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4-Functionally Substituted 3-Heterylpyrazoles: IV. Benzylamino[3-aryl(heteryl)-4-pyrazolyl]methylphosphonic Acids

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Abstract—Derivatives of *N*-benzyl[3-aryl(heteryl)-4-pyrazolyl]methanimines react with diethyl phosphite to afford diethyl benzylamino[3-aryl(heteryl)-4-pyrazolyl]-4-methylphosphonates that on hydrolysis with 18% hydrochloric acid yield the corresponding aminophosphonic acids.

In extension of our studies on planned construction of acyclic and heterocyclic systems with a pyrazole moiety we set a target to synthesize previously unknown benzylamino(4-pyrazolyl)methylphosphonic acids. The recent high interest in heteryl(amino)-methylphosphonic acids [2] is due mostly to application thereof as sinthons for preparation of peptidylphosphonates.

Taking into account the published data [3, 4] on the synthesis of heteryl(amino)methylphosphonic acids with 2-furyl, 2-,3-thienyl, 3-pyrazolyl, and 4-imidazolyl moieties we started the preparation of the target amino[3-aryl(heteryl)-4-pyrazolyl]methylphosphonic acids from 3-aryl(heteryl)-4-formylpyrazoles (**Ia–f**) that underwent a chain of successive transformations: formylpyrazoles **Ia–f** → aldimines **IIa–f** → diethyl aminomethylphosphonates **IIIa–f** → aminomethylphosphonic acids **IVa–f**.

The synthesis of aldimines **IIa–f** (Table 1) was performed by heating aldehydes **Ia–f** with benzylamine in boiling benzene in the presence of catalytic amounts of acetic acid. We selected as amine in this reaction just benzylamine since it might be easily transformed if required into an unsubstituted amino group by reductive hydrogenation [3]. The reaction of azomethines **IIa–f** with diethyl phosphite is carried out in toluene at boiling for 4 h and results in diethyl benzylamino(4-pyrazolyl)methylphosphonates **IIIa–f** in high yield. The latter when subjected to acid hydrolysis with18% hydrochloric acid afford the corresponding methylphosphonic acids **IVa–f** (see the Scheme).

Diethyl aminomethylphosphonates **IIIa–f** (Table 2) and aminomethylphosphonic acids proper **IVa–f** (Table 3) are colorless crystalline substances whose structure is consistent with the corresponding

Table 1. Yields, melting points, IR spectra and elemental analyses of *N*-benzyl[3-aryl(heteryl)-1-phenyl-1*H*-pyrazolyl]-methanimines **IIa**–**f**

Compd. no.	Yield, %	mp, °C (ethanol)	IR spectrum, ν(C=N), cm^{-1}	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
IIa	87	67–68	1650	81.44	5.31	12.12	$C_{23}H_{19}N_3$	81.89	5.63	12.46
IIb	84	105–107	1655	73.98	4.61	11.08	$C_{23}H_{18}ClN_3$	74.29	4.84	11.30
IIc	83	90–92	1650	66.12	4.11	9.88	$C_{23}H_{18}BrN_3$	66.34	4.32	10.09
IId	76	132–136	1645	84.02	5.38	9.92	$C_{29}H_{23}N_3$	84.26	5.56	10.16
IIe	81	75–76	1650	73.19	4.76	12.03	$C_{21}H_{17}N_3S$	73.46	4.95	12.24
IIf	90	179–181	1655, 1750[a]	76.86	4.42	10.10	$C_{26}H_{19}N_3O_2$	77.03	4.69	10.37

[a] ν(O–C=O).

