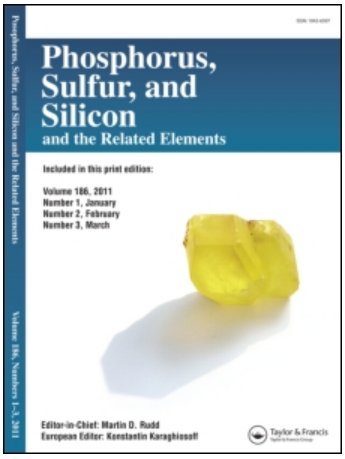

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A SYNTHESIS OF 1,3,4-OXADIAZOLES VIA THE AZA-WITTIG REACTION OF N-ACYLAMINO IMINOTRIPHENYLPHOSPHORANES

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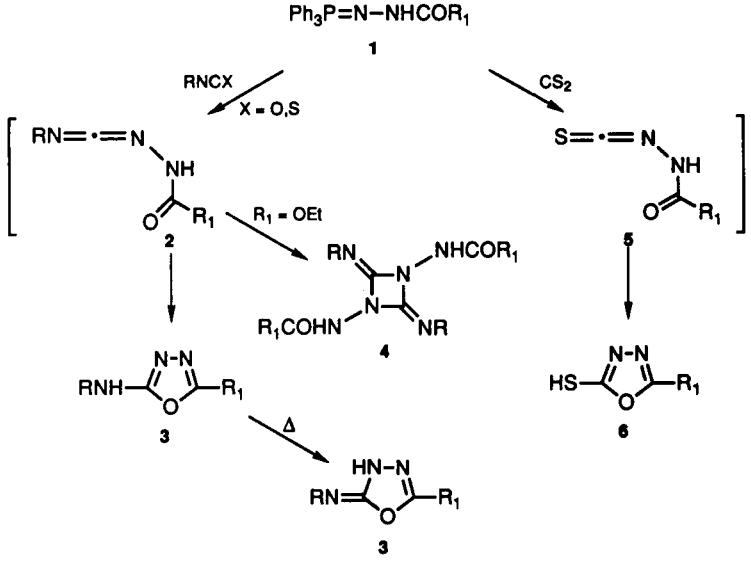
The aza-Wittig reaction of N-acylamino iminotriphenylphosphoranes with carbon disulfide, isocyanates and isothiocyanates, lead to the very reactive heterocumulenic systems (**5**) and (**2**) which undergo spontaneous cyclization to 5-substituted 2-mercapto-1,3,4-oxadiazoles (**6**) and 2-amino-1,3,4-oxadiazoles (**3**), respectively.

Key words: Synthesis; N-acylamino iminotriphenylphosphoranes; N-acylamino carbodiimides; N-acylamino isothiocyanates; 1,3,4-oxadiazoles; aza-Wittig reaction.

The aza-Wittig (Staudinger-Meyer-Hauser[1,2]) reaction of iminophosphoranes has drawn considerable attention in later years because of its high synthetic potential, e.g., in the preparation of nitrogen heterocycles.[3,4] We now report a method for the preparation of the unstable N-acylamino carbodiimides (**2**) and N-acylamino isothiocyanates (**5**) which, without isolation, undergo spontaneous cyclization to 2-amino-1,3,4-oxadiazoles (**3**) and 2-mercapto-1,3,4-oxadiazoles (**6**) in good yields.



Scheme 1.

In continuing our studies of iminophosphoranes we have investigated the reactions of N-acylamino iminotriphenylphosphoranes (**1**), Table II, with some heterocumulenes, i.e., isocyanates, isothiocyanates, and carbon disulfide (Scheme I).

As shown in Table I, iminophosphoranes (**1a–e**) and (**1f**) exhibit striking differences in their reactions toward these compounds. In the case of (**1a–e**), the resulting N-acylamino carbodiimides (**2a–k**) undergo an intramolecular ring closure to 2-amino-1,3,4-oxadiazoles (**3**). In the case of **1f**, however, the forming carbodiimides undergo cycloadditions, yielding, among numerous by-products, 1,3-diazetidine-2,4-diimines (**4**) (Scheme I). We attribute this difference in reaction path to the reduced nucleophilicity of the carbonyl oxygen in (**21-m**) as compared to (**2a–k**). It is reasonable to suppose that the electrocyclic ring closure of the latter compounds is initiated by a nucleophilic attack of the carbonyl oxygen on the sp-hybridized carbon atom of the carbodiimide moiety as depicted in Scheme II. In the case of (**21-m**), however, where reduced electron density on the carbonyl oxygen makes the intramolecular reaction energetically less favorable, the highly reactive carbodiimides undergo cycloaddition, either by a 1,4-dipolar intermediate or by the allowed concerted $[\pi 2_s + \pi 2_a]$ mechanism.

