Diastereofacial Selectivity in 1,3-Dipolar Cycloaddition to Methylphenylvinylphosphine Oxide

Alberto Brandi*,[1] and Patrizia Cannavò

Centro dei Composti Eterociclici-CNR, Dipartimento di Chimica Organica, Università di Firenze, via G. Capponi 9, I-50121 Firenze, Italy

K. Michał Pietrusiewicz* and Maria Zabłocka

Polish Academy of Sciences, Centre of Molecular and Macromolecular Studies, Boczna 5, 90-362 Lodz, Poland

Michał Wieczorek

Institute of General Chemistry, Technical University of Lodz, Zwirki 36, 90-924 Lodz, Poland

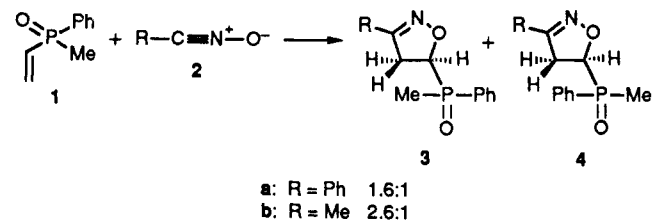
Received March 22, 1988

1,3-Dipolar cycloaddition reactions of nitrile oxides and nitrones with racemic methylphenylvinylphosphine oxide (1) have been found to provide phosphinylisoxazolines and -isoxazolidines, respectively, in very good yields. 5-Substituted regioisomers either prevailed in the product mixtures or were the only product formed. The studied cycloadditions have been found to occur with considerable (ca. 40% de) diastereofacial selectivity, which compares very well with similar literature data recorded for other chiral allylic systems. Possible transition-state structures are proposed and discussed in terms of conformational preferences about the carbon–phosphorus bond to the alkene in the ground state, in the transition state, and in the product. The crystal structure of **3a** has been determined to confirm the spectral assignments; **3a** has the erythro configuration and exists in a conformation possessing the C—O and P=O bonds in the anti arrangement.

Introduction

The control of regio- and stereochemistry, particularly in conformationally flexible acyclic systems, is of fundamental concern to rational synthetic design. The stereoselectivity of additions to allylic double bonds has attracted considerable interest in the recent literature, and numerous reports of diastereofacial selectivity have appeared.[2] Generally, the best selectivity is achieved in cases in which the chiral allylic carbon subunit bears a heteroatom substituent.[2,3] It follows now from our work that an allylic phosphorus stereogenic center can also be capable of considerable stereocontrol in cycloaddition of nitrile oxides and nitrones to chiral vinylphosphine oxides. Chiral phosphinylisoxazolines and -isoxazolidines resulting from such a process offer many novel synthetic possibilities,[4] all the more that the homochiral vinylphosphine oxides have recently been made available.[5] In this work racemic methylvinylphosphine oxide[6] 1 was used as a model.

Scheme I



Results and Discussion

The cycloaddition reactions of benzonitrile oxide and acetonitrile oxide with 1 were carried out at room temperature in methylene chloride and each gave a mixture of the two diastereomeric 5-(methylphenylphosphinyl)-isoxazolines in good yields (Scheme I). The assignment of regiochemistry to the products followed unequivocally from their ^{13}C NMR spectra[7] in which only C-5 ring carbons were found strongly coupled to phosphorus ($^1J_{PC} \simeq 81$ Hz).[7]

As the isomeric isoxazolines **3a**, **4a** and **3b**, **4b** gave the ^1H NMR spectra that were markedly distinct within each pair, it appeared also possible to assess their relative stereochemistry. The minor isomers had one of their H-4 protons (syn to the phosphinyl group, as judged from the corresponding vicinal H–H and P–H coupling constants) decidedly more shielded ($\Delta\delta \simeq 0.6$ ppm) and their H-5 proton somewhat less shielded ($\Delta\delta \simeq 0.15$ ppm), as compared to the major isomers, respectively. With the reasonable assumption that the observed differences in shielding are due to the diamagnetic ring current of the proximal P-phenyl ring, the detailed assignment of structure to **3a,b** and **4a,b** was proposed as depicted in Scheme I. Additionally, in the case of **3a** the assignment was made unequivocal through a single-crystal X-ray diffraction analysis. An ORTEP of **3a** is shown in Figure 1.

As indicated in Scheme I, preferential formation of one of the two isomeric isoxazolidines took place in both cases.

(1) Present address: Università della Basilicata, Istituto di Chimica, via N. Sauro 85, 85100 Potenza, Italy.

(2) For general references, see: *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York; Vol. 2, 1983; Vol. 3, 1984. Symposia-in-print, Control of Acyclic Stereochemistry; Mukaiyama, T., Ed. *Tetrahedron* **1984**, *40*, 2197–2343.

(3) For some leading references, see the following. (a) Oxidation: Gao, Y.; Hauson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, Hauson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Electrophilic addition: Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650. (c) 1,3-Dipolar cycloadditions: Annunziata, R.; Cinquini, M.; Cozzi, F.; Gennari, C.; Raimondi, L. *J. Org. Chem.* **1987**, *52*, 4674. Koizumi, T.; Hirai, H.; Yoshii, E. *J. Org. Chem.* **1982**, *47*, 4005. (d) Diels–Alder reactions: Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663. See also references cited therein.

(4) (a) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience, New York, 1984. (b) Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, Organic Nitro Chemistry Series; Feuer, H., Ed.; VCH Publishers: New York, 1988. (c) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1–174.

