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# A Convenient Procedure for Introducing Arylsulfanyl and Heterylsulfanyl Groups into the 5 Position of the Oxazole Ring

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**Abstract** — Available (2-aryl-5-mesyl-1,3-oxazol-5-yl)triphenylphosphonium salts readily react with sodium thiophenolates and their heterocyclic analogs by way of substitution of the mesyl group by an arylsulfanyl or a heterylsulfanyl group. Treatment of the products with sodium hydroxide results in their mild dephosphorylation, which was used for preparative synthesis of a series of 2-aryl-5-arylsulfanyl(heterylsulfanyl)-1,3-oxazoles.

Previously we found that substituted vinylphosphonium salts of the general formula $Cl_2C{=}C^{+}\cdot(NHCOR)PPh_3An^{-}$ regioselectively react with sodium sulfide to form stable mesomeric ylide betaines **I** and used the latter to success for preparing a series of 5-alkylsulfanyl-2-R-1,3-oxazoles [1–3]. In the present work, as seen from the scheme below, we studied the conversions of ylide betaines **I**, leading not only to S-methylation products **II**, but also to substituted oxazoles **III**–**VII**. The most important of the products were found to be new available reagents **III** containing adjacent mesyl and triphenylphosphonium groups in the oxazole ring. They readily and selectively reacted with sodium thiophenolates or their heterocyclic analogs, and this reaction proved to be a key step in the synthetic sequence **III** → **V** → **VI** → **VII**. As a result, we could introduce into the 5 position of the oxazole ring four types of sulfur-containing groups: ArS, HtS, $ArSO_2$, and $HtSO_2$. Furthermore, the 4-$Ph_3P^+$ group could be replaced by hydrogen. The application scope of this convenient synthetic approach to 5-mercapto-1,3-oxazole derivatives is not restricted by the examples in the scheme below, since each of the steps of the sequence **I** → **II** → **III** → **V** is obviously rather general in nature. Moreover, this approach, even though it involves many steps, offers advantages over other known syntheses of a few representatives of phosphonium salts **V**, such as condensation of reagent **IV** and its analogs with thiols [3, 4] or reaction of ylide betaines **I** with arenediazonium salts [3]. The latter method has a fairly narrow field of uses and, in addition, is insufficiently selective. The condensation **IV** → **V** occurs much more selectively, but the chlorination of ylide betaines **I** is complicated [3, 4] and fails to provide isolable (2-aryl-5-chloro-1,3-oxazol-4-yl)triphenylphosphonium chlorides. Therefore, in the synthesis of phosphonium salts **V**, we considered it expedient to replace them by the available and analytically pure reagents **III**.

In summary it can be said that the assignment of compounds **I**–**VIII** to 1,3-dioxazole derivatives casts no doubts, since the structure of one of the first members of the series of ylide betaines **I** with R = H, as well as its reaction product with methyl iodide was rigorously proved by X-ray diffraction analysis [5]. Moreover, successive treatment of ylide betaine **Ia** with hydrogen peroxide and sodium hydroxide gave 2-phenyl-1,3-dioxazole which was also synthesized by independent methods [2]. In addition, the modification of the 5-substituent was followed, as seen from Table 1, by $^1$H NMR spectroscopy which gave evidence for the conversion of the methylsulfanyl group into mesyl in the course of the nucleophilic substitution reaction **II** → **V** and the elimination of the triphenylphosphonium group by the alkaline cleavage **V** → **VI**. It is interesting that related phosphonium salts **V** and **VII** differently react with alkalis. In the first case, the major process is C–P bond cleavage and in the second, dephosphorylation is attended with C–S bond cleavage. Therefore, 5-arylsulfonyl-2-R-1,3-oxazoles should be prepared using the sequence **V** → **VI** → **VII**.

## EXPERIMENTAL

The IR spectra were obtained on a Specord M-80 instrument in KBr pellets. The 1H NMR spectra were measured on a Varian VXR-300 spectrometer in $CDCl_3$ or $(CD_3)_2SO$, internal reference TMS (Table 1).

