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Synthesis of Sydnone Compounds Substituted by Heteroatom Groups at the 4-Positions

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A general method for the introduction of heteroatoms to the 4-position of a sydnone ring was developed. Various 4-alkylthio- and 4-arylthiosydnones were prepared in excellent yields by the reaction of 3-aryl-4-lithiosydnones (**2**) with dialkyl and diaryl disulfides. Treatment of **2** with diaryl diselenides, diphenylphosphinous chloride, and arsenic trichloride provided 3-aryl-4-(arylseleno)sydnones, (3-aryl-4-sydnonyl)diphenylphosphine and tris(3-aryl-4-sydnonyl)arsine, respectively, in good yields. It was also found that the reactivity of sydnonyl anions derived from **2** was quite different in some cases from that of the corresponding ordinary aromatic analogues, though the sydnone ring has a somewhat aromatic nature.

Sydnone is a typical mesoionic compound and has been investigated extensively because of its unique electronic structure and biological activity.[1]

As a part of a broad program to study on the synthesis of sydnone compounds and their properties, we reported the synthesis of sydnone derivatives having various kinds of heterocyclic groups at the 4-positions from derivatives of sydnone-4-carboxylic acid[2,3] and 4-(haloacety)sydnones.[4–7]

Although a number of sydnone derivatives have been prepared, relatively few studies on the direct substitution by heteroatoms at the 4-position have been reported.[8–14] All attempts to introduce electron-donating substituents such as hydroxyl, alkoxyl, and amino groups at this position have been unsuccessful so far. Recently, Masuda and Okutani have successfully introduced methylthio and phenylthio groups, i.e. analogues of an alkoxyl group, to the 4-position of sydnones by the use of dimethyl sulfoxide and methyl phenyl sulfoxide, respectively.[10] However, their method has limitation and some problems, because the yields are low except for a few cases and the reaction conditions are not so mild. Since the sydnone ring is unstable to acid, alkali, heat, oxidation, and reduction, the successful synthesis of sydnone derivatives requires quite mild reaction conditions in general. Although 4-lithiosydnone (**2**) can be easily prepared from sydnone (**1**) and butyllithium, very few synthetic studies using **2** have been reported: Especially, very few sydnone derivatives substituted by heteroatoms have been prepared from **2**.[13,14]

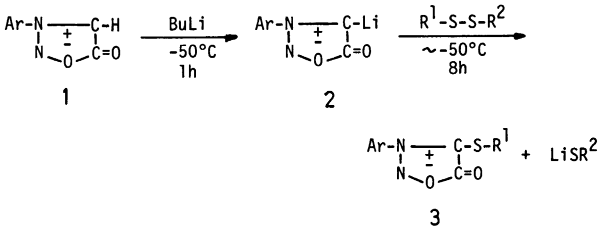
From these aspects, at first, a general method for the introduction of sulfur and its analogue, selenium, to the 4-position was developed using **2** as the starting material in this work. And then, some attempts to introduce phosphorus, arsenic, antimony, and tin atoms were also made.

Results and Discussion

Synthesis of 4-Alkylthio- and 4-Arylthiosydnone Compounds (3).

It is known that carbanions readily react with disulfides to provide the corresponding sulfides.[15] This method seems suitable for the introduction of thio groups to carbon atoms which have active hydrogens. This prompted us to explore the possibilities of direct introduction of alkylthio and arylthio groups to the 4-position of a sydnone ring by the reaction of 4-lithiosydnone (**2**) with various disulfides. We found that the initial lithiation of sydnones and the subsequent reaction of the resulting **2** with disulfides could be run in sequence in THF below −50 °C.

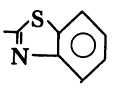
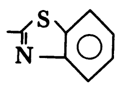
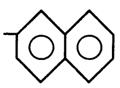
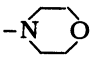
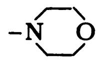
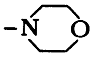
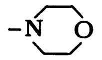
As shown in Table 1, 4-alkylthio- and arylthiosydnone compounds (**3**) were successfully prepared in excellent yields. Bis(2-Benzothiazolyl) disulfides provided 4-(2-benzothiazolylthio)-sydnone (**3d**) in a good yield whereas dimorpholino disulfide did not and large amount of the starting sydnone was recovered. This unsuccessful result may be attributable to higher electron density on the sulfur atoms compared with those of the other disulfides. The higher electron density may be due to the presence of the electron-donating morpholino groups. Two possible products, 4-(2-naphthylthio)sydnone (**3e**) and 4-sydnonyl thiocyanate, were expected to be formed from **2** and 2-naphthalenesulfenyl thiocyanate, however **3e** was obtained as a sole product in a good yield as shown in Scheme 2.



