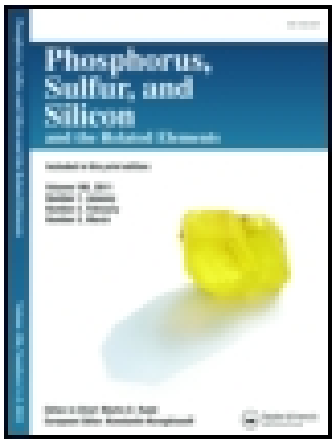

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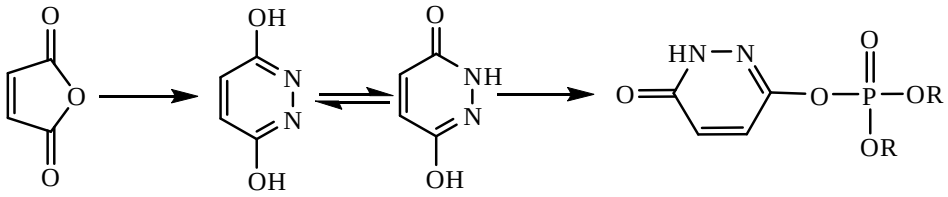
Abstract: 6-*O*-Phosphorylated pyridazine-3(*2H*)-one derivatives were conveniently prepared by a facile method. Maleic hydrazide was prepared by the condensation of maleic anhydride with 85% hydrazine hydrate. It was then chemoselectively phosphorylated at the 6-*O* position using the Atherton–Todd reaction. An efficient, highly chemoselective method to synthesize 6-*O*-phosphorylated pyridazin-3(*2H*)-one derivatives is provided and the approach has the merits of mild reaction conditions.



Keywords: Maleic hydrazide; phosphorylation; chemoselective; Atherton–Todd reaction

INTRODUCTION

Pyridazinone derivatives, a class of compounds containing the N-N bond, have been reported to exhibit a wide variety of biological activities such as herbicide[1], fungicidal[2] and antibacterial[3] activities well as to act as aldose reductase inhibitors[4] and as hepatoprotective agents[5]. Recently pyridazine-3(2H)-one was reported to be a stable and good leaving group and to show electron withdrawing ability[6,7]. Also various organophosphorus compounds have been developed as carboxylic acid activators. Pyridazine-3(*2H*)-one containing phosphate esters were synthesized by the reaction of pyridazine-3(*2H*)-ones and *O,O*-dialkyl phosphorochloridates as carboxylic acid activator.[8]

Pyridazinyl-substituted phosphorothioate esters are potent broad-spectrum insecticides. A derivative of 6-hydroxy-3(*2H*)-pyridazinone, more commonly known as maleic hydrazide, is a sparingly soluble, high melting monobasic acid, which has pK_a 7.6 in 90 % ethanol.[9] Substitution at the (*2H*) position by alkyl or aryl groups does not affect the acidity appreciably, but the solubility in organic solvents is improved. It was reported that these compounds react with *O,O*-dialkyl phosphoro- chloridothioates similarly to phenols. *O,O*-Dialkyl phosphorochloridothioates or *O,O*-dialkyl phosphorochloridates are highly reactive phosphoryl reagents, however, and a regioselective phosphorylation of polyhydroxyphenols is difficult.[10]

The Atherton-Todd reaction is a powerful classical phosphorylation method, which is not only widely used for the preparation of phosphates and related phosphorus compounds,[11-14] but also provides a method for the selective phosphorylation of different active groups. In a previous paper we reported on the highly regioselective 4-*O*-phosphorylation of 2,4-dihydroxyacetophotone with *O,O*-dialkyl phosphites.[15] In addition the dialkylphosphite reagent

showed also different chemoselectivities towards the different hydroxy functionalities in puerarin.[16] In this paper, we report on the effective and highly chemoselective *O*-phosphorylation of maleic hydrazide with *O*,*O*-dialkyl phosphites by the Atherton–Todd reaction (Scheme 1). The structures of the phosphorylated products were confirmed by electrospray ionization–mass spectrometry (ESI–MS), nuclear magnetic resonance (NMR) and infrared (IR) spectroscopy.

RESULTS AND DISCUSSION

Maleic hydrazide was synthesized by the condensation of maleic anhydride (**1**) with 85% hydrazine hydrate. In order to obtain 6-*O*-phosphorylated maleic hydrazide, possible routes for 6-*O*-phosphorylation of maleic hydrazide are shown in Scheme 2.

