Journal of Organometallic Chemistry 943 (2021) 121841

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

4-lithiosydnone imines: Generation and stability. Plant growth regulating activity of 4-hydroxymethyl derivatives of sydnone imines

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ARTICLE INFO

Article history:
Received 11 February 2021
Revised 9 April 2021
Accepted 12 April 2021
Available online 15 April 2021

Keywords:
sydnone imines
deprotonation
lithium amides
4-lithiosydnone imines
1-methoxy-*N*,*N*-dimethylmethanaminium methylsulfate
plant growth regulators

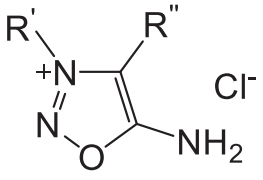
ABSTRACT

The C(4)-deprotonation of N_6-substituted sydnone imines with lithium hexamethyldisilazide (LHDMS), lithium diisopropylamide (LDA), lithium diethylamide (LDEA), and *n*-BuLi was studied. A thermal stability of 4-lithiosydnone imines was investigated and an efficiency of subsequent reactions of the generated C(4)-lithio derivatives with electrophiles was shown to depend on the exploited deprotonating reagent. It was found that 4-(α-arylhydroxymethyl)sydnone imines, when used for pre-sowing treatment of corn seeds at very low doses (0.25-5 g t^{-1}), promoted a plant growth up to 60%.

1. Introduction

Sydnone imines (**1a,b** and **2**) are important representatives of mesoionic heterocyclic compounds [1-4]. Compounds that are unsubstituted on the exocyclic N_6 atom are not stable as free bases **1a**, but they can form stable salts **1b** or the N_6-substituted derivatives **2**. Sydnone imines are of special interest primarily due to the wide spectrum of their biological activities [3,4]. These compounds have manifested themselves as effective exogenous donors of nitric oxide (NO), the signaling molecule playing a role in a variety of biological processes [5-9]. Some of sydnone imine derivatives are used as medicines (Molsidomine, Sydnophen, Mesocarb). Resently, sydnone imines have been shown to exhibit plant growth regulating properties [10-12].

1a



1b

2

R'''=C(O)R, CO_2R, $C(O)NR_2$, SO_2R, etc.

Therefore, a search for new biologically active sydnone imine based molecules is being actual. So, effective synthetic methods for preparation of the diversity of these heterocyclic compounds

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https://doi.org/10.1016/j.jorganchem.2021.121841
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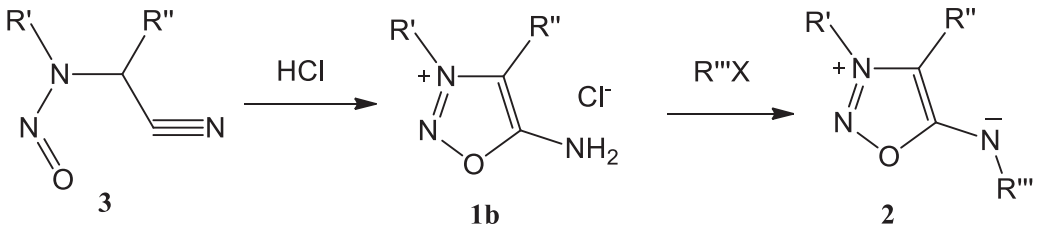
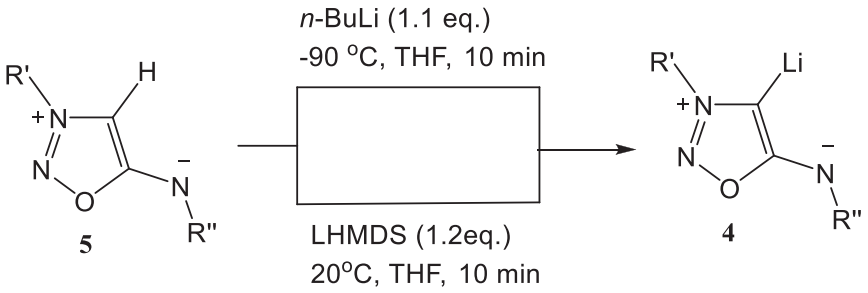


Scheme 1. Cyclization of *N*-nitroso derivatives **3** to sydnone imine derivatives **1b, 2**.



Scheme 2. Formation of 4-lithio derivatives by a deprotonation of sydnone imines with *n*-BuLi or LHMDS.

are highly desirable. Nowadays, there are two main approaches to the preparation of sydnone imine derivatives. The first one is cyclization of the appropriately substituted *N*-nitroso derivatives of α-aminoacetonitriles **3** (Scheme 1) and the alternative approach is modification of the pre-synthesized sydnone imine framework [4]. The second way seems to be more preferable for preparation of families of the structurally similar derivatives for SAR studies.

4-Lithio derivatives are among the most important conventional reactive intermediates in the sydnone imine chemistry providing the way to a diversity of the C(4)-substituted sydnone imines [4]. However, the molecular structures of 4-lithio sydnone imines are still not known in detail because of the lack of single crystal X-ray studies data for these compounds. This is due to the fact that 4-lithio sydnone imines are stable only in solutions at low temperature and do not survive in a solid state. Nevertheless, the fact that the C(4)-H deprotonation in sydnone imines with strong lithiated bases leads to a formation of the corresponding 4-lithio derivatives has never been questioned by experts in the art. There have been numerous reports on the use of 4-lithio sydnone imines for the preparation of a variety of C(4)-substituted derivatives. Specifically, they have been exploited in the syntheses of 4-hydroxymethyl [13-15], 4-alkoxycarbonyl [13,14], 4-thioalkyl [15-17], 4-formyl [18,19] and 4-diphenylphosphino sydnone imines [20]. In some cases the molecular structures of the resulting products, *i. a.* substitution at C(4), have been proven by X-ray single crystal studies or X-ray powder diffraction analysis (for examples, see [15,17,18,20]). Moreover, the transmetalation reactions of 4-lithio sydnone imines were used to prepare the corresponding cuprio [13,14], selenio, aurio, and palladio derivatives [21]. Further Pd-catalyzed cross-coupling reactions of the cuprio derivatives were found to produce the corresponding 4-substituted sydnone imines [13,14]. As for the selenio, aurio, and palladio derivatives, a presence of the direct bonds of C(4) with Se, Au or Pd in these molecules was shown [21], with the Au-C(4) and Pd-C(4) bonds were proved by X-ray study.

