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Thermolyses of α-phosphorylmethyl tetrazolyl sulfoxides in the presence of 2,3-dimethyl-1,3-butadiene and their reactions with several amines

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Abstract

We have synthesized α-(phosphoryl)methyl tetrazolyl sulfoxides and examined the reactivities in the thermolyses and in the presence of several amines, such as aniline, benzylamine, piperidine, pyrrolidine, and morpholine. Thermolyses of the derivatives in the presence of 2,3-dimethyl-1,3-butadiene afforded 2-phosphoryl substituted 4,5-dimethyl-3,6-dihydro-2*H*-thiopyran *S*-oxide. In addition, novel phosphinecarbothioamides were obtained in the reaction of the derivatives with amines.

Keywords: α-Phosphoryl sulfoxide; Tetrazole; Phosphinecarbothioamide; Hetero Diels–Alder reaction

1. Introduction

Previously, we reported thioaldehyde and/or sulfine formation in the thermal reaction of heteroaryl substituted β-ketosulfoxides in the presence or absence of bases.[1] Namely, thermolyses of benzothiazolyl phenacyl sulfoxides in the presence of 2,3-dimethyl-1,3-butadiene afforded thiopyran derivatives, which is considered to be formed by the hetero Diels–Alder reaction of diene with the corresponding thioaldehyde formed initially.[1a] On the other hand, in the reaction of tetrazolyl phenacyl sulfoxides under the same conditions, the corresponding cycloadducts with sulfines were formed in excellent yields.[1b] These results revealed that different mechanistic pathways were operating depending on the heteroaryl moieties, resulted in the formation of two different types of products, i.e., thioaldehydes or sulfines.

Recently, we have reported the phosphinecarbothioamide formation in the reactions of α-(dimethylphosphoryl)methyl tetrazolyl sulfoxides with several amines as a short communication.[2] In order to obtain the scope and limitations of the reactions, we further prepared several tetrazolyl substituted α-phosphorylmethyl sulfoxides and studied their thermolyses in the presence of 2,3-dimethyl-1,3-butadiene and also their reactions with several amines. Herein, we report the results of thermolyses and the reactions in the presence of amines.

2. Results and discussion

2.1. Preparation of 5-(1-phenyl)-1H-tetrazolyl α-(dimethylphosphoryl)-, α-(diphenylphosphoryl)-, and α-(diethoxyphosphoryl)methyl tetrazolyl sulfoxides

α-(Dimethylphosphoryl)methyl 5-(1-phenyl)-1*H*-tetrazolyl sulfide (**1**) was prepared by the reaction of chloromethyl(dimethyl)phosphine oxide with 1-phenyl-5-mercapto-1*H*-tetrazole in the presence of triethylamine. The corresponding sulfoxide, i.e., α-(dimethylphosphoryl)methyl 5-(1-phenyl)-1*H*-tetrazolyl sulfoxide (**2**) was obtained by the oxidation of **1** with *m*-CPBA as shown in Scheme 1.

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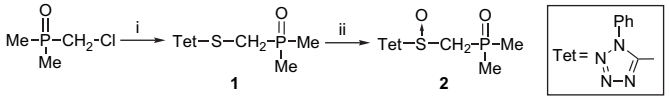
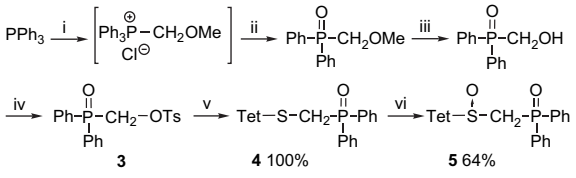
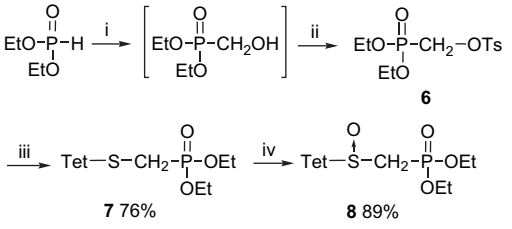


Scheme 1. Preparation of **2**. (i) Tet–SH, Et_3N, $CHCl_3$, 70 °C, 6 h, 85%; (ii) *m*-CPBA, $CHCl_3$, rt, 3 h, 57%.

α-(Diphenylphosphoryl)methyl 5-(1-phenyl)-1*H*-tetrazolyl sulfoxide (**5**) was prepared by following the procedure shown in Scheme 2. Diphenylphosphorylmethyl tosylate (**3**) was obtained by the reaction of tosylchloride with the corresponding alcohol prepared via three steps starting from triphenylphosphine by the Michaelis–Arbuzov type reaction.[3] Sulfide **4** was prepared by the reaction of **3** with 1-phenyl-5-mercapto-1*H*-tetrazole in the presence of K_2CO_3 as a base. The corresponding sulfoxide **5** was obtained by the oxidation of **4** with *m*-CPBA.



Scheme 2. Preparation of **5**. (i) Chloromethoxymethane, $CHCl_3$, rt, 5.5 h; (ii) 30% aqueous NaOH, 0–100 °C, 10 h, 75%; (iii) 47% HBr, 120 °C, 12 h, 83%; (iv) TsCl, Et_3N, CH_2Cl_2, rt, 8 h, 98%; (v) Tet–SH, K_2CO_3, DMF, 90 °C, 4 h, 100%; (vi) *m*-CPBA, $CHCl_3$, rt, 1 h, 64%.



Scheme 3. Preparation of **8.** (i) Paraformaldehyde, Et_3N, 120 °C, 5 h, 42%; (ii) TsCl, Et_3N, rt, 6 h, 60%; (iii) Tet–SH, K_2CO_3, DMF, 80 °C, overnight, 76%; (iv) *m*-CPBA, $CHCl_3$, rt, 1 h, 89%.