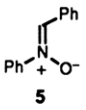
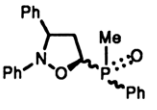
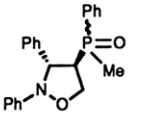
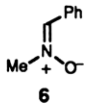
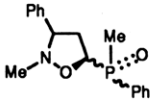
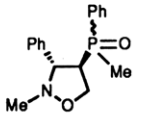
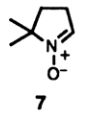
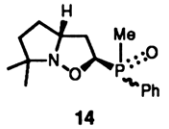
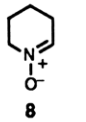
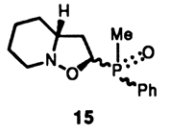
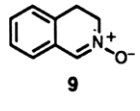
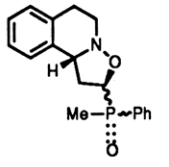
(5) (a) Bodalski, R.; Rutkowska-Olma, E.; Pietrusiewicz, K. M. *Tetrahedron* **1980**, *36*, 2353. (b) Pietrusiewicz, K. M.; Zablocka, M.; Monkiewicz, J. *J. Org. Chem.* **1984**, *49*, 1522. (c) Johnson, C. R.; Imamoto, T. *J. Org. Chem.* **1987**, *52*, 2170. (d) Pietrusiewicz, K. M.; Zablocka, M. *Tetrahedron Lett.*, submitted.

(6) Kabachnik, M. I.; Chang, C.-Y.; Tsvetkov, E. N. *Dokl. Akad. Nauk SSSR* **1960**, *135*, 603; *Chem. Abstr.* **1961**, *55*, 12272a.

(7) Pietrusiewicz, K. M.; Brandi, A. *Phosphorus Sulfur*, in press.

0022-3263/89/1954-3073$01.50/0

Table I. Nitrone Cycloadditions to Methylphenylvinylphosphine Oxide (1)

entry	nitrones	yield, %	adducts (diastereoisomer ratio)[a]		regioisomer ratio[b]
1	 **5**	92	 **10** (42:29:17:12)	 **11** (70:30)	60:40
2	 **6**	84	 **12** (62:21:17)[c]	 **13** ( )[d]	87:13
3	 **7**	91	 **14** (72:28)		>95:5
4	 **8**	91	 **15** (41:29:15:15)		>95:5
5	 **9**	97	 **16** (48:24:24:4)		>95:5

[a] Yield of isolated compounds. [b] Molar ratio determined from ^{31}P NMR spectra of the crude mixtures. [c] Only three out of the four possible isomers were detected. [d] Only one out of the two possible isomers was detected.

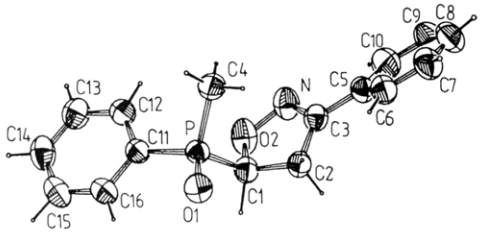


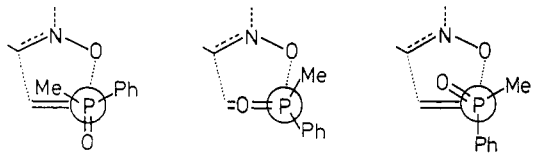
Figure 1. ORTEP drawing of **3a**.

It is important to note that the observed selectivity compares very well with those recorded[8,9] for the analogous cycloadditions of nitrile oxides to olefins possessing a stereogenic Ph,Me-substituted carbon center in the allylic position. By analogy, this selectivity should be a subject of considerable control through a judicious choice of the two reactants.[8,9]

The results of the closely related cycloaddition reactions of **1** with some representative nitrones (**5–9**) are displayed in Table I. The reactions occurred with similar facility and afforded phosphinylisoxazolidines in high yields though in the form of mixtures of regio- and stereoisomers. The isolation of individual components from these mixtures was not always possible, but nevertheless the combined ^{31}P and ^{13}C NMR analysis of either the individual isomers or some enriched fractions (obtained in the course of the separation of the mixtures by flash chromatography) allowed the assignment of regiochemistry to all the isomeric compounds. The large $^{1}J_{PC}$ coupling constant was again highly diagnostic for the prompt assignment of the phosphorus bearing C-4 or C-5.[7]

From the stereochemical assignment viewpoint, the reaction of **1** with 3,4-dihydro-2,2-dimethyl-2*H*-pyrrole 1-oxide (DMPO) (**7**) provides the most straightforward example. The two bicyclic products of this reaction (**14a** and **14b**) were easily separated and were individually analyzed by spectroscopic means, which included also 2D-NMR techniques. The ^{13}C NMR chemical shift of carbons coupled directly to phosphorus (δ 74.24, J = 86 Hz and δ 75.42, J = 87 Hz, respectively) indicated that the two compounds had the methylphenylphosphinyl substituent in the 5-position (isoxazoline numbering). The lack of correlation between protons H-3 and H-5 (isoxazoline numbering) in the 2D-NOESY spectra of **14a** and **14b** suggested in turn that these protons were in the trans relationship in both isomers, implying that **14a** and **14b** differed only in the configuration at phosphorus. In addition, the two isomers exhibited the same distinct pattern of ^{1}H NMR chemical shifts for their isoxazolidine ring methylene and H-5 protons, which was previously seen for the pairs of isomeric isoxazolidines **3a**,**4a** and **3b**,**4b**. The minor isomer **14b** had its methylene protons (δ 2.33–2.12) more shielded and the H-5 proton (δ 4.33) less shielded as compared to the major isomer **14a** (δ 2.72 and 2.32, and δ 4.09, respectively). Hence, by analogy, we assigned the stereochemistry of **14a** the same as in **3a**, and of **14b** the same as **4a**.

