New, simple and versatile synthesis of 4,6-disubstituted pyridazin-3(2*H*)-ones†

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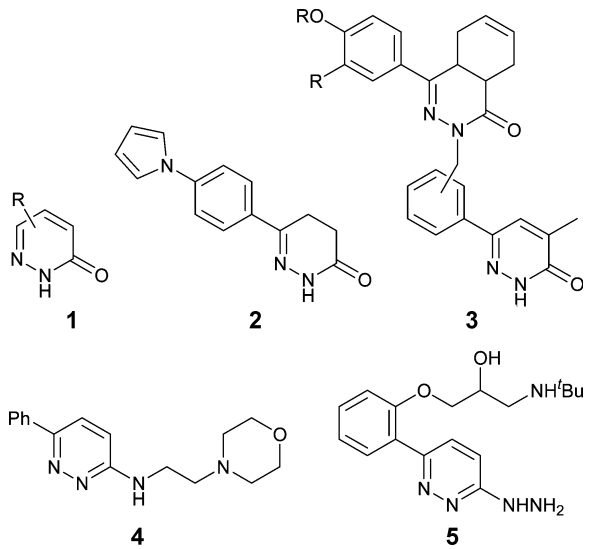
A simple, two-step synthesis of 4,6-disubstituted pyridazin-3(2*H*)-ones starting from 2-diethoxyphosphoryl-4-oxoalkanoates and hydrazines is described. The intermediate 4-diethoxyphosphoryl-4,5-dihydropyridazin-3(2*H*)-ones obtained in this way are used in a Horner–Wadsworth–Emmons olefination of aldehydes to give a variety of disubstituted pyridazin-3(2*H*)-ones.

Introduction

The pyridazin-3(2*H*)-ones **1** and their 4,5-dihydro derivatives show wide biological activity: they constitute the pyridazinone class of herbicides, which are carotenoid biosynthesis inhibitors,[1] and can also act as fungicides and insecticides.[2] Even more importantly, the pyridazin-3(2*H*)-one ring is present in many compounds that possess a variety of pharmacological properties, and therefore plays the role of a pharmacophore. Particularly well recognized is the antihypertensive activity of pyridazin-3(2*H*)-one derivatives such as imazodan **2**.[3] Also, the immunosuppressant activity of 4-cyano derivatives of **1**,[4] the gastric antisecretory and antiulcer activity of 2-cyanoguanidine derivatives of **1**,[5] as well as the hypotensive activity of 6-aryl-4-methyl derivatives of **1**,[6] have been reported. Recently, pharmacological investigations of phthalazinone/pyridazinone hybrids **3**, displaying both relaxation and antiinflamatory activities, have been undertaken with the aim of finding a new drug therapy for bronchial asthma.[7] Furthermore, pyridazin-3(2*H*)-ones **1** are the key intermediates in the synthesis of the psychotropic drug minaprine **4** and its analogs[8] as well as in the synthesis of the vasodilator antihypertensive agent prizidilol **5**.[9] Simple conversion of the appropriate derivative of **1** into the imino chloride and the nucleophilic displacement of the chlorine atom by the primary amine gives **4** or **5**.

The synthesis of pyridazin-3(2*H*)-ones **1** can be accomplished in several ways. Classic methods[10] involve (i) condensation of 4-oxoalkanoic acid with hydrazine and its derivatives to produce 4,5-dihydropyridazinones, which may be oxidized to the corresponding pyridazinones or (ii) the reaction of α-diketones with hydrazine derivatives in the presence of an ester containing active methylene protons. A more recent variant of the first method involves heating of 2-hydroxy-4-oxoalkanoic acids or esters with hydrazine. These acids or esters can be prepared from glyoxylic acid and methyl ketones,[11] or by catalytic hydrogenation of 4,5-dihydroisoxazoles.[12] The synthesis of **1** has also been accomplished by condensation of 4,5-dihydropyridazin-3(2*H*)-ones with some aromatic aldehydes.[13] The main drawback of these methods is the scarcity of the appropriately substituted substrates *e.g.* α-diketones or 4-oxoalkanoic acids.