α-(Diethoxyphosphoryl)methyl 5-(1-phenyl)-1*H*-tetrazolyl sulfoxide (**8**) was prepared by following the procedure shown in Scheme 3.

Diethoxyphosphorylmethyl tosylate (**6**) was obtained in 60% yield by the reaction of tosylchloride with the corresponding alcohol prepared by hydroxymethylation with paraformaldehyde starting from phosphonic acid diethyl ether.[4] Sulfide **7** was prepared by the reaction of tosylate **6** with 1-phenyl-5-mercapto-1*H*-tetrazole in the presence of K_2CO_3. The corresponding sulfoxide **8** was obtained similarly as compound **5**.

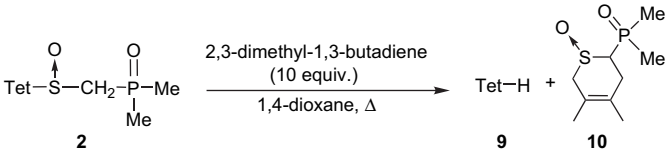
2.2. Thermolyses of 2, 5, and 8 in the presence of 1,3-dimethyl-2,3-butadiene

As mentioned in Section 1, the thermolyses of tetrazolyl phenacyl sulfoxides in the presence of 2,3-dimethyl-1,3-butadiene afforded the thiopyran oxide derivatives in excellent yields, which is considered to be formed by the hetero Diels–Alder reaction of the diene with the corresponding sulfines formed initially.[1b] Therefore, the thermolysis of **2** in the presence of the same diene was studied in 1,4-dioxane at several temperatures. The results are summarized in Table 1. 4,5-Dimethyl-2-(dimethylphosphoryl)-3,6-dihydro-2*H*-thiopyran *S*-oxide (**10**) was expectedly observed to be formed in high yields (entry 1). In the presence of triethylamine, the reaction proceeded more smoothly even at low temperature (entry 2). The thermolyses of **5** and **8** in the presence of the same diene were studied. The results are summarized in Table 2. In the case of entry 1, the thermolysis of **5** at 140 °C for 1 h afforded 4,5-dimethyl-2-(diphenylphosphoryl)-3,6-dihydro-2*H*-thiopyran *S*-oxide (**11**) and tetrazole **9** in almost quantitative yields. After 2 h at the same temperature, **11** and **9** were obtained in 28 and 32% yields, respectively (entry 2). In this case, 3,4-dimethyl-6-(diphenylphosphoryl)-2*H*-thiopyran (**12**) was formed in 27% yield. Compound **12** was considered to be formed by the dehydration of **11**, probably due to the strong acidic nature of hydrogens both at α- and β-position of phosphoryl group. The controlled reaction of **11** in 1,4-dioxane at 140 °C revealed to produce **12** exclusively by the elimination of H_2O as depicted in Scheme 4. When the thermolysis of **5** was carried out in the presence of triethylamine at the same temperature for 1 h, **12** and **9** were obtained in 73 and 37% yields, respectively (entry 3). The formation of **12** from **11** also seems to proceed in a relatively short time. The thermolysis of **8** was carried out at 160 °C. The obtained products were the corresponding cycloadducts 4,5-dimethyl-2-(diethoxyphosphoryl)-3,6-dihydro-2*H*-thiopyran *S*-oxide (**13**) and the successive dehydrated product, i.e., 3,4-dimethyl-6-(diethoxyphosphoryl)-2*H*-thiopyran (**14**) (entry 4).

2.3. Reactions of α-(phosphoryl)methyl sulfoxides 2, 5, and 8 with several amines

It is reported that sulfines reacted with amines to afford the corresponding sulfinamide derivatives;[5] we studied the reactions of **2** with several amines. The results are summarized in Table 3. In all cases, the expected corresponding sulfinamides were not obtained, but unexpected formation of novel phosphinecarbothioamide derivatives were observed.[2]

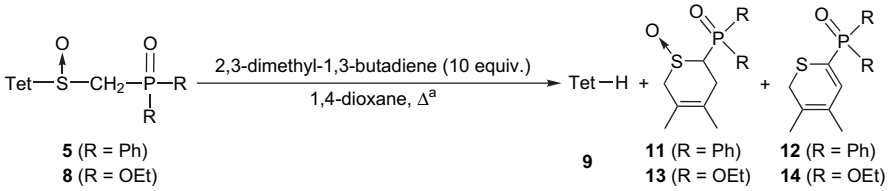
Table 1
Thermolysis of **2** in the presence of 2,3-dimethyl-1,3-butadiene



Entry	Conditions	Yields[a] (%)	
		9	**10**
1	100 °C, 20 h	97	85
2	70 °C, 3 h, Et_3N (1.5 equiv)	99	72

[a] Isolated yields.

Table 2
Thermolyses of **5** and **8** in the presence of 2,3-dimethyl-1,3-butadiene



5 (R = Ph)
8 (R = OEt)

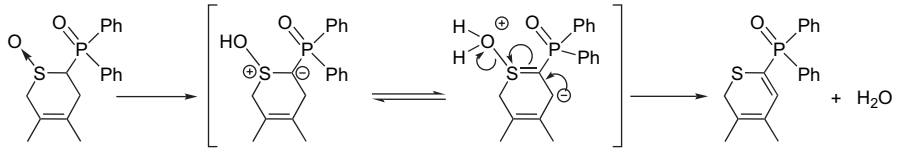
9

11 (R = Ph)
13 (R = OEt)

12 (R = Ph)
14 (R = OEt)

Entry	Sulfoxide	Conditions	Yields[b] (%)		
			9	**11/13**	**12/14**
1	**5**	140 °C, 1 h	99	97	Trace
2	**5**	140 °C, 2 h	32[c]	28	27
3	**5**	140 °C, 1 h, Et_3N (1.5 equiv)	37[c]	0	73
4	**8**	160 °C, 2 h	12[c]	21	58

[a] In sealed tubes.
[b] Isolated yields.
[c] Low yield of **9** is due to the thermal decomposition of **9** itself at the higher temperature.



