Facile Synthesis of Symmetric and Unsymmetric 1,3,4-Oxadiazoles Using 2-Acyl(or aryl)pyridazin-3-ones

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Abstract: Symmetric and unsymmetric 1,3,4-oxadiazoles were synthesized in situ from hydrazine hydrate and the corresponding 2-acyl(or aryl)-4,5-dichloropyridazin-3-ones as acylating agents in polyphosphoric acid or BF₃·OEt₂ in excellent yields.

Key words: 2-acyl-4,5-dichloropyridazin-3-ones, 1,3,4-oxadiazoles, cyclodehydration

1,3,4-Oxadiazoles have attracted significant interest in medicinal chemistry,1–7 pesticide chemistry,8 polymer science,9 and material science.10 This has, in recent years, led to the discovery of a variety of cyclodehydrating agents including the solid phase methodology for the synthesis of 1,3,4-oxadiazoles.11 Because the biological6,8a,b or electrochemical properties9a,b,10c,d of unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles are different from symmetrically 2,5-disubstituted 1,3,4-oxadiazole has been of considerable interest. The synthesis of symmetrically 2,5-disubstituted 1,3,4-oxadiazoles from diacylhydrazines prepared from acid chloride and hydrazine can be performed by using several cyclodehydrating agents such as thionyl chloride,12 phosphorus oxychloride,13 sulfuric acid,14 phosphorus pentoxide/phosphorus oxychloride,11e 1,1,1,3,3,3-hexamethyldisilazane,8b and BF₃·OEt₂.11d,e Although these methods are useful for the synthesis of symmetrically 2,5-disubstituted 1,3,4-oxadiazoles, they are not suitable for the one-pot synthesis of unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles since the diacylhydrazines as the precursors of 2,5-disubstituted 1,3,4-oxadiazoles are mostly prepared from acid chlorides.5a,10b,11d,e The drawback of the synthetic method for unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles using hydrazine and acid chloride is that acid chlorides are overly reactive. In fact, the reaction of acid chlorides with unprotected hydrazine always gave the corresponding diacylhydrazines.6 Therefore, a mild and stable acylating agent is required for synthesizing unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles.

We had reported in our previous paper on the excellent ability of the acyl transfer to amines shown by 2-acyl(or aryl)-4,5-dichloropyridazin-3-ones. Since they are also stable in air and not hygroscopic, we successfully synthesized both symmetrically and unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles by using 2-acyl(or aryl)-4,5-dichloropyridazin-3-ones as acylating agents. We report here on a facile one-pot procedure for the synthesis of either unsymmetrically or symmetrically 2,5-disubstituted 1,3,4-oxadiazoles using 2-acyl(or aryl)-4,5-dichloropyridazin-3-ones (Scheme 1).

After the reaction of 1a–e with hydrazine hydrate, the resulting mixture was treated with polyphosphoric acid or boron trifluoride diethyl etherate in dioxane to give the symmetrically 2,5-disubstituted 1,3,4-oxadiazoles in 81–98% yields, except for 1,3,4-oxadiazoles 2f and 2g were not formed from the corresponding diacylhydrazines of 1f and 1g using BF₃·OEt₂ (Table 1).

On the other hand, we attempted to synthesize in situ unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles using two different 2-acyl(or aryl)-4,5-dichloropyridazin-3-ones and polyphosphoric acid as cyclodehydrating agent. A typical reaction procedure in situ involves the addition of a 2-acyl(or aryl)-4,5-dichloropyridazin-3-one to a so-
lution of hydrazine hydrate in THF, stirring for 10 minutes at room temperature and then adding another 2-acyl(or aroyl)-4,5-dichloropyridazin-3-one to furnish the corresponding unsymmetric N-acyl(or aroyl)-N'-aryloxydiazidine. After evaporating the solvent under reduced pressure, polyphosphoric acid was added to the residue, and the reaction mixture was refluxed for 1.5–3.5 hours. The yields of unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles were good to excellent. 4,5-Dichloropyridazin-3-one was also isolated in quantitative yields in all cases (Table 1 and 2).

Unsymmetric 2,5-dialkyl-1,3,4-oxadiazoles, however, could not be prepared from the different 2-acyl-4,5-dichloropyridazin-3-one under our conditions.

In conclusion, our method for the synthesis of either symmetrically or unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles has several advantages: (1) the precursors such as diaroylhydrazines or N,N'-diarylhydrazines need not be isolated before cyclodehydration; (2) 2-acyl(or aroyl)-4,5-dichloropyridazin-3-ones are mild and stable sources of acyl (or aroyl) group for the synthesis of unsymmetrically N,N'-disubstituted hydrazines; (3) cyclodehydration can be accomplished in situ; and (4) reusable 4,5-dichloropyridazin-3-one can be recovered quantitatively.

