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3-Lithiomethyl-4-phenylsydnone: a new type of organometallic derivatives of sydnones

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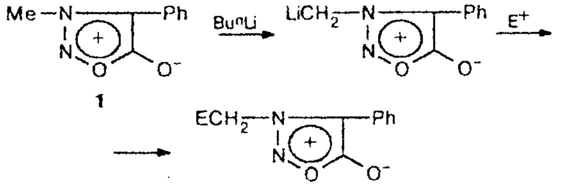
An α-lithium derivative of 3-alkyl-substituted sydnone was first synthesized by direct metallation of 3-methyl-4-phenylsydnone with *n*-butyllithium. The reactivity of the compound obtained was studied. Reactions of 3-lithiomethyl-4-phenylsydnone with various electrophiles can serve as a convenient method for preparation of functionalized sydnones.

Key words: 3-methyl-4-phenylsydnone, metallation, *n*-butyllithium; 3-lithiomethyl-4-phenylsydnone, reactions with electrophiles; functionalized sydnones.

Sydnones are representatives of an important class of mesoionic heterocyclic compounds. There is great interest in them due to their unusual structure and broad spectrum of pharmacological activity.[1,2]

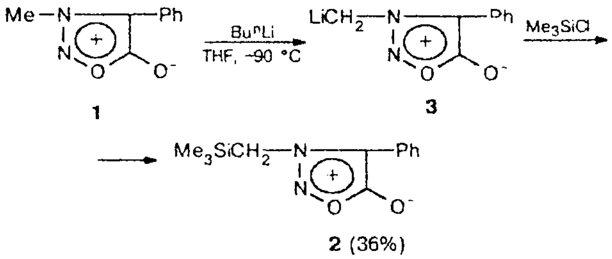
At present, substituted sydnones are mainly synthesized by heterocyclization of the corresponding substituted starting compounds. Direct introduction of substituents into the ring of a mesoionic compound or modification of already present substituents seems to be preferred ways but are often impossible because of insufficient stability of the mesoionic fragment.

In the present work, we attempted to obtain an α-lithium derivative of 3-methyl-4-phenylsydnone (3-methyl-4-phenyl-1,2,3-oxadiazolium-5-olate, **1**) and, based on it, develop preparative methods for introduction of various substituents into the α-position of the alkyl substituent of the sydnone ring.



α-Metallation of the alkyl substituent at position 3 of the sydnone has hitherto not been described in the literature. We assumed that because of the high electron-withdrawing influence of the sydnone ring,[3] the CH acidity of the α-proton of the alkyl substituent would be substantially increased, which would allow direct metallation at the α-position of 3-alkylsydnone.

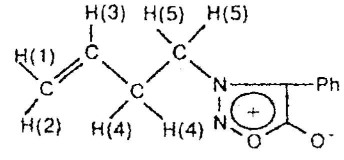
The first attempts to deprotonate sydnone **1** with *n*-butyllithium in THF at −60 °C resulted in complete destruction of the sydnone ring. However, carrying out the metallation at −90 °C for 5 min followed by treatment of the reaction mixture with an excess of chlorotrimethylsilane yielded 3-trimethylsilylmethyl-4-phenylsydnone (**2**). This unambiguously attests to the formation of an α-lithium derivative of sydnone (**3**).



As expected, our lithium derivative **3** is unstable. Thus, extension of the duration of metallation at −90 °C to 20 min resulted in a decreasing yield of compound **2** to 15%.

We found that the acidity of the α-protons is so high that lithium diisopropylamide can be used as a deprotonating agent. However, in this case, the yield of sydnone **2** decreases to 20%, which is probably due to a lower rate of metallation.

We studied the reactivity of the lithium derivative **3**. The data obtained are given in Table 1. Because compound **3** is unstable, the range of electrophiles that react with it to give target products in quite high yields is significantly restricted. Nevertheless, the lithium derivative **3** reacts with allyl bromide to give the corresponding allyl-substituted product **4** in 67% yield.



4

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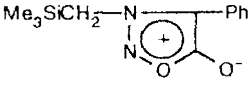
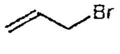
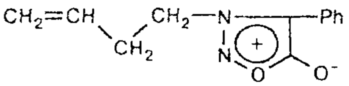
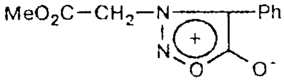
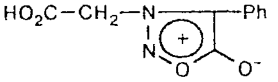
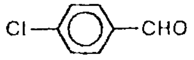
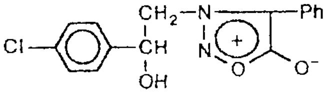
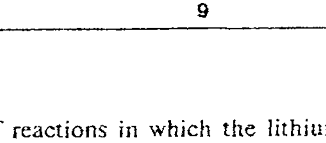
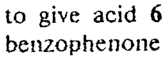
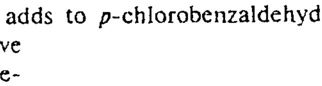
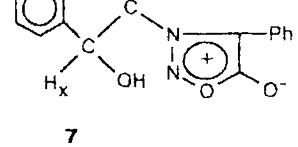
Table 1. Reactions of the α-lithium derivatives of 3-methyl-4-phenylsydnone with various electrophiles

Electrophile	Product	Yield (%)
Me_3SiCl	 **2**	36
	 **4**	67
$ClCO_2Me$	 **5**	21
CO_2	 **6**	70
	 **7**	80
	 **8**	70
	 **9**	12

Another type of reactions in which the lithium derivative **3** enters is addition at the carbonyl group. Thus, compound **3** is smoothly carboxylated by carbon dioxide to give acid **6** and adds to *p*-chlorobenzaldehyde and benzophenone to give alcohols **7** and **8**, respectively.

