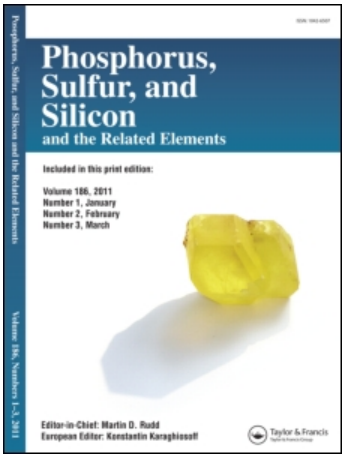

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A Simple Synthesis of Dimethylphosphinyl-Substituted Tetrahydropyrroles

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*New dimethylphosphinyl-substituted tetrahydropyrroles **3**, **5**, **6** and **8** have been synthesized via 1,3-cycloaddition reaction of the N-(4-chlorophenylmethylene)aminomethyl-dimethylphosphinoxide (**1**) to benzylideneacetophenone, ethyl cinnamate and cinnamonitrile. The structure of the compounds was confirmed by elemental analysis, IR, ^{1}H-, and $^{31}P\{^{1}H\}$-NMR spectroscopy and in some cases by mass spectrometry, as well.*

Keywords 1,3-cycloaddition reaction; dimethylphosphinyl-substituted tetrahydropyrroles; N-(4-chlorophenylmethylene)aminomethyl-dimethylphosphinoxide; phase-transfer catalysis

INTRODUCTION

Due to their unique biological properties, the aminophosphonic acids as analogues of the natural aminoacids have played a central role in the investigation of biologically active molecules during the last 20 years.[1] For the preparation of a series of substituted 2-diethoxyphosphonylpyrrolidines—the phosphonyl analogues of proline—Dehnell has applied a method based on the 1,3-cycloaddition

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of deprotonated (with strong bases) 2-azaallylphosphonates to 2,3-unsaturated esters.[2,3] This new method to generate 1,3-dipoles is of great interest due to its ability to provide diastereoselective route to a variety of 5-membered heterocyclic compounds, substituted with functional groups containing phosphorus.

The present work is a continuation of our previous investigations on the application of the Michael reaction for the preparation of functionalized heterocyclic compounds.[4] In order to investigate the possibility of introducing a phosphinyl group in the pyrrolidine ring we turned our attention to the Schiff bases of the aminomethyl-dimethylphosphine oxide. The synthesis of dialkylphosphinyl derivatives has been of interest because of their higher biological activity in some cases in comparison with the corresponding phosphonic and phosphinic esters.[5] On the other hand some of the nitrosourea derivatives and platinum complexes of dimethylphosphinyl derivatives exhibit antitumor activity being of low toxicity;[6,7] triazolo- and pyrazolopyrimidine derivatives have plant-growth regulating activity.[8]

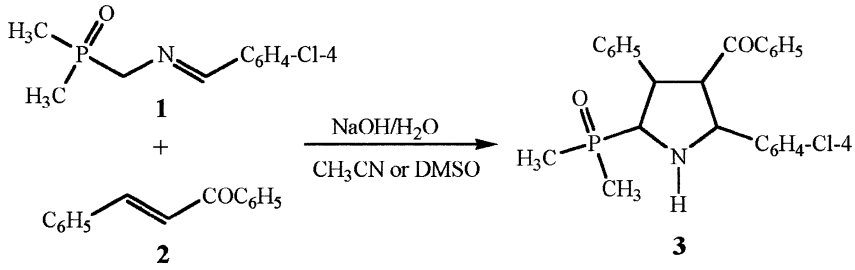
We report here the synthesis and characterization of dimethylphosphinyl-substituted tetrahydropyrroles via 1,3-cycloaddition reaction of N-arylmethyleneaminomethyl-dimethylphosphinoxide (**1**) to electron-deficient alkenes (α,β-unsaturated ketones, esters, and nitriles) in different reaction conditions.

RESULTS AND DISCUSSION

The reaction between the Schiff base **1** and benzylideneacetophenone (**2**) was carried out in acetonitrile and in the presence of 10 equivalents of aqueous NaOH (50%). We obtained a crude reaction product free from starting compounds (TLC, ^{1}H-NMR). The absence of a signal for the imine proton —CH=N— (δ ~8.2-8.3 ppm) in the ^{1}H-NMR spectra means that no acyclic product of 1,4-addition was formed.