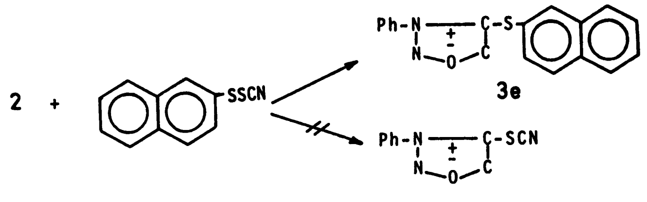
Scheme 1.

This procedure seems to be an excellent general method for the preparation of 4-alkylthio- and arylthiosydnone derivatives, since the reaction proceeds

Table 1. Synthesis of 4-Thiosydnone Compounds (3)

Compd (3)			R^2	Yield[a]	Mp
No.	Ar	R^1		%	θ_m/°C
3a	Ph	Me	Me	87	101—102 (101.5—102.0)[10]
3b	Ph	Ph	Ph	93	65.0—65.5
3c	Ph	*p*-Tolyl	*p*-Tolyl	98	91—92
3d	Ph			95	107—108
3e	Ph		CN	92	134—135 (decomp)
3f	Ph			0	—
3g	*p*-Tolyl	Me	Me	90	90.5—91.5
3h	*p*-Tolyl	Ph	Ph	100	—[b]
3i	*p*-Tolyl	*p*-Tolyl	*p*-Tolyl	98	87.5—88.5
3j	*p*-Tolyl			0	—

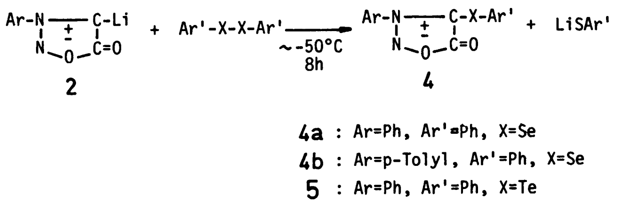
a) Crude yield. b) Brown viscous oil.



Scheme 2.

under quite mild conditions and almost pure products can be directly obtained.

Synthesis of 4-(Arylseleno)sydnones (4). We extended this process for the preparation of 4-(arylseleno)sydnones (**4**) and 4-(phenyltelluro)sydnone (**5**) using diaryl diselenide and diphenyl ditelluride, respectively. As shown in Tables 2, **4** was obtained in a good yield whereas **5** was not. Although disulfide, diselenide, and ditelluride are analogues, the reactivity of ditelluride to **2** was found to be quite different.



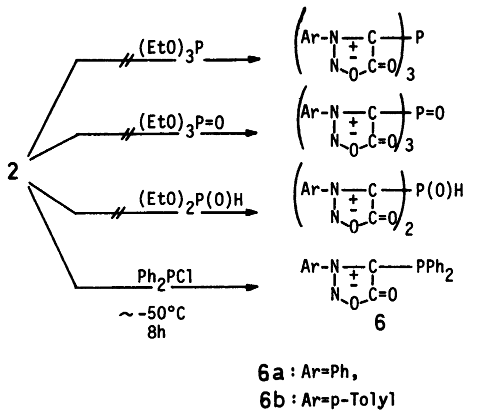
Scheme 3.

Introduction of Phosphorus Atoms to the 4-Positions of Sydnones. Since it is known that aryllithiums react with various kinds of phosphorus acid esters and halophosphorus compounds to give the corresponding compounds having a C–P bond, the following reactions were examined using **2** as shown in Scheme 4. 4-Lithiosydnone **2** did not react with the phosphorus acid esters used, whereas diphenylphosphinous chloride reacted with **2** to provide 4-(diphenylphosphino)sydnone (**6**) in a good yield. These unsuccessful results may indicate that the reactivity of 4-sydnonyl anion is lower than that of ordinary aryl

Table 2. Synthesis of Sydnone Derivatives (4—7)

Compound	Yield[a]	Mp
	%	θ_m/°C
4a	99	83—84
4b	100	90—91
5	0	—
6a	92	175—176
6b	97	164.5—165
7a	99	92
7b	100	91

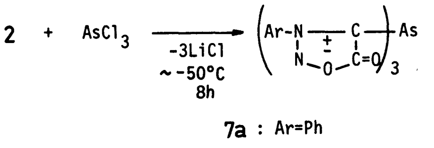
a) Crude yield.