It should be noted that the nucleophilicity of the carbanion **3** is rather high; even in the case of acetophenone, which is capable of enolization, alcohol **9** is formed (see Table 1), although in only 12% yield. The low yield of ester **5** from the reaction of the lithium derivative **3** with methyl chloroformate is apparently due to addition of the initial organolithium compound **3** at the carbonyl group of the product **5** formed.



7

However, the yields of the products of the reactions studied are as a whole satisfactory and therefore α-lithium derivatives of sydnones can be used for preparative introduction of various functions into the α-position of the alkyl substituent of the sydnone ring.

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer. IR spectra were recorded on a Specord M-80 spectrometer. Melting points were determined in a glass capillary placed in a metal box. All reactions involving organometallic compounds were carried out in an atmosphere of dry argon in dehydrated solvents.

3-Methyl-4-phenylsydnone was obtained from α-methylaminophenylacetic acid according to the known procedure.[4]

4-Phenyl-3-(trimethylsilyl)methylsydnone (2). A 2.3 *M* solution of Bu^{n}Li (1.3 mL) in hexane (3.10 mmol) was added to a solution of 3-methyl-4-phenylsydnone (0.5 g, 2.80 mmol) in 50 mL of THF at −90 °C. The solution was stirred at the same temperature for 4 min, and then chlorotrimethylsilane (0.43 mL, 3.40 mmol) was added. After 10 min stirring at −90 °C, the cooling was removed. The reaction mixture was allowed to attain room temperature. Water (1 mL) was added, THF removed *in vacuo*, the residue dissolved in chloroform and filtered through an Al_2O_3 layer (2×3 cm), the latter washed with chloroform, and the combined filtrate concentrated *in vacuo*. The product was isolated by TLC on silica gel (ether—hexane, 1 : 1, as eluent). Sydnone **2** isolated was recrystallized from a chloroform—ether mixture. Yield 0.25 g (36%), m.p. 79—80 °C. Found (%): C, 58.73; H, 6.74; N, 11.63; Si, 11.40. $C_{12}H_{16}N_2O_2Si$. Calculated (%): C, 58.03; H, 6.49; N, 11.28; Si, 11.31. ^{1}H NMR ($CDCl_3$), δ: 0.02 (s, 9 H, Me_3Si); 3.80 (s, 2 H, CH_2); 7.30—7.40 (m, 5 H, C_6H_5). IR ($CHCl_3$), ν/cm^{-1}: 1738 (C=O).

3-(But-1-en-4-yl)-4-phenylsydnone (4) was synthesized by analogy with compound **2** from 3-methyl-4-phenylsydnone (0.5 g, 2.80 mmol), a 2.3 *M* solution of Bu^{n}Li (1.3 mL, 3.10 mmol) in hexane, and 3-bromoprop-1-ene (0.3 mL, 3.40 mmol). Yield 0.4 g (67%), m.p. 56—57 °C. Found (%): C, 66.63; H, 5.74; N, 13.01. $C_{12}H_{12}N_2O_2$. Calculated (%): C, 66.65; H, 5.59; N, 12.95. ^{1}H NMR ($CDCl_3$), δ: 2.55 (m, 2 H, H(4), $^3J_{H(3)H(4)}$ = 8 Hz, $^3J_{H(4)H(5)}$ = 8 Hz); 4.47 (t, 2 H, H(5)); 5.05 (m, 1 H, H(2), $^3J_{H(2)H(3)}$ = 17 Hz, $^3J_{H(1)H(2)}$ = 2 Hz, $^4J_{H(2)H(4)}$ = 1 Hz); 5.10 (m, 1 H, H(1), $^3J_{H(1)H(3)}$ = 10 Hz); 5.60 (m, 1 H, H(3)); 7.38 (m, 5 H, C_6H_5). IR ($CHCl_3$), ν/cm^{-1}: 1740 (C=O).

3-Carbomethoxymethyl-4-phenylsydnone (5) was synthesized by analogy with compound **2** from 3-methyl-4-phenylsydnone (0.5 g, 2.80 mmol), a 2.3 *M* solution of Bu^{n}Li (1.3 mL, 3.10 mmol) in hexane, and MeOCOCl (1.1 mL, 3.40 mmol). Yield 0.27 g (21%), m.p. 121—122 °C. Found (%): C, 56.66; H, 4.67; N, 11.97. $C_{11}H_{10}N_2O_4$. Calculated (%): C, 56.41; H, 4.30; N, 11.96. ^{1}H NMR ($CDCl_3$), δ: 3.81 (s, 3 H, CH_3); 5.11 (s, 2 H, CH_2); 7.41—7.48 (m, 5 H, C_6H_5). IR ($CHCl_3$), ν/cm^{-1}: 1765 (CO_2CH_3); 1750 (C=O).