(8) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.
(9) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754.



TS A TS B TS C

Figure 2. Favored transition states for the exo approach proposed for the 1,3-dipolar cycloaddition of nitrile oxides and nitrones to 1.

In the reactions of 1 with acyclic (**5** and **6**) and with the six-membered cyclic nitrones (**8** and **9**) the formation of all four 5-(methylphenylphosphinyl)isoxazolidines resulted. However, even after partial separations and some equilibration experiments, it was not possible to assign the individual configurations or to conclude with certainty from the NMR data which of the two pairs of isomers in each case originated from the exo and which from the endo approach.

On the other hand, the stereochemistry of the minor regioisomers, i.e., 4-(methylphenylphosphinyl)isoxazolidines (**11** and **13**), was assessed to be 3,4-trans in all cases, as suggested by their ^1H NMR spectra as well as by comparison with the analogous 4-(diphenylphosphinyl)isoxazolidines[7] assigned unambiguously in one case by the single-crystal X-ray diffraction technique.[10]

The data collected in Scheme I and Table I point to a significant regiochemical preference favoring the formation of the 5-substituted isoxazolines and isoxazolidines in these cycloadditions. A comparison of regiochemistry recorded in this work with that recently described for cycloaddition of nitrones to diphenylvinylphosphine oxide[7] reveals that on replacing the P-Ph by the P-Me substituent in the vinylphosphine oxide, the regioselectivity of these cycloadditions increases in favor of the 5-substituted isomer. This brings about the almost complete regioselectivity in reactions of 1 with cyclic nitrones and is in agreement with the reduced electron-withdrawing ability of the methylphenylphosphinyl group as compared to the diphenylphosphinyl group.[11]

The considerable diastereofacial selectivity observed in the studied cycloadditions of both the nitrile oxides and the nitrones[12] to 1 is noteworthy.[13] The striking similarity of stereoisomeric ratios and relative configurations of the products derived from the two processes suggests a common rationale for the observed preferences. However, more than one conceivable suggestion regarding the transition-state structure of the studied cycloadditions could be put forward.

If one considers the conformation about the (C-5)–P bond assumed by **3a** in the crystal (Figure 1) to be indicative of the preferred transition-state geometry, as inferred by Houk et al.[9] for an analogous all-carbon allylic system, then a Felkin-type transition state (TS) A (Figure 2) with the most polar substituent in the anti position[14] should apply in our case.

On the other hand, an analogy could be also drawn between the vinylphosphine oxide and structurally related sulfoxide systems. For the latter, the s-cis conformation possessing the S–O dipole and the double bond in the syn coplanar array was considered[15] to be the reactive conformation and was also found to be preferred in the crystal.[15b] With this premise, TS B could account for the preferential formation of the **3a**, **4a**, and **14a** isomers.

By the same reasoning, the transition-state structure C involving only somewhat distorted s-cis conformation of 1 (to better accommodate the steric and dipolar interactions) could also apply. This in turn would best conform to the "oxygen inside" model suggested recently by Houk and Jäger[8] for the 1,3-dipolar cycloaddition to allyl ethers.

From this brief discussion no definitive conclusion regarding the preferred transition state for the 1,3-dipolar cycloadditions to chiral vinylphosphine oxides is yet apparent and further studies should follow in order to obtain the most clear-cut picture of this synthetically useful process.

Experimental Section

All reactions were carried out under nitrogen. R_f values refer to TLC, carried out on 0.25-mm silica gel plates (Merck F254), with the same eluant indicated for the column chromatography. IR spectra were recorded on Perkin-Elmer 283 and 881 spectrophotometers and NMR spectra ($CDCl_3$ solutions, unless otherwise stated) on Varian XL 300 (^1H, 300 MHz) and Varian FT-80 A (^{13}C, 20 MHz; ^{31}P, 32.203 MHz) spectrometers: the chemical shifts for ^1H and ^{13}C NMR spectra are given in ppm from TMS; for ^{31}P NMR spectra in ppm from 85% H_3PO_4. Coupling constants (J) are reported in hertz. Diastereomeric ratios were calculated from ^{31}P spectra, unless otherwise stated. ^1H and ^{13}C NMR signals of aromatic substituents were not reported. Microanalyses were carried out with a Perkin-Elmer 240 C elemental analyzer. Methylphenylvinylphosphine oxide was synthesized according to ref 6. Nitrile oxides were prepared in situ from the corresponding chloroximes.[4a,b] Nitrones were synthesized by standard procedures according to the literature.[4]

3-Phenyl-5-(methylphenylphosphinyl)isoxazoline (*erythro*-3a and *threo*-4a). Triethylamine (0.350 mL, 2.5 mmol) was added, in 2 h, to a solution of *N*-hydroxybenzenecarboximidoyl chloride (0.387 g, 2.5 mmol) and 1 (0.332 g, 2 mmol) in CH_2Cl_2 (10 mL) kept at 0 °C. The reaction mixture was allowed to warm up to room temperature and, after stirring for 15 h, the solution was washed three times with water, dried over Na_2SO_4, and concentrated. ^1H NMR analysis showed that two isomers **3a** and **4a** were formed in a 1.6:1 ratio. The two isomers showed only one spot on TLC with R_f 0.45 (eluant CH_2Cl_2–MeOH, 10:1) and could be partially separated by column chromatography (same eluent): first fraction 202 mg (35%), **3a** and **4a** in 7:1 ratio; second fraction 356 mg (63%), **3a** and **4a** in 1:1 ratio.