In this paper we present a new, simple, and general two-step route to 4,6-disubstituted pyridazin-3(2*H*)-ones **9** and **10**.

Results and discussion

The 2-diethoxyphosphoryl-4-oxoalkanoates **6** that are substrates in our synthesis are readily available through the application of methods recently developed in our laboratory.[14]

In the first step oxoalkanoates **6a–h** were treated with hydrazine and phenylhydrazine. The reaction with hydrazine proceeded smoothly in boiling ethanol, yielding crude 4-diethoxyphosphoryl-4,5-dihydropyridazin-3(2*H*)-ones **7a–h**, which were purified by column chromatography (Table 1). In contrast, the reaction of oxoalkanoates **6b**,**f–h** with phenylhydrazine, which gave 4-diethoxyphosphoryl-2-phenyl-4,5-dihydropyridazin-3(2*H*)-ones **7i–l**, required more vigorous conditions (boiling toluene) and longer reaction times (Table 1). Crude products were purified by column chromatography. All compounds **7** were obtained in good to excellent yields and their structures were unequivocally confirmed by spectroscopic methods. Evidently, the first-formed hydrazones lactamize spontaneously to pyridazinones **7**.

In the second step, diethoxyphosphorylpyridazinones **7** were used in the Horner–Wadsworth–Emmons olefination of aldehydes.

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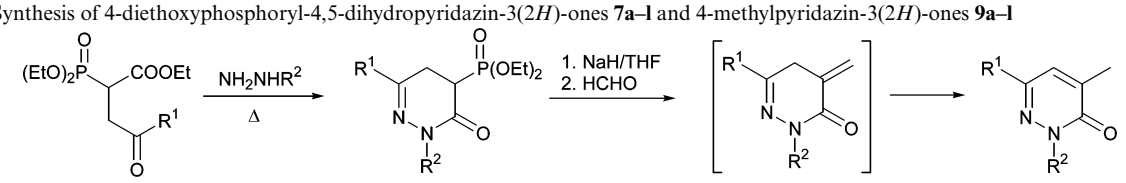
† Electronic supplementary information (ESI) available: Characterisation data for compounds **7b,c,e,f,h,j,k**, **9a,b,d,f–k** and **10b,c**, and NMR spectra for the new pyridazinones **9c,e,k,l** and **10a–d**. See DOI: 10.1039/b718734c

Table 1 Synthesis of 4-diethoxyphosphoryl-4,5-dihydropyridazin-3(2*H*)-ones **7a–l** and 4-methylpyridazin-3(2*H*)-ones **9a–l**



6a-h **7a-l** **8a-l** **9a-l**

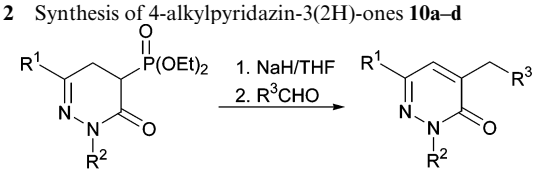
	R^1	R^2	Reaction time/h	Solvent	Yield of **7**[a] (%)	Yield of **9**[b] (%)
a	Me	H	10	Ethanol	94	75
b	Et	H	10	Ethanol	95	85
c	*n*-Pentyl	H	10	Ethanol	86	79
d	Bn	H	10	Ethanol	84	70
e	3,4-$(MeO)_2C_6H_3CH_2$	H	10	Ethanol	85	50
f	Ph	H	10	Ethanol	92	88
g	4-BrC_6H_4	H	10	Ethanol	76	89
h	4-$MeOC_6H_4$	H	10	Ethanol	65	60
i	Et	Ph	90	Toluene	61	49
j	Ph	Ph	34	Toluene	69	67
k	4-BrC_6H_4	Ph	45	Toluene	78	50
l	4-$MeOC_6H_4$	Ph	20	Toluene	61	40

[a] Yields of pure, isolated products based on **6**. [b] Yields of pure, isolated products based on **7**.

