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Synthesis of Phosphorylated 1,3,5-Oxadiazines via *N*-Acyltrifluoroacetimidoylphosphonates

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ABSTRACT: N-*Benzoyl- and* N-*methoxycarbonyltrifluoroacetimidoylphosphonates react with dimethylcyanamide in a [4+2]-cycloaddition to give 4-phosphorylated 1,3,5-oxadiazines. The structures of the products were confirmed by NMR (^1H, ^{13}C, ^{19}F, ^{31}P) and IR spectra and by XRD analysis.* © 2002 John Wiley & Sons, Inc. Heteroatom Chem 13:22–26, 2002; DOI 10.1002/hc.1102

INTRODUCTION

Recently we have developed several preparative approaches to α-acylimino-substituted polyhaloalkylphosphonates, a novel class of phosphorylated heterodienes [1]. Owing to the presence of electron-withdrawing substituents at the carbon and nitrogen atoms of the C=N bond these compounds show high reactivity and can be used as promising precursors in syntheses of biologically important α-aminoalkylphosphonic acids and their derivatives.

In the present work, we studied the cycloaddition of the indicated heterodienes to a donor dienophile, dimethylcyanamide. In principle, *N*-acylimines can react either as a 4π- or a 2π-component to give [4+2]- or [2+2]-cycloaddition products, respectively (see Scheme 1). Both reaction routes have been reported in the literature [2]. In this connection, the prime problem is to clarify in which way the reaction in question takes place.

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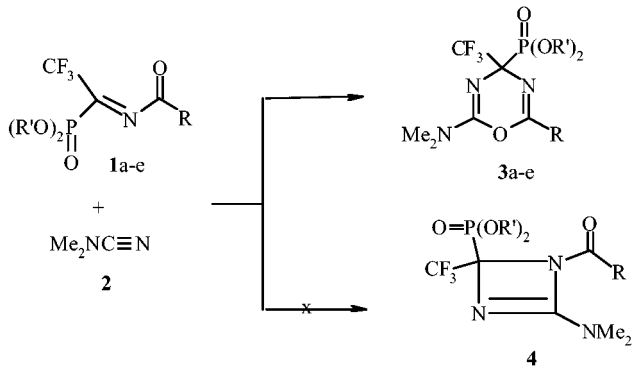
RESULTS AND DISCUSSION

Diisopropyl *N*-benzoyltrifluoroacetimidoylphosphonate (**1a**) reacts with dimethylcyanamide (**2**) under mild conditions (diethyl ether, 20°C) to give **3a** as the sole product.

The reaction is accompanied by characteristic changes in the NMR spectra of the reaction mixture, which allows one to follow the progress of the process. Thus, the ^{31}P NMR signal of the phosphoryl group exhibits a downfield shift (16.5 ppm) caused by the change in hybridization of the carbon atom directly bonded to the phosphorus center. This is consistent with the position of the signal from this atom in the ^{13}C NMR spectrum of the product (δ 77.08 ppm), identified by its characteristic coupling to the phosphorus and fluorine nuclei ($^1J_{CP} = 182$ Hz, $^2J_{CF} = 30$ Hz). Moreover, this atom becomes chiral, as can be judged from the diastereotopic alkoxy groups disclosed in the ^1H and ^{13}C NMR spectra. The ^{19}F NMR signal of the CF_3 group shows a substantial upfield shift.

Strictly speaking, the above spectral data are consistent with both reaction routes outlined in Scheme 1 and cannot provide a distinction between the alternative structures **3** or **4**. This is particularly



1, **3**: R = Ph, R′ = *i*-Pr (a), Me (b), Et (c), Pr (d); R = MeO, R′ = *i*-Pr (e)

SCHEME 1

true for the IR spectra, where intense bands are observed in the absorption regions of C=N and C=O bonds (1635 and 1712 cm^{-1}) seemingly in favor of the oxadiazete **4**. It should be noted, however, that just on the basis of similar IR spectra, the structures of the cycloaddition products of perhalogenoketones and cyanamides were first incorrectly identified [3] and then reexamined [4].