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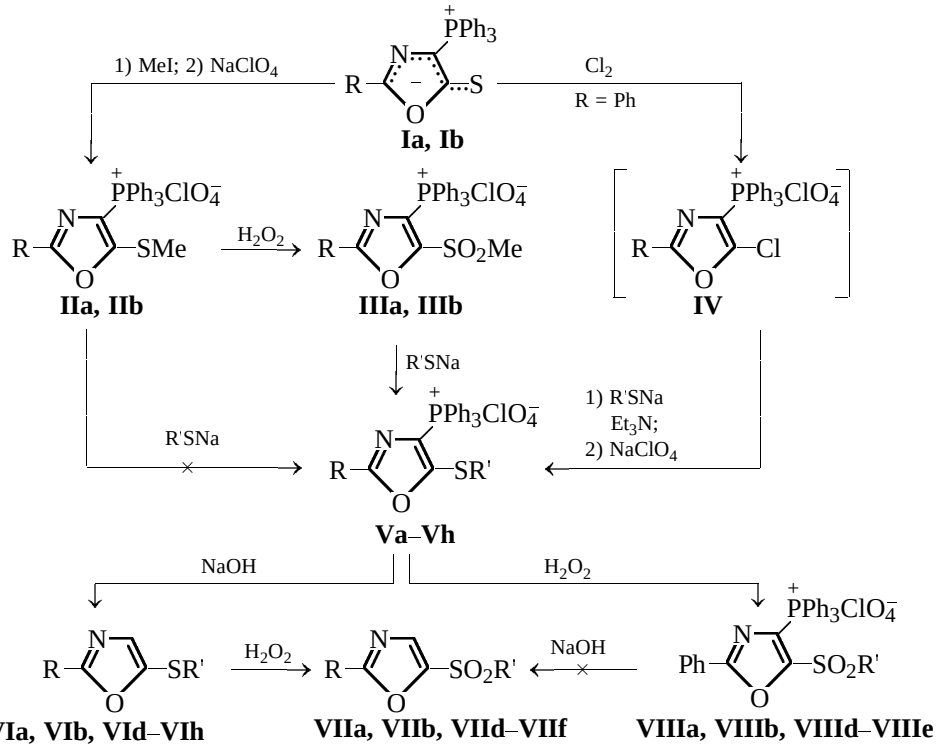


R = $C_6H_5$ (**Ia**–**IIIa, Va, Vc, VIa**–**VIIIa**), 4-$CH_3C_6H_4$ (**Ib**–**IIIb, Vb, Vd**–**Vh, VIb, VId**–**VIg, VIIb, VIId**–**VIIf, VIIIe, VIIIg**); R' = $C_6H_5$ (**Vb**–**VIIb**), 4-$ClC_6H_4$ (**Va, Vd**–**VIIa, VIId, VIIIa**), 4-$CH_3C_6H_4$ (**Vc, Ve, VIe**–**VIIIe**), benzotriazol-2-yl (**Vf**–**VIIf**), 5-(4-bromophenyl)-1,2,4-triazol-3-yl (**Vg, VIg, VIIIg**), 4-hydroxy-6-methylpyrimidin-2-yl (**Vh, VIh**).

