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Regioselective aza-Michael addition of azoles to 4-(diphenylphosphoryl)but-3-en-2-one

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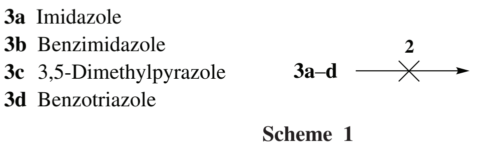
Aza-Michael reaction of (*E*)-4-(diphenylphosphoryl)but-3-en-2-one with mono- and bicyclic nitrogen heterocycles proceeds regioselectively in the absence of catalysts to give the corresponding β-diphenylphosphoryl-β-azahetarylalkanones. Its reaction with imidazole in the presence of chiral organocatalysts affords the corresponding enantiomerically enriched adduct in higher yield.

Aza-Michael addition of nitrogen nucleophiles to electron-deficient alkenes is an efficient method for the formation of carbon–nitrogen bond, which fits requirements of green chemistry.[1–3] Addition of azoles[4,5] and aliphatic amines[6,7] at common acceptors including (*E*)-4-phenylbut-3-en-2-one proceeds, as a rule, in the presence of basic catalysts. Addition of organophosphorus compounds (OPC) to double C=C bond is well studied.[8] However, the employment of unsaturated OPC as Michael acceptors is very confined[9] and no examples of preparation of nitrogen heterocycles containing diarylphosphoryl substituents by this reaction are documented. At the same time, interest in compounds of this type increases.[10–12] We anticipated that the reaction of phosphorylated enones with amino-containing compounds could afford a new series of promising hybrid phosphorus-nitrogen compounds. The nootropic properties of a number of hydrazides of diarylphosphorylacetic acids are reported,[13] while (carbamoylmethyl)phosphine oxides[14] and *N*-phosphorylureas[15] show the highest efficiency among nitrogen-containing organophosphorus extractants.

In this work, we tested (*E*)-4-(diphenylphosphoryl)but-3-en-2-one **1** and (*E*)-5-(diphenylphosphoryl)-1,5-diphenylpent-1-en-3-one **2** as Michael acceptors (Scheme 1). Compounds **1** and **2** were obtained using the Conant reaction.[16] The C=C bond in compound **2** is distant from the diphenylphosphoryl fragment and sterically more available for attack by nucleophile than in compound **1**. However, on attempting various versions of aza-Michael reaction, we did not observe the formation of adducts between compound **2** and azoles. This is in agreement with the data[4–7] that relative benzylidenacetone would add NH-heterocycles only on using catalysts. In contrast, phosphoryl enone **1** readily reacted with azoles **3a–d** even in the absence of catalysts (see Scheme 1, *cf.* ref. 1). The reaction was performed in an argon flow on refluxing in anhydrous acetonitrile or toluene (Table 1).[†]



Scheme 1

According to 2D COSY NMR data, the addition occurs regioselectively at the carbon atom bearing diphenylphosphoryl group, which is not obvious for the reaction with disubstituted Michael acceptors.[1] The second possible regioisomer was not detected even in trace amounts. This fact agrees well with the data on the smaller electron-withdrawing effect of diphenylphosphoryl group as compared to acetyl one.[17]

The results show that imidazole is the most reactive among azoles tested, while the lowest yield was achieved with benzotriazole. This is in a good agreement with the basicity (pK_b) of these azoles.

The use of known chiral organocatalysts of Michael reaction such as amino alcohols, diols, and binaphthols[3,18–20] dramatically

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[†] ^{1}H, ^{1}H{^{31}P} and ^{31}P{^{1}H} NMR spectra were recorded on a Bruker AV-400 spectrometer (400.13 MHz for ^{1}H and ^{1}H{^{31}P} and 161.98 MHz for ^{31}P{^{1}H}) at 30 °C in CDCl$_3$. The signals of residual protons of the deuterated solvent were used as an internal reference for ^{1}H/^{1}H{^{31}P} NMR spectra, 85% H$_3$PO$_4$ was employed as an external reference for ^{31}P{^{1}H} NMR spectra. IR spectra were obtained on an UR-20 spectrophotometer in CHCl$_3$. Mass spectra were measured on a Finigan SSQ-7000 mass spectrometer. Elemental analysis was performed in the Laboratory of Microanalysis, A. N. Nesmeyanov Institute of Organoelement Compounds. Melting points were determined on an Electrothermal IA 9000 melting point indicator in sealed capillary tubes. Initial phosphoryl enones **1** and **2**,[16] and *N*-benzyl-(*S*)-proline[22] were prepared by published procedures.