3a: mp 130–131 °C (from ligroin (100–150 °C)). Anal. Calcd for $C_{16}H_{16}NO_2P$: C, 67.36; H, 5.65; N, 4.90. Found: C, 67.58; H, 5.69; N, 4.82. ^{31}P NMR: 3.522. ^1H NMR: 4.98 (ddd, J_{PH} = 6.1, J_{vic} = 12.4, 9.3, H-5), 3.92 (ddd, J_{PH} = 21.3, J_{gem} = 17.3, J_{vic} = 9.2, 1 H-4), 3.68 (ddd, J_{PH} = 19.0, J_{gem} = 17.3, J_{vic} = 12.4, 1 H-4), 1.77 (d, J_{PH} = 12.9, 1 H). ^{13}C NMR: 156.53 (J_{PC} = 4.6), 78.33 (J_{PC} = 81.3), 36.11, 10.96 (J_{PC} = 70.3). IR ($CDCl_3$): 3064, 2960, 2940, 1602, 1448, 1438, 1354, 1297, 1180 (vs), 1113.

4a: mp 141–142 °C (from ligroin (100–150 °C)). Anal. Calcd for $C_{16}H_{16}NO_2P$: C, 67.36; H, 5.65; N, 4.90. Found: C, 67.62; H, 5.79; N, 5.30. ^{31}P NMR: 34.90. ^1H NMR: 5.11 (ddd, J_{PH} = 2.6, J_{vic} = 12.2, 9.7, H-5), 3.65 (ddd, J_{PH} = 18.2, J_{gem} = 17.1, J_{vic} =

(10) Wieczorek, M.; Bujacz, G., to be published.

(11) More detailed discussion on regiochemistry of 1,3-dipolar cycloadditions involving structurally diversified phosphorus compounds will be presented in the forthcoming paper: Brandi, A.; Cicchi, S.; Goti, A.; Pietrusiewicz, K. M.; Wisniewski, W., in preparation.

(12) Even though the precise assignment for each isomeric product in entries 1, 2, 4, and 5 could not be made, a plausible pairing of the two out of the four stereoisomers would indicate considerable excess of one isomer over another for both the exo and the endo approach.

(13) The issue of diastereofacial selection in addition reactions to double bonds carrying a chiral (either racemic or nonracemic) phosphorus substituent has been very rarely addressed in the literature. Cf. ref 4b and also Bodalski et al. [Bodalski, R.; Koszuk, J.; Krawczyk, H.; Pietrusiewicz, K. M. *J. Org. Chem.* **1982**, *47*, 2219. Kashman, Y.; Awerbouch, O. *Tetrahedron Lett.* **1973**, 3217] for a few examples.

(14) Kozikowski, A. P.; Gosh, A. K. *J. Org. Chem.* **1984**, *49*, 2762. Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1987**, *43*, 2369.

(15) For the most recent references, see: (a) Pyne, S. G.; Griffith, R.; Edwards, M. *Tetrahedron Lett.* **1988**, *29*, 2089. (b) Koizumi, T.; Arai, Y.; Takayama, H. *Tetrahedron Lett.* **1987**, *28*, 3689. (c) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7399.

12.2, 1 H-4), 3.30 (ddd, J_{PH} = 21.7, J_{gem} = 17.1, J_{vic} = 9.7, 1 H-4), 1.97 (d, J_{PH} = 13.5, 1 H). ^{13}C NMR: 156.25 (J_{PC} = 4.6), 78.24 (J_{PC} = 80.4), 6.25, 13.56 (J_{PC} = 70.6). IR (CCl_4) 3064, 1590, 1448, 1438, 1354, 1294, 1195 (vs), 1112 cm^{-1}.

3-Methyl-5-(methylphenylphosphinyl)isoxazoline (*erythro*-3b and *threo*-4b). A 6% solution of NaOCl (commercial bleach) (6 mL) was added to a solution of acetaldoxime (168 mg, 3 mmol) and **1** (166 mg, 1 mmol) in CH_2Cl_2 (10 mL), at 0 °C. The two-phase mixture was vigorously stirred for 10 min and triethylamine (152 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise in 3 h. After stirring at room temperature for 24 h, the organic layer was separated, washed twice with water (10 mL), dried (Na_2SO_4), and concentrated to afford a mixture of adducts **3b** and **4b** in a 2.6:1 ratio (^1H NMR). The adducts have been purified, without separation, by passing through a short pad of silica gel (eluant CH_2Cl_2–MeOH, 10:1, only one spot R_f = 0.3): yield 142 g (64%). Anal. Calcd for $C_{11}H_{14}NO_2P$: C, 59.19; H, 6.32; N, 6.27. Found: C, 58.82; H, 6.39; N, 5.91. IR (CCl_4) 3062, 2924, 2860, 1591, 1438, 1385, 1324, 1293, 1194 (vs), 1114 cm^{-1}.

3b. ^{31}P NMR: 34.79. ^1H NMR: 4.72 (ddd, J_{PH} = 7.3, J_{vic} = 12.3, 9.3, H-5), 3.42 (ddd, J_{PH} = 20.8, J_{gem} = 17.8, J_{vic} = 9.2, 1 H-4), 3.18 (dt, J_{PH} = 18.7, J_{gem} = 18.7, J_{vic} = 11.7, 1 H-4), 1.70 (d, J_{PH} = 13.2, 1 H), 1.99 (s, 3 H). ^{13}C NMR: 154.78 (J_{PC} = 4.7), 76.80 (J_{PC} = 82.4), 38.95, 11.71, 10.73 (J_{PC} = 70.5).