**Table 1.** $^1$H NMR spectra of the synthesized compounds

| Comp. no. | δ, ppm ($CDCl_3$) |
|---|---|
| **IIa** | 2.63 s (3H, $CH_3S$), 7.56–8.10 m (20H, $4C_6H_5$) |
| **IIIa** | 3.35 s (3H, $CH_3SO_2$), 7.65–8.12 m (20H, $4C_6H_5$) |
| **IIIb** | 2.46 s (3H, $CH_3$), 3.34 s (3H, $CH_3SO_2$), 7.42–8.15 m (19H, $3C_6H_5$, $C_6H_4$) |
| **Vb** | 2.42 s (3H, $CH_3$), 7.25–7.96 m (24H, $4C_6H_5$, $C_6H_4$) |
| **Vd** | 2.41 s (3H, $CH_3$), 7.26–7.94 m (23H, $3C_6H_5$, $2C_6H_4$) |
| **Ve** | 2.34 s (3H, $CH_3$), 2.41 s (3H, $CH_3$), 7.20–8.05 m (23H, $3C_6H_5$, $2C_6H_4$) |
| **Vf** | 2.43 s (3H, $CH_3$), 7.27–8.02 m (23H, $3C_6H_5$, $2C_6H_4$) |
| **Vg** | 2.41 s (3H, $CH_3$), 7.29–7.95 m (24H, $3C_6H_5$, $2C_6H_4$, NH) |
| **Vh** | 2.31 s (3H, $CH_3$), 3.41 s (3H, $CH_3$), 7.27–7.96 m (21H, $3C_6H_5$, CH)[a] |
| **VIa** | 7.22–8.09 m (9H, $C_6H_5$, $C_6H_4$), 7.49 s (1H, $C^4$–H) |
| **VIb** | 2.40 s (3H, $CH_3$), 7.21–7.93 m (9H, $C_6H_5$, $C_6H_4$), 7.45 s (1H, $C^4$–H) |
| **VId** | 2.40 s (3H, $CH_3$), 7.20–7.95 m (8H, $2C_6H_4$), 7.45 s (1H, $C^4$–H) |
| **VIe** | 2.31 s (3H, $CH_3$), 2.40 s (3H, $CH_3$), 7.10–7.92 m (8H, $2C_6H_4$), 7.40 s (1H, $C^4$–H) |
| **VIf** | 2.45 s (3H, $CH_3$), 7.26–8.10 m (8H, $2C_6H_4$), 7.67 s (1H, $C^4$–H) |
| **VIg** | 2.44 s (3H, $CH_3$), 3.26 s (3H, $CH_3$), 7.33 d, 8.00 d (4H, $C_6H_4$), 7.26 s, 7.81 s (2H, CH, $C^4$–H)[a] |
| **VIIa** | 7.45–8.05 m (9H, $C_6H_5$, $C_6H_4$), 7.85 s (1H, $C^4$–H) |
| **VIIb** | 2.41 s (3H, $CH_3$), 7.27–8.12 m (9H, $C_6H_5$, $C_6H_4$), 7.83 s (1H, $C^4$–H) |
| **VIId** | 2.42 s (3H, $CH_3$), 7.26–8.14 m (8H, $2C_6H_4$), 7.83 s (1H, $C^4$–H) |
| **VIIe** | 2.41 s (3H, $CH_3$), 2.44 s (3H, $CH_3$), 7.26–7.92 m (8H, $2C_6H_4$), 7.79 s (1H, $C^4$–H) |
| **VIIf** | 2.41 s (3H, $CH_3$), 7.26–8.24 m (8H, $2C_6H_4$), 8.08 s (1H, $C^4$–H) |
| **VIIIe** | 2.44 s (3H, $CH_3$), 2.46 s (3H, $CH_3$), 7.27–7.98 m (23H, $3C_6H_5$, $2C_6H_4$) |

[a] Signal of the N–H proton was not found.

**Table 2.** Constants, yields, and elemental analyses of phosphorylated oxazoles **II, III, V**, and **VIII**

| Comp. no. | Yield, % | mp, °C[a] | Found, % | | | Formula | Calculated, % | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Cl | P | S | | Cl | P | S |
| **IIa** | 95 | 234–235 | 6.33 | 5.52 | 5.68 | $C_{28}H_{23}ClNO_5PS$ | 6.42 | 5.61 | 5.81 |
| **IIb** | 97 | 195–198 | 6.15 | 5.35 | 5.56 | $C_{29}H_{25}ClNO_5PS$ | 6.26 | 5.46 | 5.66 |
| **IIIa** | 90 | 242–244 | 5.94 | 5.22 | 5.39 | $C_{28}H_{23}ClNO_7PS$ | 6.07 | 5.30 | 5.49 |
| **IIIb** | 88 | 220–221 | 5.79 | 5.09 | 5.28 | $C_{29}H_{25}ClNO_7PS$ | 5.93 | 5.19 | 5.37 |
| **Va** | 73 | 169–171 | 10.85 | 4.63 | 4.89 | $C_{33}H_{24}Cl_2NO_5PS$ | 10.93 | 4.78 | 4.94 |
| **Vb** | 75 | 180–182 | 5.49 | 4.80 | 5.05 | $C_{34}H_{27}ClNO_5PS$ | 5.64 | 4.93 | 5.11 |
| **Vc** | 70 | 151–152 | 5.53 | 4.83 | 5.02 | $C_{34}H_{27}ClNO_5PS$ | 5.64 | 4.93 | 5.11 |
| **Vd** | 71 | 182–184 | 10.31 | 4.57 | 4.75 | $C_{34}H_{26}Cl_2NO_5PS$ | 10.70 | 4.66 | 4.84 |
| **Ve** | 78 | 150–152 | 5.49 | 4.68 | 4.81 | $C_{35}H_{29}ClNO_5PS$ | 5.52 | 4.82 | 4.99 |
| **Vf** | 83 | 162–163 | 5.06 | 4.40 | 9.25 | $C_{35}H_{26}ClN_2O_5PS_2$ | 5.17 | 4.52 | 9.36 |
| **Vg** | 64 | 196–198 | 4.37 | 3.89 | 4.02 | $C_{36}H_{27}BrClN_4O_5PS$ | 4.58 | 4.00 | 4.14 |
| **Vh** | 66 | 245–246 (decomp.) | 5.26 | 4.52 | 4.77 | $C_{33}H_{27}N_3O_6PS$ | 5.37 | 4.69 | 4.86 |
| **VIIIa** | 78 | 151–152 | 10.24 | 4.39 | 4.62 | $C_{33}H_{24}Cl_2NO_7PS$ | 10.42 | 4.52 | 4.71 |
| **VIIIe** | 75 | 150–152 | 5.12 | 4.49 | 4.65 | $C_{35}H_{29}ClNO_7PS$ | 5.26 | 4.59 | 4.76 |
| **VIIIg** | 60 | 251–253 | 4.32 | 3.60 | 3.92 | $C_{36}H_{27}BrClN_4O_7PS$ | 4.40 | 3.84 | 3.98 |