Thus, treatment of pyridazinines **7a–h** (R^2 = H) with sodium hydride at room temperature, and then with paraformaldehyde in boiling THF gave, after purification by column chromatography, 4-methylpyridazin-3(2*H*)-ones **9a–h**, usually in very good yields (Table 1). However, pyridazinones **7i–l** (R^2 = Ph) subjected to the same procedure gave unacceptably low yields of 4-methylpyridazinones **9i–l**. Pleasingly, however, when the formation of enolate anion and the reaction with paraformaldehyde was performed at 0 °C, satisfactory yields of **9i–l** were obtained (Table 1). IR, ^{1}H and ^{13}C NMR spectra confirmed their structures unambiguously. The aromatic character of the final pyridazinones **9** is certainly the driving force in the rearrangement of initially formed 4-methylidene-4,5-dihydropyridazin-3(2*H*)-ones **8** to pyridazin-3(2*H*)-ones **9**.

To broaden the scope of our method, we diversified the range of substituents in position 4. To achieve this, selected diethoxyphosphorylpyridazin-3(2*H*)-ones **7c**,**j** were tested in the Horner–Wadsworth–Emmons olefination of isobutyraldehyde, benzaldehyde and 1-naphthylaldehyde (Table 2). These reactions proceeded well in THF, in the presence of NaH as a base and, after standard work up and purification of the crude products by column chromatography, gave the expected rearranged pyridazin-3(2*H*)-ones **10a–d** in moderate to good yields (Table 2).

Table 2 Synthesis of 4-alkylpyridazin-3(2H)-ones **10a–d**



7c,j **10a-d**

	R^1	R^2	R^3	Yield of **10**[a] (%)
a	*n*-Pentyl	H	1-Naphthyl	35
b	*n*-Pentyl	H	*i*-Pr	60
c	Ph	Ph	Ph	76
d	Ph	Ph	*i*-Pr	75

[a] Yields of pure, isolated products based on **7c** (for **10a,b**) or **7j** (for **10c,d**).

Conclusions

We have developed an efficient, general, and simple approach to 4,6-disubstituted pyridazin-3(2*H*)-ones **9** and **10**, a class of compounds displaying broad biological activity. The easy accessibility and great diversity of the starting 2-diethoxyphosphoryl-4-oxoalkanoates **6** allows for the introduction of a variety of alkyl and aryl substituents into position 6. Also, substituents in position 4 can be easily modified by using selected aldehydes in the Horner–Wadsworth–Emmons olefination step. Furthermore, substituents at positions 4 and 6 can be introduced independently, which substantially increases the scope of our method.

Experimental

Organic solvents and reagents were purified by the appropriate standard procedures. Column chromatography was performed on Fluka® silica gel 60 (230–400 mesh). IR spectra were recorded on a Specord M 80 spectrometer. ^{1}H NMR (250 MHz), ^{13}C NMR (62.9 MHz), and ^{31}P NMR (101 MHz) spectra were recorded on a Bruker DPX-250 spectrometer with TMS as an internal standard for ^{1}H-NMR and ^{13}C-NMR, and 85% H_3PO_4 as an external standard for ^{31}P NMR. ^{31}P NMR spectra were recorded using broad-band proton decoupling. *J* values are given in Hz. Characterization data for compounds **7b**,**c**,**e**,**f**,**h**,**j**,**k**, **9a**,**b**,**d**,**f–k** and **10b**,**c** as well as ^{1}H and ^{13}C NMR spectra for the new pyridazinones **9c**,**e**,**k**,**l** and **10a–d** can be found in the ESI.†

General method for the synthesis of 4-diethoxyphosphoryl-4,5-dihydropyridazin-3(2*H*)-ones 7a–l

To a solution of 2-diethoxyphosphoryl-4-oxoalkanoate **6** (2.0 mmol) in an appropriate solvent (60 cm^3) (Table 1), 80% hydrazine hydrate (0.40 g, 4.0 mmol) or phenylhydrazine (0.43 g, 4.0 mmol) was added. The mixture was refluxed for the period of time given in Table 1. Progress of the reaction was occasionally monitored with ^{31}P NMR. After the oxoalkanoate was completely consumed, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography ($CHCl_3$–methanol, 95:5).