4b. ^{31}P NMR: 34.79. ^1H NMR: 4.87 (ddd, J_{PH} = 2.9, J_{vic} = 12.1, 9.0, H-5), 3.18 (m, 1 H-4), 2.83 (ddd, J_{PH} = 21.6, J_{gem} = 17.7, J_{vic} = 9.3, 1 H-4), 1.86 (d, J_{PH} = 13.5, 1 He, 1.63 (s, 3 H). ^{13}C NMR: 154.55 (J_{PC} = 4.5), 76.62 (J_{PC} = 83.0), 39.18, 12.71 (J_{PC} = 70.1), 11.39.

Reaction of *N*-(Phenylmethylene)benzenamine *N*-Oxide (5) with 1. A solution of nitrone **5** (217 mg, 1.1 mmol) and phosphine oxide **1** (166 mg, 1 mmol) in benzene (1 mL) was heated at 55 °C for 33 h. ^{31}P NMR analysis of the dark brown solution showed a mixture of six isomers **10a**, **10b**, **10c**, **10d**, **11a**, and **11b** was formed with the ratio shown in Table I. Attempted separation of the complex mixture by flash chromatography (eluant CH_2Cl_2–MeOH, 30:1) afforded only fractions enriched of the individual isomers with 92% overall yield of isolated compounds. Anal. Mixture of isomers. Calcd for $C_{22}H_{22}NO_2P$: C, 72.71; H, 6.10; N, 3.85. Found: C, 72.45; H, 6.34; N, 3.70. IR (CCl_4) 3060, 3030, 2960, 2925, 2875, 2855, 1600, 1490, 1440, 1290, 1190 (vs), 1110 cm^{-1}.

10a. ^{31}P NMR: 33.45. ^1H NMR: 4.65 (dd, J = 8.1, 5.1, H-3), 4.55 (dt, J = 8.0, 9.0, H-5), 3.12 (ddt, J = 15.9, 12.9, 8.4, 1 H-4), 2.49 (ddt, J = 12.9, 5.4, 7.5, 1 H-4), 1.88 (d, J_{PH} = 13.2, 3 H). ^{13}C NMR: 75.45 (J_{PC} = 83.3), 69.44 (J_{PC} = 4.9), 39.56, 12.71 (J_{PC} = 71.0).

10b. ^{31}P NMR: 35.31. ^1H NMR: 4.79 (m, 1 H), 4.21 (m, 1 H), 2.83 (m, 1 H), 1.70 (d, J_{PH} = 13.1, 3 H). ^{13}C NMR: 75.90 (J_{PC} = 83.1), 70.02 (J_{PC} = 5.9), 41.07, 11.52 (J_{PC} = 70.0).

10c. ^{31}P NMR: 35.61. ^1H NMR: 1.97 (d, J_{PH} = 13.2, 3 H), other signals covered. ^{13}C NMR: 76.08 (J_{PC} = 83.5), 70.46 (J_{PC} = 6.3), 41.43, 14.48 (J_{PC} = 70.0).

10d. ^{31}P NMR: 35.10. ^1H NMR: 1.90 (d, J_{PH} = 13.2, 3 H), other signals covered. ^{13}C NMR: 74.76 (J_{PC} = 83), 69.02 (J_{PC} = 4.7), 40.49, 14.20 (J_{PC} = 70).

11a. ^{31}P NMR: 34.25. ^1H NMR: 4.80 (dd, J = 15.6, 6.6, H-3), 4.41 (dt, J = 10.8, 8.7, 1 H-5), 4.28 (dt, J = 12.9, 7.6, 1 H-5), 3.19 (quintet, J = 7.2, H-4), 1.59 (d, J_{PH} = 13, 3 H). ^{13}C NMR: 70.12 (J_{PC} = 0.9), 66.85, 55.57 (J_{PC} = 69.9), 14.22 (J_{PC} = 70.1).

11b. ^{31}P NMR: 33.90. ^1H NMR: 1.56 (d, J_{PH} = 13, 3 H), other signals covered. ^{13}C NMR: 70.48 (J = 1.4). ^{13}C NMR: 70.48 (J_{PC} = 1.4), 67.25, 55.79 (J_{PC} = 69.6), 14.97 (J_{PC} = 70.8).

Reaction of *N*-(Phenylmethylene)methanamine *N*-Oxide (6) with 1. A solution of nitrone **6** (270 mg, 2 mmol) and **1** (332 mg, 2 mmol) in $CHCl_3$ (1 mL) was heated at 60 °C for 4 days. ^{31}P NMR analysis of the dark brown solution showed the four isomers **12a**, **12b**, **12c**, and **13** were formed with the ratio shown in the Table I. Attempted separation of the complex mixture by flash chromatography (eluant CH_2Cl_2–MeOH, 20:1) afforded only fractions enriched of the individual isomers with 84% overall yield of isolated compounds. Anal. Mixture of isomers. Calcd for $C_{17}H_{20}NO_2P$: C, 67.76; H, 6.69; N, 4.65. Found: C, 67.47; H, 6.33; N, 4.48. IR (CCl_4): 3064, 3032, 2992, 2961, 2919, 2874, 2850, 1604, 1493, 1455, 1437, 1293, 1195 (vs), 1114 cm^{-1}.

12a. ^{31}P NMR: 33.41. ^1H NMR: 4.48–4.32 (m, H-5), 3.68 (m, H-3), 3.05–2.22 (m, 2 H-4), 2.60 (s, 3 H), 1.74 (d, J_{PH} = 13.5, 3 H). ^{13}C NMR: 75.30 (J_{PC} = 84.4), 72.21, 43.28, 38.88, 12.32 (J_{PC} = 70.8).