4-Diphenylphosphoryl-4-(imidazol-1-yl)butan-2-one **4a**. Imidazole **3a** (0.076 g, 1.11 mmol) was added to a solution of compound **1** (0.30 g, 1.11 mmol) in MeCN (10 ml). The mixture was kept at 80 °C with stirring for 15 h (^{31}P{^{1}H} NMR monitoring). The solvent was evaporated to dryness and the product was extracted with diethyl ether. Crystals precipitated on standing at 0 °C were separated and dried at 50 °C in a drying cabinet until constant weight to give 0.23 g (53%) of **4a**, mp 139–141 °C. An additional portion of compound **4a** (0.11 g, 25%) was obtained from the solution. ^{31}P{^{1}H} NMR, δ: 30.43 (s). ^{1}H{^{31}P} NMR, δ: 2.02 (s, 3H, Me), 2.93 (dd, 1H, CH_AH$_B$, $^3J_{H_AH}$ 2.0 Hz, $^2J_{H_AH_B}$ 18.4 Hz), 3.34 (dd, 1H, CH$_A$$H_B$, $^3J_{H_BH}$ 10.1 Hz, $^2J_{H_BH_A}$ 18.2 Hz), 5.49 (dd, 1H, PCH, $^3J_{HH_A}$ 2.1 Hz, $^3J_{HH_B}$ 9.8 Hz), 6.92 (s, 1H, H^4-Het), 7.15 (s, 1H, H^5-Het), 7.34 (t, 2H, *m*-H$_{Ph}$, $^3J_{HH}$ 7.6 Hz), 7.45 (t, 1H, *p*-H$_{Ph}$, $^3J_{HH}$ 7.6 Hz), 7.48 (s, 1H, H^2-Het), 7.48 (d, 2H, *o*-H$_{Ph}$, $^3J_{HH}$ 7.5 Hz), 7.57 (t, 2H, *m*-H$_{Ph}$, $^3J_{HH}$ 7.3 Hz), 7.63 (t, 1H, *p*-H$_{Ph}$, $^3J_{HH}$ 7.3 Hz), 7.88 (d, 2H, *o*-H$_{Ph}$, $^3J_{HH}$ 7.9 Hz). IR (ν/cm^{-1}): 1203 (P=O), 1719 (C=O). Found (%): C, 67.61; H, 5.74; N, 8.34; P, 9.16. Calc. for C$_{19}$H$_{19}$N$_2$O$_2$P (%): C, 67.45; H, 5.66; N, 8.28; P, 9.15.

Table 1 The reaction of enone **1** with azoles **3a**–**d**.

Entry	Azole	T/°C	t/h	Solvent	Product	Yield (%)
1	**3a**	80	15	MeCN	**4a**	78
2	**3b**	110	16	PhMe	**4b**	37
3	**3c**	110	65	PhMe	**4c**	80
4	**3d**	110	48	PhMe	**4d**	41

accelerates the reaction and increases the yield, although the enantioselectivity of formation of adduct **4a** is relatively low. The higher *ee* value of only 9% was reached with (*S*)-BINOL. Table 2 shows the results of conjugated addition of imidazole **3a** to enone **1** in the presence of 5 mol% of chiral catalysts at 110 °C in toluene. The acceleration of the reaction is likely to result from the known ability of bifunctional catalysis *via* both activation of Michael acceptor **1** due to hydrogen bonding at the carbonyl group and increase in nucleophilicity of heterocycle **3a** on account of coordination.[3,18–20]

Table 2 Addition of imidazole **3a** to enone **1** in the presence of 5 mol% of chiral catalysts.

