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Synthesis of Phosphonyl 1,2,3-Thiadiazoles

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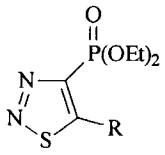
ABSTRACT: *In accord with the Hurd-Mori reaction conditions, 1- or 2-phosphonyl hydrazones reacted with thionyl chloride to afford 4- or 5-phosphonyl 1,2,3-thiadiazoles in good yields and purity. A synthesis of 1- or 2-phosphonyl hydrazones using two methods is described.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 16:413–416, 2000

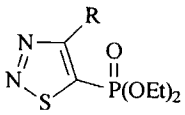
INTRODUCTION

Several reports have appeared in recent years detailing with the bioactivity of 1,2,3-thiadiazole derivatives [1–6]. The biological activity is to a great degree attributed to the nature of substituents on the thiadiazole ring. Therefore, it is conceivable that modification of the thiadiazole ring by introduction of a phosphonyl group, which could regulate biological functions, might be expected to exhibit potential pesticide activity. However, in the course of surveying the literature on the preparation of phosphonyl 1,2,3-thiadiazole, we found only a report by Khokhlov et al. [7] detailing the conversion of a cyanodiazomethylphosphonate to a phosphonyl thiadiazole (Scheme 1). Thus, we deemed it necessary to develop an efficient and facile strategy for the synthesis of phosphonyl thiadiazoles.

As part of our research on herbicidal thiadiazoles, we have been interested in synthetic methods that might apply to the synthesis of 4-phosphonyl-1,2,3-thiadiazoles **1** or to 5-phosphonyl-1,2,3-thiadiazoles **2**.

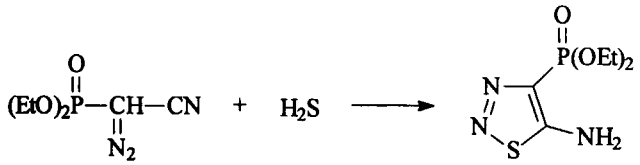


1

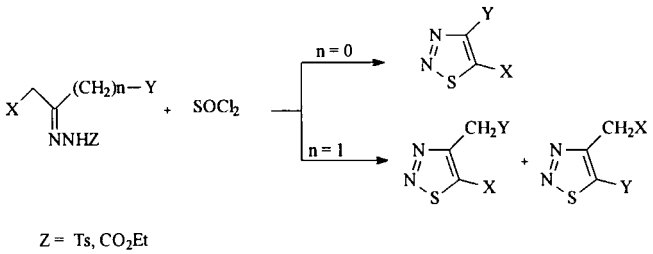


2

It is known that the Hurd-Mori reaction is the most convenient methodology for construction of a 1,2,3-thiadiazole ring (Scheme 2). As depicted in Scheme 2, when *n* equals 1, two products could be obtained. Indeed, the regioselectivity changed, depending on the nature of substituents X and Y [8,9].



SCHEME 1



SCHEME 2

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We have also found that phosphonyl hydrazones undergo reaction with thionyl chloride to provide 4- or 5-phosphonyl 1,2,3-thiadiazoles by the Hurd-Mori reaction.

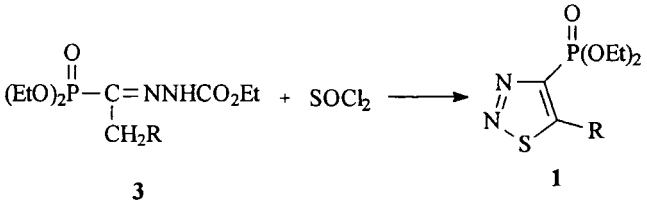
RESULTS AND DISCUSSIONS

4-Phosphonyl-1,2,3-thiadiazoles **1** were synthesized by the following reaction (Scheme 3). The structures of compounds **1** were confirmed by ^{1}H NMR, ^{31}P NMR, MS, and elemental analyses (see Table 1 and Table 2).

