stirred suspension of the appropriate salicylic semicarbazide **2** (3 mmol) in 30 mL of CH_2Cl_2 was added Ph_3P (1.18 g, 4.5 mmol), CCl_4 (1.16 mL, 12 mmol), and Et_3N (0.63 mL, 4.5 mmol) and the mixture was heated to reflux temperature for 1-2 h. After cooling to room temperature the reaction mixture was partitioned between water and CH_2Cl_2 (2 × 30 mL), and combined each other, and the solvent was removed after drying over $MgSO_4$. The residue was chromatographed on a silica gel column and eluted with hexane-ethyl acetate 5 : 1 to yield **3i-3n**. The

physical and spectral data are listed in Table 1.

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