Reagents and solvents were used as received from commercial sources. TLC was performed on silica gel 60 F254 (Merck). The spots were located by UV light. Column chromatography was carried out on silica gel 60 (70–230 mesh). Melting points were determined with a Thomas–Hoover capillary apparatus and are uncorrected. 1H and 13C NMR spectra were recorded on a Bruker FT NMR-DRX 500 or a Varian Inova 500 spectrometer and with chemical shift values reported in δ units (part per million) relative to an internal standard (tetramethylsilane). IR spectra were obtained on a Hitachi 270-50 or Mattson Genesis Series FT-IR spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240C. Mass spectra were recorded using JEOL JMS-700 spectrometer.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Synthesis of Symmetrically 2,5-Disubstituted 1,3,4-Oxadiazoles</th>
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<tr>
<td>Entry</td>
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<td>lh  PPA  BF&lt;sub&gt;3&lt;/sub&gt;OET&lt;sub&gt;2&lt;/sub&gt;</td>
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</table>

<sup>a</sup> PPA = polyphosphoric acid.

<sup>b</sup> Isolated yield. 4,5-Dichloropyridazin-3-one was recovered quantitatively.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Synthesis of Unsymmetrically 2,5-Disubstituted 1,3,4-Oxadiazoles in Polyphosphoric Acid</th>
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<td>Entry</td>
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<sup>a</sup> Isolated yield. 4,5-Dichloropyridazin-3-one was recovered quantitatively.
2,5-Diphenyl-1,3,4-oxadiazole (2a)
Mp 132–133 °C (Lit. 11 mp 137–139 °C; Lit. 12 mp 138 °C).
IR (KBr): 3050, 2950, 1620, 1560, 1500, 1440, 1260, 1080, 1020, 710, 690 cm⁻¹.
¹H NMR (CDCl₃): δ = 7.52–7.58 (m, 6 H), 8.14–8.16 (m, 4 H).
¹³C NMR (CDCl₃): δ = 123.9, 126.9, 129.0, 131.7, 164.6.
HRMS (EI, 80 eV): m/z calcd for C₁₆H₁₄N₂O₂: 222.0793; found: 222.0792.
Anal. Calcd for C₁₆H₁₄N₂O₂: C, 75.66; H, 5.45; N, 12.60. Found: C, 75.78; H, 4.65; N, 12.71.

2,5-Bis(4-chlorophenyl)-1,3,4-oxadiazole (2c)
Mp 220–222 °C (Lit. 11 mp 242 °C).
IR (KBr): 3050, 2950, 1610, 1500, 1440, 1300, 1260, 1180, 1080, 1020, 820, 740 cm⁻¹.
¹H NMR (CDCl₃): δ = 2.40 (s, 6 H), 7.32 (d, 4 H, J = 6.5 Hz), 8.01 (d, 4 H, J = 6 Hz).
¹³C NMR (CDCl₃): δ = 21.1, 121.1, 126.7, 129.6, 142.0, 164.4.
HRMS (EI, 80 eV): m/z calcd for C₁₆H₁₄N₂O: 250.1106; found: 250.1103.

2,5-Bis(4-methylphenyl)-1,3,4-oxadiazole (2b)
Mp 171–173 °C (Lit. 11 mp 175 °C).
IR (KBr): 3050, 3000, 2950, 1610, 1500, 1440, 1300, 1260, 1180, 1080, 1020, 800, 740 cm⁻¹.
¹H NMR (CDCl₃): δ = 2.40 (s, 6 H), 2.42 (s, 6 H), 7.32 (d, 4 H, J = 6.5 Hz), 8.01 (d, 4 H, J = 6 Hz).
¹³C NMR (CDCl₃): δ = 21.1, 121.1, 126.7, 129.6, 142.0, 164.4.
HRMS (EI, 80 eV): m/z calcd for C₁₆H₁₄N₂O: 250.1106; found: 250.1103.

2,5-Bis(4-chlorophenyl)-1,3,4-oxadiazole (2e)
Mp 155–157 °C.
IR (KBr): 3000, 1650, 1500, 1450, 1340, 1320, 1280, 1180, 1040, 850 cm⁻¹.
¹H NMR (CDCl₃): δ = 3.88 (s, 6 H), 7.01–7.03 (m, 4 H), 8.04–8.06 (m, 4 H).
¹³C NMR (CDCl₃): δ = 55.5, 114.5, 116.5, 128.6, 162.2, 164.1.
HRMS (EI, 80 eV): m/z calcd for C₁₆H₁₄N₂O: 282.1004; found: 282.1007.
Anal. Calcd for C₁₆H₁₄N₂O: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.12; H, 5.21; N, 10.03.