Scheme 4.

anions.

Introduction of Arsenic Atom to the 4-Positions of Sydnones. Since diarylphosphinous chloride and phosphorus trichloride[13] reacted smoothly with **2**, the reaction of **2** with arsenic trichloride was successfully attempted in a similar manner to provide the corresponding tri(4-sydnonyl)arsine (**7**) which is a compound containing three sydnone rings bound to the same central arsenic atom.



7a : Ar=Ph
7b : Ar=p-Tolyl

Scheme 5.

Attempts to Introduce Tin and Antimony to the 4-Positions of Sydnones. It is known that **2** reacts with chlorotrimethylsilane to give 4-sydnonylsilane.[14] In a similar manner, the reactions of **2** with tin(II) chloride, trimethyltin chloride, antimony trichloride, and antimony pentachloride were carried out. However, all attempts were unsuccessful. Since ordinary aryllithium readily reacts with halostannanes, the unsuccessful result also clearly indicates that the nucleophilicity of 4-sydnonyl anion is weaker than that of ordinary aryl anions.

The new types of sydnone compounds thus prepared are expected to be pharmacologically active and screening tests of several biological activities of these sydnones are currently under investigation.

Experimental

^{1}H NMR spectra were recorded at 60 MHz on a Varian EM-360 spectrometer using $CDCl_3$ and Me_4Si as a solvent and an internal standard, respectively. IR spectra were obtained on a Hitachi 295 infrared spectrometer. Electron impact mass spectra were determined at 30 eV on a JEOL JMS-D100 mass spectrometer by direct introduction via solid probe.

Typical Procedure for the Synthesis of 4-Alkylthio- and Arylthiosydnones (3). Synthesis of 4-Methylthio-3-phenyl-sydnone (3a): To a stirred suspension of 6.2 mmol of 4-phenylsydnone in 10 ml of anhydrous THF was added dropwise 6.5 mmol of a solution of butyllithium in hexane (15%, 4 ml) below −50 °C. After about 1 h of stirring, a solution of 6.2 mmol of diphenyl disulfide in 5 ml of THF was added dropwise to the resulting brown solution below −50 °C. After additional 8 h of stirring, the reaction mixture was poured into ice-water. The precipitating colorless pure product, **3a** was collected by filtration, washed with water, and dried. The yield was 1.15 g; IR (KBr): 3060 (νCH of Ph), 2950 (νCH of Me), 1790, and 1770 cm^{-1} (νC=O). *m/z* 208 (M^+) and 150 (M^+−NO-CO). ^{1}H NMR: δ=2.20 (s, 3H, $C\underline{H}_3$) and 7.67 (s, 5H, $C_6\underline{H}_5$). Found: C, 51.99; H, 3.96; N, 13.50; S, 15.69%. Calcd for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45; S, 15.40%.

3-Phenyl-4-(phenylthio)sydnone (3b): A yellow solid (from ethanol). IR (KBr): 3060 (νCH of Ph) and 1770 cm^{-1} (νC=O). *m/z* 270 (M^+) and 212 (M^+−NO-CO). ^{1}H NMR δ=7.16 (s, 5H, $C_6\underline{H}_5S$) and 7.60 (s, 5H, $C_6\underline{H}_5$). Found: C, 62.32; H, 3.68; N, 10.44; S, 11.65%. Calcd for $C_{14}H_{10}N_2O_2S$: C, 62,21; H, 3.73; N, 10.36; S, 11.86%.

3-Phenyl-4-(*p*-tolylthio)sydnone (3c): A pale yellow solid (from ethanol). IR (KBr): 3070 (νCH of aromatic), 2930 (νCH of Me), 1790 and 1770 cm^{-1} (νC=O). *m/z* 284 (M^+) and 226 (M^+−NO-CO). ^{1}H NMR δ=2.30 (s, 3H, $C\underline{H}_3$), 7.07 (s, 4H, *p*-$MeC_6\underline{H}_4$), and 7.30—7.80 (m, 5H, $C_6\underline{H}_5$). Found: C, 63.33; H, 3.97; N, 9.76; S, 11.18%. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85; S, 11.28%.