Entry	Catalyst	t/h	Isolated yield[a] (%)	*ee* of **4a**
1	(*S*,*S*)-TADDOL	6	53	4
2	(4*S*-*trans*)-2,2-Dimethyl-α,α,α′,α′-tetra-(1-naphthyl)-1,3-dioxolane-4,5-dimethanol	6	60	4
3	Cinchonidine	6	68	3
4	*N*-Benzyl-(*S*)-proline	6	71	2
5	(*S*)-BINOL	21	98	9

[a] The mixture was concentrated and the product was analyzed by ^{1}H and ^{31}P NMR and by HPLC (Aligent 1100 Series system) on chiral column (Daicel Chiracel OD-H): hexane/propan-2-ol (95:15) + 0.2% DEA; 0.75 ml min^{-1}, UV detector 225 nm.

A computation using PASS software[21] indicates a large probability of nootropic physiological activity for compounds **4a**–**d**.

In conclusion, we prepared the first representatives of β-diphenylphosphoryl-β-hetarylalkanones by the aza-Michael reaction, which are of interest as compounds with potential biological activity and hybrid phosphorus–nitrogen ligands for *f*-block elements.

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4-Diphenylphosphoryl-4-(benzimidazol-1-yl)butan-2-one **4b**. Similarly, the refluxing of 0.10 g (0.37 mmol) of enone **1** with 0.044 g (0.37 mmol) of benzimidazole **3b** in 15 ml of toluene at 110 °C for 16 h gave 0.053 g (37%) of **4b**, mp 162–164 °C (from $\mathrm{Et_2O}$). $^{31}\mathrm{P}\{^1\mathrm{H}\}$ NMR, δ: 30.93 (s). ^{1}H NMR, δ: 1.97 (s, 3H, Me), 3.16 (ddd, 1H, $\mathrm{C}H_\mathrm{A}\mathrm{H}_\mathrm{B}$, $^3J_{\mathrm{H_AH}}$ 3.0 Hz, $^3J_{\mathrm{H_AP}}$ 8.2 Hz, $^2J_{\mathrm{H_AH_B}}$ 18.5 Hz), 3.47 (ddd, 1H, $\mathrm{CH_A}H_\mathrm{B}$, $^3J_{\mathrm{H_BH}}$ 9.1 Hz, $^3J_{\mathrm{H_BP}}$ 5.0 Hz, $^2J_{\mathrm{H_AH_B}}$ 18.5 Hz), 5.80–5.86 (m, 1H, PCH), 7.10–7.30 (m, 5H, *m*,*p*-$\mathrm{H_{Ph}}$ + 2$\mathrm{H_{Het}}$), 7.44 (dd, 2H, *o*-$\mathrm{H_{Ph}}$, $^3J_{\mathrm{HH}}$ 7.4 Hz, $^3J_{\mathrm{HP}}$ 11.4 Hz), 7.55–7.68 (m, 5H, *m*,*p*-$\mathrm{H_{Ph}}$ + 2$\mathrm{H_{Het}}$), 7.95 (dd, 2H, *o*-$\mathrm{H_{Ph}}$, $^3J_{\mathrm{HH}}$ 7.7 Hz, $^3J_{\mathrm{HP}}$ 10.2 Hz), 8.20 (br. s, 1H, $\mathrm{H^2}$-Het). IR (ν/cm^{-1}): 1194 (P=O), 1720 (C=O). Found (%): C, 71.20; H, 5.74; N, 6.51; P, 7.49. Calc. for $\mathrm{C_{23}H_{21}N_2O_2P}$ (%): C, 71.12; H, 5.45; N, 7.21; P, 7.97.