4-Diethoxyphosphoryl-6-methylpyridazin-3(2*H*)-ones (7a). (0.41 g, 94%) colorless oil (Found: C, 43.6; H, 6.8. $C_9H_{17}N_2O_4P$ requires C, 43.55; H, 6.9%); ν_{max} (film)/cm^{-1} 1684, 1254 and 1008; $\delta_H(CDCl_3)$ 1.21–1.38 (6H, m, 2 × CH_3CH$_2$O), 2.07 (3H, s, CH_3), 2.65–3.12 (3H, m, CH_2, CH), 4.12–4.26 (4H, m, 2 × CH$_3$CH_2O) and 8.51 (1H, s, NH); $\delta_C(CDCl_3)$ 15.72 (d, *J* 5.6 2 × *C*H$_3$CH$_2$O), 22.22 (s, *C*H$_3$), 26.67 (d, *J* 5.6, *C*-5), 35.84 (d, *J* 134.5, *C*-4), 62.45 (d, *J* 8.7, CH$_3$*C*H$_2$O), 62.47 (d, *J* 8.7, CH$_3$*C*H$_2$O),150.91 (d, *J* 5.0, *C*-6) and 162.01 (d, *J* 4.3, *C*-3); $\delta_P(CDCl_3)$ 22.34.

6-Benzyl-4-diethoxyphosphorylopyridazin-3(2*H*)-one (7d). (0.57 g, 84%) colorless crystals, mp 150 °C (from Et_2O) (Found: C, 55.7; H, 6.4. $C_{15}H_{21}N_2O_4P$ requires C, 55.55; H, 6.5%); ν_{max}(film)/cm^{-1} 1684, 1616, 1256 and 1004; $\delta_H(CDCl_3)$ 1.27–1.34 (6H, m, 2 × CH_3CH$_2$O), 2.52–3.05 (3H, m, CH_2, CH), 3.61, 3.68 (2H, AB, *J* 15.0, CH_2), 4.03–4.20 (4H, m, 2 × CH$_3$CH_2O), 7.23–7.37 (5H, m, 5 × CH_{Ar}) and 8.51 (1H, s, NH); $\delta_C(CDCl_3)$ 16.01 (d, *J* 3.1, *C*H$_3$CH$_2$O), 16.10 (d, *J* 3.1, *C*H$_3$CH$_2$O), 25.48 (d, *J* 5.0, *C*-5), 34.47 (d, *J* 137.7, *C*-4), 36.23 (s, *C*H$_2$), 42.84 (s, *C*H$_2$Ph), 62.68 (d, *J* 6.9, 2 × CH$_3$*C*H$_2$O), 126.86 (s, 2 × *C*-Ar), 128.48 (s, 2 × *C*-Ar), 128.92 (s, *C*-Ar), 135.37 (s, *C*-Ar), 152.95 (d, *J* 5.0, *C*-6) and 162.35 (d, *J* 4.4, *C*-3); δ_P ($CDCl_3$) 21.37.

6-(4-Bromophenyl)-4-diethoxyphosphorylopyridazin-3(2*H*)-one (7g). (0.59 g, 76%) yellow oil (Found: C, 43.5; H, 4.8. $C_{14}H_{18}BrN_2O_4P$ requires C, 43.2; H, 4.7%); ν_{max}(film)/cm^{-1} 1684, 1616, 1324, 1256, 1104 and 1020; $\delta_H(CDCl_3)$ 1.10–1.40 (6H, m, 2 × CH_3CH$_2$O), 3.00–3.56 (3H, m, CH_2, CH), 3.92–4.33 (4H, m, 2 × CH$_3$CH_2O), 7.40–7.65 (4H, m, 4 × CH_{Ar}) and 8.76 (1H, s, NH); $\delta_C(CDCl_3)$ 16.10 (d, *J* 6.2, 2 × *C*H$_3$CH$_2$O), 23.78 (d, *J* 5.6, *C*-5), 36.36 (d, *J* 134.5, *C*-4), 62.98 (d, *J* 4.9, CH$_3$*C*H$_2$O), 63.07 (d, *J* 6.8, CH$_3$*C*H$_2$O), 124.09 (s, *C*-Ar), 127.40 (s, 2 × *C*-Ar), 131.58 (s, 2 × *C*-Ar), 134.05 (s, *C*-Ar), 148.14 (d, *J* 4.9, *C*-6) and 162.66 (d, *J* 4.3, *C*-3); $\delta_P(CDCl_3)$ 21.40.