12b. ^{31}P NMR: 35.38. ^1H NMR: 4.70–4.58 (m, H-5), 4.20–3.93 (m, H-3), 3.13–2.12 (m, 2 H-4), 2.47 (s, 3 H), 1.83 (d, J_{PH} = 13.5). ^{13}C NMR: 74.68 (J_{PC} = 81.3), 72.40, 42.89, 39.63, 13.69 (J_{PC} = 69.6).

12c. ^{31}P NMR: 38.07. ^1H NMR: 3.53 (m, H-3), 2.50 (s, 3 H), 1.77 (d, J_{PH} = 13.3, 3 H); other signals covered. ^{13}C NMR: 74.27 (J_{PC} = 80.5), 72.05, 42.67, 39.46, 11.66 (J_{PC} = 67.9).

13. ^{31}P: 34.78. ^1H NMR: 4.55–4.35 (m, 2 H-5), 3.67–3.53 (m, H-3), 3.15–3.05 (m, H-4), 2.52 (s, 3 H), 1.63 (d, J_{PH} = 12.5, 3 H). ^{13}C NMR: 72.80 (J_{PC} = 0.8), 65.60, 53.23 (J_{PC} = 71.4), 42.40, 15.47 (J_{PC} = 70.4).

Reaction of 3,4-Dihydro-2,2-dimethyl-2*H*-pyrrole 1-Oxide (7) with 1. A solution of nitrone **7** (212 mg, 1.87 mmol) and **1** (303 mg, 1.82 mmol) in CH_2Cl_2 (1 mL), after 7 days at room temperature, afforded a mixture of two isomers **14a** and **14b** in a 2.5:1 ratio (^{31}P NMR). The two isomers can be separated by flash chromatography (eluant CH_2Cl_2–MeOH, 10:1): first fraction R_f = 0.40, 78 mg (15%), isomer **14b**; second fraction 90 mg (18%), isomers **14b** and **14a** in a 1.1:1 ratio; third fraction R_f = 0.35, 294 mg (58%), isomer **14a**.

14a. Anal. Calcd for $C_{15}H_{22}NO_2P$: C, 64.44; H, 7.94; N, 5.01. Found: C, 64.53; H, 7.96; N, 5.18. ^{31}P NMR: 37.64. ^1H: 4.20 (ddd, J = 9.9, 6.9, 5.4, H-5), 4.01–3.86 (m, H-3), 2.82 (dddd, J = 19.4, 12.6, 9.9, 6.6, 1 H-4), 2.43 (dt, J = 12.6, 6.3, 1 H-4), 2.00 (m, 1 H), 1.72 (d, J_{PH} = 13.2, 3 H), 1.65–1.20 (m, 3 H), 1.26 (s, 3 H), 1.03 (s, 3 H). ^{13}C NMR: 74.24 (J_{PC} = 86.4), 69.07, 63.69 (J_{PC} = 5.4), 37.65, 36.03, 30.88, 26.90, 23.73, 11.13 (J_{PC} = 68.6). IR (CCl_4): 3090, 3070, 2980, 2950, 2880, 1595, 1465, 1440, 1385, 1370, 1310, 1290, 1190 (vs), 1110 cm^{-1}.

14b. Anal. Calcd for $C_{15}H_{22}NO_2P$: C, 64.44; H, 7.94;, N, 5.01. Found: C, 64.80; H, 7.97; N, 4.78. ^{31}P NMR: 37.49. ^1H: 7.80 (m, 2 H), 7.45 (m, 3 H), 4.31 (ddd, J = 9.9, 6.3, 3.3, 1 H), 3.66–3.61 (m, 1 H), 2.33–1.98 (m, 3 H), 1.78 (J_{PH} = 13.2, 3 H), 1.75–1.40 (m, 3 H), 1.28 (s, 3 H), 0.96 (s, 3 H). ^{13}C NMR: 75.42 (J_{PC} = 86.9), 68.93, 63.87 (J_{PC} = 6.6), 38.09, 36.37, 30.65, 24.78, 23.55, 13.98 (J_{PC} = 69.2). IR (CCl_4); 3061, 2971, 2871, 1592, 1466, 1438, 1382, 1366, 1305, 1291, 1191 (vs), 1113 cm^{-1}.

Reaction of 2,3,4,5-Tetrahydropyridine 1-Oxide (8) with 1. A solution of **1** (457 mg, 2.7 mmol) and the nitrone **8** [obtained by oxidation of *N*-hydroxypiperidine (505 mg, 5 mmol) with yellow HgO (2.83 g, 12.5 mmol)][16] in $CHCl_3$ (5 mL) was heated at 60 °C for 48 h. ^{31}P NMR analysis of the crude reaction mixture showed the isomers **15a**, **15b**, **15c**, and **15d** were formed in the ratio shown in Table I. Attempted separation of the complex mixture by flash chromatography (eluant CH_2Cl_2/MeOH, 10:1) gave only fractions enriched of the individual isomers with 91% overall yield of isolated compounds. Anal. Mixture of isomers. Calcd for $C_{14}H_{20}NO_2P$: C, 63.14; H, 7.57; N, 5.28. Found: C, 63.25; H, 7.93; N, 5.60. IR (CCl_4): 3061, 2944, 2858, 1591, 1438, 1292, 1195 (vs), 1113 cm^{-1}.

