Synthesis of 5-Substituted Pyrrolo[1,2-*b*]pyridazines with Antioxidant Properties

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Summary

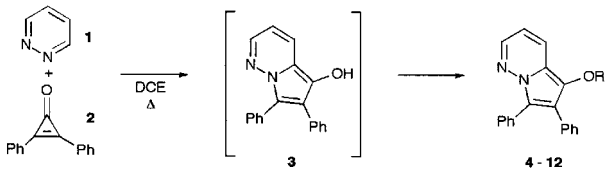
5-Substituted pyrrolo[1,2-*b*]pyridazines have been prepared by cyclisation of pyridazine with diphenylcyclopropenone followed by further functionalisations in the pyrrolo[1,2-*b*]pyridazine 5-position. Several compound exhibit profound inhibition of lipid peroxidation *in vitro*. Lipid peroxidation of boiled rat liver microsomes was induced by ascorbic acid/$FeSO_4$ and the peroxidation was determined by measuring the thiobarbituric acid reactive material.

Introduction

Free radical mediated processes have been implicated in numerous serious pathological conditions and development of novel antioxidants may therefor lead to new drugs [1]. We have recently reported derivatives of 1-indolizinols which are strong inhibitors of lipid peroxidation *in vitro*, and hence may have a therapeutic potential as antioxidants / radical scavengers [2,3]. Indolizinyl esters, ethers, carbonates, and carbamates [2] as well as sulfonates [3] were active, and we proposed that the compounds were not cleaved to indolizinols but that they inhibited peroxidation themselves by an electron donation mechanism [2]. An extension of this work is the study of azaindolizines, and in this paper we report synthesis and antioxidant properties of 5-substituted pyrrolo[1,2-*b*]pyridazines (1-substituted 5-azaindolizines).

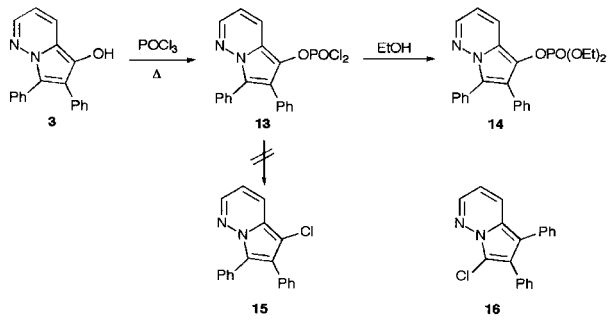
Results and Discussion

We chose to prepare the pyrrolo[1,2-*b*]pyridazines **4**–**12** by cyclization of pyridazine **1** with diphenylcyclopropenone **2** to give the pyrrolo[1,2-*b*]pyridazin-5-ol **3** [4] followed by further functionalisation of the hydroxy group (Scheme 1, Table 1). The esters **4**–**6**, ethers **7** and **8**, carbonate **9**, and carbamate **10** were prepared essentially as reported before for similar structures [2,4]; treatment of the intermediate hydroxy compound **3** with acid chloride or anhydride, alkyl halide, chloroformate, or isocyanate in the presence of a suitable base.



Scheme 1

The triflate **11** was available when the pyrrolo[1,2-*b*]pyridazin-5-ol **3** was reacted with triflic anhydride in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) at low temperatures. Sodium hydride was a much less efficient base in this reaction, and the use of ethereal solvents (THF, DME, or diethyl ether) instead of dichloromethane resulted in extensive polymerisation. Reaction of the pyrrolo[1,2-*b*]pyridazin-5-ol **3** with tosyl chloride in the presence of DMAP and triethylamine gave the tosylate **12**. It has been reported that 5-chloropyrrolo[1,2-*b*]pyridazine **15*** is formed when pyrrolo[1,2-*b*]pyridazin-5-ol **3** is reacted with phosphorus oxychloride [5], but this procedure gave, in our hands, only the phosphate **14** after work-up using ethanol. Work-up without nucleophilic solvents gave compound **13** (Scheme 2).



Scheme 2

* Lown and Matsumoto actually reported the synthesis of 5-chloropyrrolo[1,2-*b*]pyridazin **16** (see Scheme 2) from pyrrolo[1,2-*b*]pyridazin-5-ol [5], but later Weidner *et al.* showed that the hydroxy group in the starting material must have been situated in the indolizine 1-position [4].