The indicated considerations require a more reliable proof of the structures of the cycloaddition products of **1** with **2**, and, towards this end, we performed a single-crystal X-ray diffraction analysis of the compound isolated in the reaction of **1a** with **2**. The analysis confirmed unambiguously the 1,3,5-oxadiazine structure **3a** of the product (see Fig. 1). Bond distances and bond angles in the molecule are reported in Table 1.

The central heterocycle $O^1N^1N^2C^1C^2C^3$ is planar within 0.07 Å. The benzene ring C^4—C^9 is turned out from this plane by 10.6°. The valence bonds of the N^3 atom have the trigonal planar configuration (the sum of bond angles, 359.81(1.3)°). The dimethylamino group lies practically in the plane of the six-membered heterocycle; the corresponding dihedral angle is only 2.9°. Such orientation allows effective $n(N^3)$—$\pi(N^2=C^3)$ conjugation. Indeed, the $N^3=C^3$ bond (1.342(6) Å) is substantially shorter than a normal single bond N (sp^2)—C (sp^2) (1.43–1.45 Å) [5,6]. The geometric parameters of the phosphoryl group are unexceptional [7,8].

TABLE 1 Selected Bond Lengths (Å) and Bond Angles (deg) in **3a**

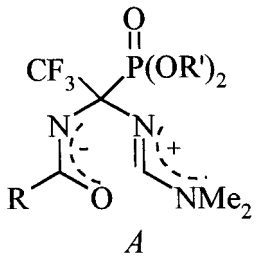
Bond	*Bond Length*	*Bond*	*Bond Angle*
P(1)—O(2)	1.458(4)	O(2)—P(1)—O(3)	116.6(2)
P(1)—O(3)	1.570(4)	O(2)—P(1)—O(4)	117.9(2)
P(1)—O(4)	1.552(4)	O(3)—P(1)—O(4)	99.9(2)
P(1)—C(2)	1.857(5)	O(2)—P(1)—C(2)	109.1(2)
O(1)—C(1)	1.385(6)	O(3)—P(1)—C(2)	107.0(2)
O(1)—C(3)	1.360(6)	O(4)—P(1)—C(2)	105.4(2)
N(1)—C(1)	1.259(6)	C(1)—O(1)—C(3)	116.3(4)
N(1)—C(2)	1.453(7)	C(1)—N(1)—C(2)	117.9(4)
N(2)—C(2)	1.441(6)	C(2)—N(2)—C(3)	117.0(4)
N(2)—C(3)	1.276(6)	O(1)—C(1)—N(1)	124.5(4)
N(3)—C(3)	1.342(6)	N(1)—C(2)—N(2)	117.6(4)
C(1)—C(4)	1.461(7)	O(1)—C(3)—N(2)	125.4(4)

The two C=N bonds in the heterocycle differ in length insignificantly (Table 1). The difference in chemical shifts of the corresponding carbon atoms in the ^{13}C NMR spectrum (149.8 and 154.3 ppm) is also small. Therefore, the assignment of the absorption bands at 1635 and 1712 cm^{-1} in the IR spectrum of compound **3a** to stretching vibrations of almost equivalent C=N bonds would be unjustified. It is most likely that they are associated with symmetrical and antisymmetrical coupled vibrations of the fragment N=C—O—C=N [4].

N-Benzoylimines **1b–d** and *N*-methoxycarbonylimine **1e** react with dimethylcyanamide in a similar way to form oxadiazines **3b–e**. The reactivity of the imines declines as the electron-withdrawing power of the substituent at the nitrogen atom decreases (COPh > COOMe) or as the steric volume of the phosphoryl group increases ($P(O)(OMe)_2 > P(O)(OPr\text{-}i)_2$). Thus, the cycloaddition of **1b** with **2** at room temperature is almost complete within 20 h whereas **1a** and **1e** react with **2** in this time only to the extent of 80 and 20%, respectively. For complete reaction, the mixture of **1e** and **2** should be refluxed in diethyl ether for several hours.