We have previously shown [13,14], that 4-lithio derivatives of sydnone imines (**4**) can be easily generated by direct deprotonation of sydnone imines **5** unsubstituted at C4 with *n*-BuLi at -90°C in THF (Scheme 2). The 4-lithio derivatives **4** are stable only at the temperature below -80°C. According to our data, lithium amides cannot be used for production of compounds **4** at -90°C. However, some recent papers [21-23] reported about deprotonation of sydnone imines with lithium hexamethyldisilazide (LHMDS) at room temperature in THF (Scheme 2). The authors argued that 4-lithio derivatives **4** are formed quantitatively under these conditions and are stable at room temperature for several weeks [21]. These data are contradictory to our observations.

Taking into account the great importance of this issue for practice of synthesis, it was decided to thoroughly reexamine the process of generation of the lithio derivatives **4** from sydnone imines **5** under the action of various deprotonating reagents and the thermal stability of compounds **4**. Aims of this study were to compare lithium hexamethyldisilazide, lithium diisopropylamide, lithium diethylamide and *n*-BuLi as deprotonating agents for generation of 4-lithio derivatives **4**, to evaluate the stability of the last ones, and to use them for preparation of 4-formyl and 4-(α-arylhydroxymethyl) derivatives, the putative plant growth regulating compounds.

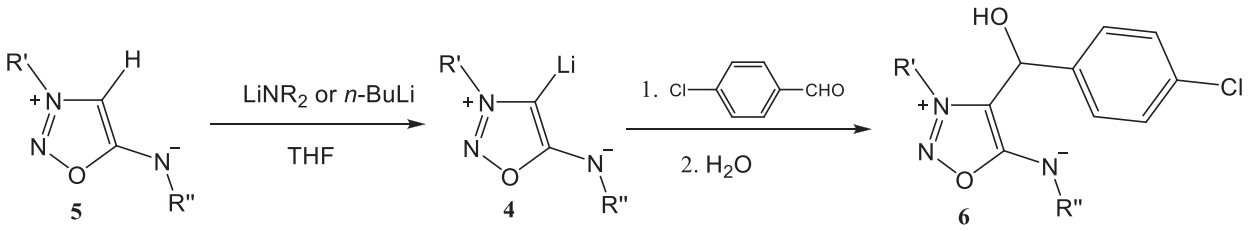
2. Results and discussion

2.1. C(4)-Deprotonation of sydnone imines and stability of 4-lithio derivatives

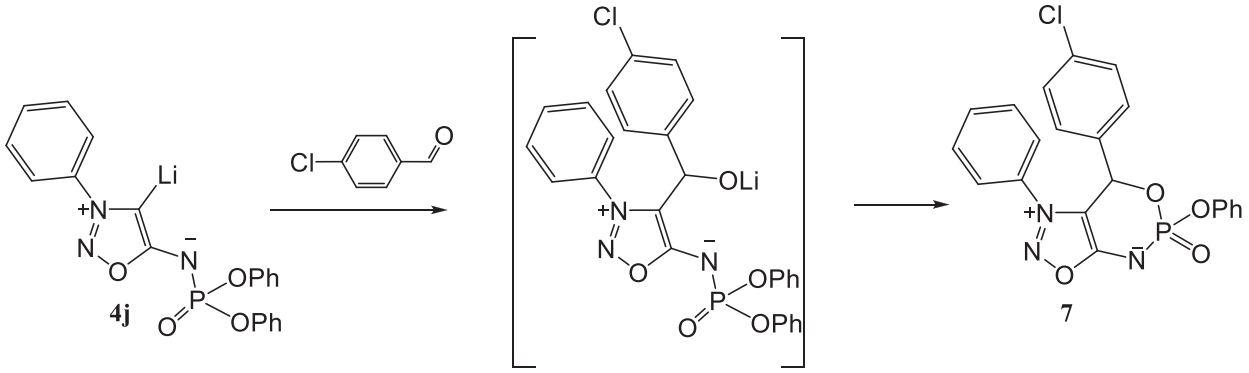
2.1.1. Deprotonation procedure and stability monitoring

As sydnone imines unsubstituted at N_6 position are unstable (see above), the direct C(4)-lithiation of compounds **1b** is impossible. So, N_6-substituted derivatives **5** were used as the starting materials for deprotonation. Because the direct evaluation of the yields of the resultant 4-lithio derivatives **4**was impossible, the reaction mixtures after the deprotonation step were treated with 4-chlorbenzadehyde to form, after hydrolytic work-up, the corresponding alcohols **6** (Scheme 3).

As one could expect [15], the lithium derivative **4j** reacted with 4-chlorobenzaldehyde affording the bicyclic derivative **7** instead



Scheme 3. Preparation of alcohols **6** from sydnone imines **5***via* an intermediate formation of 4-lithiosydnone imines **4**.



Scheme 4. Formation of bicyclic derivative **7** from **4j**.

of the alcohol **6** as a result of the cyclization reaction shown in Scheme 4.

Since reactions of organolithium derivatives with aromatic aldehydes usually give high yields and are not accompanied by side processes (see, for example, [24]), a content of alcohol **6** among the reaction products after hydrolysis should generally corresponds to the content of the lithio derivative **4** in the reaction mixture. Quantities of alcohol **6** and the unreacted starting sydnone imine **5** in reaction mixtures were calculated from the ^{1}H NMR data after hydrolysis and evaporation of the solvent using hexamethylbenzene (HMB) or 4,4′-bis-*tert*-butyldiphenyl (DTBBP) as the internal standard. The standard was added to the reaction mixtures after hydrolysis.