15a. ^{31}P NMR: 34.38. ^1H NMR: 4.25 (dt, J = 4.4, 10.5, H-5 isoxazoline numbering), 3.50–3.35 (m, H-3 isoxazoline numbering), 3.05–1.10 (m, 10 H), 1.72 (d, J_{PH} = 13.2, 3 H). ^{13}C NMR: 73.56 (J_{PC} = 86.3), 66.25, 54.92, 34.97, 28.66, 24.37, 23.07, 12.21 (J_{PC} = 70.7).

15b. ^{31}P NMR: 36.94. ^1H NMR: 4.54 (ddd, J = 10.3, 7.0, 5.1, H-5 isoxazoline numbering), 3.60–3.48 (m, H-3 isoxazoline numbering), 1.71 (d, J_{PH} = 13.2, 3 H), other signals covered. ^{13}C NMR: 74.34 (J_{PC} = 87.3), 59.99 (J_{PC} = 2.9), 49.43, 31.37, 24.77, 23.95, 18.52, 13.68 (J_{PC} = 69.3).

15c. ^{31}P NMR: 35.38. ^1H NMR: 4.70–4.58 (m, H-5 isoxazoline numbering), 4.43–4.34 (m, H-3 isoxazoline numbering), 1.78 (d, J_{PH} = 13.4, 3 H), other signals covered. ^{13}C NMR: 73.00 (J_{PC} = 87.1), 65.67, 54.79, 34.97, 28.68, 24.37, 23.07, 11.46 (J_{PC} = 68.5).

15d. ^{31}P NMR: 38.78. ^1H NMR: 4.30–4.20 (m, H-5 isoxazoline numbering), 3.53–3.38 (m, H-3 isoxazoline numbering), 3.12–1.10 (m, 10 H), 1.75 (d, J_{PH} = 13.5, 3 H). ^{13}C NMR: 73.12 (J_{PC} = 86.6), 65.89, 54.99, 35.08, 28.91, 24.49, 23.26, 11.76 (J_{PC} = 67.7).

Reaction of 3,4-Dihydroisoquinoline 1-Oxide (9) with 1. A solution of the nitrone **9** (176 mg, 1.2 mmol) and **1** (166 mg,

(16) Thesing, J.; Sirrenberg, W. *Chem. Ber.* **1959**, *92*, 1748.

1 mmol) in $CHCl_3$ (1 mL) was set aside at room temperature for 7 days. Analysis by ^{31}P NMR of the crude reaction mixture showed the four isomers **16a**, **16b**, **16c**, and **16d** were formed in the ratio shown in the Table I. Purification of the mixture on a short pad of silica gel (eluant CH_2Cl_2–MeOH, 20:1) afforded 304 mg (97%) of a mixture of crystalline products. Isomers **16a** and **16c** can be isolated pure by repeated crystallization from ligroin. Anal. Mixture of isomers. Calcd for $C_{16}H_{20}NO_2P$: C, 69.00; H, 6.43; N, 4.47. Found: C, 68.84; H, 6.54; N, 4.75. IR (CCl_4): 3063, 3025, 2925, 2855, 1591, 1490, 1454, 1438, 1293, 1195 (vs), 1114 cm^{-1}.

16a: mp 155–156 °C (ligroin 100–150 °C). Anal. Calcd for $C_{18}H_{20}NO_2P$: C, 69.00; H, 6.43; N, 4.47. Found: C, 69.25; H, 6.56; N, 4.34. ^{31}P NMR: 36.17. ^1H NMR: 7.86–7.77 (m, 1 H), 7.58–7.45 (m, 1 H), 7.25–7.07 (m, 2 H), 4.70 (t, J = 8.4, H-3 isoxazoline numbering), 4.59 (ddd, J = 10.0, 7.8, 5.9, H-5 isoxazoline numbering), 3.33–2.51 (m, 6 H), 1.84 (d, J_{PH} = 13.0). ^{13}C NMR: 75.30 (J_{PC} = 86.0), 63.19, 47.76, 37.42, 28.05, 11.17 (J_{PC} = 70.4).

16b. ^{31}P NMR: 36.40. ^1H NMR: 4.78 (ddd, J = 10.3, 5.1, 3.2, H-5 isoxazoline numbering), 3.55 (t, J = 8.8, H-3 isoxazoline numbering), 1.88 (d, J_{PH} = 13.0, 3 H), other signals covered. ^{13}C NMR: 75.15 (J_{PC} = 86.8), 63.62, 47.76, 37.20, 28.61, 13.74 (J_{PC} = 69.4).

16c: mp 150–151 °C (ligroin 100–150 °C). Anal. Calcd for $C_{18}H_{20}NO_2P$: C, 69.00; H, 6.43; N, 4.47. Found: C, 69.30; H, 6.65; N, 4.34. ^{31}P NMR: 32.52. ^1H NMR: 7.77–7.65 (m, 1 H), 7.58–7.45 (m, 1 H), 7.25–7.00 (m, 1 H), 4.69 (t, J = 8.5, H-3 isoxazoline numbering), 4.49–4.36 (m, 1 H), 3.47–3.28 (m, 2 H), 3.12–2.60 (m, 4 H), 1.73 (d, J_{PH} = 13.2). ^{13}C NMR: 78.62 (J_{PC} = 81.1), 63.07, 49.78, 36.73, 28.17, 12.74 (J_{PC} = 72.0).

16d. ^{31}P NMR: 35.74.