These data suggest that the cycloaddition proceeds through the interaction of the acceptor four-center LUMO in heterodiene **1** with the donor HOMO in cyanamide **2**. In line with this, the cycloaddition of **1** across the C≡N bond occurs only in the case of nitrile **2**, which is activated by the donor Me_2N group. Less nucleophilic nitriles, such as benzonitrile and acetonitrile, are unreactive in this reaction.

Putatively, it may be assumed that the cycloaddition is realized as a charge-controlled process, with the intermediacy of the dipolar adduct A:



A

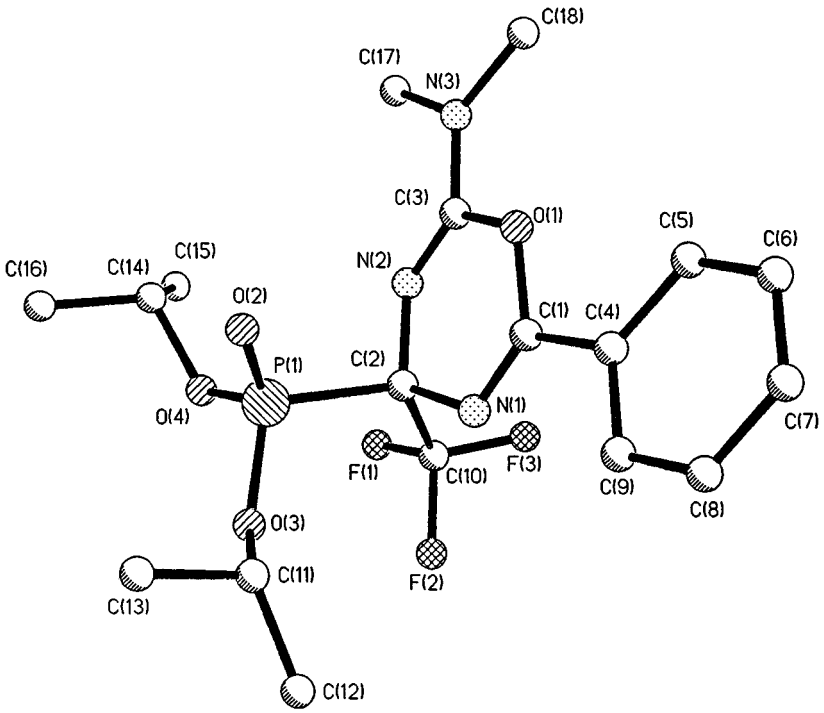


FIGURE 1 Molecular structure of compound **3a** (hydrogen atoms are omitted for clarity).

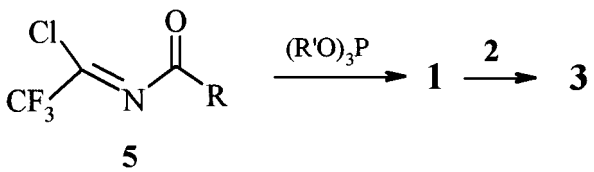
Owing to stabilization by effective delocalization of charges, the intermediate closes to form the six- rather than four-membered ring, in accordance with Burger's concept [9].

Since the starting imines are easily prepared from the corresponding imidoyl chlorides **5** and trialkyl phosphites, the syntheses of oxadiazines **3** can be conducted in a one-pot manner as shown in Scheme 2.

In summary, the [4+2]-cycloaddition of *C*-phosphorylated *N*-acylimines to cyanamides is a convenient method for preparation of phosphorylated oxadiazines. Its potentialities in the synthesis of other heterocycles are now under investigation.