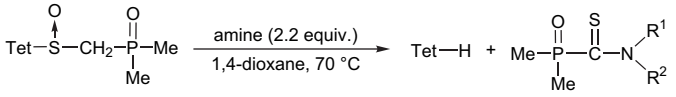
11 **12**

Scheme 4. The probable elimination mechanism for **11** to **12**.

Further, we have prepared the tetrazolyl sulfoxides bearing several similar phosphoryl groups, such as α-(diphenylphosphoryl)- and α-(diethoxyphosphoryl)methyl groups, and studied the reaction in the presence of several amines. The results are summarized in Table 4.

The reactions of **5** with 2.2 equiv of amines in 1,4-dioxane at 90 °C were found to afford the corresponding phosphine-carbothioamide derivatives **16a–e** (entries 1–5). In the case of **8** under similar conditions at 100 °C the corresponding

Table 3
Reaction of **2** with several amines

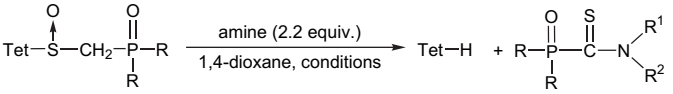


2 **9** **15a-e**

Entry	Amine (2.2 equiv)	Time (h)	Yields[a] (%)	
			9	**15**
1	a, Ph—NH_2	1.5	83	50 (**15a**)
2	b, Ph⌒NH_2	2.5	99	50 (**15b**)
3	c, NH	0.75	99	52 (**15c**)
4	d, O NH	1.0	75	53 (**15d**)
5	e, NH	0.75	82	52 (**15e**)

[a] Isolated yields.

Table 4
Reaction of **5** and **8** with several amines



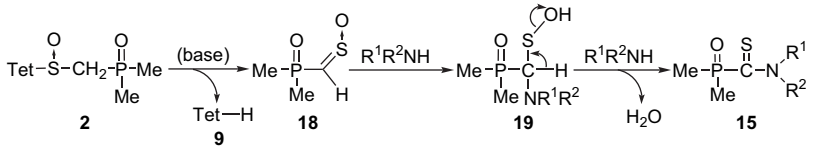
5 R = Ph
8 R = OEt

9

16a-e R = Ph
17a-e R = OEt

Entry	Sulfoxide	Amide	Temp (°C)	Time (h)	Yield[a] (%)	
					9	**16/17**
1	**5**	a, Ph—NH_2	90	12.0	42	42 (**16a**)
2	**5**	b, Ph⌒NH_2	90	1.75	98	49 (**16b**)
3	**5**	c, NH	90	1.5	69	30 (**16c**)
4	**5**	d, O NH	90	2.0	98	44 (**16d**)
5	**5**	e, NH	90	1.0	99	87 (**16e**)
6	**8**	a, Ph—NH_2	100	0.8	42	50 (**17a**)
7	**8**	b, Ph⌒NH_2	100	0.8	98	50 (**17b**)
8	**8**	c, NH	100	0.5	78	47 (**17c**)
9	**8**	d, O NH	100	0.5	75	53 (**17d**)
10	**8**	e, NH	100	0.5	80	57 (**17e**)

[a] Isolated yields.



Scheme 5.

phosphinecarbothioamide derivatives **17a–e** were obtained in almost similar yields (entries 6–10).

In conclusion, the reactions of **2**, **5** and **8** with amines were found to afford novel phosphinecarbothioamides **15–17** in moderate isolated yields. The relatively low yields of **15–17** are probably due to their unstable nature, because the TLC monitoring showed that the reaction proceeded cleanly to afford **9** and **15–17**.

The probable mechanism for the formation of phosphinecarbothioamides **15–17** is shown in Scheme 5 (the scheme was drawn using **2** as the representative of **2**, **5**, and **8**). First, the thermolytic reaction of starting sulfoxides **2**, **5**, and **8** afforded the corresponding sulfines **18**. Successively, the nucleophilic attacking of amines at the oxythiocarbonyl carbon occurred to afford the sulfenic acid intermediate **19**. Finally, the elimination of H_2O from the intermediate leads to the product **15**.

In contrast to our results, it is reported that in the reactions of common sulfines with nucleophiles, attacking of nucleophiles takes place on the partially positive-charged sulfur (thiophilic attack) predominantly. In the case of primary and secondary amines, the products were the corresponding sulfine amides.[6a–d] However, in the reaction of tetrazolyl α-phosphorylmethyl sulfoxides, the sulfines formed initially have a strong electron withdrawing phosphoryl group at α-position probably controlling the reaction pathway of the attack on the carbon (carbophilic attack) to produce phosphinecarbothioamide derivatives. Similar results in the case of chlorosulfines were reported.[7a–d]

3. Conclusion

Several tetrazolyl substituted phosphorylmethyl sulfoxides **2**, **5** and **8** were prepared and their thermolysis and their reactions with amines were examined. In the thermolysis in the presence of 2,3-dimethyl-1,3-butadiene, the hetero Diels–Alder reaction adducts **10**, **11**, and **13** were formed. Compounds **11** and **13** were found to lead to 2*H*-thiopyrane derivatives **12** and **14**. In the reaction of tetrazolyl sulfoxides **2**, **5**, and **8**, the formation of phosphinecarbothioamides **15–17** was considered to be via sulfine, which was formed initially by the elimination of tetrazole due to the high leaving ability.

4. Experimental

4.1. General

All the melting points were uncorrected using micromelting point apparatus. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ using TMS as an internal standard. The elemental analyses were performed at Micro analytical Laboratory of the Department of Material Systems Engineering and Life Science, University of Toyama. All the reactions were monitored with TLC and the products were separated by column chromatography using Silica Gel 60 and also by preparative layer chromatography using Silica Gel 60 PF_{254} with UV detection. All the reagents were of highest quality and further purified by distillation or recrystallization. The solvents were further purified by general method.