The phosphonyl hydrazones **3** were easily prepared according to a known procedure [10] using the reaction of ethyl hydrazinocarboxylate with 1-oxoalkylphosphonates **4**, which was generated by an Arbuzov reaction between an acyl chloride and triethyl phosphite (Scheme 4).

The procedure provides sole products **1** because there is only one α-carbon to react with thionyl chloride in the phosphonyl hydrazones **3**.

The hydrazones could have two isomers in theory. However, when the phosphonyl hydrazones **3** and the phosphonyl methylene hydrazones **5** were prepared, only one isomer could be detected in each case. The isomeric configurations were not assigned, but each was readily converted to the corresponding thiadiazoles **1** or **2** in good yields.



3 **1**

a R = H, **b** R = Me, **c** R = Ph, **d** R = CO_2Et

SCHEME 3

TABLE 1 Yields and Quantitative Elemental Analyses Data of Compounds **1** and **2**

Compounds	R	Yield (%)	Elemental Analyses Calculated (Found) C	H	N
1a	H	84.7	32.43 (32.52)	4.95 (4.88)	12.61 (12.73)
1b	Me	69.2	35.59 (35.37)	5.51 (5.57)	11.86 (11.62)
1c	Ph	79.6	48.32 (48.56)	5.03 (5.35)	9.40 (9.59)
1d	CO_2Et	72.1	36.73 (36.91)	5.10 (5.04)	9.52 (9.37)
2a	H	92.3	32.43 (32.09)	4.95 (5.08)	12.61 (13.10)
2b	Me	88.5	35.59 (35.27)	5.51 (5.66)	11.86 (12.12)
2c	Ph	86.4	48.32 (47.92)	5.03 (4.82)	9.40 (9.70)

The 5-Phosphonyl 1,2,3-thiadiazoles **2** were obtained by the reaction of phosphonyl methylene hydrazones **5** with thionyl chloride (Scheme 5). The structures of compounds **2** were confirmed by ^{1}H NMR, ^{31}P NMR, MS, and elemental analysis (see Table 1 and Table 2).

The compounds **5** were prepared in good yields by two methods (Scheme 6). The first involved the Arbuzov reaction of triethyl phosphite with iodoalkyl ketones **6** leading to formation of 2-oxoalkylphosphonates **7**, which were then converted to compounds **5** with ethyl hydrazinocarboxylate [10] (method A). The second method involved the reaction of 1-chloro (or 1-bromo) alkyl ketones **8** with ethyl hydrazinocarboxylate to give the hydrazone derivatives **9**, which then reacted with triethyl phosphite to afford compounds **5** [11] (method B).

The obvious difference between method A and method B is the order of introducing the phosphonyl group in compounds **5**. Since chloro (or bromo) alkyl ketones react with triethyl phosphite to favor the Perkow reaction, which leads to formation of vinyl phosphates, iodoalkyl ketones **6** must be used to obtain 2-oxoalkylphosphonates **7**. However, the reaction of compounds **9** with triethyl phosphite yields only the phosphonyl methylene hydrazones **5** according to the Arbuzov reaction whether X is chloro, bromo, or iodo. The compounds **5** prepared by the two methods were pure enough to be used in the next step without further purification.

In the case of the phosphonyl methylene hydrazone **5b** (R = CH_3), 5-diethoxyphosphonyl-4-methyl-1,2,3-thiadiazole **2b** was obtained instead of 4-diethoxyphosphonyl methylene 1,2,3-thiadiazole **10** (Scheme 7). This may be rationalized on the basis that the electrophilic substitution of thionyl chloride at the methylene group took place more readily than at the methyl group because of the electron-withdrawing effect of the phosphonyl group.