EXPERIMENTAL

^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were recorded on a Varian VXR-300 spectrometer at 299.95, 50.23, 282.20, and 121.42 MHz, respectively. Chemical shifts are reported relative to internal TMS (^{1}H, ^{13}C), $CFCl_3$ (^{19}F), and external 85% H_3PO_4 (^{31}P). IR spectra were run on an UR-20 instrument.



SCHEME 2

*4-Dialkoxyphosphoryl-2-dimethylamino-4-trifluoromethyl-6-R-4H-1,3,5-oxadiazines (**3a–e**). General Procedure*

A. To a cooled solution of imidoylphosphonate **1** (1.0 mmol) in 3 ml of diethyl ether was added dimethylcyanamide (4.0 mmol) and the mixture was maintained at room temperature for 2 days (R=Ph) or heated at reflux for 6 h (R=MeO). The solvent was evaporated and the residue was washed with petroleum ether, then diethyl ether and crystallized from diethyl ether or purified by chromatography on silica gel with diethyl ether as eluent.

B. Equimolar amounts of the appropriate imidoyl chloride **5** and trialkyl phosphite were mixed at 5–10°C and allowed to react for 3 h at room temperature. Then, cyanamide **2** was added in a fourfold excess and the mixture was treated as described earlier.

4-Diisopropoxyphosphoryl-2-dimethylamino-6-phenyl-4-trifluoromethyl-4H-1,3,5-oxadiazine (**3a**). Yield 88% (Method A), mp 106–107°C (from diethyl ether). ^{1}H NMR ($CDCl_3$): δ 1.34, 1.37, 1.38, and 1.40

(each 3H, d, J_{HH} 6.5 Hz, $\underline{Me}_2CH$), 3.07 (6H, s, Me_2N), 4.7–4.9 (2H, m, OCH), 7.45 (2H, m, *m*-H_{Ph}), 7.54 (1H, m, *p*-H_{Ph}), 7.99 (2H, m, *o*-H_{Ph}). ^{19}F NMR ($CDCl_3$): δ −77.8. ^{31}P NMR ($CDCl_3$): δ 10.3. ^{13}C NMR ($CDCl_3$): δ 23.36 (d, $^3J_{CP}$ 6.8 Hz), 23.45 (d, $^3J_{CP}$ 6.5 Hz), 24.40 (d, $^3J_{CP}$ 2.0 Hz) and 24.49 (d, $^3J_{CP}$ 2.0 Hz) ($\underline{Me}_2CH$), 36.04 (s, Me_2N), 73.32 (d, $^2J_{CP}$ 7.9 Hz) and 73.76 (d, $^2J_{CP}$ 7.7 Hz) (OCH), 77.08 (dq, $^1J_{CP}$ 182, $^2J_{CF}$ 30 Hz, C-4), 122.78 (qd, $^1J_{CF}$ 282, $^2J_{CP}$ 6.5 Hz, CF_3), 127.48 and 128.44 (s, *o*- and *m*-C_{Ph}), 130.20 (d, $^4J_{CP}$ 2.5 Hz, *ipso*-C_{Ph}), 132.31 (s, *p*-C_{Ph}), 149.79 (d, $^3J_{CP}$ 4 Hz) and 154.30 (d, $^3J_{CP}$ 7.7 Hz) (C-2, C-6). IR (KBr): ν 1010 (POC), 1268 (P=O), 1635, 1712 (N=C–O–C=N). Anal. calcd for $C_{18}H_{25}F_3N_3O_4P$: C, 49.66; H, 5.79; F, 13.09; N, 9.65; P, 7.11. Found: C, 49.89; H, 5.94; F, 12.94; N, 9.48; P, 7.34.

