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Synthesis and reactivity of 4-lithium and 4-copper derivatives of sydnone imines

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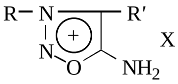
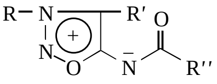
4-Lithium and 4-copper sydnone imines have been obtained, and preparative methods for the direct introduction of hydroxyalkyl, acyl, carbalkoxyl, vinyl and aryl groups into the 4-position of sydnone imines have been developed on this basis.

Sydnone imines **1** and their exocyclic N_6-derivatives **2** hold a special place among mesoionic heterocycles.[1–4]



1



2

R = alkyl, aryl, NR_2
R′ = H, alkyl, aryl, alkenyl, alkynyl
R′′= alkyl, aryl, OR, NR_2

This unique class of synthetic compounds has no analogues among the known natural substances. Sydnone imines exhibit biological activity,[2,4] and a number of medicines were created on this basis.

The cyclization of substituted *N*-nitroso-α-aminonitriles in acid media is the most productive method for the preparation of sydnone imines.

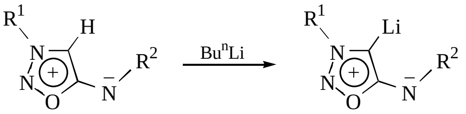
However, this method has a significant drawback because the necessary α-aminonitriles are not easily accessible, and their functional groups may hinder the cyclization.

The direct introduction of substituents into the already formed sydnone imine ring using organometallic derivatives can solve the problem of the direct synthesis of sydnone imines. Unfortunately, only 4-mercurio sydnone imines obtained by the direct mercuration of sydnone imines are presently known.[5] However, these compounds found no synthetic applications.

All attempts to obtain lithium derivatives of sydnone imines by the replacement of bromine with lithium in 4-bromo-N_6-acetyl sydnone imines by analogy with sydnones were unsuccessful.[6]

In this study, we developed a method for the direct functionalization of sydnone imines using their organometallic derivatives.

We supposed that 4-lithium-N_6-acyl derivatives of sydnone imines can be synthesised by the direct metallation of sydnone imines unsubstituted at the 4-position in the presence of butyllithium:



The following two side reactions can occur in the synthesis of 4-lithium-N_6-acyl derivatives of sydnone imines by this method: the addition of a metallation agent to the carbonyl group and decomposition of the obtained lithium derivatives.

In our opinion, the carbonyl activity in N_6-acyl derivatives of sydnone imines is essentially suppressed because of a high negative charge of the exocyclic nitrogen. The influence of the latter side reaction is significant only in the case of low-reactivity electrophiles, when the rate of the reaction of 4-lithium derivatives with electrophiles is comparable to the rate of decomposition.

The reaction mixture changed from colourless to yellow-brown within 30 min on the treatment of 3-cyclohexyl-N_6-pivaloyl sydnone imine in THF with Bu^nLi at –78 °C. The solution became light yellow on the addition of benzaldehyde.

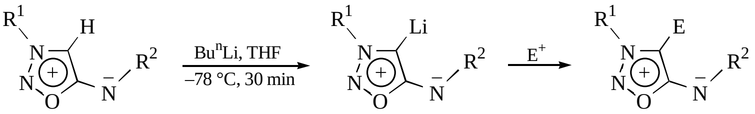
The treatment of the reaction mixture with water followed by chromatography resulted in the formation of an alcohol (53% yield) as a product of addition of 4-lithium sydnone imine to benzaldehyde.

We found that the metallation of other sydnone imines can also be performed, and other substrates that react with lithium sydnone imines can be used (Table 1).†

Unfortunately, 4-lithium sydnone imine derivatives exhibit low nucleophilicity and are thermally unstable. At –78 °C, these derivatives do not react with active electrophiles such as trimethylsilyl chloride, methyl iodide and allyl bromide, and they decompose at higher temperatures.

Carbonyl compounds that are incapable of enolization were

Table 1 Reactivity of 4-lithium derivatives of sydnone imines.



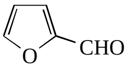
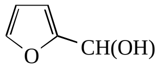
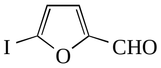
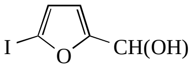
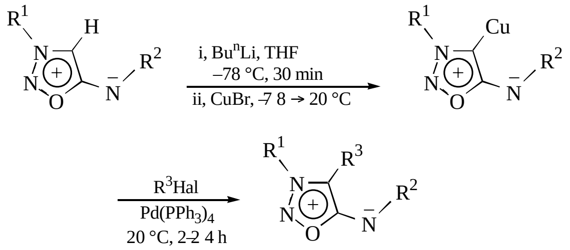
Run	R¹	R²	E⁺	E	Yield (%)	mp/°C
1	cyclo-C_6H_{11}	$Bu^tC(O)$	PhCHO	PhCH(OH)	53	168–169
2	cyclo-C_6H_{11}	$Bu^tC(O)$	*p*-ClC_6H_4CHO	*p*-$ClC_6H_4CH(OH)$	63	185 (decomp.)
3	cyclo-C_6H_{11}	$Bu^tC(O)$			53	130–132
4	cyclo-C_6H_{11}	$Bu^tC(O)$			33	134 (decomp.)
5	cyclo-C_6H_{11}	$Bu^tC(O)$	AcOCl	MeOC(O)	83	70–71
6	cyclo-C_6H_{11}	PhC(O)	PhCHO	PhCH(OH)	45	173–175
7	cyclo-C_6H_{11}	$CF_3C(O)$	PhCHO	PhCH(OH)	47	118–120
8	cyclo-C_6H_{11}	MeC(O)	PhCHO	PhCH(OH)	30	137 (decomp.)
9	cyclo-C_6H_{11}	MeOC(O)	PhCHO	PhCH(OH)	65	142–144
10	cyclo-C_6H_{11}	*p*-$MeC_6H_4SO_2$	PhCHO	PhCH(OH)	44	160–161
11	1-morpholine	PhC(O)	PhCHO	PhCH(OH)	62	181–182
12	1-morpholine	PhC(O)	AcOCl	MeOC(O)	60	124–125
13	1-morpholine	PhC(O)	CH_2O	$HOCH_2$	36	147–149

Table 2 Reactivity of 4-copper derivatives of sydnone imines.