4.2. α-(Dimethylphosphoryl)methyl 5-(1-phenyl)-1H-tetrazolyl sulfide (*1*)

To a stirred solution of 1-phenyl-5-mercapto-1*H*-tetrazole (2.0 g, 11.2 mmol) in $CHCl_3$ were added triethylamine (2.34 mL, 16.8 mmol) and chloromethyl(dimethyl)phosphine oxide (2.13 g, 16.8 mmol) at rt. This reaction mixture was stirred for 24 h at 70 °C. After cooling and addition of H_2O, the reaction mixture was extracted with $CHCl_3$. The organic layer was washed with H_2O and dried over anhydrous $MgSO_4$, and then evaporated to give 2.5 g of **1** as colorless oil in 85% yield. This oily product was used for the preparation of **2** without further purification. Spectral data: oil product (without further purification); ^{1}H NMR ($CDCl_3$) δ 1.67 (d, J=12.8 Hz, 6H), 3.80 (d, J=8.0 Hz, 2H), 7.58–7.60 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.1 (d, $^1J_{C-P}$=71.0 Hz), 31.8 (d, $^1J_{C-P}$=70.7 Hz), 123.7, 130.0, 130.5, 133.2, 153.3; IR (KBr): 3700–3100, 1504, 1171 cm^{-1}. HRMS (EI) calcd for $C_{10}H_{13}N_4OPS$: 268.0548; found: *m/z* 268.0550.

4.3. General procedure for the preparation of α-(diphenylphosphoryl)- and α-(diethoxyphosphoryl)-methyl sulfide *4* and *7*

To a stirred solution of **3** or **6** (1.0 mmol) and 1-phenyl-5-mercapto-1*H*-tetrazole (1.2 mmol) in DMF (5.0 mL) was added K_2CO_3 (3.0 mmol) at rt. The reaction mixture was stirred at 90 or 80 °C. After consumption of the starting materials, DMF was evaporated off under reduced pressure. The residue was dissolved in $CHCl_3$ and then the precipitate was filtered off. The organic layer was washed with H_2O and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography on silica gel.

4.3.1. α-(Diphenylphosphoryl)methyl 5-(1-phenyl)-1H-tetrazolyl sulfide (*4*)

Yield 100%; mp 111–113 °C (CH_2Cl_2–AcOEt–hexane); ^{1}H NMR ($CDCl_3$) δ 4.34 (d, J=7.6 Hz, 2H), 7.40–7.58 (m, 11H), 7.78–7.84 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 31.8 (d, $^1J_{C-P}$=66.1 Hz), 123.7, 128.8 (d, $^2J_{C-P}$=12.3 Hz), 129.8, 130.3, 130.3 (d, $^1J_{C-P}$=103.2 Hz), 131.1 (d, $^3J_{C-P}$=9.1 Hz),

132.6 (d, $^4J_{C-P}$=3.37 Hz), 133.1, 153.3; IR (KBr): 1498, 1200, 756, 696 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{17}N_4OPS$: 392.0861; found: *m/z* 392.0879.

4.3.2. α-(Diethoxyphosphoryl)methyl 5-(1-phenyl)-1H-tetrazolyl sulfide (**7**)

Yield 73%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, *J*=6.8 Hz, 6H), 3.76 (d, *J*=6.8 Hz, 2H), 4.13–4.20 (m, 4H), 7.56–7.69 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.3 (d, $^3J_{C-P}$= 6.2 Hz), 26.3 (d, $^1J_{C-P}$=148.1 Hz), 63.2 (d, $^2J_{C-P}$=6.6 Hz), 123.8, 129.9, 130.4, 133.4, 153.2; IR (KBr): 1500, 1392, 1254, 1049, 1022, 972 cm^{-1}. HRMS (EI) calcd for $C_{12}H_{17}O_3N_4PS$: 328.0759; found: *m/z* 328.0722.

4.4. General procedure for the preparation of α-(dimethylphosphoryl)-, α-(diphenylphosphoryl)-, and α-(diethoxyphosphoryl)methyl sulfoxide **2**, **5**, and **8**

To a stirred solution of sulfide (1.0 mmol) in $CHCl_3$ (20 mL) was added *m*-CPBA (1.2 mmol) in $CHCl_3$ (20 mL) at rt. After stirring for 1 or 3 h at rt, the reaction mixture was washed with aqueous saturated solution of $NaHCO_3$ three times. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography on silica gel.

4.4.1. α-(Dimethylphosphoryl)methyl 5-(1-phenyl)-1H-tetrazolyl sulfoxide (**2**)

Spectral data: yield 57%; mp 125–127 °C (CH_2Cl_2–hexane); ^{1}H NMR ($CDCl_3$) δ 1.72 (d, *J*=13.2 Hz, 3H), 1.80 (d, *J*=13.2 Hz, 3H), 4.19–4.31 (m, 2H), 7.59–7.65 (m, 3H), 7.72–7.74 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 18.6 (d, $^1J_{C-P}$= 70.8 Hz), 18.8 (d, $^1J_{C-P}$=70.7 Hz), 53.3 (d, $^1J_{C-P}$=56.0 Hz), 124.9, 130.1, 131.4, 132.7, 156.9; IR (KBr): 1080 cm^{-1}. Anal. Calcd for $C_{10}H_{13}N_4O_2PS$: C, 42.25; H, 4.61; N, 19.71. Found: C, 41.77; H, 4.54; N, 19.61.