Maleic hydrazide was phosphorylated with $POCl_3$ or $(RO)_2P(O)Cl$ to yield the title compounds with very low yields under harsh experimental conditions. When maleic hydrazide was allowed to react with $(RO)_2P(O)H$ under Atherton–Todd reaction conditions, five 6-*O*-phosphorylated maleic hydrazides were synthesized with good yields under mild reaction conditions. It is well known that the rate of phosphorylation in an Atherton–Todd reaction depends on the rate of nucleophilic attack. The Atherton–Todd reaction, under the present experimental conditions, was found to proceed chemoselectively, favoring attack at 6-hydroxy group of maleic hydrazide (**2**). Maleic hydrazide can, in principle, exist as equilibrium of two tautomeric forms: the lactim and the lactam forms (Scheme 3). It has been reported that spectroscopic studies of maleic hydrazide tautomers indicate the lactam form to be the most

stable species in ethanol solution.[17] This observation is in agreement with experimental and theoretical data on the parent phthalhydrazide and its methyl isomers.[17-20]

The greater reactivity of the phenolic hydroxyl group in comparison to the amide function results in a chemoselective reaction affording the *O*-phosphorylated maleic hydrazide. This conclusion was also confirmed by ^{13}C NMR and FT–IR spectra of compound **3a**. For example, the ^{13}C NMR spectrum of compound **3a** showed the signal of the carbon atom in 3-position at δ = 161.3 ppm, which is in accord with the chemical shift of carbonyl carbon atom. In addition, the infrared peaks in the region of 3300–3100 cm^{-1} and a broad band at 1680 cm^{-1} represented the N–H stretching and bending modes, respectively. This indicates the presence of N-H and not O-H functionality in the structure of compound **3a**. The maleic hydrazide (**2**) reacts with various dialkyl phosphites to form a series of 6-*O*-phosphorylated maleic hydrazide derivatives **3** (Table 1). The ^{1}H, ^{13}C and ^{31}P NMR spectra of compound **3a** are presented as an example in Figures S1–S3 in the Supplemental Material.

Under the same experimental conditions dialkyl phosphites with different structures gave different yields, as shown in Table 1. Compound **3a** is obtained in 86 % isolated yield due to small steric hindrance in the case of dimethyl phosphite. Diethyl phosphite, di-*n*-propyl phosphite and di-*n*-butyl phosphite give the corresponding compound **3b**, **3c** and **3d** in 84 %, 81 % and 80 % isolated yield, respectively. The compound **3e** is obtained in only 76 % isolated yield because of great steric hindrance in the case of di-*i*-butyl phosphite.

In conclusion, a convenient procedure for the preparation of novel 6-*O*-phosphorylated maleic hydrazide derivatives was reported using commercially available materials. These compounds were synthesized by the condensation of maleic anhydride with 85% hydrazine hydrate and subsequent Atherton–Todd reaction. Phosphorylation of maleic hydrazide was found to proceed chemoselectively, favoring the attack at the oxygen atom in 6-position of maleic hydrazide.

EXPERIMENTAL

Maleic hydrazide (**2**) was synthesized according to the literature[21] and was purified by sublimation before use. Other starting materials were obtained from commercial sources and used without further purification. Melting points were recorded with a microscopical determinator XT4 (the thermometer was not calibrated). IR spectra were recorded with a Shimadazu IR-408 spectrophotometer. ^{1}H, ^{13}C and ^{31}P NMR spectra were obtained with a Bruker Avance DPX-400 spectrometer; chemical shifts are given in ppm with positive values downfield from internal tetramethylsilane (TMS) and external 85% H_3PO_4 (^{31}P). Coupling constants are in Hertz. ESI–MS spectra were recorded with a Bruker Esquire-3000 instrument. Elemental analyses of the new compounds were performed with a Vario EL III 0 serial no. 11024054 instrument. Sample ^{1}H, ^{13}C and ^{31}P NMR spectra for **3a** are presented in the Supplemental Materials (Figures S 1 – S 3)

General Experimental Procedure for the Synthesis of Compounds 3a-e

A solution of dialkyl phosphonite (2.2 mmol) in CCl_4 (0.6 mL) was added dropwise to the solution of maleic hydrazide (2 mmol) in a mixture of Et_3N (0.3 mL) and the corresponding

alcohol (1 mL) at 0 °C during 30 min. Then the reaction mixture was stirred at room temperature for approximately 8-10 h. After water (5 mL) was added to the solution it was extracted with 3 × 5 mL of ethyl acetate. The ethyl acetate solution was dried over anhydrous magnesium sulfate. From the resulting solution the solvent was evaporated under reduced pressure to yield compound **3**. Finally the residue was purified by column chromatography on silica gel with ethyl acetate / corresponding alcohol (5:1) as eluent to yield pure compounds **3**.