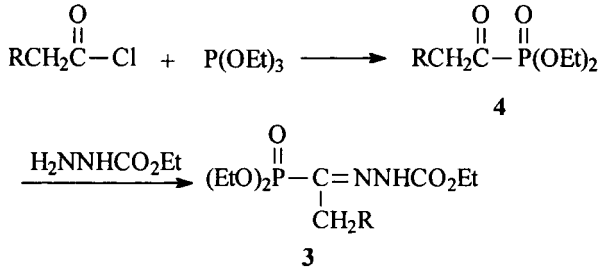
We also investigated the possibility of synthesizing compounds **2** by the reaction of 5-chloro-1,2,3-thiadizzoles **11** with triethyl phosphite. When R = H, the compound **2a** was obtained. However, analogous attempts to carry out the reaction of compound **11b** or **11c** with triethyl phosphite have met with failure. The failure may be ascribed to the steric hindrance of the R group (Scheme 8).

It should be pointed out that the synthesis of compounds **1** by a method similar to that used for preparing the compound **2a** (Scheme 8) is precluded by the difficulty of synthesizing 4-chloro-1,2,3-thiadiazoles.

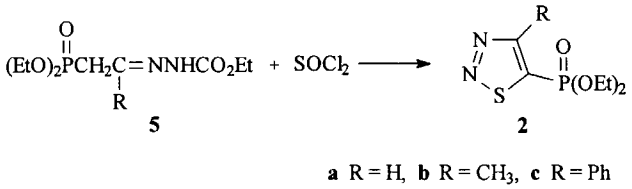
In summary, we have developed a convenient method for preparing 4- or 5-phosphonyl-1,2,3-thiadiazoles, respectively. The method has many advan-

TABLE 2 ^{1}H NMR, ^{31}P NMR, and MS Data of Compounds **1** and **2**

Compounds	*^{1}H NMR ($CDCl_3$)*	*^{31}P NMR ($CDCl_3$)*	*MS*
1a	1.38 (t, 6H, OCH_2CH_3), 4.36 (m, 4H, OCH_2CH_3), 9.87 (d, 1H, 5-H, $^{3}J_{PH}$ = 4.0Hz)	5.37	221 (M − 1)
1b	1.33 (t, 6H, OCH_2CH_3), 4.23 (m, 4H, OCH_2CH_3), 2.86 (d, 3H, CH_3, $^{4}J_{PH}$ = 2.0Hz)	5.28	237 (M + 1)
1c	1.20 (t, 6H, OCH_2CH_3), 4.18 (m, 4H, OCH_2CH_3), 7.24 ~ 7.66 (m, 5H, C_6H_5)	5.41	298 (M)
1d	1.31 (t, 9H, OCH_2CH_3), 4.31 (m, 6H, OCH_2CH_3),	2.69	295 (M + 1)
2a	1.35 (t, 6H, OCH_2CH_3), 4.19 (m, 4H, OCH_2CH_3), 9.00 (d, 1H, 5-H, $^{3}J_{PH}$ = 3.2Hz)	5.95	221 (M − 1)
2b	1.35 (t, 6H, OCH_2CH_3, 4.18 (m, 4H, OCH_2CH_3), 2.91 (d, 3H, CH_3, $^{4}J_{PH}$ = 2.0Hz)	7.32	237 (M + 1)
2c	1.17 (t, 6H, OCH_2CH_3), 4.05 (m, 4H, OCH_2CH_3),	6.98	298 (M)



SCHEME 4



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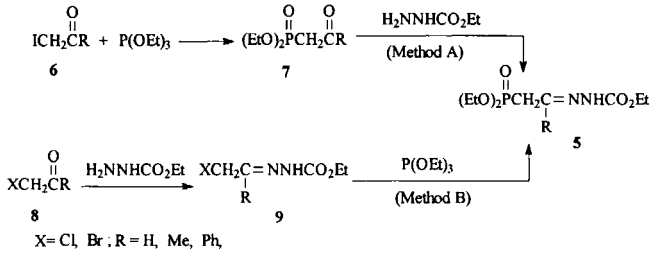


SCHEME 6

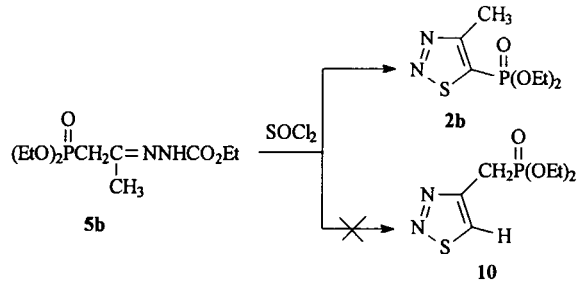
tages such as high yields and high regioselectivity. The procedure is relatively simple, the isolation and purification of products is straightforward, and the formation of side products is minimized.