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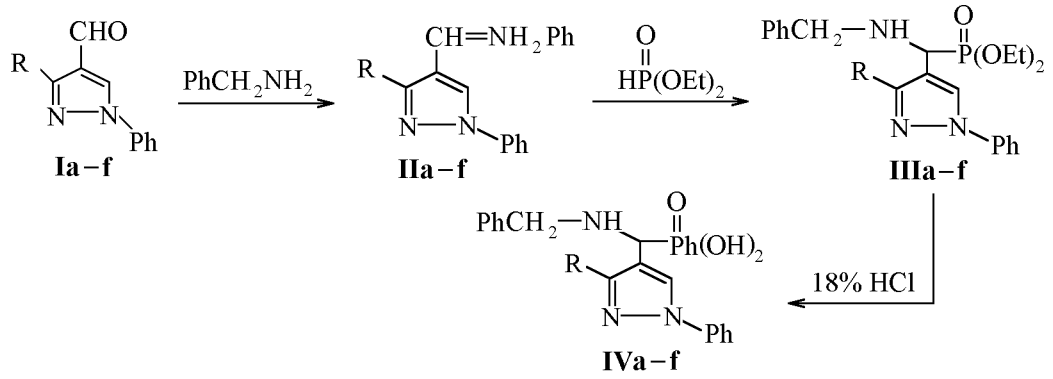
Scheme.



R = Ph (**a**), C_6H_4Cl-4 (**b**), C_6H_4Br-4 (**c**), C_6H_4Ph-4 (**d**), 2-thienyl (**e**), 2-oxo-2*H*-chromen-3-yl (**f**).

Table 2. Yields, melting points, ^1H and ^{31}P NMR spectral data, and elemental analyses of diethyl benzylamino[3-aryl-(heteryl)-1-phenyl-4-pyrazolyl]methylphosphonates **IIIa**–**f**

Compd. no.	Yield, %	mp, °C[a]	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIa	67	131–132	67.91	6.17	8.59	$C_{27}H_{30}N_3O_3P$	68.21	6.31	8.84
IIIb	72	126–127	63.21	5.48	8.01	$C_{27}H_{29}ClN_3O_3P$	63.59	5.69	8.24
IIIc	78	134–135	58.23	5.02	7.35	$C_{27}H_{29}BrN_3O_3P$	58.48	5.23	7.58
IIId	61	127–128	71.61	5.97	7.41	$C_{33}H_{34}N_3O_3P$	71.86	6.17	7.62
IIIe	67	107–108	62.12	5.68	8.50	$C_{25}H_{28}N_3O_3PS$	62.37	5.82	8.73
IIIf	67	172–173	66.03	5.21	7.48	$C_{30}H_{30}N_3O_5P$	66.29	5.49	7.73