4-Dimethoxyphosphoryl-2-dimethylamino-6-phenyl-4-trifluoromethyl-4H-1,3,5-oxadiazine (**3b**). Yield 86% (Method A), mp 167–168°C (from diethyl ether). ^1H NMR ($CDCl_3$): δ 3.08 (6H, s, Me_2N), 3.91 and 3.95 (each 3H, d, $^3J_{HP}$ 10.5 Hz, POMe); 7.45 (2H, m, *m*-H_{Ph}), 7.55 (1H, m, *p*-H_{Ph}), 7.99 (2H, m, *o*-H_{Ph}). ^{19}F NMR ($CDCl_3$): δ −78.8 (d, $^3J_{FP}$ 1.1 Hz). ^{31}P-{H} NMR ($CDCl_3$): δ 14.6 (q, $^3J_{PF}$ 1.1 Hz). ^{13}C NMR (acetone-d_6): δ 34.58 (s, Me_2N), 54.20 (d, $^2J_{CP}$ 6.4 Hz, MeO), 54.86 (d, $^2J_{CP}$ 6.6 Hz, MeO), 78.36 (dq, $^1J_{CP}$ 177.6, $^2J_{CF}$ 30.5 Hz, C-4), 123.14 (qd, $^1J_{CF}$ 282.5, $^2J_{CP}$ 7 Hz, CF_3), 127.52 and 128.82 (s, *o*- and *m*-C_{Ph}), 129.99 (d, $^4J_{CP}$ 3 Hz, *ipso*-C_{Ph}), 132.82 (s, *p*-C_{Ph}), 150.10 (d, $^3J_{CP}$ 4.8 Hz) and 154.90 (d, $^3J_{CP}$ 8.1 Hz) (C-2, C-6). IR (KBr): ν 1060, 1180 (POMe), 1280 (P=O), 1630, 1710 (N=C–O–C=N). Anal. calcd for $C_{14}H_{17}F_3N_3O_4P$: F, 15.03; N, 11.08; P, 8.17. Found: F, 15.12; N, 10.97; P, 8.35.

4-Diethoxyphosphoryl-2-dimethylamino-6-phenyl-4-trifluoromethyl-4H-1,3,5-oxadiazine (**3c**). Yield 48% (based on 5, R = Ph, Method B), mp 129–130°C (from diethyl ether). ^1H NMR ($CDCl_3$): δ 1.37 (6H, t, J_{HH} 7 Hz, $\underline{Me}CH_2$), 3.07 (6H, s, Me_2N), 4.3 (4H, m, OCH_2), 7.45 (2H, m, *m*-H_{Ph}), 7.55 (1H, m, *p*-H_{Ph}), 7.98 (2H, m, *o*-H_{Ph}). ^{19}F NMR ($CDCl_3$): δ −78.34. ^{31}P NMR ($CDCl_3$): δ 11.9. IR (KBr): ν 1070 (POC), 1290 (P=O), 1650, 1740 (N=C–O–C=N). Anal. calcd for $C_{16}H_{21}F_3N_3O_4P$: F, 13.99; P, 7.60. Found: F, 13.76; P, 7.73.

2-Dimethylamino-4-dipropoxyphosphoryl-6-phenyl-4-trifluoromethyl-4H-1,3,5-oxadiazine (**3d**). Yield 51% (based on 5, R = Ph, Method B), mp 76–78°C (from diethyl ether). ^1H NMR ($CDCl_3$): δ 0.959 and 0.961 (each 3H, t, J_{HH} 7 Hz, $\underline{Me}CH_2$), 1.73 (4H, m, $C-CH_2-C$), 3.07 (6H, s, Me_2N), 4.1–4.2 (4H, m, OCH_2), 7.44 (2H, m, *m*-H_{Ph}), 7.54 (1H, m, *p*-H_{Ph}), 7.99 (2H, m, *o*-H_{Ph}). ^{19}F NMR ($CDCl_3$): δ −78.31. ^{31}P NMR ($CDCl_3$): δ 12.2. IR (KBr): ν 1070 (POC), 1280 (P=O), 1650, 1730 (N=C–O–C=N). Anal. calcd for $C_{18}H_{25}F_3N_3O_4P$: F, 13.09; P, 7.11. Found: F, 12.91; P, 7.27.