4-Diphenylphosphoryl-4-(3,5-dimethylpyrazol-1-yl)butan-2-one **4c**. Analogously, from 0.1 g (0.37 mmol) of enone **1** and 0.035 g (0.37 mmol) of 3,5-dimethylpyrazole **3c** in 5 ml of toluene at 110 °C for 65 h a mixture was obtained, which was subjected to preparative TLC on glass plates (180×240 mm) coated with silica gel (60 $\mathrm{PF_{254}}$ with 30% of gypsum) using $\mathrm{CHCl_3}$–ethyl acetate (1 : 3) as an eluent to give 0.107 g (80%) of **4c**, mp 170–172 °C. $^{31}\mathrm{P}\{^1\mathrm{H}\}$ NMR, δ: 30.82 (s). ^{1}H NMR, δ: 1.82 (s, 3H, $\mathrm{C^3H_3}$-Het), 2.05 (s, 3H, COMe), 2.18 (s, 3H, $\mathrm{C^5H_3}$-Het), 3.14 (ddd, 1H, $\mathrm{C}H_\mathrm{A}\mathrm{H}_\mathrm{B}$, $^3J_{\mathrm{H_AH}}$ 1.8 Hz, $^3J_{\mathrm{H_AP}}$ 5.8 Hz, $^2J_{\mathrm{H_AH_B}}$ 18.2 Hz), 3.75 (ddd, 1H, $\mathrm{CH_A}H_\mathrm{B}$, $^3J_{\mathrm{H_BH}}$ 10.8 Hz, $^3J_{\mathrm{H_BP}}$ 4.2 Hz, $^2J_{\mathrm{H_AH_B}}$ 18.1 Hz), 5.28 (ddd, 1H, PCH, $^3J_{\mathrm{HH_A}}$ 1.6 Hz, $^3J_{\mathrm{HH_B}}$ 10.8 Hz, $^2J_{\mathrm{HP}}$ 11.1 Hz), 5.56 (s, 1H, $\mathrm{H^4}$-Het), 7.34–7.58 (m, 8H, *o*,*m*,*p*-$\mathrm{H_{Ph}}$), 7.99 (dd, 2H, *o*-$\mathrm{H_{Ph}}$, $^3J_{\mathrm{HH}}$ 7.8 Hz, $^3J_{\mathrm{HP}}$ 11.3 Hz). IR (ν/cm^{-1}): 1188 (P=O), 1721 (C=O). Found (%): C, 68.54; H, 6.04; N, 7.14. Calc. for $\mathrm{C_{21}H_{23}N_2O_2P}$ (%): C, 68.84; H, 6.33; N, 7.65.

4-Diphenylphosphoryl-4-(benzotriazol-1-yl)butan-2-one **4d**. Similarly, the refluxing of 0.20 g (0.74 mmol) of enone **1** and 0.088 g (0.74 mmol) of benzotriazole **3d** in 15 ml of toluene at 110 °C for 48 h gave 0.12 g (41%) of **4d**, mp 148–150 °C. $^{31}\mathrm{P}\{^1\mathrm{H}\}$ NMR, δ: 30.07 (s). ^{1}H NMR, δ: 2.07 (s, 3H, Me), 3.44 (ddd, 1H, $\mathrm{C}H_\mathrm{A}\mathrm{H}_\mathrm{B}$, $^3J_{\mathrm{H_AH}}$ 2.8 Hz, $^3J_{\mathrm{H_AP}}$ 6.8 Hz, $^2J_{\mathrm{H_AH_B}}$ 18.4 Hz), 3.90 (ddd, 1H, $\mathrm{CH_A}H_\mathrm{B}$, $^3J_{\mathrm{H_BH}}$ 10.1 Hz, $^3J_{\mathrm{H_AP}}$ 4.8 Hz, $^2J_{\mathrm{H_BH_A}}$ 18.4 Hz), 6.25–6.32 (m, 1H, PCH), 7.25–7.29 (m, 1H, $\mathrm{H^5}$-Het), 7.32–7.55 (m, 7H, *m*,*p*-$\mathrm{H_{Ph}}$ + $\mathrm{H^6}$-Het), 7.61 (d, 1H, $\mathrm{H^7}$-Het, $^3J_{\mathrm{HH}}$ 8.4 Hz), 7.70–7.83 (m, 4H, *o*-$\mathrm{H_{Ph}}$), 7.92 (d, 1H, $\mathrm{H^4}$-Het, $^3J_{\mathrm{HH}}$ 8.3 Hz). MS, *m*/*z*: 390.1363 $[\mathrm{M+H}]^+$, 412.1188 $[\mathrm{M+Na}]^+$ (calc. for $\mathrm{C_{22}H_{21}N_3O_2P}$, *m*/*z*: 390.137140; calc. for $\mathrm{C_{22}H_{20}N_3NaO_2P}$, *m*/*z*: 412.119085).