3-Carboxymethyl-4-phenylsydnone (6). A 2.3 *M* solution of Bu^{n}Li (2.6 mL, 6.20 mmol) in hexane was added to a solution of 3-methyl-4-phenylsydnone (1 g, 5.60 mmol) in 60 mL of THF at −90 °C. The solution was stirred at the same temperature for 4 min, and then solid CO_2 (5 g) was added. The cooling was removed after 10 min. The reaction mixture was allowed to attain room temperature, and 5% NaOH (20 mL) was added. The resulting solution was washed with ether, and the aqueous layer was acidified to pH 5 with conc. HCl and cooled. The precipitate of sydnone **6** that formed was filtered off and recrystallized from an ethanol—ethyl acetate mixture. Yield 0.85 g (70%), m.p. 194—196 °C (decomp.). Found (%): C, 54.95; H, 3.80; N, 12.84. $C_{10}H_8N_2O_4$. Calculated (%): C, 54.55; H, 3.66; N, 12.72. ^{1}H NMR (DMSO-d_6), δ: 5.30 (s, 2 H, CH_2); 7.44—7.50 (m, 5 H, C_6H_5). IR (KBr), ν/cm^{-1}: 1732 (C=O).

3-(2-*p*-Chlorophenyl-2-hydroxyethyl)-4-phenylsydnone (7) was synthesized by analogy with compound **2** from 3-methyl-4-phenylsydnone (0.5 g, 2.80 mmol), a 2.3 *M* solution of Bu^nLi (1.3 mL, 3.10 mmol) in hexane, and *p*-chlorobenzaldehyde (0.48 g, 3.40 mmol). Yield 0.7 g (80%), m.p. 116—118 °C. Found (%): C, 61.10; H, 4.36; Cl, 11.34; N, 8.82. $C_{16}H_{13}ClN_2O_3$. Calculated (%): C, 60.67; H, 4.14; Cl, 11.19; N, 8.84. ^{1}H NMR ($CDCl_3$), δ: 4.42 (m, 1 H, H_A); 4.50 (m, 1 H, H_B); 5.23 (m, 1 H, H_X, ABX system, $^3J_{BX}$ = 9.28 Hz, $^3J_{AX}$ = 3.22 Hz, $^2J_{AB}$ = 13.55 Hz); 7.19, 7.23 (dd, 4 H, C_6H_4); 7.48—7.50 (m, 5 H, C_6H_5). IR ($CHCl_3$), ν/cm^{-1}: 1740 (C=O).

3-(2-Hydroxy-2,2-diphenylethyl)-4-phenylsydnone (8) was synthesized by analogy with compound **2** from 3-methyl-4-phenylsydnone (0.5 g, 2.80 mmol), a 2.3 *M* solution of Bu^nLi (1.3 mL, 3.10 mmol) in hexane, and benzophenone (0.62 g, 3.40 mmol). Yield 0.7 g (70%), m.p. 195—196 °C. Found (%): C, 73.98; H, 5.37; N, 7.80. $C_{22}H_{18}N_2O_3$. Calculated (%): C, 73.73; H, 5.06; N, 7.82. ^{1}H NMR ($CDCl_3$), δ: 5.11 (s, 2 H, CH_2); 7.19—7.32 (m, 10 H, PhCPh); 7.44—7.50 (m, 5 H, Ph). IR ($CHCl_3$), ν/cm^{-1}: 1748 (C=O).

3-(2-Hydroxy-2-phenylpropyl)-4-phenylsydnone (9) was synthesized by analogy with compound **2** from 3-methyl-4-phenylsydnone (0.5 g, 2.80 mmol), a 2.3 *M* solution of Bu^nLi (1.3 mL, 3.10 mmol) in hexane, and acetophenone (0.4 g, 3.40 mmol). Yield 0.1 g (12%), m.p. 115—116 °C. ^{1}H NMR ($CDCl_3$), δ: 1.61 (s, 3 H, CH_3); 4.56, 4.68 (dd, 2 H, CH_2, AB system, J_{AB} = 13.6 Hz); 7.19—7.31 (m, 5 H, $C_6H_5C(OH)CH_3$); 7.40—7.42 (m, 5 H, C_6H_5). IR ($CHCl_3$), ν/cm^{-1}: 1744 (C=O).

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References

1. M. Ohta and H. Kato, *Nonbenzenoid Aromatics*, Ed. J. P. Snyder, Academic, New York, 1969, 117 pp.
2. C. G. Newton and C. A. Ramsden, *Tetrahedron*, 1982, **38**, 2965.
3. H.-J. Tien, S.-T. Lin, and J.-T. Sheu, *Can. J. Chem.*, 1994, **72**, 1610.
4. R. A. Eade and J. C. Earl, *J. Chem. Soc.*, 1948, **72**, 2307.

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