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N-Substituted *C*-diethoxyphosphorylated nitrones as useful synthons for the synthesis of α-aminophosphonates

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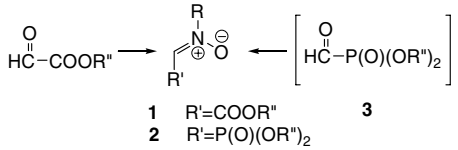
Abstract—A convenient method for the synthesis of N-substituted *C*-phosphorylated nitrones **2** from hydroxymethylphosphonates via successive Swern oxidation and treatment with respective hydroxylamines is reported for the first time. Moderate (20%) to excellent (up to 90%) diastereoselectivities in cycloadditions of nitrone **2a** and terminal alkenes were observed with trans C5-substituted isoxazolidines predominating. In $ZnCl_2$-catalysed cycloadditions, mixtures enriched in cis diastereoisomers were produced.

Cycloaddition reactions are among the most powerful chemical transformations available to organic chemistry, because the regio- and stereochemistry of cycloadducts are often controlled by both steric and electronic effects.[1–4] 1,3-Dipolar cycloadditions of nitrones to alkene dipolarophiles are of special interest, since substituted isoxazolidines have found numerous applications as enzyme inhibitors,[5,6] furanoside ring mimics,[7–10] as well as key intermediates in the synthesis of a variety of compounds after cleavage of the N–O bond.[1]

C-Alkoxycarbonyl nitrones **1** are easily available by condensation of the corresponding *N*-hydroxylamines and alkyl glyoxylates and consequently they have been employed in the synthesis of several amino acids as well as other biologically important compounds (Scheme 1).[11–19]

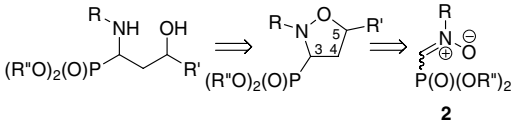
It was reasoned that analogous N-substituted *C*-phosphorylated nitrones **2** would be useful intermediates for the synthesis of a wide range of substituted α-aminophosphonates, after reductive cleavage of the isoxazolidine ring (Scheme 2).



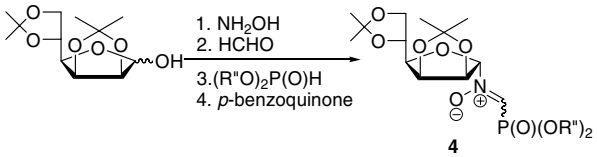
Scheme 1. Synthetic approaches to *C*-alkoxycarbonyl- and *C*-phosphorylated nitrones.

Previously, attempts at synthesizing nitrones **2** from formylphosphonates **3** had failed. Dialkyl formylphosphonates are chemically unstable and at −10 °C undergo decomposition to carbon monoxide and a dialkyl phosphite.[20] To overcome this problem, Vasella accomplished a multi-step synthesis of *N*-glycosyl-*C*-dialkoxyphosphorylated nitrones **4** (Scheme 3),[21] which without isolation were subjected to 1,3-dipolar cycloaddition with ethylene.

Prompted by a recent letter by Chiacchio et al.[22] which utilised the *N*-methyl nitrone obtained from



Scheme 2. Retrosynthesis of substituted α-aminophosphonates from nitrones **2**.



Scheme 3. Synthesis of the *N*-chiral Vasella nitrone **4**.

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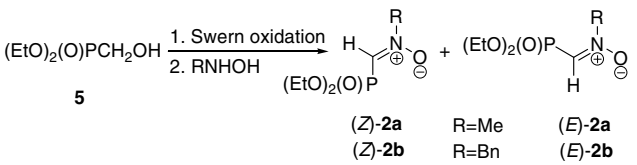
commercially available diethylphosphonoacetaldehyde diethylacetal for the synthesis of phosphonylated *N*,*O*-nucleoside analogues, a general method for the synthesis of N-substituted *C*-phosphorylated nitrones **2** from formylphosphonates and their reactivity in 1,3-dipolar cycloadditions with a range of terminal alkenes is reported herein.