4-(2-Benzothiazolylthio)-3-phenylsydnone (3d): Colorless needles (from ethanol-acetone). IR (KBr): 3070 (νCH of aromatic), 1795, and 1775 cm^{-1} (νC=O). *m/z* 239 (M^+−NO-CO). ^{1}H NMR δ=7.00—8.00 (m, aromatic C-$\underline{H}$). Found: C, 55.08; H, 2.71; N, 12.65; S, 19.65%. Calcd for $C_{15}H_9N_3O_2S$: C, 55.03; H, 2.77; N, 12.84; S, 19.59%.

4-(2-Naphthylthio)-3-phenylsydnone (3e): The product **3e** was obtained as a pale yellow solid, which contains ethanol of crystallization after recrystallization from ethanol. IR (KBr): 3070 (νCH of aromatic), 1785, and 1765 cm^{-1} (νC=O). *m/z* 320 (M^+), 262 (M^+−NO-CO), and 46 ($EtOH^+$). ^{1}H NMR δ=1.27 (t, 3H, $C\underline{H}_3CH_2OH$), 1.67 (s, 1H, $CH_3CH_2O\underline{H}$), 3.75 ($CH_3C\underline{H}_2OH$), and 7.10—8.10 (m, 12H, aromatic C-$\underline{H}$). Found: C, 65.36; H, 4.82; N, 7.41%. Calcd for $C_{20}H_{18}N_3O_3S$: C, 65.56; H, 4.95; N, 7.63%.

4-Methylthio-3-(*p*-tolyl)sydnone (3g): Colorless prisms (from ethanol). IR (KBr): 3070 (νCH of aromatic), 2930 (νCH of Me), and 1770 cm^{-1} (νC=O). *m/z* 222 (M^+) and 164 (M^+−NO-CO). ^{1}H NMR δ=2.28 (s, 3H, $C\underline{H}_3S$), 2.53 (s, 3H, *p*-$C\underline{H}_3C_6H_4$), and 7.47 (s, 4H, *p*-$MeC_6\underline{H}_4$). Found: C, 53.75; H, 4.59; N, 12.36%. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60%.

4-Phenylthio-3-(*p*-tolyl)sydnone (3h): After reaction, the reaction mixture was poured into ice-water and was repeatedly extracted with dichloromethane. The extracts were dried over anhydrous sodium sulfate and then evaporated to give pure **3h** as brown viscous oil. IR (KBr): 3070 (νCH of aromatic), 2930 (νCH of Me), and 1780 cm^{-1} (νC=O). *m/z* 284 (M^+) and 226 (M^+−NO-CO). ^{1}H NMR δ=2.40 (s, 3H, $C\underline{H}_3$), 7.13 (s, 5H, $C_6\underline{H}_5$), and 7.26 (s, 4H, *p*-$MeC_6\underline{H}_4$). Found: C, 63.23; H, 4.18; N, 9.92; S, 11.27%. Calcd for $C_{15}H_{12}N_2O_2S$ C, 63.36; H, 4.25; N, 9.85; S, 11.28%.

3-(*p*-Tolyl)-4-(*p*-tolylthio)sydnone (3i): A yellow solid (from ethanol). IR (KBr): 3070 (νCH of aromatic), 2930 (νCH of Me), 1790, and 1775 cm^{-1} (νC=O). *m/z* 298 (M^+) and 240 (M^+−NO-CO). ^{1}H NMR δ=2.30 (s, 3H, *p*-$C\underline{H}_3C_6H_4S$), 2.50 (s, 3H, *p*-$C\underline{H}_3C_6H_4$), 7.10 (s, 4H, *p*-$MeC_6\underline{H}_4S$), and 7.30 (s, 4H, *p*-$MeC_6\underline{H}_4$). Found: C, 64.20; H, 4.54; N, 9.32; S, 10.83%. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39; S, 10.75%.