4.4.2. α-(Diphenylphosphoryl)methyl 5-(1-phenyl)-1H-tetrazolyl sulfoxide (**5**)

Yield 64%; mp 137–139 °C (CH_2Cl_2–AcOEt–hexane); ^{1}H NMR ($CDCl_3$) δ 4.48 (dd, *J*=14.0, 14.0 Hz, 1H), 5.23 (dd, *J*=8.8, 8.9 Hz, 1H), 7.45–7.68 (m, 11H), 7.71–7.73 (m, 2H), 7.78–7.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 54.2 (d, $^1J_{C-P}$=60.3 Hz), 124.9, 129.0 (d, $^3J_{C-P}$=7.4 Hz), 129.1 (d, $^3J_{C-P}$=8.2 Hz), 129.5 (d, $^1J_{C-P}$=107.3 Hz), 130.0, 130.5 (d, $^1J_{C-P}$=116.5 Hz), 130.7 (d, $^2J_{C-P}$=10.7 Hz), 131.0 (d, $^2J_{C-P}$=9.9 Hz), 131.2, 132.7, 132.96 (d, $^4J_{C-P}$=3.3 Hz), 132.99 (d, $^4J_{C-P}$=3.3 Hz), 157.2 (d, $^3J_{C-P}$=4.92 Hz); IR (KBr): 1497, 1438, 1197, 1121, 1069, 761, 745, 691 cm^{-1}. Anal. Calcd for $C_{20}H_{17}N_4O_2PS$: C, 58.82; H, 4.20; N, 13.72. Found: C, 58.85; H, 4.26; N, 13.73.

4.4.3. α-(Diethoxyphosphoryl)methyl 5-(1-phenyl)-1H-tetrazolyl sulfoxide (**8**)

Yield 89%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.27–1.34 (m, 6H), 3.95 (dt, *J*=0.8, 14.4 Hz, 1H), 4.06–4.20 (m, 4H), 4.59 (dt, *J*=0.8, 14.4 Hz, 1H), 7.60–7.65 (m, 3H), 7.71–7.76 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.1 (d, $^3J_{C-P}$=6.6 Hz), 49.7 (d, $^1J_{C-P}$=136.1 Hz), 63.3 (d, $^2J_{C-P}$=6.6 Hz), 63.5 (d, $^2J_{C-P}$=6.6 Hz), 124.9, 129.9, 131.3, 132.7, 156.9; IR (KBr): 2985, 2910, 1498, 1255, 1043, 1018, 976, 766, 692 cm^{-1}. HRMS (EI) calcd for $C_{12}H_{17}N_4O_4PS$: 344.0708; found: *m/z* 344.0706.

4.5. General procedure for the thermal reaction of sulfoxides **2**, **5**, and **8** in the presence of 2,3-dimethyl-1,3-butadiene

Sulfoxide **2**, **5**, or **8** (0.1 mmol) and 2,3-dimethyl-1,3-butadiene (1.0 mmol) were dissolved in 1,4-dioxane (2.0 mL). The solution was placed and sealed in a Pyrex tube under nitrogen. The reaction was carried out for appropriate reaction time at the applied temperature. The separation and purification of the products were made by preparative thin layer chromatography on silica gel.

4.5.1. 4,5-Dimethyl-2-(dimethylphosphoryl)-3,6-dihydro-2H-thiopyran S-oxide (**10**)

^{1}H NMR ($CDCl_3$) δ 1.72–1.78 (m, 12H), 2.44–2.54 (m, 1H), 2.82 (d, *J*=18.8 Hz, 1H), 3.23–3.29 (m, 1H), 3.49 (d, *J*=15.6 Hz, 1H), 3.69 (dd, *J*=15.2, 15.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9 (d, $^1J_{C-P}$=68.5 Hz), 18.5 (d, $^1J_{C-P}$= 70.3 Hz), 19.0, 19.9, 29.9 (d, $^3J_{C-P}$=1.71 Hz), 56.1 (d, $^2J_{C-P}$= 6.63 Hz), 59.0 (d, $^1J_{C-P}$=63.7 Hz), 118.5, 128.0. HRMS (EI) calcd for $C_9H_{17}O_2PS$: 220.0687; found: *m/z* 220.0676.

4.5.2. 4,5-Dimethyl-2-(diphenylphosphoryl)-3,6-dihydro-2H-thiopyran S-oxide (**11**)

Mp 162–164 °C (CH_2Cl_2–AcOEt–hexane); ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 3H), 1.74 (s, 3H), 2.32–2.41 (m, 1H), 2.74–2.83 (m, 1H), 3.49 (dd, *J*=15.8, 15.6 Hz, 2H), 3.77 (q, *J*=6.8 Hz, 1H), 7.50–7.60 (m, 6H), 7.81–7.91 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.4, 20.1, 27.5 (d, $^3J_{C-P}$=1.6 Hz), 53.4 (d, $^2J_{C-P}$=3.3 Hz), 58.1 (d, $^1J_{C-P}$=64.5 Hz), 118.5, 127.3 (d, $^3J_{C-P}$=6.6 Hz), 128.7 (d, $^3J_{C-P}$=6.6 Hz), 128.8 (d, $^3J_{C-P}$= 6.6 Hz), 130.3 (d, $^1J_{C-P}$=100.8 Hz), 130.9 (d, $^1J_{C-P}$= 101.6 Hz), 131.2 (d, $^2J_{C-P}$=9.1 Hz), 131.5 (d, $^2J_{C-P}$=9.1 Hz), 132.3 (d, $^4J_{C-P}$=3.3 Hz), 132.5 (d, $^4J_{C-P}$=3.3 Hz); IR (KBr): 1198, 1049 cm^{-1}. Anal. Calcd for $C_{19}H_{21}O_2PS$: C, 66.26; H, 6.15. Found: C, 66.57; H, 6.44.

4.5.3. 3,4-Dimethyl-6-(diphenylphosphoryl)-2H-thiopyran (**12**)

Unstably brown crude compound; ^{1}H NMR ($CDCl_3$) δ 1.85 (s, 3H), 1.90 (s, 3H), 3.19 (s, 2H), 6.98 (d, *J*=16.2 Hz, 1H), 7.45–7.58 (m, 6H), 7.79–7.83 (m, 4H). HRMS (EI) calcd for $C_{19}H_{19}OPS$: 326.0894; found: *m/z* 326.0875.