Stability of lithium derivatives **4** was deduced from their decomposition rates at room temperature. These rates were evaluated by the time dependent decrease of the yields of alcohols **6.** Measurements were carried out using the ^{1}H NMR as described above. In the case of deprotonations with lithium amides, a lithium amide was added to a solution of sydnone imine **5**, the mixture was kept at 20°C and quenched with 4-chlorbenzadehyde 10-720 min after adding the amide. With *n*-BuLi, deprotonation was carried out at -80°C for 10 min followed by either an addition of 4-chlorbenzadehyde at -80°C, keeping the mixture for 5 min at this temperature, warming it to 20°C and keeping for an additional 10 min before the hydrolytic work-up, or quick (1 min) heating of the **5**/*n*-BuLi mixture to 20°C, keeping it for 1-480 minutes at this temperature, and quenching with 4-chlorobenzaldehyde followed by hydrolysis after additional stirring for 20 minutes. The results are presented in Table 1.

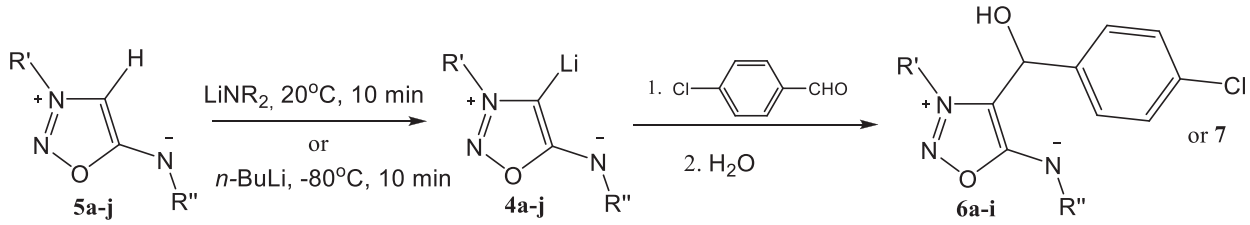
2.1.2. Generation of 4-lithiosydnone imines

To study the deprotonation reaction and to examine stabilities of the arising 4-lithio derivatives **4**, sydnone imines **5** bearing conventional types of substituents on the *N*(3) nitrogen of the oxadiazole ring, such as alkyl (isopropyl), dialkylamino (morpholyl), and aryl (phenyl), were used as the starting materials (Table 1). In addition, starting sydnone imines **5** had the most important substituents (acetyl, trifluoroacetyl, benzoyl, ethoxycarbonyl, *tert*-butoxycarbonyl, *p*-toluenesulfonyl, diphenylphosphinyl, and diphenylphosphoryl) on the exocyclic N_6 nitrogen.

Lithium diisopropylamide (LDA) and diethylamide (LDEA) were used as the deprotonating agents along with lithium hexamethyldisilazide (LHDMS); the application of the last one was described earlier [21-23]. The use of cheaper LDA or LDEA for the deprotonation instead of LHMDS makes the preparation of lithium derivatives **4** less expensive. Deprotonations of sydnone imines **5** with lithium amides were carried out under the conditions reported in ref. [22] (**5**: lithium amide ratio was 1: 1.2, THF, 20°C, 10 min). Deprotonations of compounds **5** using *n*-BuLi (1.1 eq.) were carried out in THF at -80°C for 10 min. The 4-lithio derivatives **4** were quenched with 4-chlorobenzaldehyde either at -80°C or at 20°C, with the retention times of **4** at 20°C before the addition of 4-chlorobenzaldehyde varied within 1-480 min interval. The results are shown in Table 1.

The data presented in Table 1 obviously allows to divide the examined sydnone imines into the following three groups: **5a,h,i** (1st group), **5b,c,e,j** (2nd group), and **5d,f,g** (3rd group). In the first group of compounds, yields of alcohols **6** are high and do not depend on a type of the deprotonating agent although the use of lithium amides usually afforded some higher yields than the use of *n*-BuLi. In the second group, yields of alcohols are generally slightly lower than those in the first group (excepting **5i**) and the best results in the most cases were observed when *n*-BuLi was used as the deprotonating agent, especially in comparison with LDA or LDEA. As for the third group of the sydnone imines, alcohols **6** were prepared in moderate yields (25-78%) using only n-BuLi. The use of LHMDS, LDA or LDEA as the deprotonating reagents gave very poor yields (1-6%) of compounds **6**, if any. These results can be explained by the difference in the stabilities of 4-lithio derivatives **4a-j**.

Table 1
Deprotonation of sydnone imines **5** with lithium amides or *n*-BuLi followed by a derivatization of 4-lithiosydnone imines **4** with 4-chlorobenzaldehyde.



Starting sydnone imine			Deprotonation with R_2NLi				Deprotonation with *n*-BuLi		
5	R'	R"	Method A[a]	R_2NLi, yields of **4**(**5**), %[b]			Method B[c]		Method C[d]
			Time period, min	LHDMS	*i*-Pr_2NLi	Et_2NLi	Time period, min	Yields of **4**(**5**), %[b]	Yields of **4**(**5**), %[b]
5a	*i*-Pr	CO-Ph	10	96(1)	84(5)	96(3)	5	93(6)	-
			30	93(1)	57(8)		15	85(11)	
			60	93(1)	53(7)	24(25)			
			120		34(7)	1(38)	30	77(6)	
			180	89(5)	0(9)				
			360	60(13)			60	28(25)	
			600	0(20)					
5b	*i*-Pr	CO-CH_3	10	85(12)	34(23)	27(40)	5	62(17)	76(22)
			30	66(11)			15	25(33)	
			60	2(41)			30	0(48)	
5c	*i*-Pr	CO-CF_3	10	58(14)	1(15)	0(14)	0	1(34)	60(19)
			30	32(29)					
			60	22(41)					
5d	*i*-Pr	SO_2-C_6H_4-CH_3	10	6(9)	1(34)	1(24)	0	1(65)	77(15)
5e	*i*-Pr	CO-$OC(CH_3)_3$	10	63(13)	0(17)	0(20)	1	67(30)	80(20)
			30	0(29)			10	50(20)	
							30	0(28)	
5f	*i*-Pr	$P(O)Ph_2$	10	4(36)	0(0)	0(0)	0	1(33)	25(72)
5g	*i*-Pr	$P(O)(OPh)_2$	10	0(12)	0(27)	0(43)	0	0(24)	78(1)
5h	*N*-morpholine	CO-OEt	10	93(2)	85(9)	86(3)	10	94(3)	-
			60	93(6)					
			120	87(2)			60	57(14)	
			240	54(8)					
			360	35(20)			120	45(18)	
			720	0(11)					
5i	Ph	CO-$OC(CH_3)_3$	10	53(8)	59(25)	58(34)	5	58(14)	-
			60	50(13)			30	45(38)	
			120	49(17)			60	40(39)	
			240	40(22)			120	24(51)	
			480	14(29)			240	22(42)	
							480	8(54)	
5j	Ph	$P(O)(OPh)_2$	10	36[e](47)	17[e](69)	20[e](52)	30	21[e](17)	45[e](18)
			60	25[e](40)			60	7[e](60)	
			120	3[e](56)					