The crystalline reaction product (99% yield) represents a mixture of at least three of the possible eight diastereomers of the pyrrolidine **3** (Scheme 1) in the ratio of **3C**: **3A**: **3X** = 4: 3: 1, determined by integration of the signals for the dimethylphosphinyl groups in the ^{1}H-NMR spectra. Separation of the diastereomers could not be achieved chromatographically, but we obtained fractions, enriched of one of them, enabling us to make the assignment of the proton spectra. After two recrystallizations from ethyl acetate, one of the diastereomers (**3A**), probably the most insoluble of them, was isolated and identified as

3-benzoyl-2-(4-chlorophenyl)-5-dimethylphosphinyl-4-phenyl-2,3,4,5-tetrahydropyrrole (**3**) by means of the elemental analysis, IR, ^{1}H-, and ^{31}P{^{1}H}-NMR and mass spectra.



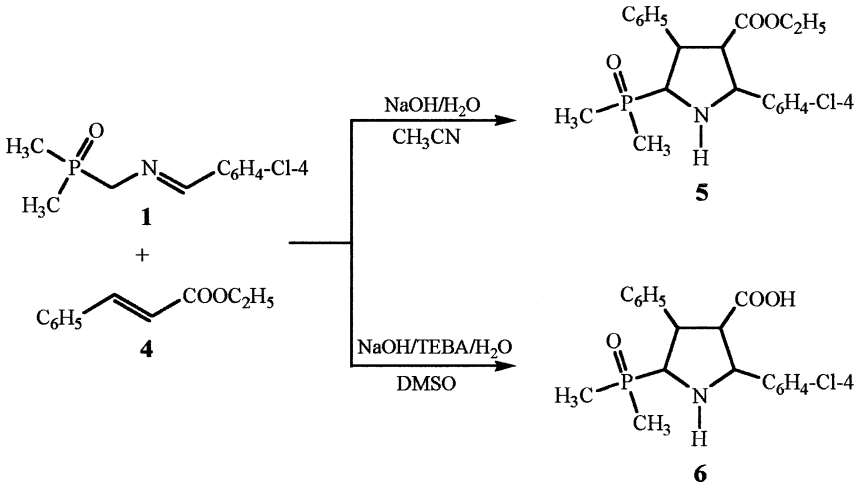
SCHEME 1

In dimethyl sulfoxide (DMSO) as a solvent the same pyrrolidine **3** was obtained, but with lower yield (77%) and lower stereoselectivity. At least six diastereoisomers (the main three of them in the ratio of **3C**:**3B**:**3A** = 3:1:1) were observed in the ^{1}H-NMR spectra of the crude reaction product. High yields but low diastereoselectivity were found also when the reaction was carried out in acetonitrile but in the presence of solid potassium carbonate and triethylbenzyl-ammonium chloride (TEBA) (94%, five isomers) or in tetrahydrofuran and NaH as deprotonating agent (92%, five isomers).

The reaction of **1** with ethyl cinnamate (**4**) was carried out in the same reaction conditions (10 equivalents of 50%-aqueous NaOH in acetonitrile). The reaction mixture crystallized in 5 min. After standard workup we obtained the corresponding pyrrolidine **5** in 79% yield at room temperature, resp. 84% yield at 0°C (Scheme 2). In this case the reaction occurred with high stereoselectivity—only one (**5A**) of all possible diastereomers was present in the crude reaction product according to the ^{1}H-NMR spectra. The yield after recrystallization from ethyl acetate was 72%.

From the aqueous layer after acidification we isolated 7% of cinnamic acid, as a result of hydrolysis of the starting ethyl cinnamate in basic conditions. In tetrahydrofuran and in the presence of NaH we obtained the pyrrolidine **5** (75%) as a mixture of two diastereoisomers (**5D**: **5A** = 3: 1). After twofold recrystallization of the reaction product from ethyl acetate one of the isomers was isolated (**5A**, ^{1}H-NMR spectra).