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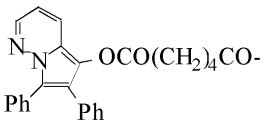
Table 1. Synthesis and antioxidant properties of pyrrolo[1,2-*b*]pyridazine derivatives.

Reagents and conditions	R-	Compound No.	Yield (%)	IC_{50} values[a]
$(CH_3CO)_2O$, DMAP, DCE	CH_3CO-	**4**	55	0.07
$CH_3(CH_2)_{14}COCl$, cat. DMAP, Et_3N, DCE	$CH_3(CH_2)_{14}CO$-	**5**	46	49.5
$ClOC(CH_2)_4COCl$, cat. DMAP, Et_3N, DCE		**6**	45	47.8
CH_3I, NaH, THF	CH_3-	7	54	26.0
CH_3CH_2I, NaH, THF	CH_3CH_2-	**8**	52	6.50
CH_3OCOCl, NaH, DME	CH_3OCO-	**9**	61	29.5
PhNCO, DMAP, DCE	PhNHCO-	**10**	52	3.20
$(CF_3SO_2)_2O$, DMAP, CH_2Cl_2	CF_3SO_2-	**11**	55	0.47
p-CH_3-C_6H_4-SO_2Cl, cat. DMAP, Et_3N, DCE	*p*-CH_3-C_6H_4-SO_2-	**12**	55	24.5
$POCl_3$, Δ	Cl_2OP-	**13**	69	n.d.
1. $POCl_3$, Δ; 2. CH_3CH_2OH	$(CH_3CH_2O)_2OP$-	**14**	59	>100

[a] IC_{50} (mM) is the concentration which causes 50% inhibition of lipid peroxidation after 30 min. The values are given as the mean of 3 separate experiments and the accuracy of the data is within 25%.

The ability of the indolizine derivatives to inhibit lipid peroxidation *in vitro* was examined and the results are summarised in Table 1. The testing was performed as we have described before [2]. Lipid peroxidation of boiled rat liver microsomes was induced by ascorbic acid/$FeSO_4$ and the peroxidation was determined by measuring the thiobarbituric acid reactive material. Except for the phosphate **14**, all compounds examined had IC_{50} values well below 100 μM and must be considered as potent antioxidants. In the same assay, the IC_{50} value for rutin was found to be 10 μM and cyanidine had an IC_{50} value of 27 μM. The acetate **4** and triflate **11** were extremely active. Comparison of the esters **4**, **5**, and **6**, as well as the sulfonates **11** and **12** indicate that increased lipophilisity, lowers the activity. The same trend is seen before when benzoindolizines were much less active than indolizines [2].

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Experimental

The ^{1}H NMR spectra were recorded at 500 MHz with a Bruker Avance DRX 500 instrument, at 300 MHz with a Bruker Avance DPX 300 instrument or at 200 MHz with a Bruker Avance DPX 200 or a Varian Gemini 200 instrument and the ^{13}C NMR spectra were recorded at 125, 75 or 50 MHz using the above mentioned spectrometers. Mass spectra were recorded at 70 eV ionising voltage with a VG Prospec instrument, and are presented as *m/z* (% rel. int.). Methane was used for chemical ionisation (CI). Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. Melting points are uncorrected. Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 9385). THF was distilled from Na/benzophenone. 1,2-Dichloroethane and triethylamine were distilled from calcium hydride. All other reagents were commercially available and used as received. The lipid peroxidation inhibition tests were performed as previously reported [2].

6,7-Diphenylpyrrolo[1,2-b]pyridazin-5-yl Acetate ***4***

Synthesis see ref. [4]. Yield 55%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.25 (s, 3H, CH_3), 6.50 (dd, *J* = 9.1 and 4.4 Hz, 1H), 7.18–7.35 (m, 8H, Ph), 7.43–7.50 (m, 2H, Ph), 7.59 (dd, *J* = 9.1 and 1.8 Hz, 1H) and 7.97 (dd, *J* = 4.4 and 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.6, 109.6, 117.3, 119.4, 124.0, 124.1, 124.4, 126.9, 127.7, 128.1, 128.3, 129.8, 130.1, 130.7, 132.2, 142.1 and 169.7; MS (EI) 328 (15%, M^+), 286 (100), 285 (32), 255 (8), 178 (21), 176 (16), 152 (9), 126 (5) and 107 (9).