When diethyl hydroxymethylphosphonate **5** was subjected to Swern oxidation and the resulting crude product treated in situ with *N*-methylhydroxylamine (Scheme 4), an 86:4:10 mixture containing nitrone **2a** (R = Me), unreacted hydroxymethylphosphonate **5** and diethyl phosphite was produced, as judged from the ^{31}P NMR spectra. Pure nitrone **2a**[23] was isolated in 75% yield after column chromatography followed by crystallisation. In the same manner, nitrone **2b**[24] (R = Bn) was obtained in 70% yield as a colourless oil. Nitrones **2a** and **2b** are stable compounds and could be stored at room temperature without decomposition for several months.

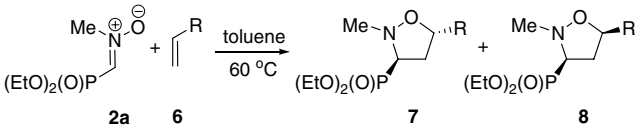
In a chloroform-*d* solution at room temperature, nitrones **2** exist as equilibrium mixtures of *E*/*Z* isomers [15:85 for **2a** (R = Me) and 14:86 for **2b** (R = Bn)]. However, nitrone **2a** (R = Me) crystallises as pure (*Z*)-isomer. The ^{1}H NMR spectrum of nitrone **2a** in C_6D_6 recorded immediately after dissolving (2 min) showed signals for the (*Z*)-isomer only. After 30 min, a 5:95 mixture of (*E*)-**2a** and (*Z*)-**2a** was present, while after 2 h a 15:85 ratio was observed which remained unchanged for 24 h at room temperature. This equilibrium was not influenced by heating a benzene-d_6 solution at 60 °C for 18 h. The equilibrium (15:85) ratio was immediately attended after dissolving crystals of **2a** in $CDCl_3$.

In the ^{1}H NMR spectrum of nitrone **2a** in $CDCl_3$, signals for the methyl groups were observed at $\delta = 4.08$ ppm (minor) and $\delta = 3.84$ ppm (major), while in the spectrum of nitrone **2b** singlets for the CH_2Ph appeared at $\delta = 5.52$ ppm (minor) and $\delta = 4.98$ ppm (major). Significant downfield shifts were observed for the minor isomers, which resulted from deshielding of the CH_3–N and PhCH_2–N protons by the P=O groups in both (*E*)-isomers.[25] Moreover, *H*–CP resonances in (*E*)-nitrones **2** (**2a**—6.99 ppm; **2b**—6.94 ppm) were also shifted downfield, when compared to the (*Z*)-isomers (6.82 ppm in **2a**, 6.70 ppm in **2b**).

1,3-Dipolar cycloadditions of nitrone **2a** were first examined with terminal alkenes in toluene at 60 °C (Scheme 5). The reactions were monitored by ^{31}P NMR spectroscopy and continued until the starting nitrone had disappeared. The trans/cis ratios of the resulting diastereoisomeric isoxazolidines **7** and **8** were



Scheme 4. Synthesis of nitrones **2**.



Scheme 5. 1,3-Dipolar cycloadditions of nitrone **2a** and terminal alkenes.

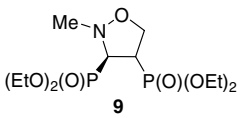
Table 1. Isoxazolidines **7** and **8** produced via Scheme 5

Entry	R	Reaction time (h)	Trans/cis ratio (**7**:**8**)	Yield[a]
a	CH_2OH	48	62:38	**7a**—38%; **8a**—20%
b	CH_2NHBoc	48	72:28	Inseparable
c	CH_2Br	40	65:35	Inseparable
d	CH_2SiMe_3	40	95:5	**7d**—64%
e	COOMe	24	90:10	**7e**—73%
f	OAc	40	90:10	**7f**—62%
g	Ph	24	90:10	**7g**—60%; **8g**—2%
h	$P(O)(OEt)_2$	24	74:19[b]	**7h**—29%; **8h**—7%
i	$CH_2P(O)(OEt)_2$	50	74:26	**7i**—23%; **8i**—4%

[a] Yield of pure materials obtained after silica gel chromatography.
[b] C4-regioisomer **9** (7%) was also produced.

calculated from the ^{31}P NMR spectra of the crude reaction mixtures and in some instances confirmed by analysis of the ^{1}H NMR spectra (Table 1).