When we carried out the reaction of the Schiff base **1** and ethyl cinnamate in phase-transfer catalysis conditions (10 equivalents of aqueous NaOH (50%)/TEBA/DMSO) we did not obtain the ester

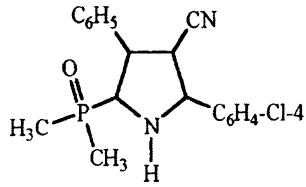


SCHEME 2

of pyrrolidinecarboxylic acid **5** but the acid **6** itself (86% yield of a crude product) as a mixture of two diastereomers in the ratio of **6A**: **6C** = 1: 1 (^{1}H-NMR spectra). It was dissolved in the basic medium and isolated by acidification of the aqueous layer at pH~5.5. After twofold recrystallization from methanol, one of the two isomers of 2-(4-chlorophenyl)-5-dimethylphosphinyl-4-phenyl-2,3,4,5-tetrahydropyrrole-3-carboxylic acid (**6A**) was isolated (20%). Obviously due to the better solubility of the ester **5** in DMSO than in acetonitrile the reaction mixture remains homogeneous and allows the hydrolysis to take place. The IR spectra of the acid **6** (nujol) showed a low frequency shifting of the **CO**OH (1690 cm^{-1}) and OH (broad multiplet at 1930–2370 cm^{-1}) due to the strong intermolecular H-bond between P=O and COOH. Performing the reaction in DMSO but with a catalytic amount of aqueous NaOH (4%) we obtained again the ester **5** (79%) as a mixture of two diastereomers in the ratio of **5A**: **5C** = 3: 1 (^{1}H-NMR spectra).

Reaction of **1** with cinnamonitrile (**7**) in the same reaction conditions (ten equivalents of aqueous NaOH (50%) in acetonitrile, in DMSO or in dichloromethane) produced again the pyrrolidine adduct **8** with high yields (93–97%) of the crude reaction product as a mixture of several diastereomers. After recrystallization from ethyl acetate we obtained the most insoluble of them and confirmed its structure as 2-(4-chlorophenyl)-3-cyano-5-dimethylphosphinyl-4-phenyl-2,3,4,5-tetrahydropyrrole (**8C**).

All products were fully characterized by elemental analysis, IR, ^{1}H- and ^{31}P{^{1}H}-NMR and in some cases by mass spectra data (Tables I and



8

II). A detailed study of the relative configuration of the synthesized pyrrolidines **3**, **5**, **6** and **8** by combined use of 1D and 2D homo- and heteronuclear pulse sequences is in progress. It shows that the main two isomers (**A** and **C**) of **3**, **5**, **6** and **8** have the same relative configuration and that the substituents at the C-3 and C-4 of the pyrrole ring have trans orientation one towards another and these at C-2 and C-5 have cis orientation one towards another.

EXPERIMENTAL

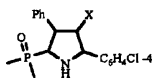
Melting points (uncorrected): microhot stage Boetius PHMK 05. Infrared spectra: Specord 75 IR spectrometer in $CHCl_3$or in nujol. ^{1}H-NMR spectra: Bruker DRX 250 and Bruker DRX-500 NMR spectrometers, DMSO-d_6 as a solvent. $^{31}P\{^1H\}$-NMR spectra: Bruker Avance (81 MHz), DMSO-d_6 as a solvent. Chemical shifts are measured towards TMS as internal standard (^{1}H-NMR spectra) or 85% H_3PO_4 ($^{31}P\{^1H\}$-NMR spectra). The electron impact (EI) mass spectra were measured on a Varian MAT 311A at 70 eV using the direct inlet system. TLC: Silicagel 60 F_{254} on aluminium sheets, layer thickness 0.2 mm, Merck. Mobile phase: dichloromethane:methanol = 20 : 1.The column chromatography separation was carried out on Silicagel 60 (0.063–0.250 mm), Merck. Dry tetrahydrofuran was distilled over $LiAlH_4$ before use. NaH, 60% suspension in oil, Aldrich.

The aminomethyl-dimethyl-phosphine oxide [9] and the starting Schiff base **1**[10] were prepared according to literature procedures.