[a] Method A. A mixture of**5** and $LiNR_2$ was stirred at 20°C for the time period indicated in the table and 4-chlorobenzaldehyde was added. The mixture was stirred for 20 min and quenched with water.
[b] Calculated from the ^{1}H MNR data using the internal standard.
[c] Method B. A mixture of**5** and *n*-BuLi was stirred at -80°C for 10 min, warmed up to 20°C for 1 min and kept at 20°C for the time period indicated in the table followed by an addition of 4-chlorobenzaldehyde. The mixture was stirred for 20 min and quenched with water.
[d] Method C. A mixture of**5** and *n*-BuLi was stirred at -80°C for 10 min and 4-chlorobenzaldehyde was added. Themixturewas warmed up to 20°C stirred for 20 min and quenched with water.
[e] Yieldofcompound**7**.

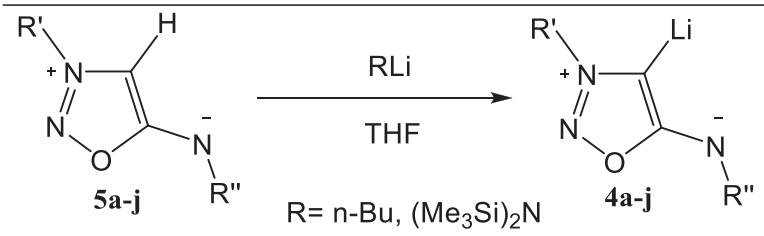
Taken together, the data presented in Table 1 outline the suitability of the 4-lithio derivatives derived from structurally varied sydnone imines for synthetic purposes.

2.1.3. Stability of 4-lithiosydnone imines

The experimental data presented in Table 1 show that the stability of lithio derivatives **4** depends on the substituents at *N*(3) and N_6. It additionally depends on the deprotonating reagent used to obtain compounds **4**. Some of 4-lithio derivatives suddenly turned out to be rather stable. Unlike the majority of the 4-lithio derivatives, which rapidly decomposed at room temperature, that ones generated from the 1st group of sydnone imines (**5a,h,i**) by the action of LHMDS were found to undergo only minor decomposition while keeping at 20°C for 2-3 h. However, they fully decomposed at room temperature within 10 h. These data contradict the statement [21,22] that 4-lithio derivatives of sydnone imines (including those generated from **5h**) are stable for several weeks.

It is convenient to use the "half-decomposition" time ($T_{1/2}$) at 20°C as a measure of the *apparent* thermal stability of the 4-lithio derivatives **4**. $T_{1/2}$ is the time period for which the reaction mixture prepared by mixing a sydnone imine **5** and a lithium amide should be kept at 20°C before the addition of 4-chlorobenzaldehyde to reduce the yield of the corresponding alcohol **6** by two folds. In the case of deprotonations with *n*-BuLi, $T_{1/2}$ is the time of keeping the reaction mixture at 20°C after warming it from -80°C to 20°C before the addition of 4-chlorobenzaldehyde.

Table 2
The apparent "half-decomposition" time ($T_{1/2}$, min) of 4-lithio derivatives **4a-j** generated from **5a-j**by the action of LHMDS or *n*-BuLi.



RLi	Compound 4									
	R', R"	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j
	R'	i-Pr	i-Pr	i-Pr	i-Pr	i-Pr	i-Pr	i-Pr	N-morphlyl	Ph	Ph
	R"	-CO-Ph	-CO-CH_3	-CO-CF_3	-SO_2-C_6H_4-CH_3	-CO-OC(CH_3)$_3$	-P(O)Ph_2	-P(O)(OPh)$_2$	-CO-OEt	-CO-OC(CH_3)$_3$	-P(O)(OPh)$_2$
LHMDS		450	40	40	-[a]	15	-[a]	-[a]	300	300	100
n-BuLi		45	10	0[b]	0[b]	15	0[b]	0[b]	120	120	20

[a] Alcohol **6** was not formed.
[b] The lithio derivative was completely decomposing while warming up to 20°C.

The approximate apparent $T_{1/2}$ values of 4-lithio derivatives **4a-j** generated from compounds **5a-j** by treatment with LHMDS or *n*-BuLi are shown in Table 2. As on can see, the stability values given in Table 2 for a specific lithio derivative vary depending on the deprotonating reagent used for generation of the compound. As a result, the features of the specific deprotonation process (see below in this section) affect the values. Therefore, it should be specially noted, that these are the apparent, not true, values.

The data presented in Table 2 show that the substituent on the N_6 nitrogen exerts a significant impact on the stability of 4-lithio derivatives generated from 3-alkyl substituted sydnone imines. Among them, the most stable is the N_6-benzoyl derivative **4a**. The corresponding alkylcarbonyl and alkoxycarbonyl derivatives are less stable. The 4-lithio derivatives bearing a heteroatomic substituent, such as 4-tolylsulfonyl (**4d**), diphenylphosphinyl (**4f**) or diphenylphosphoryl (**4g**) groups, at N_6 have the least stability and were completely decomposing while warming up to room temperature.