The cycloadditions to nitrone **2a** were regiospecific (except for entry h) and afforded trans/cis mixtures of C5-substituted isoxazolidines **7a**–**i** and **8a**–**i**. In the ^{1}H NMR spectra of compounds **7** and **8**, diagnostic resonances for the H_2C(4) protons in the isoxazolidine ring were observed in the 2.0–2.9 ppm range, while the C(5) signals in the ^{13}C NMR spectra appeared as doublets ($^{3}J_{P-C} = 5$–10 Hz) at 70–79 ppm (except for **7f**/**8f**). From diethyl vinylphosphonate **6h**, the C4-regioisomer **9** was also produced (entry h). Although this compound was not isolated, its formation was evident from the appearance of two doublets at 27.40 and 21.53 ppm ($J = 30.5$ Hz) in the ^{31}P NMR spectrum of the crude product.



In most cases, isolation of pure major isoxazolidines **7** was accomplished chromatographically (Table 1). Furthermore, some minor isomers of **8** were also obtained as pure compounds and were fully characterised.

The assignment of the relative configurations of 3,5-disubstituted isoxazolidines has never been a trivial task. In recent letters, NOE experiments have been employed in most instances. The trans and cis configurations in diastereoisomers **7a** and **8a**, respectively, were assigned based on 2D NOE experiments (Fig. 1). Positive NOE

signals between the H_3–$H_{4\alpha}$, H_5–$H_{4\alpha}$ and H_3–H_5 pairs in isoxazolidine **8a** unambiguously supported the cis relationship between the H_3, $H_{4\alpha}$ and H_5 protons. The observation of a positive NOE signal for the H_5–$H_{4\beta}$ and H_3–$H_{4\alpha}$ pairs in adduct **7a** clearly identified their trans relationship.

The presence of the diethoxyphosphoryl group at C3 in compounds **7** and **8** provides new opportunities in the conformational analysis of substituted isoxazolidines, since vicinal coupling constants between H_4CCP and C_5CCP can be applied in addition to $^3J(H_3CCH_4)$ and $^3J(H_4CCH_5)$. After extraction of all the vicinal couplings available, the conformational homogeneity of isoxazolidines **8h**, **8g** and **7f** could be proved (Fig. 2).

From the ^1H and ^{13}C NMR spectra of isoxazolidine 3,5-diphosphonate **8h**, the following couplings were extracted: $J(H_3–H_{4\alpha}) = 7.0$ Hz, $J(H_3–H_{4\beta}) = 10.3$ Hz, $J(H_{4\alpha}–P_3) = 7.0$ Hz, $J(H_{4\alpha}–P_5) = 3.3$ Hz, $J(H_{4\beta}–P_3) = 18.0$ Hz, $J(H_{4\beta}–P_5) = 16.5$ Hz, $J(H_{4\alpha}–H_5) = 7.0$ Hz, $J(H_{4\beta}–H_5) = 10.3$ Hz and $J(CCCP) = 9.8$ Hz. These values[26,27] clearly showed that the isoxazolidine ring in **8h** exists in a single ^4E conformation having both bulky diethoxyphosphoryl groups in pseudoequatorial positions (Fig. 2) and thus reveal the cis relationship of H_3 and H_5. Similarly, the cis configuration of the minor isomer **8g** was also established from corresponding couplings [$J(H_3–H_{4\alpha}) = 8.1$ Hz, $J(H_3–H_{4\beta}) = 9.3$ Hz, $J(H_{4\alpha}–P_3) = 6.6$ Hz, $J(H_{4\beta}–P_3) = 18.6$ Hz, $J(H_{4\alpha}–H_5) = 6.6$ Hz, $J(H_{4\beta}–H_5) = 8.7$ Hz and $J(CCCP) = 8.3$ Hz], indicating the analogous ^4E conformation of the isoxazolidine ring with both diethoxyphosphoryl and phenyl groups in pseudoequatorial positions. Furthermore, the vicinal couplings found for **7f** [$J(H_3–H_{4\alpha}) = 6.6$ Hz, $J(H_3–H_{4\beta}) = 12.0$ Hz, $J(H_{4\alpha}–P) = 3.0$ Hz, $J(H_{4\beta}–P) = 17.4$ Hz, $J(H_{4\alpha}–H_5) = 0$ Hz, $J(H_{4\beta}–H_5) = 4.5$ Hz and $J(CCCP) = 9.5$ Hz] support the ^4E conformation of the isoxazolidine ring, in which the $P(O)(OEt)_2$ and OAc groups occupy the pseudoequatorial and axial positions, respectively (Fig. 2). The anomeric effect of the AcO–C5 group additionally stabilizes this conformation.