General Procedure for the Preparation of 3, 5, 6 and 8

Aqueous sodium hydroxide (0.5 mL of 50% or 0.2 mL of 4% solution) was added at room temperature to a magnetically stirred solution of the Schiff base **1** (0.46 g, 2 mmol) and 2 mmol of the corresponding 2,3-unsaturated compound **2** (0.42 g), **4** (0.35 g) or **7** (0.25 mL) in acetonitrile (1 mL), DMSO (3 mL) or dichloromethane (1 mL). When reactions were

TABLE I Preparative and Analytical Data of the Main Isomers of the Pyrrolidines 3, 5, 6 and 8



No.	X	M.p.,°C	General formula (Mol. mass)	Elemental analysis					
				% C		% H		% N	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
3A	COC_6H_5	212–215 (ethyl acetate)	$C_{25}H_{25}ClNO_2P$ (437.91)	68.57	68.46	5.75	5.54	3.20	3.48
5A	$COOCH_2CH_3$	176–178 (ethyl acetate)	$C_{21}H_{25}ClNO_3P$ (405.86)	62.15	62.45	6.21	6.09	3.45	3.81
6C	COOH	258–260 (ethyl acetate)	$C_{19}H_{21}ClNO_3P$ (377.80)	60.40	60.60	5.60	5.84	3.71	4.15
8C	CN	252–255 (ethyl acetate-ethanol)	$C_{19}H_{20}ClN_2OP$ (358.80)	63.60	63.44	5.62	5.30	7.81	8.07

TABLE II Spectral Data of the Main Isomers of Compounds 3, 5, 6 and 8

No.	IR ($CHCl_3$) ν (cm^{-1})	^{1}H NMR (DMSO-d_6)[a] δ (ppm), J (Hz)	^{31}P NMR (DMSO-d_6) δ (ppm)
3A[b]	3370, 1685, 1600, 1300, 1165	0.94 (d, 3H, CH_3-P, $^2J_{PH} = 12.8$), 1.35 (d, 3H, CH_3-P, $^2J_{PH} = 12.8$), 3.6–3.7 (m, 2H, H-5 and NH), 4.11 (dt, 1H, 12H, H_{ar}), 7.7 (m, H-4, $^3J_{PH} = 12.5$, $^3J_{HH} = 10.3$), 4.80 (t, 1H, H-3, $^3J_{HH} = 10.3$), 5.11 (dd, 1H, H-2, $^3J_{HH} = 9.8$, $^3J_{HH} = 6.8$), 7.1–7.5 (m, 2H, o-H_{ar})	41.40
3C	3360, 1685, 1600, 1290, 1165	0.49 (d, 3H, CH_3-P, $^2J_{PH} = 12.3$), 1.27 (d, 3H, CH_3-P, $^2J_{PH} = 12.3$), 3.77 (dd, 1H, H-5, $^2J_{PH} = 9.1$, $^3J_{HH} = 9.0$), 4.06 (bs, 1H, NH), 4.29 (ddd, 1H, H-4, $^3J_{PH} = 24.6$, $^3J_{HH} = 10.8$, $^3J_{HH} = 9.0$), 4.50 (dd, 1H, H-2, $^3J_{HH} = 9.6$, $^4J_{PH} = 1.6$), 5.01 (dd, 1H, H-3, $^3J_{HH} = 10.7$, $^3J_{HH} = 9.6$) 7.2–7.5 (m, 12H, H_{ar}), 7.6 (m, 2H, o-H_{ar})	43.78
5A	3360, 1725, 1600, 1290, 1150	0.76 (t, 3H, C**H**$_3$$CH_2O$, $^3J_{HH} = 7.1$), 0.95 (d, 3H, CH_3-P, $^2J_{PH} = 12.8$), 1.34 (d, 3H, CH_3-P, $^2J_{PH} = 12.8$), 3.4–3.6 (m, 5H, H-3, H-5, CH_3C**H**$_2$O, NH), 3.82 (dt, 1H, H-4, $^3J_{PH} = 12.9$, $^3J_{HH} = 10.2$), 4.87 (dd, 1H, H-2, $^3J_{HH} = 9.6$, $^3J_{HH} = 6.6$), 7.2–7.4 (m, 7H, H_{ar}), 7.5 (m, 2H, o-H_{ar})	44.61
5C	3360, 1725, 1600, 1300, 1150	0.42 (d, 3H, CH_3-P, $^2J_{PH} = 12.3$), 0.91 (t, 3H, C**H**$_3$$CH_2O$, $^3J_{HH} = 7.1$), 1.23 (d, 3H, CH_3-P, $^2J_{PH} = 12.2$), 3.5–3.8 (m, 2H), 3.90 (q, 2H, CH_3C**H**$_2$O, $^3J_{HH} = 7.1$), 4.0–4.2 (m, 2H), 4.51 (t, 1H, $^3J_{HH} = 7.7$) 7.2–7.5 (m, 7H, H_{ar}), 7.6 (m, 2H, o-H_{ar})	45.55
6A[c,d]	3370, 3330, 1850–2800, 1690, 1300, 1120	0.95 (d, 3H, CH_3-P, $^2J_{PH} = 12.7$), 1.34 (d, 3H, CH_3-P, $^2J_{PH} = 12.7$), 3.4–3.6 (m, 2H, H-3, H-5), 3.77 (dt, 1H, H-4, $^3J_{PH} = 12.8$, $^3J_{HH} = 10.7$), 4.85 (d, 1H, H-2, $^3J_{HH} = 9.8$), 7.2–7.5 (m, 7H, H_{ar}), 7.5 (m, 2H, o-H_{ar})	41.55
6C[d]	3370, 3330, 1850–2800, 1690, 1300, 1120	0.44 (d, 3H, CH_3-P, $^2J_{PH} = 12.3$), 1.22 (d, 3H, CH_3-P, $^2J_{PH} = 12.3$), 3.6–3.7 (m, 2H, H-3 and H-5), 4.05 (ddd, 1H, H-4, $^3J_{PH} = 25.0$, $^3J_{HH} = 11.7$, $^3J_{HH} = 9.0$), 4.52 (dd, 1H, H-2, $^3J_{HH} = 9.7$, $^4J_{PH} = 2.0$), 7.2–7.5 (m, 7H, H_{ar}), 7.6 (m, 2H, o-H_{ar})	43.35
8C	3380, 2250, 1600, 1300, 1160	0.41 (d, 3H, CH_3-P, $^2J_{PH} = 12.4$), 1.25 (d, 3H, CH_3-P, $^2J_{PH} = 12.4$), 3.74 (dd, 1H, H-5, $^2J_{PH} = 11.0$, $^3J_{HH} = 8.9$), 3.92 (dd, 1H, H-3, $^3J_{HH} = 12.5$, $^3J_{HH} = 10.0$), 4.22 (ddd, 1H, H-4, $^3J_{PH} = 21.4$, $^3J_{HH} = 12.5$, $^3J_{HH} = 8.9$), 4.64 (dd, 1H, H-2, $^3J_{HH} = 10.1$, $^4J_{PH} = 2.5$), 7.3–7.5 (m, 7H, H_{ar}), 7.8 (m, 2H, o-H_{ar})	43.62