Dimethyl (6-Oxo-1,6-dihydropyridazin-3-yl) Phosphate (3a)

Colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.83 (b s, 1H, NH), 7.19 (d, *J* = 8.0 Hz, 1H, CH=CH), 7.04 (d, *J* = 8.0 Hz, 1H, CH=CH), 3.93 (d, *J* = 11.6 Hz, 6H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.3 (C-3), 147.6 (d, $^{2}J_{PC}$ = 6.4 Hz, C-6), 133.9 (C-4), 128.5 (d, $^{3}J_{PC}$ = 6.0 Hz, C-5), 55.5 (d, $^{2}J_{PC}$ = 6.0 Hz, -OCH_3); ^{31}P NMR ($CDCl_3$, 162 MHz) δ = -5.3; IR (KBr): ν = 3180 (N-H), 1685 (C=O), 1277 (P=O), 3085 (=C-H), 2975, 2880, 1600 cm^{-1}. ESI–MS, m/z: 221.2 $[M+H]^{+}$. Anal. Calcd. for $C_6H_9N_2O_5P$: C, 32.74; H, 4.12; N, 12.73. Found: C, 32.91; H, 4.22; N, 12.53 %.

Diethyl (6-Oxo-1,6-dihydropyridazin-3-yl) Phosphate (3b)

Colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.69 (b s, 1H, NH), 7.12 (d, *J* = 8.0 Hz, 1H, CH=CH), 6.96 (d, *J* = 8.0 Hz, 1H, CH=CH), 4.18 (dq, $^{3}J_{PH}$ = 11.6 Hz, *J* = 7.2 Hz, 4H, OCH_2), 1.25 (t, *J* = 7.1 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.3 (C-3), 147.6 (d, $^{2}J_{PC}$ = 6.3 Hz, C-6), 133.7 (C-4), 128.5 (d, $^{3}J_{PC}$ = 5.6 Hz, C-5), 65.4 (d, $^{2}J_{PC}$ = 6.0 Hz, OCH_2), 15.9 (d, $^{3}J_{PC}$ = 6.7 Hz, CH_3); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = -7.8; IR (KBr): ν = 3168 (N-H),

1680 (C=O), 1277 (P=O), 3080 (=C-H), 2970, 2880, 1600 cm^{-1}. ESI–MS, m/z: 249.2 $[M+H]^+$. Anal. Calcd. for $C_8H_{13}N_2O_5P$: C, 38.72; H, 5.28; N, 11.29. Found: C, 38.90; H, 5.16; N, 11.20 %.

Dipropyl (6-Oxo-1,6-dihydropyridazin-3-yl) Phosphate (3c)

White solid. ^1H NMR ($CDCl_3$, 400 MHz): δ = 11.54 (b s, 1H, NH), 7.18 (d, *J* = 9.9 Hz, 1H, CH=CH), 7.01 (d, *J* = 9.9 Hz, 1H, CH=CH), 4.14 (dt, $^3J_{PH}$ = 11.5 Hz, *J* = 6.7 Hz, 4H, OCH_2), 1.70 (m, 4H, CH_2), 0.94 (t, *J* = 7.2 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.3 (C-3), 147.7 (d, $^2J_{PC}$ = 6.0 Hz, C-6), 133.7 (C-4), 128.6 (d, $^3J_{PC}$ = 5.4 Hz, C-5), 70.8 (d, $^2J_{PC}$ = 6.3 Hz, OCH_2), 23.5 (d, $^3J_{PC}$ = 7.1 Hz, CH_2), 9.9 (CH_3); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = -7.5; IR (KBr): ν = 3170 (N-H), 1682 (C=O), 1275 (P=O), 3080 (=C-H), 2975, 2881, 1602 cm^{-1}. ESI–MS, m/z: 277.2 $[M+H]^+$. Anal. Calcd. for $C_{10}H_{17}N_2O_5P$: C, 43.48; H, 6.20; N, 10.14. Found: C, 43.67; H, 6.41; N, 10.02 %.

Dibutyl (6-Oxo-1,6-dihydropyridazin-3-yl) Phosphate (3d)

White solid. ^1H NMR ($CDCl_3$, 400 MHz): δ = 11.48 (b s, 1H, NH), 7.16 (d, *J* = 8.0 Hz, 1H, CH=CH), 7.00 (d, *J* = 8.0 Hz, 1H, CH=CH), 4.15 (dt, $^3J_{PH}$ = 11.5 Hz, *J* = 7.0 Hz, 4H, OCH_2), 1.64 (m, 4H, CH_2), 1.34 (m, 4H, CH_2), 0.87 (t, *J* = 7.4 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.3 (C-3), 147.7 (d, $^2J_{PC}$ = 6.0 Hz, C-6), 133.6 (C-4), 128.5 (d, $^3J_{PC}$ = 5.6 Hz, C-5), 69.0 (d, $^2J_{PC}$ = 6.4 Hz, OCH_2), 32.0 (d, $^3J_{PC}$ = 6.9 Hz, CH_2), 18.5 (CH_2), 13.4 (CH_3); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = -7.5; IR (KBr): ν = 3172 (N-H), 1681 (C=O), 1270 (P=O), 3082 (=C-H),

2970, 2880, 1600 cm^{-1}. ESI–MS, m/z: 305.2 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{21}N_2O_5P$: C, 47.37; H, 6.96; N, 9.21. Found: C, 47.56; H, 7.05; N, 9.08 %.