X-ray Crystallography. Crystal data: **3a** ($C_{16}H_{16}NO_2P$) was recrystallized from ligroin in the orthorhombic system, space group *Pbca* with a = 7.823 (1) Å, b = 17.084 (3) Å, c = 22.211 (5) Å, Z = 8, V = 2968.5 (7) Å^3, and D_{calcd} = 1.223 mg/m^3. Intensity data were collected on a CAD4 diffractometer in the range $1 < \theta < 75°$ with graphite-monochromatized Cu Kα radiation (λ = 1.54178 Å) in the $\omega/2\theta$ scan mode, lattice constants refined by least-squares fit of 25 reflections in the θ range 21.9–27.4°, no absorption correction was applied. A total of 3486 integrated reflections were collected up to ($(\sin\theta)/\lambda$ = 0.6 Å^{-1}); $\omega/2\theta$ scan technique, scan width (1.1 + 0.14 tan θ)°; $0 < h < 9$; $0 < k < 21$; $0 < l < 27$; decline in intensities of three standard reflections (4,3,–3; 8,–2; 2,9,–2) 0.1% during 57.9 h. A total of 2733 reflections observed [$I > 3\sigma(I)$] were used to solve the structure by direct methods (by SHELX-86 program)[17] and to refine it by full-matrix least squares (by SHELX-76 program)[18] using F's; H atoms were found on a Fourier map and refined with isotropic thermal parameters; anisotropic thermal parameters were applied for all other atoms; refinement converged to R = 0.0555, R_w = 0.0702 with weight $w = 1.0/(\sigma^2(F) + 0.01441F^2)$, for 246 refined parameters; largest shift over esd in the last cycle 0.02; largest residual peak in final difference Fourier map 0.011 e Å^3. Scattering factors were from ref 19.

Acknowledgment. This work was supported by the Italian National Research Council (CNR) and the Polish Academy of Sciences (CPBP-01-13). Partial support from PR-II-10 is also acknowledged.

Supplementary Material Available: Tables of crystallographic experimental details—unit cell packing diagram, positional parameters, anisotropic temperature factors, hydrogen atom positional parameters, bond lengths, bond angles, and torsion angles (7 pages). Ordering information is given on any current masthead page.

(17) SHELX 86: Sheldrick, G. M.; Krüger, C.; Goddard, R. *Crystallographic Computing 3*; Oxford University Press: 1985; pp 175–189.
(18) Sheldrick, G. M. SHELX 76. Program for Crystal Structure Determination, University of Cambridge, England, 1976.
(19) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974.

3-Oxo- and 3-Imino-4-substituted-1,2,5-thiadiazolidine 1,1-Dioxides: Synthesis, Spectral Properties, and Selected Chemistry

Chai-Ho Lee, James D. Korp, and Harold Kohn*

Department of Chemistry, University of Houston, Houston, Texas 77204-5641

Received January 24, 1989

A general synthesis for the preparation of 3-oxo- and 3-imino-4-substituted-1,2,5-thiadiazolidine 1,1-dioxides has been developed beginning with an aldehyde, metal cyanide, and sulfamide. The selected chemistry and spectral properties of these compounds are detailed, as well as an X-ray crystallographic structure of a representative member of each class of heterocyclic compound. 3-Imino-4-phenyl-1,2,5-thiadiazolidine 1,1-dioxide crystallizes in space group $P2_12_12_1$, with a = 5.156 (1) Å, b = 7.418 (2) Å, c = 24.407 (5) Å, and Z = 4. 4-(1'-Naphthyl)-3-oxo-1,2,5-thiadiazolidine 1,1-dioxide crystallizes in space group $P2_1/c$, with a = 19.018 (7) Å, b = 5.335 (1) Å, c = 11.544 (3) Å, β = 103.63 (2)°, and Z = 4.

Introduction

The diverse chemical reactivity and pharmacological properties of hydantoins (**1**) have commanded the interest of organic and medicinal chemists.[1] Unfortunately, little is known about the sulfur dioxide equivalent of 1, 3-oxo-1,2,5-thiadiazolidine 1,1-dioxides (**2**). The early description of the preparation of 4,4-diphenyl-3-oxo-1,2,5-thiadiazolidine 1,1-dioxide[2] and the recent articles by Unterhalt and Hanewacker on the synthesis of 2,4-disubstituted derivatives of **2**[3] are our major sources of knowledge for these compounds. The need for additional information is further magnified by the many useful biological properties (i.e., anticonvulsant,[4] hypoglycemic,[5] antihypertensive,[6] hist-

(1) (a) Lopez, C. A.; Trigo, G. G. *Adv. Heterocycl. Chem.* **1985**, *38*, 177. (b) Ware, E. *Chem. Rev.* **1950**, *46*, 403.
(2) Vorreither, H. K.; Ziegler, E. *Monatsh. Chem.* **1965**, *96*, 216.
(3) Unterhalt, B.; Hanewacker, G.-A. *Arch. Pharm. (Weinheim, Ger.)* **1988**, *321*, 375.
(4) Aeberli, P.; Gogerty, J.; Houlihan, W. J. *J. Med Chem.* **1967**, *10*, 636.
(5) (a) McManus, J. M.; McFarland, J. W.; Gerber, C. F.; McLamore, W. M.; Laubach, G. D. *J. Med. Chem.* **1965**, *8*, 766. (b) Wiseman, E. H.; Pereira, J. N.; Finger, K. F.; Pinson, R. *Ibid.* **1965**, *8*, 777. (c) McFarland, J. W.; Gerber, C. F.; McLamore, W. M. *Ibid.* **1965**, *8*, 782. (d) Sarges, R.; Kuhla, D. E.; Wiedermann, H. E.; Mayhew, D. A. *Ibid.* **1976**, *19*, 695.

0022-3263/89/1954-3077$01.50/0