Entry	R^1	R^2	R^3Hal	Yield (%)	mp/°C
1	cyclo-C_6H_{11}	$Bu^tC(O)$	PhCH=CHBr	53	206 (decomp.)
2	cyclo-C_6H_{11}	$CF_3C(O)$	PhI	63	156–158
3	cyclo-C_6H_{11}	$CF_3C(O)$	PhCH=CHBr	53	199 (decomp.)
4	cyclo-C_6H_{11}	$CF_3C(O)$	MeCOCl	33	92–93
5	cyclo-C_6H_{11}	$CF_3C(O)$	PhCOCl	30	150–151
6	Me	$Bu^tC(O)$	*p*-$O_2NC_6H_4I$	45	132–133
7	Me	$Bu^tC(O)$	CH_2=CHBr	65	92–94
8	Me	$Bu^tC(O)$	PhCH=CHBr	47	210 (decomp.)
9	Me	$CF_3C(O)$	PhCH=CHBr	44	200–201

found to be the only type of electrophiles that react with 4-lithium sydnone imines.

The low stability of 4-lithium sydnone imines and a small number of electrophiles that react with 4-lithium derivatives significantly restrict the preparative capabilities of using 4-lithium sydnone imines for the direct functionalization of a sydnone imine ring. 4-Copper sydnones, which are oxygen analogues of sydnone imines, are known to be highly stable. Convenient preparative methods for introducing different substituents at the 4-position of sydnones *via* palladium-catalysed cross-coupling reactions were developed for 4-copper sydnones.[7,8] We suppose that 4-copper sydnone imines are as stable as the sydnones.

On the addition of copper bromide (1 equiv.) to a solution of 4-lithium-3-cyclohexyl-N_6-pivaloyl sydnone imine at –78 °C, the colour of the reaction mixture became deeper, and copper bromide underwent dissolution. This suggests the formation of 4-copper sydnone imines. An increase in the temperature to room temperature and even the refluxing of the solution for several hours did not result in decomposition of 4-copper sydnone imine.

We also examined the applicability of 4-copper derivatives to palladium-catalysed cross-coupling reactions with different organohalides (Table 2).[‡]

Preparative methods for the direct introduction of hydroxyalkyl, acyl, carbalkoxyl, vinyl, and aryl groups at the 4-position of a sydnone imine ring were developed on the basis of the synthesised organometallics.

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References

1 H. U. Daeniker and J. Druey, *Helv. Chim. Acta*, 1962, **45**, 2426.
2 V. G. Yashunskii and L. E. Kholodov, *Usp. Khim.*, 1980, **49**, 54 (*Russ. Chem. Rev.*, 1980, **49**, 28).
3 L. B. Clapp, in *Comprehensive Heterocyclic Chemistry*, ed. K. T. Potts, Pergamon Press, Oxford, 1984, vol. 6, p. 365.
4 C. G. Newton and C. A. Ramsden, *Tetrahedron*, 1982, **38**, 2967.
5 H. Kato, M. Hashimoto and M. Otha, *Nippon Kagaku Zasshi*, 1957, **78**, 707.
6 S. A. Zotova and V. G. Yashunskii, *Zh. Org. Khim.*, 1965, **1**, 2218 [*J. Org. Chem. USSR* (*Engl. Transl.*), 1965, **1**, 2258].
7 V. N. Kalinin and F. M. She, *J. Organomet. Chem.*, 1988, **352**, C34.
8 V. N. Kalinin, D. N. Pashchenko and F. M. She, *Mendeleev Commun.*, 1992, 60.

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[†] *Typical experimental procedure*. A solution of Bu^nLi (2.1 mmol) in hexane was added to a solution of sydnone imine (2.0 mmol) in 50 ml of absolute THF at –78 °C. The mixture was stirred at –78 °C for 30 min; then, 3.0 mmol of an electrophile was added. After the mixture was heated to room temperature, 1 ml of water was added, the mixture was diluted with 100 ml of methylene chloride and filtered through a layer of Al_2O_3. The solvent was removed by evaporation, and the residue was chromatographed on SiO_2 (chloroform–diethyl ether, 10:1). The resulting product was crystallised from diethyl ether–hexane. Satisfactory elemental analysis and ^{1}H NMR data were obtained for all substances.

[‡] *Typical experimental procedure*. A solution of Bu^nLi (2.1 mmol) in hexane was added to a solution of sydnone imine (2.0 mmol) in 50 ml of absolute THF at –78 °C. The mixture was stirred at –78 °C for 30 min; then, 2.1 mmol of copper(I) bromide was added. The mixture was additionally stirred for 20 min. After the mixture was heated to room temperature, 3.0 mmol of an organohalide and 0.1 mmol of tetrakis-triphenylphosphinepalladium(0) were added. The mixture was stirred for 2–24 h until the reaction completed (monitoring by TLC). The reaction mixture was decomposed with water, then diluted with 100 ml of methylene chloride and filtered through a layer of Al_2O_3. The solvent was removed by evaporation, and the residue was chromatographed on SiO_2 (chloroform–diethyl ether, 10:1). The resulting product was crystallised from diethyl ether–hexane. Satisfactory elemental analysis and ^{1}H NMR data were obtained for all substances.