A stability of 4-lithio derivatives **4** also strongly depends on the substituent at *N*(3) of the oxadiazole ring. With N_6-alkoxycarbonyl derivatives, the thermal stability of the N_6-ethoxycarbonyl substituted compound **4h** bearing an amino functionality at *N*(3) is significantly higher than that of the *N*(3)-isopropyl substituted derivative **4e** with the *tert*-butoxycarbonyl group at the N_6 nitrogen. The phenyl substituent at *N*(3) of the oxadiazole ring increases the stability of **4**. The 3-phenyl derivatives **4i** and **4j** are significantly more stable than their 3-alkyl analogs**4e** and **4g**.

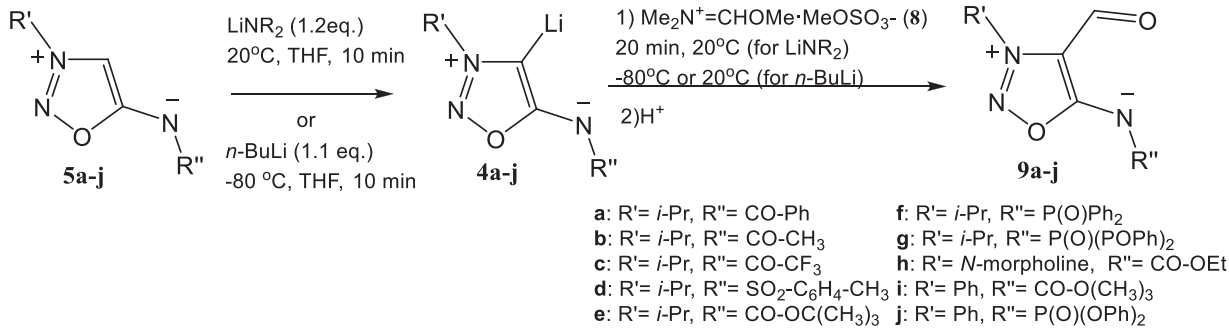
It should be noted that compounds **4** obtained by deprotonation of **5** with *n*-BuLi exhibited lower apparent stability then their relatives prepared using LHMDS as the base. This observation would be explained by stabilization of lithio derivatives **4** upon their coordination with the amine formed from LHMDS during the deprotonation reaction. However, the use of LDA or LDEA as deprotonating reagents resulted in a formation of compound **4a** that demonstrated the low apparent stability (Table 1) comparable to that one exhibited by this lithio compound obtained using *n*-BuLi as the base. In our opinion, the equilibrium character of the deprotonation process can explain the higher apparent stability of compounds **4** obtained using LHMDS. Unlike the reaction with *n*-BuLi, the equilibrium in the case of LHMDS is shifted towards the starting compound **5**, so that the low concentration of the generated 4-lithio derivative **4** leads to a decrease in the rate of the decomposition reaction and, consequently, to an increase of the apparent stability. The use LDA or LDEA, the stronger bases compared to LHDMS, as the deprotonating agents leads to a shift of the equilibrium towards the lithio derivatives **4**, thus decreasing the apparent stability of compounds **4**. In the case of *n*-BuLi, the deprotonation reaction is irreversible.

Our assumption that the equilibrium at deprotonation of **5** under the action of LHMDS is shifted towards the starting materials contradicts the statement[16, 17] that 4-lithio derivatives **4** are formedin this reaction quantitatively. It should be taken into account that the quantitative formation of **4** was deduced [21,22] only from the NMR data, although this method is not applicable to the fast dynamic processes. The almost quantitative yields of the products in some reactions of **4** with electrophiles both reported in [21,22] and observed by us can be easily explained by a gradual shift of the equilibrium "to the right" as the lithio derivatives **4** are consumed by the electrophiles.

Lithium dialkylamides have been reported to add the carbonyl group of benzaldehydes affording the lithium α-dialkylamino alkoxides [25,26]. In turn, LHMDS reacts with benzaldehyde to form the corresponding *N*-trimethylsilyl imine [27]. However, these reactions proceed at moderate rates taking in some cases more then 10 minutes at room temperature. Therefore, an addition reaction of lithium amides to the carbonyl group of benzaldehydes is only weakly able to compete with both the deprotonation of compounds **5** and the reaction of the 4-lithio derivative **4** with benzaldehyde. In addition, it should be taken into account that we used the excesses of both lithium amides (1.2 equiv) and *p*-chlorobenzaldehyde (1.3 equiv) in the reactions under consideration. This also reduces the possible effect of the side reaction of the deprotonating reagent with the electrophile on the reaction consequence**5**→ **4**→**6**.

As one can see from the data presented in Table 1 the first group sydnone imines (**5a,h,i**) that give the relatively stable 4-lithio derivatives produce the alcohols **6a,h,i** in very similar yields irrespectively the type of the deprotonating reagent used for generation of the lithium intermediates **4a,h,i**. So, the use of LDA or LDEA in these cases compares favorably with more expensive LHDMS and allows deprotonation at room temperature, thus greatly simplifying the synthetic procedure. In contrast, the deprotonation of **4** with *n*-BuLi can be carried out only at low temperature (-80°C), since our attempts to carry out this reaction at room temperature resulted in resinification of the reaction mixtures. However, the sydnone imines of the second (**5b,c,e,j**) and, especially, the third (**5d,f,g**) groups producing the much less stable 4-lithio derivatives should be deprotonated with *n*-BuLi at -80°C,

Table 3
Preparation of 4-formylsydnone imines **9**.