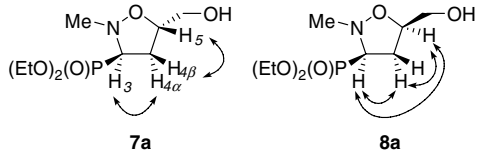


Figure 1. Observed NOEs for **7a** and **8a**.

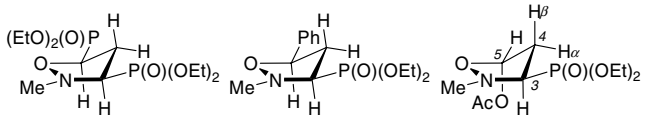


Figure 2. The preferred conformations of **8h** (left), **8g** (middle) and **7f** (right).

The relative configurations of the other isoxazolidines (*trans*-**7** and *cis*-**8**) were established by comparison of their spectral data with those of **7a** and **8a**. Similar vicinal coupling constant values were observed in all the cis and trans isomers.

The cis/trans ratios of the isoxazolidines produced in thermal cycloadditions were influenced by Lewis acids (e.g., $ZnCl_2$), especially in those cases where chelation of both alkenes and nitrones by the acid could be efficient.[3] Nitrone **2a** (R = Me) was treated with allyl alcohol in the presence of an equimolar amount of $ZnCl_2$ at room temperature to give a 20:80 mixture of isoxazolidines **7a** and **8a** in 90% total yield. In addition, the $ZnCl_2$-catalysed cycloaddition of nitrone **2a** to allyltrimethylsilane afforded a 55:45 mixture of isoxazolidines **7d** and **8d**, respectively, in 89% yield. As expected, based on the results obtained earlier with nitrone **1**,[3,28] the observed mixtures were enriched in cis isomers **8a** and **8d**. These observations further support the stereochemistries of isomers **7** and **8**, which have already been established. From these mixtures, additional amounts of **8a** as well as pure **8d** were isolated.

In conclusion, a general procedure for the synthesis of N-substituted *C*-phosphorylated nitrones **2** based on Swern oxidation of hydroxymethylphosphonates and low temperature addition of hydroxylamines was elaborated. Cycloadditions of nitrone **2a** (R = Me) and terminal alkenes led almost exclusively to the formation of C5-substituted isoxazolidines **7** and **8** with moderate (20%) to excellent (up to 90%) trans to cis diastereoselectivities. In $ZnCl_2$-catalysed cycloadditions, mixtures enriched in cis diastereoisomers were produced. Further studies on cycloadditions of nitrones **2** to more substituted alkenes are underway.

These findings pave the way for new syntheses of, for example, enantiomerically pure phosphonate analogues of homoserine, polyoxamic acids, 4-substituted glutamic acid and other α-aminophosphonates as analogues of biologically important compounds using a variety of *N*-chiral nitrones **2**. This chemistry is currently under investigation in this laboratory and will be disclosed in due course.