6,7-Diphenylpyrrolo[1,2-b]pyridazin-5-yl Palmitate ***5***

A mixture of diphenylcyclopropenone (103 mg, 0.50 mmol) and pyridazine (36 µl, 0.50 mmol) in dry 1,2-dichloroethane (20 ml) was refluxed under N_2-atm. for 2 h and cooled to 0 °C before 4-(*N*,*N*-dimethylamino)pyridine (3.0 mg, 0.024 mmol), triethylamine (72 mg, 0.53 mmol), and palmitoyl chloride (180 µl, 0.580 mmol) were added. The resulting mixture was stirred for 16 h while reaching ambient temperature. Chloroform (30 ml) was added and the reaction mixture washed with saturated aqueous $CuSO_4$ solution (4×25 ml), saturated aqueous $NaHCO_3$ solution (2×15 ml), and brine (15 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography eluting with EtOAc-hexane (1:5).

Yield 46%; mp 68–72 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81 (t, *J* = 6.9 Hz, 3H, CH_3), 1.19–1.24 (m, 24H, CH_2), 1.58–1.62 (m, 2H, CH_2), 2.46 (t, *J* = 7.5 Hz, 2H, CH_2), 6.45 (dd, *J* = 9.1 and 4.4 Hz, 1H), 7.17–7.43 (m, 10H, Ph), 7.52 (dd, *J* = 9.1 and 1.8 Hz, 1H) and 7.93 (dd, *J* = 4.4 and 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 22.7, 25.0, 29.1, 29.2, 29.4, 29.4, 29.6, 29.6, 29.7, 29.7, 31.9, 34.0, 35.3, 109.5, 117.2, 119.5, 123.8, 124.1, 124.5, 126.9, 127.6, 128.1, 128.2, 129.7, 130.1, 130.6, 132.1, 142.1 and 172.6; MS (EI) 524 (2%, M^+), 287 (25), 286 (100), 270 (2), 178 (4) and 107 (4).

Bis(6,7-diphenylpyrrolo[1,2-b]pyridazin-5-yl) Adipate ***6***

A mixture of diphenylcyclopropenone (103 mg, 0.5 mmol) and pyridazine (0.036 ml, 0.50 mmol) in dry 1,2-dichloroethane (20 ml) was refluxed under N_2-atm. for 2 h and cooled to ambient temperature before 4-(*N*,*N*-dimethylamino)pyridine (3.0 mg, 0.024 mmol), triethylamine (38 µl, 0.27 mmol) and adipoyl chloride (39 µl, 0.27 mmol) were added. The resulting mixture was stirred for 16 h. Chloroform (30 ml) was added and the reaction mixture washed with saturated aqueous $CuSO_4$ solution (4×15 ml), saturated aqueous $NaHCO_3$ solution (2×15 ml), and brine (15 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography eluting with EtOAc-hexane (1:1).

Yield 45%; mp 210–214 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.67 (m, 4H, CH_2), 2.53 (m, 4H, CH_2), 6.51 (dd, *J* = 9.0 and 4.4 Hz, 2H), 7.25–7.50 (m, 20H, Ph), 7.59 (dd, *J* = 9.0 and 1.8 Hz, 2H) and 8.00 (dd, *J* = 4.4 and 1.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.3, 35.6, 111.6, 119.3, 121.6, 126.0, 126.1, 126.5, 129.0, 129.7, 130.2, 130.3, 131.2, 132.7, 134.2, 144.1 and 174.0; MS (EI) 682 (12%, M^+), 368 (4), 287 (49), 286 (100), 285 (30), 271 (23), 270 (49), 269 (23) and 178 (33).

5-Methoxy -6,7-diphenylpyrrolo[1,2-b]pyridazine ***7***

A mixture of diphenylcyclopropenone (464 mg, 2.25 mmol) and pyridazine (0.163 ml, 2.25 mmol) in dry 1,2-dichloroethane (25 ml) was refluxed under N_2-atm. for 14 h and evaporated *in vacuo*. The residue was dissolved in dry THF (50 ml). Sodium hydride (119 mg, 4.95 mmol) was added and the mixture was stirred at ambient temperature for 1 h before iodomethane (703 mg, 4.95 mmol) was added dropwise. After further stirring for for 26 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl-solution (1 ml). The mixture was extracted with EtOAc (50 ml) and the organic extract was washed with water (2×50 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography eluting with EtOAc-hexane (1:19).