4.5.4. 4,5-Dimethyl-2-(diethoxyphosphoryl)-3,6-dihydro-2H-thiopyran S-oxide (**13**)

Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, *J*=7.07 Hz, 3H), 1.36 (t, *J*=7.03 Hz, 3H), 1.75 (s, 3H), 1.78 (s, 3H), 1.95–2.05 (m, 1H), 2.60–2.71 (m, 1H), 3.38 (d, *J*=16.1 Hz, 1H), 3.66 (d, *J*=16.1 Hz, 1H), 3.87 (dt, *J*=6.79, 6.79 Hz, 1H), 4.11–4.26

(m, 4H); IR (KBr): 3600–3100, 1246, 1022, 970, 773 cm^{-1}. HRMS (EI) calcd for $C_{11}H_{21}O_4PS$: 280.0898; found: *m/z* 280.0912.

4.5.5. 3,4-Dimethyl-6-(diethoxyphosphoryl)-2H-thiopyran (**14**)

Unstably brown oil compound; ^1H NMR ($CDCl_3$) δ 1.28 (t, J=6.79 Hz, 6H), 1.76 (s, 3H), 1.84 (s, 3H), 3.13 (s, 2H), 4.00–4.12 (m, 4H), 6.89 (d, J=18.4 Hz, 1H); IR (KBr): 1246, 1022, 970, 773 cm^{-1}. HRMS (EI) calcd for $C_{11}H_{19}O_3PS$: 262.0793; found: *m/z* 262.0815.

4.6. General procedure for the reaction of sulfoxides **2**, **5**, and **8** with amines

The solution of sulfoxide **2**, **5**, or **8** (0.1 mmol) and amine (0.22 mmol) in 1,4-dioxane (3.0 mL) was stirred for appropriate reaction time at the applied temperatures under nitrogen. The separation and purification of the products were made by preparative thin layer chromatography on silica gel eluting with AcOEt–hexane–$CHCl_3$ complex.

4.6.1. Dimethylphosphorylthioformic acid anilide (**15a**)

Mp 139–147 °C (dec) (yellow crystal from CH_2Cl_2–AcOEt–hexane); ^1H NMR ($CDCl_3$) δ 1.81 (d, J=28.4 Hz, 6H), 7.32 (t, J=7.6 Hz, 1H), 7.44 (t, J=7.6 Hz, 2H), 8.75 (d, J=7.6 Hz, 2H), 10.75 (br, 1H); ^{13}C NMR ($CDCl_3$) δ15.7 (d, $^1J_{C-P}$=74 Hz), 121.5, 127.5, 129.1, 138.2 (d, $^3J_{C-P}$=11.5 Hz), 197.0 (d, $^1J_{C-P}$=85.5 Hz); IR (KBr): 3700–2800, 1180 cm^{-1}. Anal. Calcd for $C_9H_{12}NOPS$: C, 50.70; H, 5.67; N, 6.57. Found: C, 50.71; H, 5.73; N, 6.57.

4.6.2. Dimethylphosphorylthioformic acid benzylamide (**15b**)

Mp 100–101 °C (yellow crystal from CH_2Cl_2–AcOEt–hexane); ^1H NMR ($CDCl_3$) δ 1.77 (d, J=15 Hz, 6H), 4.88 (d, J=1.6 Hz, 2H), 7.32–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.9 (d, $^1J_{C-P}$=74.1 Hz), 49.4 (d, $^3J_{C-P}$=5.8 Hz), 128.2, 128.4, 128.9, 135.2, 199.9 ($^1J_{C-P}$=83.9 Hz); IR (KBr): 3700–2900, 1170 cm^{-1}. Anal. Calcd for $C_{10}H_{14}NOPS$: C, 52.85; H, 6.21; N, 6.16. Found: C, 52.78; H, 6.24; N, 6.09.

4.6.3. Dimethylphosphorylthioformic acid piperidide (**15c**)

Mp 62–63 °C (yellow crystal from CH_2Cl_2–AcOEt–hexane); ^1H NMR ($CDCl_3$) δ 1.76 (br s, 6H), 1.91 (d, J=13.2 Hz, 6H), 4.20 (br s, 2H), 4.60 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 19.3 (d, $^1J_{C-P}$=78.1 Hz), 24.2, 25.6, 27.6, 51.8 (d, $^3J_{C-P}$=2.5 Hz), 52.5 (d, $^3J_{C-P}$=4.1 Hz), 197.3 ($^1J_{C-P}$=82.3 Hz); IR (KBr): 2944, 1483, 1442, 1247, 1179, 1110, 869 cm^{-1}. Anal. Calcd for $C_8H_{16}NOPS$: C, 46.81; H, 7.86; N, 6.82. Found: C, 46.72; H, 7.63; N, 6.79. HRMS (EI) calcd for $C_8H_{16}NOPS$: 205.0690; found: *m/z* 205.0684.

4.6.4. Dimethylphosphorylthioformic acid morpholide (**15d**)

Mp 87–88 °C (pale yellow crystal from CH_2Cl_2–AcOEt–hexane); ^1H NMR ($CDCl_3$) δ 1.95 (d, J=13.6 Hz, 6H), 3.80 (t, J=5.2 Hz, 2H), 3.84 (t, J=5.2 Hz, 2H), 4.30 (t, J=4.8 Hz, 2H), 4.70 (t, J=4.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.3 (d, $^1J_{C-P}$=78.2 Hz), 50.4 (d, $^3J_{C-P}$=2.4 Hz), 51.9 (d, $^3J_{C-P}$=3.3 Hz), 66.5, 67.4, 199.0 (d, $^1J_{C-P}$=81.4 Hz); IR (KBr): 1480, 1267, 1236, 1162, 1152, 1038 cm^{-1}; Anal. Calcd for $C_7H_{14}NO_2PS$: C, 40.57; H, 6.81; N, 6.76. Found: C, 40.73; H, 6.71; N, 6.60.