Synthesis of 4-(Arylseleno)sydnones (4). 3-Phenyl-4-(phenylseleno)sydnone (4a): In a manner similar to the synthesis of **3**, **4a** was obtained using diphenyl diselenide. A yellow solid (from ethanol). IR (KBr): 3075 (νCH of aromatic) and 1770 cm^{-1} (νC=O). *m/z* 318 (M^++2), 316 (M^+), 260 (M^++2−NO-CO), and 258 (M^+−NO-CO). ^{1}H NMR δ=7.20 (broad s, 5H, $C_6\underline{H}_5Se$) and 7.35—7.75 (m, 5H, $C_6\underline{H}_5$). Found: C, 53.03; H, 3.05; N, 8.73%. Calcd for $C_{14}H_{10}N_2O_2Se$: C, 53.01; H, 3.18; N, 8.83%.

4-Phenylseleno-3-(*p*-tolyl)sydnone (4b): A pale yellow solid (from ethanol). IR (KBr): 3070 (νCH of aromatic), 2930 (νCH of Me), 1780, and 1760 cm^{-1} (νC=O). *m/z* 332 (M^++2), 330(M^+), 274 (M^++2−NO-CO), and 272 (M^+−NO-CO). ^{1}H NMR δ=2.50 (s, 3H, $C\underline{H}_3$), and 7.10—7.50 (m, 9H, aromatic C-$\underline{H}$). Found: C, 54.48; H, 3.53; N, 8.35%. Calcd for $C_{15}H_{12}N_2O_2Se$: C, 54.39; H, 3.65; N, 8.46%.

Diphenyl(3-phenyl-4-sydnonyl)phosphine (6a). In a manner similar to the synthesis of **3** and **4**, **6a** was obtained using chlorodiphenylphosphine and 4-lithio-3-phenylsydnone. White yellow plates [from ethanol-acetone (2:1)]. IR (KBr): 3070 (νCH of phenyl) and 1760 cm^{-1} (νC=O). *m/z* 346 (M^+), 288 (M^+−NO-CO), and 185 (Ph_2P^+). ^{1}H NMR δ=7.40 (m, 10H, $C_6\underline{H}_5P$) and 7.55 (s, 5H, $C_6\underline{H}_5$). Found: C, 69.62; H, 4.17; N, 7.83%. Calcd for $C_{20}H_{15}N_2O_2P$: C, 69.36; H, 4.37; N, 8.09%.

Diphenyl[3-(*p*-tolyl)-4-sydnonyl]phosphine (6b). Colorless needles [from ethanol-acetone (2:1)]. IR (KBr): 3070 (νCH of aromatic), 1780, and 1760 cm^{-1} (νC=O). *m/z* 360 (M^+), 302 (M^+−NO-CO), and 185 (Ph_2P^+). ^{1}H NMR δ=2.47 (s, 3H, *p*-$C\underline{H}_3C_6H_4$) and 7.00—7.70 (m, 14H, aromatic C-$\underline{H}$). Found: C, 70.09; H, 4.49; N, 7.65%. Calcd for $C_{21}H_{17}N_2O_2P$: C, 70.00; H, 4.75; N, 7.77%.

Tris(3-Phenyl-4-sydnonyl)arsine (7a). In a manner similar to the synthesis of **3**, **7a** was obtained using arsenic trichloride and 4-lithio-3-phenylsydnone. A pale yellow solid [from ethanol-acetone (2:1)]. IR (KBr): 3060 (νC−H of Ph), 1785, and 1760 cm^{-1} (νC=O). ^{1}H NMR δ=7.37—7.87 (m, $C_6\underline{H}_5$]. Found: C, 51.57; H, 2.54; N, 15.21%. Calcd for $C_{24}H_{15}N_6O_6As$: C, 51. 63; H, 2.71; N, 15.05%.

Tris[3-(*p*-Tolyl)-4-sydnonyl]arsine (7b). A colorless solid [from ethanol-acetone (2:1)]. IR (KBr): 3070 (νCH of aromatic), 2940 (νCH of Me), 1790, and 1750 cm^{-1} (νC=O). ^{1}H NMR δ=2.47 (s, 9H, $C\underline{H}_3$) and 7.30 (s, 12H, *p*-$MeC_6\underline{H}_4$). Found: C, 54.18; H, 2.31; N, 13.95%. Calcd for $C_{27}H_{21}N_6O_6As$: C, 54.01; H, 2.53; N, 14.00%.

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