4-Diethoxyphosphorylo-6-ethyl-2-phenylpyridazin-3(2*H*)-one (7i). (0.412 g, 61%) brown oil (Found: C, 56.7; H, 6.8. $C_{16}H_{23}N_2O_4P$ requires C, 56.5; H, 6.7%); ν_{max}(film)/cm^{-1} 1676, 1308, 1256 and 1024; $\delta_H(CDCl_3)$ 1.21 (3H, t, *J* 7.4, CH_3CH$_2$), 1.26–1.38 (6H, m, 2 × CH_3CH$_2$O), 2.47 (2H, q, *J* 7.4, CH$_3$CH_2), 2.72–3.12 (2H, m, CH_2), 3.14–3.32 (1H, m, CH), 4.10–4.28 (4H, m, 2 × CH$_3$CH_2O), 7.22–7.28 (1H, m, CH_{Ar}), 7.34–7.44 (2H, m, 2 × CH_{Ar}) and 7.48–7.54 (2H, m, 2 × CH_{Ar}); $\delta_C(CDCl_3)$ 8.38 (s, *C*H$_3$CH$_2$), 14.52 (d, *J* 5.1, *C*H$_3$CH$_2$O), 14.60 (d, *J* 5.4, *C*H$_3$CH$_2$O), 24.57 (d, *J* 5.2, *C*-5), 28.36 (s, CH$_3$*C*H$_2$), 36.18 (d, *J* 136.0, *C*-4), 61.16 (d, *J* 6.6, CH$_3$*C*H$_2$O), 61.33 (d, *J* 7.0, CH$_3$*C*H$_2$O), 123.10 (s, 2 × *C*-Ar), 124.84 (s, *C*-Ar), 126.71 (s, 2 × *C*-Ar), 139.31 (s, *C*-Ar), 154.62 (d, *J* 5.3, *C*-6) and 159.02 (d, *J* 4.5, *C*-3); $\delta_P(CDCl_3)$ 22.21.

4-Diethoxyphosphorylo-6-(4-methoxyphenyl)-2-phenylpyridazin-3(2*H*)-one (7l). (0.51 g, 61%) yellow oil (Found: C, 60.7; H, 6.2. $C_{21}H_{25}N_2O_5P$ requires C, 60.6; H, 6.05%); ν_{max}(film)/cm^{-1} 1676, 1600, 1304, 1256 and 1028; $\delta_H(CDCl_3)$ 1.14–1.42 (6H, m, 2 × CH_3CH$_2$O), 3.08–3.62 (3H, m, CH_2, CH), 3.84 (3H, s, CH_3O) 4.04–4.28 (4H, m, 2 × CH$_3$CH_2O), 6.64–6.80 (2H, m, 2 × CH_{Ar}), 6.88–6.98 (1H, m, CH_{Ar}), 7.10–7.20 (2H, m, 2 × CH_{Ar}), 7.26–7.50 (2H, m, 2 × CH_{Ar}), 7.52–7.62 (1H, m, CH_{Ar}) and 7.72–7.82 (1H, m, CH_{Ar}); $\delta_C(CDCl_3)$ 16.17 (d, *J* 6.1, 2 × *C*H$_3$CH$_2$O), 24.28 (d, *J* 5.3, *C*-5), 38.00 (d, *J* 136.2, *C*-4), 55.19 (s, *C*H$_3$O), 62.94 (d, *J* 6.6, CH$_3$*C*H$_2$O), 63.10 (d, *J* 6.9, CH$_3$*C*H$_2$O), 113.84 (s, *C*-Ar), 114.98 (s, 2 × *C*-Ar), 118.30 (s, *C*-Ar), 124.90 (s, *C*-Ar), 126.62 (s, *C*-Ar), 127.49 (s, *C*-Ar), 127.75 (s, *C*-Ar), 128.37 (s, *C*-Ar), 129.06 (s, 2 × *C*-Ar), 141.14 (s, *C*-Ar), 146.18 (s, *C*-Ar), 149.83 (d, *J* 5.8, *C*-6) and 160.85 (d, *J* 4.4, *C*-3); $\delta_P(CDCl_3)$ 21.40.