Compd. no.	^1H NMR spectrum $(CD_3)_2SO$, δ, ppm	^{31}P NMR spectrum, $(CD_3)_2SO$, δ_P, ppm
IIIa	8.67 s (1H, = CH), 7.98 d (2H, H arom), 7.18–7.56 m (13H, H arom), 4.06 d (1H, CHP, J_{HP} 21.1 Hz), 3.82–4.03 m (4H, OCH_2), 3.67 d.d (2H, CH_2N, J_{HH} 7.0 Hz), 2.84 m (1H, NH), 1.19 t (3H, CH_3, J_{HH} 7.0 Hz), 1.04 t (3H, CH_3, J_{HH} 7.0 Hz)	25.08
IIIb	8.69 s (1H,=CH), 7.87 d (2H, H arom), 7.15–7.54 m (12H, H arom), 4.13 d (1H, CHP, J_{HP} 25.0 Hz), 3.80–3.99 m (4H, OCH_2), 3.73 d.d (2H, CH_2N, J_{HH} 11.4 Hz), 2.89 m (1H, NH), 1.21 t (3H, CH_3, J_{HH} 7.1 Hz), 1.06 t (3H, J_{HH} 7.1 Hz)	24.69
IIIc	8.74 s (1H, = CH), 7.21–7.75 m (14H, H arom), 3.85–4.07 m (4H, OCH_2), 4.01 d.d (1H, CHP, J_{HP} 23.7 Hz), 3.71 d.d (2H, CH_2N, J_{HH} 11.4 Hz), 2.89 m (1H, NH), 1.14 t (3H, CH_3, J_{HH} 7.1 Hz), 1.06 t (3H, J_{HH} 7.2 Hz)	24.73
IIId	8.80 s (1H, = CH), 7.25–7.94 m (19H, H arom), 3.80–4.01 m (4H, OCH_2), 3.96 d.d (1H, CHP, J_{HP} 23.3 Hz), 3.69 d.d (2H, CH_2N, J_{HH} 11.5 Hz), 2.81 m (1H, NH), 1.21 t (3H, CH_3, J_{HH} 7.1 Hz), 1.07 t (3H, J_{HH} 7.1 Hz)	25.12
IIIe	8.74 s (1H, = CH), 7.03–7.94 m (13H, H arom), 4.12 d (1H, CHP, J_{HP} 22.6 Hz), 3.80–4.01 m (4H, OCH_2), 3.90 d.d (2H, CH_2N, J_{HH} 11.2 Hz), 2.80 m (1H, NH), 1.11 t (3H, CH_3, J_{HH} 7.1 Hz), 1.03 t (3H, J_{HH} 7.1 Hz)	24.30
IIIf	8.73 s (1H, = CH), 7.11–7.91 m (15H, H arom), 4.09 d (1H, CHP, J_{HP} 22.2 Hz), 3.85–4.04 m (4H, OCH_2), 3.75 d.d (2H, CH_2N, J_{HH} 11.3 Hz), 2.90 m (1H, NH), 1.11 t (3H, CH_3, J_{HH} 7.2 Hz), 1.03 t (3H, CH_3, J_{HH} 7.1 Hz)	24.94

[a] Crystallization from benzene–hexane mixture, 1:1 (compound **IIIe**), 2:1 (compounds **IIIa, b, d**), 3:1 (compound **IIIc**), and 4:1 (compound **IIIf**).

Table 3. Yields, melting points, ^{1}H and ^{31}P NMR spectral data, and elemental analyses of benzylamino[3-aryl(heteryl)-1-phenyl-4-pyrazolyl]methylphosphonic acids **IVa–f**

Compd. no.	Yield, %	mp, °C	Found, %		Formula	Calculated, %	
			N	P		N	P
IVa	81	243–244	9.78	7.08	$C_{23}H_{22}O_3P$	10.02	7.39
IVb	84	264–265	9.03	6.57	$C_{23}H_{21}ClN_3O_3P$	9.26	6.83
IVc	81	271–272	8.17	5.98	$C_{23}H_{21}BrN_3O_3P$	8.43	6.22
IVd	75	247–249	8.20	6.04	$C_{29}H_{26}N_3O_3P$	8.48	6.26
IVe	71	260–261	9.59	7.05	$C_{21}H_{20}N_3O_3PS$	9.88	7.29
IVf	89	250–252	8.35	6.12	$C_{26}H_{22}N_3O_5P$	8.62	6.36