TABLE I

2-Amino-1,3,4-oxadiazoles (**3a–3k**)

Compound	R_1	R	Yield (%)	m.p. (°C)
3a	C_6H_5	C_6H_5	72	219-221 (lit.[5] 217)
3b	C_6H_5	1-$C_{10}H_7$	70	201 (lit.[6] 192-194)
3c	C_6H_5	4-NO_2-C_6H_4	79	286-288 (lit.[6] 279-280)
3d	C_6H_5	3,5-NO_2-C_6H_3	85	285
3e	4-CH_3-C_6H_4	3,5-NO_2-C_6H_3	90	285
3f	4-CH_3-C_6H_4	4-NO_2-C_6H_4	80	287-289
3g	4-NO_2-C_6H_4	4-NO_2-C_6H_4	92	330
3h	4-NO_2-C_6H_4	C_6H_5	85	270-271 (lit.[7] 270-271)
3i	3,5-NO_2-C_6H_3	4-NO_2-C_6H_4	82	340
3j	2-CH_3-C_6H_4	4-NO_2-C_6H_4	95	252
3k	2-CH_3-C_6H_4	C_6H_5	75	174-175
3l	C_2H_5O	3,5-NO_2-C_6H_3	0	
3m	C_2H_5O	4-NO_2-C_6H_4	0	

TABLE II

Iminophosphoranes $Ph_3P{=}N{-}NH{-}CO{-}R_1$

Compound	R_1	m.p. (°C)
1a	C_6H_5	200-202 (lit.[8] 177-180)
1b	4-CH_3-C_6H_4	202
1c	2-CH_3-C_6H_4	115-117
1d	4-NO_2-C_6H_4	179-181
1e	3,5-NO_2-C_6H_3	182-183
1f	C_2H_5O	99-102

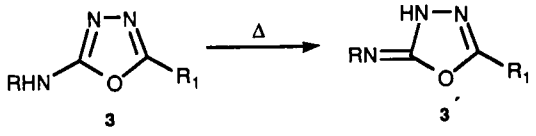
TABLE III

2-Mercapto-1,3,4-oxadiazoles

Compound	R_1	Yield (%)	m.p. °C
6a	C_6H_5	80	219 (lit.[11] 219-220)
6b	4-CH_3-C_6H_4	84	218

The reaction of (**1**) with carbon disulfide proceeds through the N-acylamino isothiocyanate (**5**). In contrast to the remarkably fast reactions of isocyanates and isothiocyanates, the aza-Wittig reaction with carbon disulfide is rather slow, although (**1a–c**) react with neat carbon disulfide at room temperature to give 2-mercapto-1,3,4-oxadiazoles (**6**) in good yields (Table III).

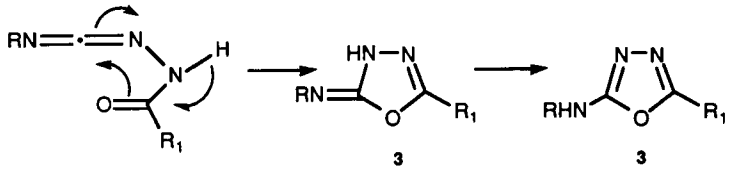
It is noteworthy that the 2-amino-1,3,4-oxadiazoles (**3**) upon heating isomerize to the corresponding 2-imino-1,3,4-oxadiazolines (3′):