General method for the synthesis of 4-alkylidenepyridazin-3(2*H*)-ones 9a–l and 10a–d

A solution of 4-diethoxyphosphorylpyridazin-3-one **7** (1.0 mmol) in THF (3 cm^3) was added, at 0 °C (for **9i–l** and **10c**,**d**) or at room temperature (for **9a–h** and **10a**,**b**), to a stirred suspension of sodium hydride (0.025 g, 1.05 mmol) in THF under an argon atmosphere. The reaction mixture was stirred at this temperature for 30 min. Then the appropriate aldehyde (1.0 mmol) was added in one portion and the reaction mixture was either stirred at 0 °C for 1.5 h (for **9i–l**) or refluxed for 1.5 h and cooled to 0 °C (for **9a–h** and **10a–d**). Then water (10 cm^3) was added, the solvent was removed under reduced pressure and the residue extracted with CH_2Cl_2 (3 × 15 cm^3). Combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure, affording the crude product which was purified by column chromatography (AcOEt–$CHCl_3$, 9:1).

4-Methyl-6-pentylpyridazin-3(2*H*)-one (9c). (0.142 g, 79%) colorless crystals, mp 76 °C (from Et_2O) (Found: C, 66.5; H, 8.7. $C_{10}H_{16}N_2O$ requires C, 66.6; H, 8.95%); ν_{max}(film)/cm^{-1} 1656, 1608 and 768; $\delta_H(CDCl_3)$; 0.89 (3H, t, *J* 6.5, CH_3), 1.26–1.43 (4H, m, 2 × CH_2), 1.63 (2H, quintet, *J* 7.5, CH_2), 2.20 (3H, d, *J* 1.2, CH_3), 2.53 (2H, t, *J* 7.5, CH_2), 7.02 (1H, d, *J* 1.2, CH) and 10.70 (1H, s, NH); $\delta_C(CDCl_3)$ 13.86 (s, *C*H$_3$), 16.16 (s, *C*H$_3$), 22.31 (s, *C*H$_2$), 28.09 (s, *C*H$_2$), 31.16 (s, *C*H$_2$), 34.43 (s, *C*H$_2$), 131.16 (s, *C*-5), 140.16 (s, *C*-4), 149.25 (s, *C*-6), and 162.96 (s, *C*-3).

6-(3,4-Dimethoxybenzyl)-4-methylpyridazin-3(2*H*)-one (9e). (0.130 g, 50%) yellow oil (Found: C, 64.4; H, 6.3. $C_{14}H_{16}N_2O_3$ requires C, 64.6; H, 6.2%); ν_{max}(film)/cm^{-1} 1648, 1600, 1512, 1460, 1264 and 1240; $\delta_H(CDCl_3)$ 2.21 (3H, d, *J* 1.2, CH_3), 3.81 (2H, s, CH_2) 3.90 (3H, s, CH_3O), 3.91 (3H, s, CH_3O), 6.76–7.00 (3H, m, 3 × CH_{Ar}), 7.32 (1H, s, CH) and 11.46 (1H, s, NH); $\delta_C(CDCl_3)$ 16.24 (s, *C*H$_3$), 40.52 (s, *C*H$_2$Ph), 55.87 (s, 2 × CH$_3$O) 111.35 (s, *C*-Ar), 111.98 (s, *C*-Ar), 120.92 (s *C*-5), 130.01 (s, *C*-Ar) 131.08 (s, *C*-Ar), 140.72 (s, *C*-4), 148.09 (s, *C*-6), 148.25 (s, *C*-Ar), 149.22 (s, *C*-Ar) and 162.68 (s, *C*-3).