Compound **5**	Deprotonation with R_2NLi			Deprotonation with *n*-BuLi	
	R_2NLi, yields of **9**(**5**), %[a,b]			Temperature, °C	Yields of **9**(**5**), %[a]
	LHDMS	*i*-Pr_2NLi	Et_2NLi		
5a	69(10)	66(35)	26(73)	20[c]	80(18)
5b	28(3)	17(6)	0(38)	-80	42(2)
				20[c]	34(4)
5c	16(26)	0(57)	0(74)	-80	19(63)
5d	0(12)	-	-	-80	52(16)
5e	9(39)	-	-	-80	60(37)
5f	0(22)	0(57)	0(51)	-80	6(21)
5g	0(17)	0(63)	0(50)	-80	38(50)
5h	66(9)	55(20)	19(73)	20[c]	66(33)
5i	29(30)	21(51)	12(65)	20[c]	28(62)
5j	1(74)	0(84)	1(79)	-80	26(62)

[a] Calculated from ^{1}H MNR data using the internal standard.
[b] The percentages of the unreacted starting compounds **5** are given in parentheses.
[c] A solution of the lithio derivative **4** was heated from -80°C to 20°C for 1 min before adding the reagent **8**.

because the use of LHMDS at room temperature leads to lower yields of the products **6**. Both LDA and LDEA are inapplicable in these cases due to very poor yields of the alcohols **6**, if any.

2.2. Synthesis of 4-formyl derivatives of sydnone imines

We have proposed previously a method for preparation of 4-formylsydnone imines by the reaction of 4-lithiosydnone imines with an adduct of dimethylformamide with dimethyl sulfate (1-methoxy-*N*,*N*-dimethylmethanaminium methylsulfate, **8**) [18,19] inasmuch as these compounds cannot be obtained by a conventional reaction of the organolithiums with DMF due to an insufficient reactivity of 4-lithiosidnone imines. In addition, 4-formylsydnone imines can be exploited as the starting materials in an alternative approach to preparation of the α-substituted or unsubstituted 4-(hydroxymethyl) derivatives similar to the alcohols reported in section 2.3, the putative plant growth regulators (see section 2.4). Herein, we compared the applicability of various deprotonating agents (LHMDS, LDA, LDEA, and *n*-BuLi) for production of lithium intermediates **4** in the syntheses of 4-formyl derivatives of sydnone imines **9**. The results are shown in Table 3.

In all cases, the use of LDEA, as compared to other deprotonating reagents, lead to lower yields of 4-formyl derivatives **9**. This may be explained by the competitive side reaction of LDEA with the highly reactive reagent **8**. In this case, the rate of the reaction of LDEA with the electrophile is comparable or exceeds the rate of the deprotonation reaction thus notably decreasing the yield of the aldehydes **9**. With the 1st group sydnone imines (**5a,h,i**), the use of sterically hindered bases (LHMDS, LDA) allows a preparation of aldehydes **9** in high yields. In contrast, with the 2nd and 3rd group sydnone imines, *n*-BuLi turned out to be the only reagent applicable for the preparation of 4-formyl derivatives, since the use of lithium amide deprotonating reagents delivered only very poor yields of **9**, if any.

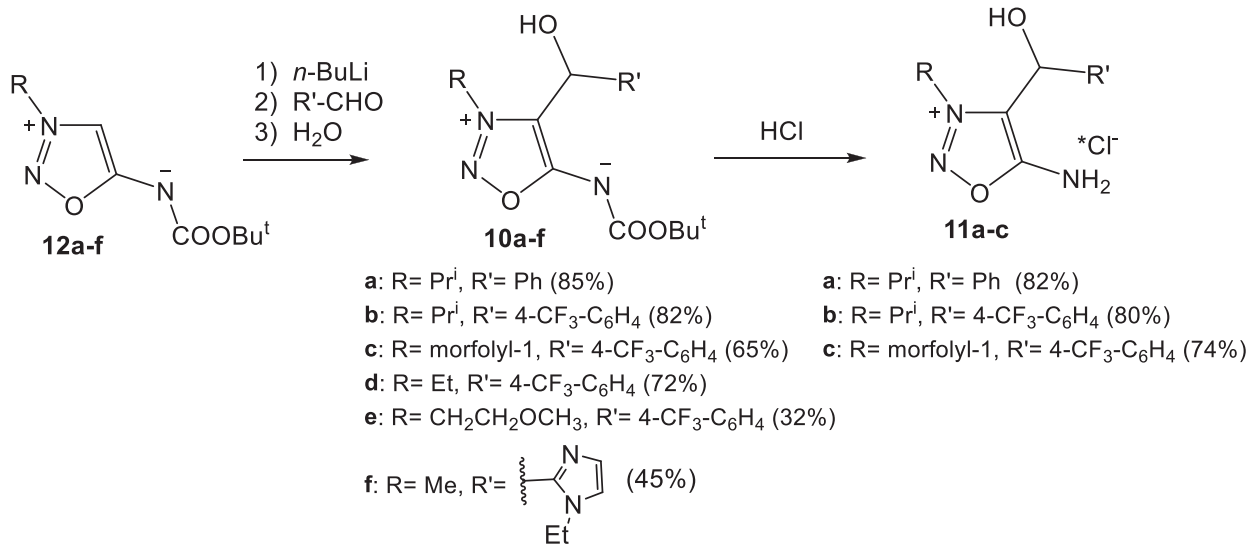
2.3. Synthesis of 4-(α-substitutedhydroxymethyl) derivatives sydnone imines for plant growth regulation studies

We prepared the α-substituted 4-hydroxymethyl derivatives of sydnone imines **10** and **11** from the corresponding 4-lithiosydnone imines (Scheme 5) to evaluate their plant growth regulating properties (see Section 2.4). To conduct SAR studies in this family, the compounds with variable substituents on the *C*(4) carbon were necessary, as well as both N_6-unsubstituted compounds (the sydnone imine salts) and their N_6-substituted relatives. Since sydnone imines unsubstituted at N_6 are stable only as salts, the direct *C*(4)-lithiation of such salts is impossible. So, we used the N_6-Boc-protected derivatives **12** as the starting materials and metalated them according the previously reported method [28].

The reaction of aromatic aldehydes with *C*(4)-lithiated intermediates formed on the deprotonation of compounds **12a-f** under the action of *n*-BuLi followed by the hydrolytic workup of the reaction mixtures led to the formation of the corresponding N_6-Boc-substituted derivatives **10**. Subsequent removal of the protective Boc-group proceeded smoothly [28] and furnished the required N_6-unsubstituted compounds **11** as the hydrochlorides.