4.6.5. Dimethylphosphorylthioformic acid pyrrolidide (**15e**)

Mp 153–155 °C (yellow crystal from CH_2Cl_2–AcOEt–hexane); ^1H NMR ($CDCl_3$) δ 1.91 (d, J=13.6 Hz, 6H), 1.94–2.00 (m, 2H), 2.06–2.13 (m, 2H), 3.86–3.90 (m, 2H), 4.29–4.33 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 18.4 (d, $^1J_{C-P}$=76.5 Hz), 22.8, 28.9, 52.7, 55.4; IR (KBr): 1474, 1441, 1292, 1178, 1153, 1023, 933, 875 cm^{-1}. HRMS (EI) calcd for $C_7H_{14}NOPS$: 191.0534; found: *m/z* 191.0518.

4.6.6. Diphenylphosphorylthioformic acid anilide (**16a**)

Mp 161–162 °C (yellow crystal from CH_2Cl_2–AcOEt–hexane); ^1H NMR ($CDCl_3$) δ 7.30 (t, J=6.7 Hz, 1H), 7.43 (t, J=8.0 Hz, 2H), 7.47–7.52 (m, 4H), 7.60 (t, J=7.4 Hz, 2H), 7.99–8.04 (m, 4H), 8.09 (d, J=8.4 Hz, 2H), 11.18 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 121.6, 127.4, 128.4 (d, $^2J_{C-P}$=13.3 Hz), 129.0 (d, $^1J_{C-P}$=108.1 Hz), 129.1, 132.7 (d, $^4J_{C-P}$=3.3 Hz), 132.9 (d, $^3J_{C-P}$=9.9 Hz), 138.4 (d, $^2J_{C-P}$=11.5 Hz), 194.0 (d, $^1J_{C-P}$=89.2 Hz); IR (KBr): 2800–3300, 1172, 1116 cm^{-1}. Anal. Calcd for $C_{19}H_{16}NOPS$: C, 67.64; H, 4.78; N, 4.15. Found: C, 67.81; H, 5.09; N, 4.28.

4.6.7. Diphenylphosphorylthioformic acid benzylamide (**16b**)

Mp 164–166 °C (pale yellow crystal from CH_2Cl_2–AcOEt–hexane); ^1H NMR ($CDCl_3$) δ 4.91–4.93 (m, 2H), 7.26–7.38 (m, 5H), 7.46–7.51 (m, 4H), 7.57–7.60 (m, 2H), 7.96–8.01 (m, 4H), 9.82 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 49.5 (d, $^1J_{C-P}$=5.8 Hz), 128.29, 128.30, 128.4 (d, $^3J_{C-P}$=5.8 Hz), 129.0, 129.2 (d, $^1J_{C-P}$=108.1 Hz), 132.6, 132.7 (d, $^3J_{C-P}$=9.9 Hz), 135.1, 197.1 ($^1J_{C-P}$=86.7 Hz); IR (KBr): 2900–3350, 1168, 1123 cm^{-1}. Anal. Calcd for $C_{20}H_{18}NOPS$: C, 68.36; H, 5.16; N, 3.99. Found: C, 68.35; H, 5.18; N, 3.89.

4.6.8. Diphenylphosphorylthioformic acid piperidide (**16c**)

Mp 153–154 °C (yellow crystal from CH_2Cl_2–AcOEt–hexane); ^1H NMR ($CDCl_3$) δ 1.40–1.43 (m, 2H), 1.67–1.71 (m, 4H), 4.21 (t, J=5.6 Hz, 2H), 4.36 (t, J=5.6 Hz, 2H), 7.45–7.57 (m, 6H), 7.81–7.86 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 24.1, 25.6, 26.7, 51.8 (d, $^3J_{C-P}$=2.9 Hz), 53.7 (d, $^3J_{C-P}$=4.2 Hz), 128.2 (d, $^2J_{C-P}$=12.3 Hz), 131.88 (d, $^1J_{C-P}$ d,=109.8 Hz), 131.95 (d, $^3J_{C-P}$=9.0 Hz), 131.97, 194.5 (d, $^1J_{C-P}$=91.8 Hz); IR (KBr): 1186, 1117 cm^{-1}. Anal. Calcd for $C_{18}H_{20}NOPS$: C, 65.63; H, 6.12; N, 4.25. Found: C, 65.47; H, 6.14; N, 4.03.

4.6.9. Diphenylphosphorylthioformic acid morpholide (**16d**)

Mp 165–167 °C (yellow crystal from CH_2Cl_2–AcOEt–hexane), lit. mp 150–151 °C;[5] ^1H NMR ($CDCl_3$) δ 3.55 (t, J=4.8 Hz, 2H), 3.79 (t, J=4.8 Hz, 2H), 4.30 (t, J=4.8 Hz, 2H), 4.48 (t, J=4.8 Hz, 2H), 7.26–7.51 (m, 4H), 7.55–7.59 (m, 2H), 7.81–7.86 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 50.4 (d,

$^{3}J_{C-P}$=2.9 Hz), 52.9 (d, $^{3}J_{C-P}$=3.9 Hz), 66.5, 66.9, 128.3 (d, $^{2}J_{C-P}$=12.4 Hz), 131.3 (d, $^{1}J_{C-P}$=110.1 Hz), 132.0 (d, $^{3}J_{C-P}$=9.0 Hz), 132.2 (d, $^{4}J_{C-P}$=3.3 Hz), 196.3 (d, $^{1}J_{C-P}$= 88.8 Hz); IR (KBr): 1183, 1173, 1109 cm^{-1}. Anal. Calcd for $C_{17}H_{18}NO_2PS$: C, 61.62; H, 5.47; N, 4.23. Found: C, 61.57; H, 5.49; N, 4.05.