EXPERIMENTAL

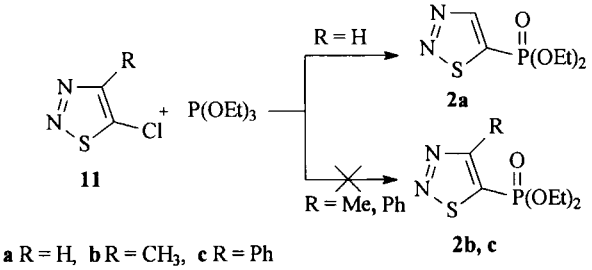
^{1}H and ^{31}P NMR spectra were taken on a BRUKER AC-P200 spectrometer. ^{1}H resonances are reported in parts per million relative to internal tetramethylsilane. ^{31}P chemical shifts are reported in parts per million relative to 85% phosphoric acid (external). Mass spectra were recorded on a Hewlett-Packard 5988 instrument. Quantitative elemental analyses were run on a Yana MT-3 instrument. All reagents and solvents were carefully dried and distilled prior to use. Compounds **4** (R = H) [11], **4** (R = CH_3) [12], **4** (R = Ph) [13], **4** (R = CO_2Et) [14], **7** (R = H) [15], **7** (R = CH_3) [16], **7** (R = Ph) [17], **11a** (R = H) [19], **11b** (R = Me) [20], and **11c** (R = Ph) [20] were synthesized by literature methods.

General Procedure for Preparation of **1**

A mixture of 0.02 mole of each phosphonyl hydrazones **3**, 0.03 g of DMF, 5 mL of ethyl acetate, and 1.1 g of sodium chloride was added with stirring to



SCHEME 7



SCHEME 8

4.4 mL (0.06 mol) thionyl chloride, cooled in an ice water bath, and the reaction mixture was stirred at room temperature for 10 hours. The mixture was added to a cold saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was separated and washed with water, dried over magnesium sulfate, and evaporated. The residue was purified by column chromatography on silica gel using ethyl acetate and petroleum ether as eluent to give **1**. The yield, ^{1}H NMR, ^{31}P NMR, MS data, and quantitative elemental analyses data are given in Table 1 and Table 2.

General Procedure for Preparation of **2** *by the Reaction of* **5**

A mixture of 0.02 mole of each phosphonylmethylene hydrazone **5**, 0.03 g of DMF, 5 mL of ethyl acetate, and 1.1 g sodium chloride was added with stirring to 4.4 mL (0.06 mol) of thionyl chloride cooled in an ice water bath, and then the reaction mixture was stirred at room temperature for 10 hours. The mixture was added to a cold saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was separated and washed with water, dried over magnesium sulfate, and evaporated. The residue was purified by column chromatography on silica gel using ethyl acetate and petroleum ether as eluent to give **2**. The yield, ^{1}H NMR, ^{31}P NMR, MS data, and quantitative elemental analysis data are presented in Table 1 and Table 2.

Preparation of **2a** *by the Reaction of* **11a**

To a solution of 1.2 g (0.01 mol) 5-chloro 1,2,3-thiadiazole in 15 mL DMF was added 1.8 g triethyl phosphite, and the reaction mixture was stirred for 15 hours at 100°C. After the solvent had been evaporated under vacuum, the residue was chromatographed on a column of silica gel using ethyl acetate and petroleum ether as eluent to give 1.2 g of **2a** (54.1%).

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