Unsymmetrically 2,5-Disubstituted 1,3,4-Oxadiazoles 3; General Procedure
To a solution of 17 (Table 2) (1.11 mmol) in anhyd THF (30 mL) was added 80% hydrazine hydrate (1.0 mmol). The mixture was stirred for 10 min, and a different (Table 2) acylpyridazin-3-one 1 (Table 2) (1.11 mol) was then added. After stirring the mixture for 10 min, the solvent was evaporated under reduced pressure, and then polyphosphoric acid (30 mL) was added. The solution was stirred for 1.5–3.5 h at 130 °C, cooled to r.t., and H₂O (100 mL) was slowly added. The pH of the solution was adjusted to about 6 by addition of sat. aq solution of NaHCO₃. The product was extracted with EtOAc (2 × 50 mL), and the combined organic layers were dried (MgSO₄) and filtered. Silica gel (1 g) was added to the filtrate and the mixture was evaporated under reduced pressure. The resulting gel was applied to the top of an open-bed silica gel column (3 × 10 cm). The column was eluted with CH₂Cl₂–THF (9.5:0.5) and fractions containing the product were combined and evaporated under reduced pressure to give 3.

2-Ethyl-5-phenyl-1,3,4-oxadiazole (3a)
Oil.
IR (KBr): 3050, 3000, 2950, 1620, 1580, 1560, 1500, 1460, 1200, 1100, 1060, 1000, 780, 720, 700 cm⁻¹.
¹H NMR (CDCl₃): δ = 1.45 (t, 3 H, J = 6.0 Hz), 2.96 (q, 2 H, J = 6.0 Hz), 7.48–7.52 (m, 3 H, 8.03–8.05 (m, 2 H).
¹³C NMR (CDCl₃): δ = 10.9, 19.2, 124.2, 126.8, 129.0, 131.5, 164.7, 167.8.
HRMS (EI, 80 eV): m/z calcd for C₁₀H₁₀N₂O: 174.0793; found: 174.0795.
Anal. Calcd for C₁₀H₁₀N₂O: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.99; H, 5.87; N, 16.21.

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2-(4-Methylphenyl)-5-phenyl-1,3,4-oxadiazole (3b)

IR (KBr): 3100, 2950, 1650, 1500, 1460, 1320, 1280, 1210, 1100, 1030, 840, 740, 700 cm−1.

1H NMR (CDCl3): δ = 7.53–7.55 (m, 3 H), 7.66–7.68 (m, 1 H), 8.12–8.14 (m, 2 H).

13C NMR (CDCl3): δ = 121.8, 123.8, 127.0, 128.3, 129.2, 129.6, 131.9, 138.1, 163.8, 164.8.

HRMS (EI, 80 eV): m/z calcd for C14H12N2O: 236.0950; found: 236.0952.


2-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (3c)

IR (KBr): 3300, 2900, 1640, 1580, 1520, 1460, 1400, 1320, 1280, 1210, 1100, 900 cm−1.

1H NMR (CDCl3): δ = 7.24 (d, 1 H, J = 1.8 Hz), 7.54–7.59 (m, 5 H), 8.06–8.09 (m, 2 H), 8.15–8.18 (m, 2 H).

13C NMR (CDCl3): δ = 112.8, 123.7, 127.1, 127.7, 129.2, 131.2, 131.9, 132.0, 133.8, 138.1, 162.4, 165.2.

HRMS (EI, 80 eV): m/z calcd for C14H11ClN2O: 242.0692; found: 242.0691.

Anal. Calcd for C14H11ClN2O: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.53; H, 4.24; N, 11.77.

2-Ethyl-5-(2-furyl)-1,3,4-oxadiazole (3h)

IR (KBr): 3150, 2950, 1650, 1580, 1520, 1460, 1400, 1320, 1280, 1210, 1100, 900 cm−1.

1H NMR (CDCl3): δ = 3.53 (t, 3 H, J = 7.5 Hz), 2.94 (q, 2 H, J = 7.5 Hz), 1.43 (t, 3 H, J = 7.5 Hz), 7.52–7.54 (m, 5 H), 8.09–8.12 (m, 2 H).

13C NMR (CDCl3): δ = 55.5, 112.1, 113.7, 114.6, 116.1, 128.8, 139.7, 145.5, 157.1, 162.5, 164.0.

HRMS (EI, 80 eV): m/z calcd for C8H8N2O2: 212.0586; found: 212.0581.

Anal. Calcd for C12H8N2O2: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.64; H, 5.03; N, 17.16.

Acknowledgments

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References


(16) Attempted synthesis of unsymmetric 1,3,4-oxadiazole 3d starting from a mixture of benzoyl chloride (1 equiv) and 2,4-dichlorobenzoyl chloride (1 equiv) gave a mixture of 2a, 3d and 2d (ca. 4:4:2 ratio by TLC).