Acknowledgements

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23. Compound **2a**: IR (KBr): 3052, 2982, 1565, 1422, 1396, 1243, 1185, 1054, 1022, 966, 854, 784 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 6.99 (d, $J = 22.2$ Hz, $0.15 \times 1H$, C*H*-P, *E*), 6.82 (d, $J = 25.8$ Hz, $0.85 \times 1H$, C*H*–P, *Z*), 4.32–4.12 (m, 4H, CH_2OP, $E + Z$), 4.08 (d, $J = 1.2$ Hz, $0.15 \times 3H$, CH_3N, *E*), 3.84 (s, $0.85 \times 3H$, CH_3N, *Z*), 1.38 (t, $J = 7.0$ Hz, $0.15 \times 6H$, CH_3CH_2OP, *E*), 1.36 (t, $J = 7.0$ Hz, $0.85 \times 6H$, CH_3CH_2OP, *Z*); ^1H NMR (C_6D_6, 300 MHz): 6.90 (d, $J = 22.2$ Hz, $0.15 \times 1H$, *E*), 6.11 (d, $J = 26.4$ Hz, $0.85 \times 1H$, *Z*), 4.30–4.15 (m, $0.85 \times 4H$, *Z*), 3.81 (d, $J = 0.6$ Hz, $0.15 \times 3H$, *E*), 3.75–3.50 (m, $0.15 \times 4H$, *E*), 2.70 (s, $0.85 \times 3H$, *Z*), 1.12 (t, $J = 6.9$ Hz, $0.85 \times 6H$, *Z*), 0.88 (t, $J = 7.1$ Hz, $0.15 \times 6H$, *E*); ^{13}C NMR ($CDCl_3$, 75.46 MHz): 127.30 (d, $J = 209.9$ Hz, *C*H–P, $E + Z$), 63.33 (d, $J = 6.0$ Hz, CH_2OP, *Z*), 63.17 (d, $J = 6.0$ Hz, CH_2OP, *E*), 55.33 (d, $J = 11.5$ Hz, CH_3N, *Z*), 52.17 (s, CH_3N, *E*), 16.40 (d, $J = 6.3$ Hz, CH_3CH_2OP, *Z*), 16.32 (d, $J = 5.7$ Hz, CH_3CH_2OP, *E*); ^{31}P NMR ($CDCl_3$, 121.47 MHz): 5.61 (*Z*) and 5.36 (*E*); ^{31}P NMR (C_6D_6, 121.47 MHz): 7.02 (*E*) and 6.68 (*Z*). Anal. calcd for $C_6H_{14}NO_4P$: C, 36.93; H, 7.23; N, 7.18. Found: C, 36.71; H, 7.35; N, 7.17.
24. Compound **2b**: IR (film): 3059, 2984, 1549, 1250, 1027, 972 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 7.45–7.32 (m, 5H, C_6H_5, $E + Z$), 6.94 (d, $J = 21.4$ Hz, $0.14 \times 1H$, C*H*–P, *E*), 6.70 (d, $J = 25.8$ Hz, $0.86 \times 1H$, C*H*–P, *Z*), 5.52 (s, $0.14 \times 2H$, CH_2Ph, *E*), 4.98 (s, $0.86 \times 2H$, CH_2Ph, *Z*), 4.29–4.23 (m, $0.86 \times 4H$, *Z*), 4.20–4.05 (m, $0.14 \times 4H$, *E*), 1.31 (t, $J = 7.0$ Hz, 3H, $E + Z$), 1.30 (t, $J = 7.0$ Hz, 3H, $E + Z$); ^{13}C NMR ($CDCl_3$, 75.46 MHz): 131.75, 129.72, 129.64, 129.38, 129.26, 128.64, 125.99 (d, $J = 209.0$ Hz, *C*H–P, $E + Z$), 72.49 (d, $J = 10.3$ Hz, CH_2Ph, *Z*), 67.55 (s, CH_2Ph, *E*), 63.56 (d, $J = 5.7$ Hz, CH_2OP, *Z*), 63.31 (d, $J = 5.7$ Hz, CH_2OP, *E*), 16.60 (d, $J = 6.3$ Hz, CH_3CH_2OP, $E + Z$); ^{31}P NMR ($CDCl_3$, 121.47 MHz): 6.99 (*Z*) and 6.08 (*E*). Anal. calcd for $C_{12}H_{18}NO_4P$: C, 53.14; H, 6.69; N, 5.16. Found: C, 52.90; H, 6.82; N, 5.22.
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