Yield 54%; mp 111–112 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 3.73 (s, 3H, OCH_3), 6.51 (dd, *J* = 9.0 and 4.4 Hz, 1H, H-3), 7.2–7.4 (m, 6H, Ph), 7.4 (m, 2H, Ph), 7.4–7.5 (m, 2H, Ph) and 7.9–8.0 (m, 2H, H-2 and H-4); ^{13}C NMR (acetone-d_6, 125 MHz) δ 62.7, 109.1, 117.1, 119.0, 123.7, 125.7, 127.4, 128.0, 128.7, 128.9, 131.1, 131.5, 134.0, 136.3, and 149.2; MS (EI) 300 (70%, M^+), 285 (100), 255 (2), 178 (5), 176 (5), 143 (3), 134 (4), 128 (4), 107 (17), and 79 (14); HRMS: Calcd. for $C_{20}H_{16}N_2O$ 300.1263, found 300.1265.

5-Ethoxy -6,7-diphenylpyrrolo[1,2-b]pyridazine ***8***

A mixture of diphenylcyclopropenone (206 mg, 1.00 mmol) and pyridazine (80 mg, 1.0 mmol) in dry 1,2-dichloroethane (20 ml) was refluxed under N_2-atm. for 24 h and evaporated under a stream of N_2-gas. The residue was dissolved in dry THF (20 ml), sodium hydride (53 mg of a ca. 55% suspension in mineral oil, ca. 2.2 mmol) was added and the resulting mixture was stirred for 1 h before addition of iodoethane (343 mg, 2.20 mmol). After further stirring for 26 h, the reaction was quenched by addition of saturated aqueous NH_4Cl-solution (1 ml). The mixture was extracted with diethyl ether (100 ml) and the organic extract was washed with water (2×30 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography eluting with EtOAc-hexane (1:19) followed by EtOAc-hexane (1:9).

Yield 52%; mp 108–109 °C; (Found: C, 79.82 H, 5.59. $C_{21}H_{18}N_2O$ requires C, 80.23; H, 5.76%); ^{1}H NMR (acetone-d_6, 200 MHz) δ 1.19 (t, *J* = 7.0 Hz, 3H, CH_3), 3.89 (q, *J* = 7.0 Hz, 2H, CH_2), 6.56 (dd, *J* = 8.8 and 4.6 Hz, 1H), 7.2–7.5 (m, 10H, Ph) and 7.9–8.0 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.5, 70.7, 107.9, 117.3, 118.8, 123.1, 124.6, 126.4, 127.3, 128.0, 128.0, 130.2, 130.3, 130.6, 133.1, 133.9 and 141.9; MS (EI) 314 (40%, M^+), 286 (23), 285 (100), 257 (2), 255 (3), 178 (6), 176 (5), 107 (11), and 99 (15).

6,7-Diphenylpyrrolo[1,2-b]pyridazin-5-yl Methylcarbonate ***9***

A mixture of diphenylcyclopropenone (103 mg, 0.50 mmol) and pyridazine (36 µl, 0.50 mmol) in dry 1,2-dichloroethane (30 ml) was refluxed under N_2-atm. for 2 h and evaporated *in vacuo*. The residue was dissolved in 1,2-dimethoxyethane (30 ml) and sodium hydride (49 mg of a ca. 55% suspension in mineral oil, ca. 1.1 mmol) and methyl chloroformate (150 µl, 2.00 mmol) were added. After stirring for 16 h, the reaction mixture was evaporated *in vacuo* and the product was purified by flash chromatography eluting with EtOAc-hexane (1:2).

Yield 61%; mp 124–128 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.82 (s, 3H, CH_3), 6.54 (dd, *J* = 9.1 and 4.4 Hz, 1H), 7.22–7.49 (m, 10H, Ph), 7.70 (dd, *J* = 9.1 and 1.8 Hz, 1H) and 7.99 (dd, *J* = 4.4 and 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.8, 109.8, 117.1, 119.2, 123.8, 124.2, 124.7, 127.0, 127.7, 128.1, 128.4, 129.7, 130.1, 130.7, 131.8, 142.1 and 154.4; MS (EI) 344 (45%, M^+), 300 (7), 286 (18), 285 (80), 183 (34), 149 (100), 141 (65), and 107 (25); HRMS: Calcd. for $C_{21}H_{16}N_2O_3$ 344.1161, found 344.1159.