6-(4-Methoxyphenyl)-4-methyl-2-phenylpyridazin-3(2*H*)-one (9l). (0.116 g, 40%) orange crystals, mp 150 °C (from Et_2O) (Found: C, 74.1; H, 5.3. $C_{18}H_{16}N_2O_2$ requires C, 73.95; H, 5.5%); ν_{max}(film)/cm^{-1} 1652, 1612, 1520 and 1252; $\delta_H(CDCl_3)$ 2.36 (3H,

d, J 1.2, CH_3), 3.86 (3H, s, CH_3O) 6.96–7.08 (3H, m, 3 × CH_{Ar}), 7.22 (1H, s, CH), 7.38–7.64 (3H, m, 3 × CH_{Ar}) and 7.70–7.84 (3H, m, 3 × CH_{Ar}); δ_C($CDCl_3$) 17.31 (s, CH$_3$), 55.35 (s, CH$_3$O), 114.23 (s, C-Ar), 125.58 (s, 2 × C-Ar), 127.32 (s, C-Ar), 127.43 (s, 2 × C-Ar), 127.58 (s, C-4), 127.82 (s, C-5), 128.55 (s, 2 × C-Ar), 129.22 (s, C-Ar), 129.37 (s, C-Ar), 141.39 (s, C-Ar), 142.17 (s, C-Ar), 144.26 (s, C-Ar), 146.39 (s, C-6) and 160.66 (s, C-3).

4-(Naphthalen-1-ylmethyl)-6-pentylpyridazin-3(2*H*)-one (10a). (0.107 g, 35%) colorless oil (Found: C, 78.3; H, 7.4. $C_{20}H_{22}N_2O$ requires C, 78.4; H, 7.2%); ν_{max}(film)/cm^{-1} 1652, 1608, 1512, 1464, 1400, 1240 and 1016; δ_H($CDCl_3$) 0.76–0.81 (3H, m, CH_3), 1.05–1.45 (6H, m, 3 × CH_2) 2.32 (2H, t, J 7.5, CH_2), 4.35 (2H, s, CH_2), 6.40 (1H, s, CH), 7.31–7.72 (4H, m, 4 × CH_{Ar}), 7.76–7.91 (3H, m, 3 × CH_{Ar}) and 10.33 (1H, s, NH); δ_C($CDCl_3$) 13.77 (s, CH$_3$), 22.18 (s, CH$_2$), 27.80 (s, CH$_2$), 30.91 (s, CH$_2$), 31.11 (s, CH$_2$), 32.29 (s, CH$_2$), 34.33 (s, CH$_2$), 124.07 (s, C-Ar), 125.55 (s, C-Ar), 125.80 (s, C-Ar), 126.32 (s, C-Ar), 127.85 (s, C-Ar), 128.14 (s, C-Ar), 128.69 (s, C-Ar), 130.60 (s, C-5), 131.83 (s, C-Ar), 133.25 (s, C-Ar), 133.91 (s, C-Ar), 142.60 (s, C-4), 149.41 (s, C-6) and 162.42 (s, C-3).