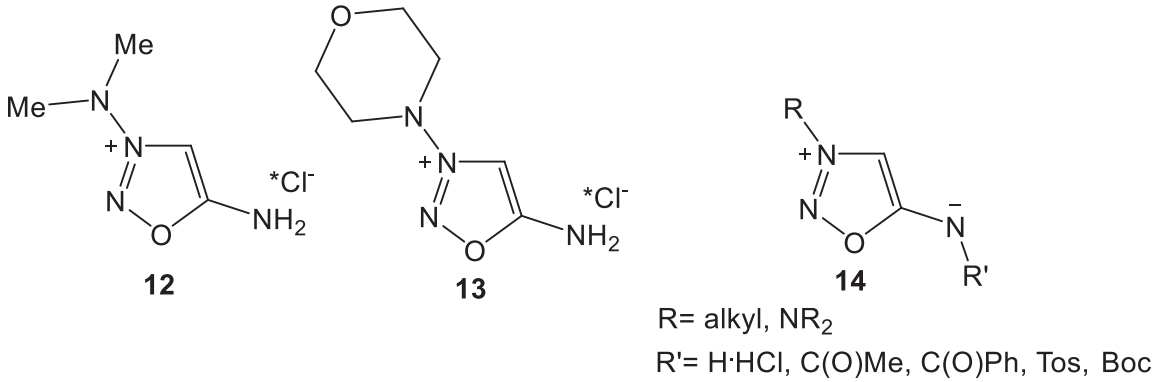
2.4. Plant growth regulating activity of sydnone imines

Recently we were the first to show that derivatives of sydnone imine have a pronounced effect on the growth and development of plants [11,12]. Specifically, compounds **12** and **13** with dimethylamino or *N*-morpholyl groups attached to the *N*(3) nitrogen showed a herbicidal effect in very small doses (1 g and 10 g per 1 ton of seeds) negatively affecting the germination of sunflower seeds [11]. In contrast, *C*(4)-unsubstituted *N*(3)-alkyl and *N*(3)-amino derivatives of sydnone imines **14** taken as either hydrochlorides or N_6-acylated relatives in the experiments on corn



Scheme 5. Synthesis of α-aryl substituted 4-hydroxymethyl derivatives **10a-f** and **11a-c**.

seeds stimulated the seed germination and the development of both shoots and roots [12].



These results have proved sydnone imines to emerge as a new family of plant growth regulating compounds. So, the data on the relationship between the molecular structures of sydnone imine derivatives and their plant growth regulating properties are of undoubted interest. As noted above, the plant growth regulating sydnone imine derivatives have so far been exemplified only by the *C*(4) unsubstituted compounds. Therefore, it was of interest to disclose whether the derivatives substituted at *C*(4) possess the growth regulating properties, and, if it would be the case, how these properties are affected by the substituents both at C(4) and at *N*(3) and N_6. With this background, we examined α-arylated 4-hydroxymethylsydnone imines **10a-f, 11a-c** readily available from the reaction of 4-lithiosidnone imines with aromatic aldehydes (see Section 2.3) for pre-sowing treatment of corn seeds, which were than evaluated in the pot experiments. The results (see the Table in Supporting Information) showed that all examined compounds, except **10e,f**, exhibited the corn growth stimulation at very low doses (0.25-5 g t^{-1} of seeds). The increase in the shoots weight of the plants compared to the control ($Ctrl_{aq.}$) reached 64% and was dose depended in many cases.

A comparison of N_6-Boc protected compounds **10a-c** with their unprotected counterparts **11a-c** proved that a Boc group can affect the activity of the compounds both qualitatively and quantitatively. But this influence is not unambiguous. For example, the growth stimulating effect is the maximum for the unprotected compound **11a** (57-64%) at higher doses (0.5 and 1.0 g t^{-1}) and essentially decreases (23%) at a dose of 0.25 g t^{-1}, whereas the corresponding Boc-protected compound **10a** is notably less active, but the activity of the last is the same at all doses (36-40%). On the contrary, the stimulating effects of compounds **10b** and **11b** at a dose of 1 g t^{-1} are similar (45-49%), with the effect of **10b** decreased with the decrease of the dose while the effect of **11b** decreased as the dose increased.

At doses of 0.5 g t^{-1}, the growth stimulating effect of the Boc-derivative **10c** was approximately 2 times higher than that of the unprotected compound **11c** (38% and 20%, respectively) and decreased to the same value (14%) at higher doses. The effect of the *N*(3)-isopropyl substituted derivatives **10a,b** and **11a,b** was more pronounced than that of the corresponding *N*(3)-morpholyl derivatives **10c** and **11c**. This testifies that the substituent at *N*(3) affects the growth stimulating ability of sydnone imines. Therefore, the relative activity of *N*(3)-alkyl substituted compounds was screened. It was found that among compounds **10b,d,e** bearing the identical substituents both at *C*(4) and at N_6, the substituent at *N*(3) strongly influenced the growth regulating effect. The *N*(3)-ethyl substituted compound **10d** turned to be less active than the isopropyl derivative **10b**, and the 2-metoxyethyl derivative **10e** containing the heteroatom in the *N*(3)-alkyl chain was found to be

inactive. The aromatic auxiliary in the substituent at *C*(4) also has some effect on the growth regulation (compounds **10a,b**). We were surprised to found that the imidazole derivative **10f** was inactive. This result may indicate that the replacement of an aryl group at the α-position to C(4) of sydnone imines with a heteroaryl substituent may affect either bioavailability of these compounds or their metabolism.

All in all, *C*(4)-substituted sydnone imines are promising plant growth regulating compounds. Specifically, the majority of the 4-hydroxymethyl derivatives investigated in this work stimulated the corn development in pot experiments (up to 64% increase of the shoots weight). This effect was shown to have, as a rule, a dose dependent character, along with the magnitude of the effect depends on a molecular structure of the sydnone imine derivative, specifically, on the substituents at *N*(3) and N_6 as well as the nature of the aromatic group in the substituent at *C*(4). Obviously, the structure-activity relationship data of biologically active compounds can be correctly interpreted only with the information on their mode of action in hands. At the moment, we associate the mode of action of the sydnone imine derivatives as the plant growth regulators with the above mentioned role of sydnone imines as the exogenous donors of nitrogen(II) oxide molecules. However, this needs the unambiguous proofs. The relative studies are now in progress and the results will be published anywhere.