[a] After recrystallization from methanol.

**Table 3.** Constants, yield, and elemental analyses of substituted oxazoles **VI** and **VII**

| Comp. no. | Yield, % | mp, °C[a] | Found, % | | Formula | Calculated, % | |
|---|---|---|---|---|---|---|---|
| | | | N | S | | N | S |
| **VIa** | 84 | 63–64 | 4.72 | 11.03 | $C_{15}H_{10}ClNOS$[b] | 4.87 | 14.14 |
| **VIb** | 80 | 76–78 | 5.18 | 12.02 | $C_{16}H_{13}NOS$ | 5.24 | 11.99 |
| **VId** | 83 | 78–80 | 4.61 | 10.70 | $C_{16}H_{12}ClNOS$[c] | 4.64 | 10.62 |
| **VIe** | 75 | 92–93 | 4.89 | 11.38 | $C_{17}H_{15}NOS$ | 4.98 | 11.40 |
| **VIf** | 60 | 136–137 | 8.62 | 19.67 | $C_{17}H_{12}N_2OS_2$ | 8.63 | 19.77 |
| **VIg** | 91 | 195–196 | 7.68 | 13.60 | $C_{18}H_{13}BrN_4OS$[d] | 7.76 | 13.56 |
| **VIh** | 65 | 270–271 (decomp.) | 14.14 | 10.82 | $C_{15}H_{13}N_3O_2S$ | 14.04 | 10.71 |
| **VIIa** | 71 | 152–154 | 4.29 | 9.94 | $C_{15}H_{10}ClNO_3S$[e] | 4.38 | 10.03 |
| **VIIb** | 70 | 160–161 | 4.64 | 10.63 | $C_{16}H_{13}NO_3S$ | 4.68 | 10.71 |
| **VIId** | 68 | 169–170 | 4.05 | 9.49 | $C_{16}H_{12}ClNO_3S$ | 4.20 | 9.61 |
| **VIIe** | 60 | 126–127 | 4.34 | 10.15 | $C_{17}H_{15}NO_3S$ | 4.46 | 10.23 |
| **VIIf** | 75 | 170–171 | 7.78 | 17.81 | $C_{17}H_{12}N_2O_3S_2$ | 7.86 | 17.99 |

[a] After recrystallization from methanol. [b] Found Cl, %: 12.26. Calculated Cl, %: 12.32. [c] Found Cl, %: 11.66. Calculated Cl, %: 11.74. [d] Found Br, %: 19.18. Calculated Br, %: 19.33. [e] Found Cl, %: 11.02. Calculated Cl, %: 11.09. [f] Found Cl, %: 10.54. Calculated Cl, %: 10.62.

The constants, yields, and elemental analyses of newly synthesized compounds are given in Tables 2 and 3.

2-Aryl-4-(triphenylphosphonio)-1,3-oxazole-5-thiolates **Ia** and **Ib** were prepared as described in [2].