2,6-Diphenyl-4-isobutylpyridazin-3(2*H*)-one (10d). (0.231 g, 76%) orange crystal mp 62 °C (from Et_2O) (Found: C, 79.1; H, 6.4. $C_{20}H_{20}N_2O$ requires C, 78.9; H, 6.6%); ν_{max}(film)/cm^{-1} 1660, 1616, 1492, 1440, 1296 and 1196; δ_H($CDCl_3$) 1.00 (6H, d, J 7.0, (CH_3)$_2$CH), 2.05–2.30 (1H, m, (CH$_3$)$_2$CH), 2.58 (2H, d, J 7.0, CH_2), 7.34–7.55 (6H, m, 5 × CH_{Ar}, CH), 7.67–7.74 (3H, m, 3 × CH_{Ar}) and 7.82–7.86 (2H, m, 2 × CH_{Ar}); δ_C($CDCl_3$) 22.55 (s, 2 × CH$_3$), 26.88 (s, (CH$_3$)$_2$$C$H), 40.02 (s, (CH$_3$)$_2CHCH_2$) 125.55 (s, 2 × C-Ar), 126.60 (s, 2 × C-Ar), 127.29 (s, C-5), 127.84 (s, C-Ar), 128.51 (s, 2 × C-Ar), 128.81 (s, 2 × C-Ar), 129.30 (s, C-Ar), 135.10 (s, C-Ar), 142.10 (s, C-4), 144.23 (s, C-Ar), 144.41 (s, C-6) and 160.30 (s, C-3).

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References

1 F. E. Dayan and S. O. Duke, in *Encyclopedia of Agrochemicals*, Vol. 2, ed. J. R. Plimmer, D. W. Gammon and N. N. Ragsdale, Wiley-Interscience, New Jersey, 2003, p. 744.
2 R. Ross, S. H. Shaber, and E. M. Szapacs, *Eur. Pat. Appl.* EP 738716, 1996 (*Chem. Abstr.*, 1996, **125**, 328724).
3 M. Thyes, H. D. Lehmann, J. Gries, H. Konig, J. Kunze, R. Lebkucher and D. Lenke, *J. Med. Chem.*, 1983, **26**, 800; J. A. Bristol, I. Sircar, W. H. Moss, D. B. Evans and R. E. Weishaar, *J. Med. Chem.*, 1984, **27**, 1099; A. A. Siddiqui and S. M. Wani, *Indian J. Chem., Sect. B*, 2004, **43**, 1574.
4 R. Norton, and M. K. A. Ibraham, *US Pat.*, US 5506228, 1996 (*Chem. Abstr.*, 1996, **125**, 33663); R. J. Bochis, A. Kotliar, W. H. Parsons and K. Rupprecht, *PCT Int. Appl.* WO 9625936, 1996 (*Chem. Abstr.*, 1996, **125**, 275896).
5 T. Yamada, H. Shimamura, Y. Tsukamoto, A. Yamaguchi and M. Ohki, *J. Med. Chem.*, 1983, **26**, 1144.
6 A. A. Siddiqui and S. M. Wani, *Indian J. Chem., Section B*, 2004, **43**, 1574.
7 M. Van der Mey, K. M. Bommele, H. Boss, A. Hatzelmann, M. Van Slingerland, G. J. Sterk and H. Timmerman, *J. Med. Chem.*, 2003, **46**, 2008.
8 C.-G. Wermuth, G. Schlewer, J.-J. Bourguignon, G. Maghiros, M.-J. Bouchet, C. Moire, J.-P. Kan, P. Worms and K. Biziere, *J. Med. Chem.*, 1989, **32**, 528.
9 E. M. Taylor, D. Cameron, R. J. Eden, R. Fielden and D. A. A. Owen, *J. Cardiac Pharmacol.*, 1981, **3**, 337.
10 A. E. A. Porter, in *Comprehensive Organic Chemistry*, Vol. 4, ed. D. Barton and W. D. Ollis, Pergamon Press, Oxford, 1979, p. 87.
11 W. J. Coates and A. McKillop, *Synthesis*, 1993, 335.
12 P. G. Baraldi, A. Bigoni, B. Cacciari, C. Caldari, S. Manfredini and G. Spalluto, *Synthesis*, 1994, 1158.
13 A. Mustafa, W. Asker, A. H. Harhash, K. M. Foda, H. H. Jahine and N. A. Kassab, *Tetrahedron*, 1964, **20**, 531; N. G. Kandile and E. A. Ahmed, *Acta Chim. Hung.*, 1990, **127**, 829.
14 E. Błaszczyk, H. Krawczyk and T. Janecki, *Synlett*, 2004, 2685; J. F. Koszuk, A. Albrecht and T. Janecki, *Synthesis*, 2007, 1671.