3 **3′**

Typically in **3a** (R_1 = R = Ph), this transformation can be discerned when the compound is heated to about 180°C. The fibrelike crystals of **3a** (strong infrared absorption at 1610–1620 cm^{-1}) gradually disappear, and new crystals (**3a′**, strong infrared absorption at 1660 cm^{-1}), form. The identities of the two isomers could not be established unambiguously by IR or NMR spectroscopies (NMR and mass spectra of **3** and **3′** are identical). The compound (**3h**) as obtained from the reaction of (1d) with phenyl isothiocyanate, however, was shown to have the constitution **3** (Scheme II) by single crystal X-ray analysis.[9] Further confirmation of the identity of the isomers was accomplished by comparison of the IR spectra (mull, KBr) with those of the related 5-phenyl-2-methylphenylamino-1,3,4-oxadiazole and 3-methyl-5-phenyl-2-phenylimino-1,3,4-oxadiazoline. The latter compounds, where the hydrogen in question has been replaced by methyl, is reported[10] to have a strong absorption at 1605 and 1660–1680 cm^{-1}, respectively, nearly the same as that of **3h** (1610–1620 cm^{-1}) and **3h′** (1660 cm^{-1}).

The transformation (**3a**) → (**3a′**) is completed well below the melting point of (**3a′**) at 219–221°C. Moreover, while infrared spectra of (**3a**) and (**3a′**) in the solid state (mull, KBr) are entirely different, the spectra in solution ($CHCl_3$) are identical. Thus no trace of the absorption at 1660 cm^{-1} can be discerned when (**3a′**) is dissolved in chloroform, demonstrating that the position of the equilibrium (**3a**) ⇌ (**3a′**) lie toward (**3a**). In view of these observations it is believed that the N-acylamino carbodiimides rearrange as depicted in Scheme II through an aromatic transition state and under kinetic control to the 2-imino-1,3,4-oxadiazoline (**3′**), which subsequently isomerize to the thermodynamically stable 2-amino-1,3,4-oxadiazole (**3**):



3 **3**

Scheme 2

The abovementioned transformation by heat into the (**3'**) isomer was observed in all the compounds (**3**) under study. When heated to about 20–50°C below the melting point, the 2-amino-1,3,4-oxadiazoles, thermodynamically stable below this temperature, are transformed into the tautomeric (**3'**), which apparently represent the more stable modification at elevated temperatures. In the solid state the 2-imino-1,3,4-oxadiazolines are fairly stable even at low temperature, but on prolonged storage they revert to 2-amino-1,3,4-oxadiazoles (**3**).

EXPERIMENTAL

The starting iminophosphoranes (**1**) were obtained from the corresponding phosphonium salts and a suitable base. Phosphonium salts were generated from triphenylphosphine dibromide and the appropriate acylhydrazides together with an equimolar amount of triethylamine in dichloromethane. The iminophosphorane (**1j**) was generated with sodium ethoxide in anhydrous ethanol. Other iminophosphoranes were prepared as follows: The phosphonium salt was taken up in DMSO and added directly to an ice cooled aqueous solution of sodium carbonate. The crystalline product was separated by filtration, washed with cold water and recrystallized to give the desired iminophosphorane (Table II). Spectroscopic data for (**1a–f**); IR (nujol), ^{1}H NMR (60 MHz, $CDCl_3$). (**1a**): $\nu_{max.}$ 1640 cm^{-1} (C=O), δ 3.85–4.55 (1H, br. s.), and 7.20–7.86 (20H, m). (**1b**): $\nu_{max.}$ 1650 cm^{-1} (C=O), δ 2.49 (3H, s), and 7.18–8.02 (19H, m). (**1c**): $\nu_{max.}$ 1650 cm^{-1} (C=O), δ 2.46 (3H, s), and 7.07–7.96 (19H, m). (**1d**): $\nu_{max.}$ 1640 cm^{-1} (C=O), δ 5.43–5.80 (1H, br. s.), 7.20–7.70 (15H, m), and 7.84–8.36 (4H, m). (**1e**): $\nu_{max.}$ 1640 cm^{-1} (C=O), δ 7.25–8.01 (15H, m), 8.60–8.80 (1H), and 8.80–9.05 (3H, m), (**1f**): $\nu_{max.}$ 1715 cm^{-1} (C=O), δ 1.20 (3H, t), 4.12 (2H, q), 4.80–5.05 (1H, br. s.), and 7.20–8.10 (15H, m).