**[5-(Methylsulfanyl)-2-aryl-1,3-oxazol-4-yl]triphenylphosphonium perchlorates IIa and IIb.** Methyl iodide, 0.03 mol, was added to a suspension of 0.01 mol of compound **Ia** or **Ib** in 30 ml of methanol, the mixture was heated at 35–40°C for 5 min until the precipitate had dissolved completely and cooled to 20–25°C, after which 5 ml of saturated aqueous sodium perchlorate and 10 ml of water were added. The precipitate was filtered off and washed with water. Compounds **IIa** and **IIb** were purified by recrystallization.

**(2-Aryl-5-mesyl-1,3-oxazol-4-yl)triphenylphosphonium perchlorates IIIa and IIIb.** Hydrogen peroxide, 30 ml of 30% aqueous solution, was added over the course of 0.5 h to a solution of 0.01 mol of compound **IIa** or **IIb** in 20 ml of glacial acetic acid, heated to 100°C. The mixture was refluxed for 2 h and cooled to 20–25°C, after which 10 ml of saturated aqueous sodium perchlorate and 20 ml of water were added. The precipitate was filtered off and washed with water. Compounds **IIIa** and **IIIb** were purified by recrystallization.

**[5-Arylsulfanyl(heterylsulfanyl)-2-phenyl(*p*-tolyl)-1,3-oxazol-4-yl)triphenylphosphonium perchlorates Va–Vh.** *a*. Sodium (arylsulfanyl)phenolate or its heteryl analog, 0.0011 mol, was added to a suspension of 0.001 mol of phosphonium salt **IIIa** or **IIIb** in 10 ml of absolute methanol. The mixture was stirred at 20–25°C for 48 h, the precipitate that formed was filtered off, and compounds **Va**–**Vh** were purified by recrystallization. Compound **Vh**: IR spectrum, $\nu$, $cm^{-1}$: 1655 (C=O), 3000–3130 (NH assoc.)

*b*. *p*-Thiocresol, 0.0021 mol, and 1 ml of pyridine were added to a suspension of 0.002 mol of phosphonium salt **IIIb** in 15 ml of dry dioxane. The mixture was refluxed for 8 h and, after addition of 3 ml of 30% aqueous sodium perchlorate, allowed to stand for 12 h. The precipitate was filtered off, washed with water and methanol, and dried at 100°C in an oil-pump vacuum. Compound **Ve**: yield 65–68%, mp 150–152°C (from methanol). Mixed sample of compound **Ve** prepared by procedures *a* and *b* gave no melting point depression.

**5-Arylsulfanyl(heterylsulfanyl)-2-phenyl(*p*-tolyl)-1,3-oxazoles VIa, Vb, and Vd–Vg.** Saturated aqueous sodium hydroxide, 0.5 ml, was added to a suspension of 0.001mol of phosphonium salt **Va**, **Vb**, or **Vd**–**Vg** in 5 ml of methanol. The mixture was refluxed for 10 min, and the precipitate that formed was filtered off. The products were purified by recrystallization. Compound **VIh**: IR spectrum, $\nu$, $cm^{-1}$: 1660 (C=O), 3050–3150 (NH assoc.)

**5-Arylsulfonyl-2-phenyl(*p*-tolyl)-1,3-oxazoles VIIa, VIIb, VIId, and VIIe.** Hydrogen peroxide, 30 ml of 30% aqueous solution, was added in three portions over the course of 3 h to a solution of 0.001 mol of compound **VIa**, **VIb**, **VId**, or **VIe** in 10 ml of glacial acetic acid, heated to 100°C. The mixture was cooled to 20–25°C and diluted with 5 ml of water. The precipitate that formed was filtered off and recrystallized.

**(5-Benzothiazol-2-yl)sulfonyl-2-*p*-tolyl-1,3-oxazole (VIIf)** was prepared from compound **VIf** as described above.

**[5-Arylsulfonyl-2-phenyl(*p*-tolyl)-1,3-oxazol-4-yl)triphenylphosphonium perchlorates VIIIa and VIIIe** were prepared like compounds **IIIa** and **IIIb** by oxidation of phosphonium salts **Va** and **Vb** with hydrogen peroxide.

**[[5-(4-Bromophenyl)-1,2,4-triazol-3-yl]sulfonyl-2-*p*-tolyl-1,3-oxazol-4-yl]triphenylphosphonium perchlorate (VIIIg)** was prepared like compounds **IIIa** and **IIIb** from phosphonium salt **Vg**. IR spectrum, $\nu$, $cm^{-1}$: 3050–3150 (NH assoc.).

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