Diisobutyl (6-Oxo-1,6-dihydropyridazin-3-yl) Phosphate (3e)

White solid. ^1H NMR ($CDCl_3$, 400 MHz): δ = 11.41 (b s, 1H, NH), 7.22 (d, *J* = 9.9 Hz, 1H, CH=CH), 7.03 (d, *J* = 9.9 Hz, 1H, CH=CH), 4.00 (dd, $^3J_{PH}$ = 11.5 Hz, *J* = 7.2 Hz, 4H, OCH_2), 2.01 (m, 2H, CH), 0.98 (d, *J* = 6.7 Hz, 12H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.8 (C-3), 147.7 (d, $^2J_{PC}$ = 6.0 Hz, C-6), 133.8 (C-4), 128.7 (d, $^3J_{PC}$ = 5.6 Hz, C-5), 75.1 (d, $^2J_{PC}$ = 6.6 Hz, OCH_2), 29.0 (d, $^3J_{PC}$ = 7.2 Hz, CH), 18.6 (CH_3); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = -7.5; IR (KBr): ν = 3169 (N-H), 1680 (C=O), 1276 (P=O), 3084 (=C-H), 2971, 2880, 1601 cm^{-1}. ESI–MS, m/z: 305.2 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{21}N_2O_5P$: C, 47.37; H, 6.96; N, 9.21. Found: C, 47.58; H, 7.08; N, 9.04 %.

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FUNDING

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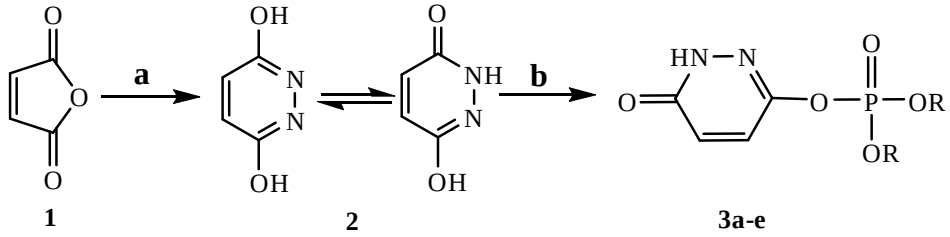
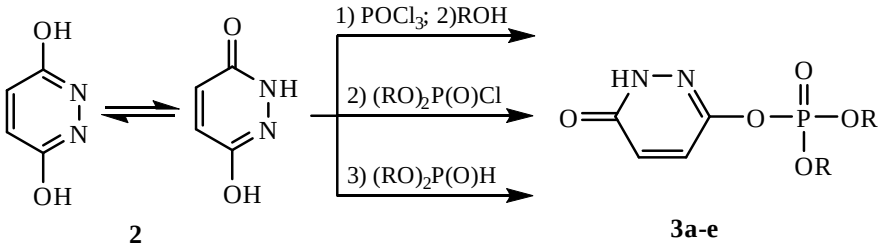
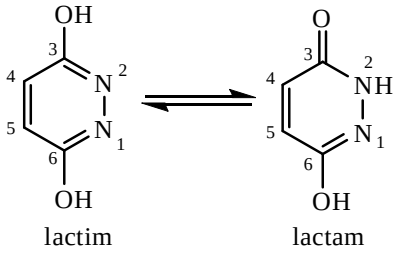


Scheme 1 Synthesis of the title compounds. Reagents and reaction conditions: (a) 85% hydrazine hydrate (1 equiv.), anhydrous ethanol, reflux 6 h; (b) Dialkyl phosphite (1.1 equiv.), Et_3N (1.1 equiv.), CCl_4 (2 equiv.), ice bath 0.5 h, room temperature 8–10 h.



Scheme 2 Possible routes for the 6-*O*-phosphorylation of maleic hydrazide.



Scheme 3 Maleic hydrazide tautomer equilibrium: lactim and lactam tautomer.

Table 1 The 6-*O*-phosphorylated maleic hydrazide derivatives prepared

3	R	Yield (%)
a	CH_3	86%
b	CH_3CH_2	84%
c	$CH_3CH_2CH_2$	81%
d	$CH_3CH_2CH_2CH_2$	80%
e	$(CH_3)_2CHCH_2$	76%