6,7-Diphenylpyrrolo[1,2-b]pyridazin-5-yl N-Phenylcarbamate ***10***

A mixture of diphenylcyclopropenone (103 mg, 0.50 mmol) and pyridazine (36 µl, 0.50 mmol) in dry 1,2-dichloroethane (30 ml) was refluxed under N_2-atm. for 2 h and cooled to 0 °C before 4-(*N*,*N*-dimethylamino)pyridine (153 mg, 1.26 mmol) and phenyl isocyanate (220 µl, 2.00 mmol) in 1,2-dichloroethane (10 ml) were added. After stirring for 12 h at 0–5 °C and at ambient temperature for 8 h, the reaction mixture was evaporated *in vacuo* and the product was purified by flash chromatography eluting with EtOAc-hexane (1:3).

Yield 52%; mp 175 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.47 (dd, *J* = 9.0 and 4.2 Hz, 1H), 6.78–7.43 (m, 15H, Ph), 7.67 (dd, *J* = 9.0 and 1.4 Hz, 1H) and 7.94 (dd, *J* = 4.2 and 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 109.6, 118.0, 118.7, 119.9, 124.0, 124.1, 124.2, 124.8, 127.1, 127.8, 128.3, 128.5, 129.3, 130.0, 130.4, 130.9, 132.3, 137.4, 142.3 and 178.0; MS (EI) 405 (1%, M^+), 287 (22), 286 (100), 285 (12), 257 (8), 178 (18), 119 (41), 107 (5), and 91 (20); HRMS: Calcd. for $C_{26}H_{19}N_3O_2$ 405.1477, found 405.1474.

6,7-Diphenylpyrrolo[1,2-b]pyridazin-5-yl Triflate ***11***

A mixture of diphenylcyclopropenone (206 mg, 1.00 mmol) and pyridazine (80 mg, 1.0 mmol) in dry 1,2-dichloroethane (10 ml) was refluxed under N_2-atm. for 15 h and cooled to ambient temperature before 4-(*N*,*N*-dimethylamino)pyridine (184 mg, 1.50 mmol) and dichloromethane (40 ml) were added. The resulting mixture was stirred under N_2-atm. at ambient temperature for 1 h and cooled to –78 °C before trifluoromethanesulfonic anhydride (141 mg, 0.50 mmol) was added. After stirring at –78 °C for 1 h, the reaction mixture was allowed to reach ambient temperature and evaporated *in vacuo*. The product was purified by flash chromatography eluting with EtOAc-hexane (1:39).

Yield 55%; mp 118–124 °C; (Found: C, 57.43; H, 3.28. $C_{20}H_{13}F_3N_2O_3S$ requires C, 57.42; H, 3.13%); ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.03 (dd, *J* = 9.3 and 4.4 Hz, 1H), 7.3–7.6 (m, 10H, Ph), 8.10 (dd, *J* = 9.3 and 1.7 Hz, 1H) and 8.29 (dd, *J* = 4.4 and 1.7 Hz, 1H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 113.5, 118.8, 119.3 (q, J_{CF} = 320 Hz), 120.6, 122.6, 124.7, 125.3, 128.6, 128.9, 128.9, 129.3, 130.0, 131.4, 131.4, 131.8 and 144.1; MS (EI): 418 (13%, M^+), 285 (100), 182 (14), 178 (11), 156 (6), 142 (5), 128 (8), 122 (8), 107 (14), and 79 (12).

6,7-Diphenylpyrrolo[1,2-b]pyridazin-5-yl Tosylate ***12***

A mixture of diphenylcyclopropenone (516 mg, 2.50 mmol) and pyridazine (200 mg, 2.50 mmol) in dry 1,2-dichloroethane (140 ml) was refluxed under a N_2-atm. for 24 h and cooled to 0 °C before 4-(*N*,*N*-dimethylamino)pyridine (61 mg, 0.50 mmol), triethylamine (506 mg, 5.00 mmol) and toluene-4-sulfonyl chloride (953 mg, 5.00 mmol) were added, and the resulting mixture was stirred at 0 °C for 1 h and at ambient temperature for 24 h. The reaction mixture was washed with water (25 ml) and saturated aqueous $NaHCO_3$ (25 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography eluting with EtOAc-hexane (1:4).