Compd. no.	^{1}H NMR spectrum $(CD_3)_2SO$, δ, ppm	^{31}P NMR spectrum, $(CD_3)_2SO$, δ_P, ppm
VIa	9.10 s (1H, = CH), 7.91 d (2H, H arom), 7.03–7.87 m (13H, H arom), 4.37 d (1H, CHP, J_{HP} 24.3 Hz), 3.97 d.d (2H, CH_2N, J_{HH} 11.5 Hz), 3.54 m (1H,NH)	8.50
VIb	9.12 s (1H, = CH), 7.10–7.89 m (14H, H arom), 4.44 d (1H, CHP, J_{HP} 25.7 Hz), 3.99 d.d (2H, CH_2N, J_{HH} 11.7 Hz), 3.59 m (1H, NH)	8.62
VIc	9.07 s (1H, = CH), 7.03–7.93 m (14H, H arom), 4.30 d (1H, CHP, J_{HP} 26.1 Hz), 4.11 d.d (2H, CH_2N, J_{HH} 11.7 Hz), 3.60 m (1H, NH)	8.42
VId	9.10 s (1H, = CH), 8.01 d (2H, H arom), 7.01–7.71 m (17H, H arom), 4.30 d (1H, CHP, J_{HP} 24.6 Hz), 4.05 d.d (2H, CH_2N, J_{HH} 11.5 Hz), 3.52 m (1H,NH)	8.57
VIe	9.12 s (1H, = CH), 7.86 d (2H, H arom), 7.00–7.54 m (11H, H arom), 4.31 d (1H, CHP, J_{HP} 25.1 Hz), 4.00 d.d (2H, CH_2N, J_{HH} 11.5 Hz), 3.59 m (1H, NH)	8.61
VIf	9.08 s (1H, = CH), 7.11–7.89 m (15H, H arom), 4.34 d (1H, CHP, J_{HP} 24.9 Hz), 4.01 d.d (2H, CH_2N, J_{HH} 11.5 Hz), 3.55 m (1H, NH)	8.52

^{1}H NMR spectra. In the downfield part of the spectra of esters **IIIa–f** appear the signals of protons C^5H of the pyrazole ring (8.6–8.8 ppm) and also multiplets of the protons from the aromatic and heterocyclic substituents. The presence of a chiral center results in magnetic nonequivalence in the benzyl and diethylphosphoryl moieties that give double sets of signals: the protons of NH_2Ph appear as two doublets at 3.6–3.8 ppm with the coupling constants 11.2–11.5 Hz, protons of CH_2O group appear as multiplet at 3.8–4.1 ppm, those of CH_3 group as triplets at 1.1–1.3 and 0.8–1.1 ppm with coupling constants 7.1–7.3 Hz. Methine proton signal in the range 4.0–4.2 ppm is split into doublet with the coupling constants 21.0–25.2 Hz due to coupling with phosphorus. The spectral pattern of the aminomethyl fragment of acids **IVa–f** consist of a doublet from CH proton (4.3–4.5 ppm) with the coupling constants 24.3–26.1 Hz and two doublets of protons NCH_2Ph (3.9–4.2 ppm) with the coupling constants 11.4–11.7 Hz. The proton of the amino group appears as unresolved broad signal in the region 2.8–2.9 ppm for esters **IIIa–f** and 3.5–3.6 ppm for acids **IVa–e**.

EXPERIMENTAL

IR spectra were recorded on spectrometer UR-20 from KBr pellets. ^{1}H NMR spectra were registered on spectrometer Varian-Gemini (300 MHz), internal reference TMS. ^{31}P NMR spectra were measured on spectrometer Varian-Gemini (121 MHz), external reference H_3PO_4.

***N*-benzyl[3-aryl(heteryl)-1-phenyl-1*H*-pyrazolyl]methanimines IIa–f.** To a solution of 0.01 mol of aldehyde **Ia–f** in 20 ml of benzene was added 1.1 g (0.01 mol) of benzylamine and 3 drops of glacial acetic acid, and the mixture was heated for 2 h in a flask equipped with a Dean–Stark trap. On cooling the separated precipitate was filtered off and crystallized from ethanol.

Diethyl benzylamino[3-aryl(heteryl)-1-phenyl-4-pyrazolyl]methylphosphonates IIIa–f. A mixture

of 0.005 mol of aldimine **IIa–f** and 0.69g (0.005 mol) of diethyl phosphite in 10 ml of toluene was heated to boiling for 4 h. The solvent was removed at reduced pressure, and the residue was crystallized from a mixture benzene–hexane.

Benzylamino[3-aryl(heteryl)-1-phenyl-4-pyrazolyl]methylphosphonic acids IVa–f. A mixture of 0.001 mol of phosphonate IIIa–f and 20 ml of 18% hydrochloric acid was heated to boiling for 6 h. On cooling the separated precipitate was filtered off, washed with ice water, dried, and crystallized from ethanol.

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