2-Amino-1,3,4-oxadiazoles (**3a–k**). To a stirred solution of 1.0 mmol of iminophosphorane (**1**) in 2 ml of dichloromethane was added a solution of 1.0 mmol of isocyanate in 1 ml of dichloromethane. The reaction occurred spontaneously and went to completion in a few minutes at ambient temperature. The resulting oxadiazoles were isolated by filtration and recrystallized from ethanol. (Table I). Mass spectra (70 eV): m/z (%) (**3a**): 237 (100, M$^+$), 179.9 (17), 144.9 (40), 118 (32.4), 104.9 (17.9), 104 (13.4), 103 (16.4). (**3b**): 287 (100, M$^+$), 286 (37.4), 245 (13.9), 230 (11.7), 184 (13.2), 169 (10.3), 145 (43.2), 143 (10.2), 118 (17.2). (**3c**): 282.4 (72.3, M$^+$), 145.2 (100), 118.2 (12.4), 105.1 (21) 103.2 (17.3). (**3d**): 327 (65.8, M$^+$), 145 (100), 118 (19.2), 105 (26.4), 103 (23.7), 77 (87.1). (**3e**): 341 (95.2, M$^+$), 159 (100), 132 (25.1), 131 (21.4), 119 (25.1), 117 (48.7), 91 (51). (**3f**): 296 (77.4, M$^+$), 159 (100), 132 (10.9), 131 (11.2), 119 (36.5), 117 (43.6), 116 (13.3), 91 (55.1), 92 (11.4). (**3g**): 327 (100, M$^+$), 191 (10.1), 190 (99.2), 163 (25.5), 150 (19.3), 144 (64.4), 133 (10.3). (**3h**): 282 (100, M$^+$), 190 (18), 163 (32.1), 144 (22), 120 (16.9), 118 (13), 104 (17.6), 102 (18.2), 92 (18), 91 (10), 89 (11.9). (**3i**): 373 (14.5), 372 (83.2, M$^+$), 235 (45.1), 208 (17.4), 195 (13), 189 (27.7), 165 (33.6), 149 (16.1), 143 (26.7), 103 (12.2), 91 (14.6), 90 (13.5), 76 (31), 75 (100). (**3k**): 252 (15), 251 (73, M$^+$), 192 (30.6), 159 (38.3), 135 (43.4), 132 (42.6), 120 (10.8), 119 (100).

2-Mercapto-1,3,4-oxadiazoles (**6a–b**). 1.0 mmol iminophosphorane (**1**) was dissolved in carbon disulfide in a glass stoppered bottle and left at ambient temperature for several days. The products, (**6a–b**), separated gradually and were recrystallized from ethanol. (**6a**): m.p. (uncorrected): 219°C not depressed by a specimen prepared by the method of Young and Wood).[11] MS (70 eV): m/z (%) 178 (100, M$^+$), 118 (74.8, M-COS), 91 (26.8), 77 (36.2). (**6b**): m.p.: 218°C; MS (70 eV): m/z (%) 192.2 (100, M$^+$), 132.2 (84.8, M-COS), 131.1 (32.2), 117.2 (13.5), 91.1 (33.2), 66.1 (11.3), 65.1 (14.2).

1,3-Diphenyl-2,4-bis-carbamoyl ethylester-1,3-diazetidine (**4**). To a stirred solution of 0.5 mmol of (**1j**) in dichloromethane was added 0.5 mmol of phenyl isocyanate. After stirring for 10 min at ambient temperature, the reaction mixture was concentrated on a rotary evaporator, yielding a yellow oil. The oil was extracted with cold anhydrous ethyl ether and the ether layer concentrated under vacuum, yielding a clear yellow oil. The oil was purified by preparative TLC (silica gel, 1:1 chloroform/ethyl acetate). The various bands were extracted from the silica gel with ethyl ether, and the ether layer concentrated under vacuum. One of the bands yielded 4.1 mg (4.5%) of (**4**) isolated as a colorless oil: IR ($CHCl_3$) 1680 cm^{-1} (C=N); MS (70 eV): m/z (relative intensity) 410 (7.5, M$^+$), 357 (2.9), 331 (4.2), 265 (2.2), 212 (21.3), 205 (29.5), 177 (20.7), 149 (10.8), 119 (62.7), 93 (100). HRMS for $C_{10}H_{11}N_3O_2$ (M$^+$/2): calcd 205.0851, found 205.0847.

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