Yield 55%; (Found: C, 71.19; H, 4.47. $C_{26}H_{20}N_2O_3S$ requires C, 70.89; H, 4.58%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.31 (s, 3H, CH_3), 6.83 (dd, *J* = 9.2 and 4.4 Hz, 1H), 6.85–6.93 (m, 2H), 7.00–7.40 (m, 12H, Ar), 7.97 (dd, *J* = 9.2 and 1.8 Hz, 1H) and 8.13 (dd, *J* = 4.4 and 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 110.8, 119.2, 119.7, 122.5, 123.6, 125.7, 126.5, 127.7, 127.7, 128.0, 128.3, 129.0, 129.4, 130.2, 130.7, 130.9, 131.1, 142.5, and 144.8; MS (EI): 440 (4%, M^+), 285 (100), 107 (12), and 79 (9).

Dichloro 6,7-diphenylpyrrolo[1,2-b]pyridazin-5-yl Phosphate ***13***

A mixture of diphenylcyclopropenone (309 mg, 1.50 mmol) and pyridazine (120 mg, 1.50 mmol) in methanol (8 ml) was refluxed under N_2-atm. for 3 h and set aside in the refrigerator for 24 h. The crystals formed was filtered off, dissolved in phosphorus oxychloride (2 ml), refluxed under N_2-atm. for 3 h and the mixture was evaporated *in vacuo*. The residue was crystallised from dichloromethane-hexane.

Yield 69%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.88 (ddd, *J* = 9.2, 4.4 and 1.7 Hz, 1H), 7.20–7.50 (m, 10H, Ph), 8.09 (dd, *J* = 9.2 and 1.7 Hz, 1H, H-4) and 8.18 (dd, *J* = 4.4 and 1.7 Hz, 1H, H-2); MS (EI) 404/402 (55/55%, M^+), 285 (100), 176 (8), 134 (8), 107 (20), and 79 (18); HRMS: Calcd. for $C_{19}H_{13}Cl_2N_2OP$ 402.009, found 402.009.

Diethyl 6,7-diphenylpyrrolo[1,2-b]pyridazin-5-yl Phosphate ***14***

A mixture of diphenylcyclopropenone (309 mg, 1.50 mmol) and pyridazine (120 mg, 1.50 mmol) in methanol (8 ml) was refluxed under N_2-atm. for 3 h and set aside in the refrigerator for 24 h. The crystals formed was filtered off, dissolved in phosphorus oxychloride (2.0 ml) and refluxed under N_2-atm. for 3 h before the mixture was evaporated *in vacuo*. The residue was crystallised from dichloromethane-hexane and the crystals formed was stirred in abs. ethanol (2.0 ml) under N_2-atm. for 24 h. The mixture was evaporated *in vacuo* and the product was purified by flash chromatography eluting with EtOAc-hexane (1:1).

Yield 59%; (Found: C, 64.91; H, 5.43. $C_{23}H_{23}N_2O_4P$ requires C, 65.40; H, 5.49%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10 (dt, *J* = 7.1 and 1.1 Hz, 6H, CH_3), 3.7–4.0 (m, 4H, CH_2), 6.45 (ddd, *J* = 9.1, 4.4 and 0.8 Hz, 1H), 7.1–7.5 (m, 10H, Ar), 7.89 (dd, *J* = 4.4 and 1.8 Hz, 1H) and 7.98 (dd, *J* = 9.1 and 1.8 Hz, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 15.8, 64.7, 117.1, 119.2, 123.6, 124.8, 126.1, 127.4, 127.9, 128.3, 128.5, 130.4, 131.1, 132.6 and 142.9; MS (EI): 422 (100%, M^+), 394 (10), 366 (14), 348 (6), 285 (25), 270 (7), 255 (3), 228 (1), 198 (1), 178 (7), 126 (1), 107 (11), and 79 (9); HRMS: Calcd. for $C_{23}H_{23}N_2O_4P$ 422.1395, found 422.1400.

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