4-Diisopropoxyphosphoryl-2-dimethylamino-6-methoxy-4-trifluoromethyl-4H-1,3,5-oxadiazine (**3e**). Yield 53% (Method A), mp 48–50°C (from diethyl ether). ^1H NMR ($CDCl_3$): δ 1.36 (12H, d, J_{HH} 6 Hz, $\underline{Me}_2CH$), 2.96 (6H, s, Me_2N), 3.89 (3H, s, MeO), 4.7–4.9 (2H, m, OCH). ^{19}F NMR ($CDCl_3$): δ −78.43. ^{31}P NMR ($CDCl_3$): δ 10.7. ^{13}C NMR ($CDCl_3$): *d* 23.28 (d, $^3J_{CP}$ 6.3 Hz), 23.36 (d, $^3J_{CP}$ 5.7 Hz), 24.33 (d, $^3J_{CP}$ 2.2 Hz) and 24.43 (d, $^3J_{CP}$ 2.2 Hz) ($\underline{Me}_2C$), 36.07 (s, Me_2N), 55.22 (s, MeO), 73.08 (d, $^2J_{CP}$ 7.6 Hz, OCH), 73.45 (d, $^2J_{CP}$ 6.6 Hz, OCH), 77.69 (dq, $^1J_{CP}$ 186, $^2J_{CF}$ 30 Hz, C-4), 122.87 (qd, $^1J_{CF}$ 283, $^2J_{CP}$ 8.5 Hz, CF_3), 149.92 (d, $^3J_{CP}$ 4.5 Hz) and 152.29 (d, $^3J_{CP}$ 6.4 Hz) (C-2, C-6). IR (film): ν 1040 (POC), 1275 (P=O), 1660, 1750 (N=C–O–C=N). Anal. calcd for $C_{13}H_{23}F_3N_3O_5P$: F, 14.64; P, 7.96. Found: F, 14.51; P, 8.11.

X-ray Structure Determination of **3a**

Crystal data: $C_{18}H_{25}F_3N_3O_4P$, $M = 435.38$, triclinic, $a = 9.303(8)$ Å, $b = 9.436(4)$ Å, $c = 14.043(5)$ Å, $\alpha = 71.25(3)°$, $\beta = 67.43(5)°$, $\gamma = 73.91(6)°$, $V = 1061.1$ Å^3, $Z = 2$, $d_{calc} = 1.36$ g cm^{-3}, space group P $\overline{1}$(N 2), $\mu = 0.18$ mm^{-1}, F(000)=456, crystal size ca. $0.19 \times 0.28 \times 0.38$ mm.

All crystallographic measurements were performed at 18°C on a CAD-4-Enraf–Nonius diffractometer operating in the $\omega - 2\theta$ scan mode (the ratio of the scanning rates $\omega/2\theta = 1.2$). Intensity data were collected within the range $2 < \theta < 25°$ ($0 \le h \le 12$, $-12 \le k \le 12$, $-17 \le l \le 17$) using graphite monochromated Mo Kα radiation ($\lambda = 0.71069$ Å). Intensities of 3966 reflections (3714 unique reflections, $R_{int} = 0.032$) were measured. Data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation using the CRYSTALS program package [10]. In the refinement 1593 reflections with $I > 4\sigma(I)$ were used. About 50% of hydrogen atoms were located in the difference Fourier maps, and the remaining H atoms were placed in calculated positions. All H atoms were included in the final refinement with fixed positional and thermal parameters. Convergence was obtained at $R = 0.055$ and $R_w = 0.062$, GOF = 1.111 (262 refined parameters;

obs/variabl. 6.1; the largest and minimal peaks in the final difference map, 0.36 and −0.24 e/Å^3). Chebyshev weighting scheme [11] with parameters 0.65, −0.11, 0.20, and −0.34 was used.

Full crystallographic details have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for these materials should quote the full literature citation and reference number CCDC 155800.

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