4.6.10. Diphenylphosphorylthioformic acid pyrrolidide (**16e**)

Mp 153–155 °C (yellow crystal from CH_2Cl_2–AcOEt–hexane); ^{1}H NMR ($CDCl_3$) δ 1.91–2.03 (m, 4H), 3.84–3.91 (m, 2H), 4.12–4.15 (m, 2H), 7.45–7.49 (m, 4H), 7.53–7.57 (m, 2H), 7.83–7.89 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 22.9, 26.6, 52.7 (d, $^{3}J_{C-P}$=2.5 Hz), 55.4 (d, $^{3}J_{C-P}$=3.3 Hz), 128.2 (d, $^{2}J_{C-P}$=12.3 Hz), 131.1 (d, $^{1}J_{C-P}$=109.0 Hz), 132.1 (d, $^{4}J_{C-P}$=2.4 Hz), 132.2 (d, $^{3}J_{C-P}$=9.0 Hz), 192.1 (d, $^{1}J_{C-P}$= 88.5 Hz); IR (KBr): 1193, 1182, 1115, 1101 cm^{-1}. Anal. Calcd for $C_{17}H_{18}NOPS$: C, 64.75; H, 5.75; N, 4.44. Found: C, 64.85; H, 5.78; N, 4.32.

4.6.11. Diethoxyphosphorylthioformic acid anilide (**17a**)

Yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.40 (dt, J=0.8, 7.2 Hz, 6H), 4.22–4.34 (m, 4H), 7.29–7.32 (m, 1H), 7.44 (t, J=8.0 Hz, 2H), 7.98 (d, J=8.1 Hz, 2H), 10.57 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 16.1 (d, $^{3}J_{C-P}$=6.6 Hz), 65.3 (d, $^{2}J_{C-P}$= 7.4 Hz), 122.0, 127.4, 129.0, 138.0 (d, $^{3}J_{C-P}$=14.9 Hz), 190.6 (d, $^{1}J_{C-P}$=181.7 Hz); IR (KBr): 3400–2900, 1360, 1230 cm^{-1}. HRMS (EI) calcd for $C_{11}H_{16}NO_3PS$: 273.0589; found: *m/z* 273.0618.

4.6.12. Diethoxyphosphorylthioformic acid benzylamide (**17b**)

Mp 75–77 °C (pale yellow crystal from CH_2Cl_2–AcOEt–hexane); ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J=7.2 Hz, 6H), 4.17–4.33 (m, 4H), 4.85 (dd, J=2.0, 5.6 Hz, 2H), 7.31–7.39 (m, 5H), 9.19 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, $^{3}J_{C-P}$= 6.6 Hz), 49.3 (d, $^{3}J_{C-P}$=8.2 Hz), 65.1 (d, $^{2}J_{C-P}$=7.4 Hz), 128.3, 128.4, 129.0, 135.0, 193.2 (d, $^{1}J_{C-P}$=180.2 Hz); IR (KBr): 3340–2850, 1520, 1500, 1394, 1250, 1050 cm^{-1}. Anal. Calcd for $C_{12}H_{18}NO_3PS$: C, 50.16; H, 6.31; N, 4.87. Found: C, 50.31; H, 6.18; N, 4.85.

4.6.13. Diethoxyphosphorylthioformic acid piperidide (**17c**)

Yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J=7.2 Hz, 6H), 1.75 (br, 6H), 4.16–4.37 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, $^{3}J_{C-P}$=6.5 Hz), 24.2, 25.4, 26.9, 50.6 (d, $^{3}J_{C-P}$=6.6 Hz), 54.6 (d, $^{3}J_{C-P}$=4.1 Hz), 64.2 (d, $^{2}J_{C-P}$=8.2 Hz), 190.3 (d, $^{1}J_{C-P}$=188.3 Hz); IR (KBr): 3700–3200, 3100–2800, 1438, 1240, 1086 cm^{-1}. HRMS (EI) calcd for $C_{10}H_{20}NO_3PS$: 265.0902; found: *m/z* 265.0882.

4.6.14. Diethoxyphosphorylthioformic acid morpholide (**17d**)

Yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.39 (dt, J=0.8, 7.2 Hz, 6H), 3.78–3.82 (m, 4H), 4.23–4.35 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, $^{3}J_{C-P}$=6.6 Hz), 49.3 (d, $^{3}J_{C-P}$=6.5 Hz), 53.8 (d, $^{3}J_{C-P}$=3.3 Hz), 64.5 (d, $^{2}J_{C-P}$=7.4 Hz), 66.4, 66.9, 191.9 (d, $^{1}J_{C-P}$=187.6 Hz); IR (KBr): 3700–2800, 1478, 1437, 1253, 1120, 1065, 1030 cm^{-1}. HRMS (EI) calcd for $C_9H_{18}NO_4PS$: 267.0694; found: *m/z* 267.0705.

4.6.15. Diethoxyphosphorylthioformic acid pyrrolidide (**17e**)

Yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.37 (dt, J=0.8, 7.2 Hz, 6H), 1.97–2.12 (m, 4H), 3.81–3.85 (m, 2H), 4.07–4.11 (m, 2H), 4.23–4.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, $^{3}J_{C-P}$=6.6 Hz), 23.4, 26.5, 53.2 (d, $^{3}J_{C-P}$=1.6 Hz), 54.3 (d, $^{3}J_{C-P}$=6.6 Hz), 64.3 (d, $^{2}J_{C-P}$=7.4 Hz), 191.9 (d, $^{1}J_{C-P}$= 187.6 Hz); IR (KBr): 3700–2700, 1450, 1250, 1168, 1062, 1030, 980 cm^{-1}. HRMS (EI) calcd for $C_9H_{18}NO_3PS$: 251.0745; found: *m/z* 251.0744.

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