[a] ^{1}H NMR spectra for compounds **3A**, **3C**, **6A** and **6C**—recorded on 500 MHz, these for **5A**, **5C**, and **8C**—on 250 MHz.
[b] MS (EI), m/z (%): 437 (2, $M^{+\cdot}$), 360 (60, $M^{+\cdot}$ - $(CH_3)_2P{=}O$), 254 (25), 105 (100, $PhC^+{=}O$), 77 (34, Ph^+).
[c] MS (EI), m/z (%): 377 (2, $M^{+\cdot}$), 300 (100, $M^{+\cdot}$ - $(CH_3)_2P{=}O$), 254 (40), 151 (82), 44 (45, $CO_2^{+\cdot}$).
[d] IR (nujol).

carried out in PTC conditions 0.1 equivalents of TEBA (0.05 g) were used. The reaction mixture was stirred for 1 h at the same temperature and then water (10 mL) was added. The resulting reaction mixture was extracted with dichloromethane (3 × 20 mL), combined extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by recrystallization or column chromatography.

The acid **6** was isolated from the clear aqueous layer, obtained after extraction, by acidification with conc. HCl to pH∼5.5 and was purified by recrystallization from methanol.

When NaH instead of NaOH was used for the preparation of pyrrolidines **3** and **5** the reaction was carried out in this way: To a stirred solution of 2 mmol of the corresponding 2,3-unsaturated compound **2** (0.42 g) or **4** (0.35 g) and 2.2 mmol NaH (0.09 g) in dry tetrahydrofuran (2 mL) a solution of 2 mmol (0.46 g) of the Schiff base **1** in 7 mL tetrahydrofuran was added drop wise. After one hour at room temperature the reaction mixture was quenched with water (20 mL) and the solvent was evaporated under reduced pressure. Then water (20 mL) was added and the resulting reaction mixture was extracted with dichloromethane (3 × 20 mL), combined extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by recrystallization or column chromatography.

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