3. Conclusion

To conclude, we re-examined the C(4)-deprotonation of sydnone imines under the action of lithium amides (LHDMS, LDA, LDEA) and *n*-BuLi. As a rule, 4-lithiosydnone imines were found to exhibit a low thermal stability. However, the stability substantially depends on the nature of the substituents at *N*(3) and N_6 of the sydnone imines. Some 4-lithiosydnone imines survive on keeping in THF solutions at room temperature for dozens of minutes. So, lithium amides, LHDMS or cheaper LDA or LDEA, can be utilized for preparation of these organolithiums as the deprotonating reagents. The use of *n*-BuLi as the base for this purpose is more general, however, the too low temperature of the process complicates it. In addition, we found that α-aryl substituted 4-hydroxymethylsydnone imines readily available from the reaction of 4-lithiosidnone imines with aromatic aldehydes exhibit plant growth regulating properties. Utilized for a pre-sowing treatment of corn seeds at very low doses (0.25-5 g per ton of seeds), these compounds in pot experiments showed a stimulation of the corn development resulting in an increase of the shoots weight up to 64% compared to the control.

4. Experimental

4.1. Materials and instrumentation

NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer with basic frequencies of 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C, 161.96 MHz for ^{31}P, and 376 MHz for ^{19}F. All chemical shifts in ^{1}H and ^{13}C spectra were referenced by TMS and residual deuterium solvents signals. In ^{31}P spectra, all chemical shifts were referenced by orthophosphoric acid. In ^{19}F chemical shifts were referenced by trichlorofluoromethane. Data are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (J, Hz). Elemental analyses were performed using a Carlo-Erba CE-1106 elemental analyzer. Melting points were determined with an Electrorthermal 1002 MEL-TEMP® capillary melting point apparatus and are uncorrected. TLC was performed on Silufol UV-254 plates; the spots were visualized in camera with iodine. Column liquid chromatography was performed using silica gel (particle size 80 μm).

All solvents were purified (dried and distilled) before use according to literature methods. All reactions were performed in an argon atmosphere in dried glassware. All reagents were used as supplied by commercial sources unless otherwise stated. Starting sydnone imines were prepared as described **5a,b** [29], **5c,d** [19], **5e,i** [28], **5f,g,j** [15], **5h** [30].1-Methoxy-*N,N*-dimethylmethanaminium methylsulphate (**8**) was obtained according to the known method [31].

4.2. Generation of 4-lithio derivatives of sydnonimines 4a-j by the action of different deprotonating agents and study of their stability

4.2.1. Deprotonation of sydnone imines with n-BuLi

To a solution of sydnone imine **5** (0.60 mmol) in THF (20 ml) was added 1.9M solution of *n*-BuLi (0.32 ml, 0.66 mmol) in hexane at -80°C. The mixture was stirred at -80°C for 10 min and 1M solution of *p*-chlorobenzaldehyde (0.72 ml, 0.72 mmol) in THF was added. The mixture was stirred for 5 min. The reaction mixture was heated on a water bath to room temperature, stirred for another 20 min, then quenched with H_2O (1 ml) and the internal standard (0.60 ml, 0.1 mmol, 0,167M solution of 4,4′-di-*tert*-butylbiphenyl or hexamethylbenzene in THF) was added. The solvent was evaporated under reduced pressure.

For the stability evaluation of the 4-lithio derivatives of sydnone imines **4**, the addition of *n*-BuLi to the solution of **5** and keeping the mixture at -80°C for 10 min was followed by quick heating the reaction mixture on a water bath to room temperature and keeping it at this temperature for 0-480 min (Table 1). Then, 1 M solution of *p*-chlorobenzaldehyde (0.72 ml, 0.72 mmol) in THF was added, the mixture was stirred for 20 min and quenched with H_2O (1 ml). An internal standard (0.60 ml, 0.1 mmol, 0,167M solution of 4,4′-di-*tert*-butylbiphenyl or hexamethylbenzene in THF) was added. The solvent was evaporated under reduced pressure.

In both cases, the residue after evaporation of the solvent was passed through a layer of SiO_2 (20 × 20 mm) using EtOAc/$CHCl_3$ (1:1) as the eluent. After removing the solvent at reduced pressure, the residue was analyzed by ^{1}H NMR spectroscopy (see Supplementary materials).

4.2.2. Deprotonation of sydnone imines with LHMDS

To a solution of sydnonimine **5** (0.60 mmol) in THF (20 ml) a 1M solution of LHMDS (0.72 ml, 0.72 mmol) in THF was added. The mixture was stirred at room temperature for 10-720 min (Table 1) and 1M solution of *p*-chlorobenzaldehyde (0.72 ml, 0.72 mmol) in THF was added. The reaction mixture was stirred for 20 min and quenched with H_2O (1 ml). The internal standard (0.60 ml, 0.1 mmol 0,167M solution of 4,4′-di-*tert*-butylbiphenyl or hexamethylbenzene in THF) was added. The solvent was evaporated under reduced pressure. The residue was passed through a layer of SiO_2 (20 × 20 mm) using EtOAc:$CHCl_3$ (1:1) as the eluent. After evaporation of the solvent at reduced pressure, the residue was analyzed by ^{1}H NMR spectroscopy (see Supplementary materials).

4.2.3. Deprotonation of sydnone imines with lithium diethylamide or diisopropylamide

A 1.9 M solution of *n*-BuLi (0.38 ml, 0.72 mmol) in hexane was added to a solution of diethylamine (0.08 ml, 0.78 mmol) or diisopropylamine (0.11 ml, 0.78 mmol) in THF (20 ml). The mixture was stirred for 10 min and sydnone imine **5** (0.6 mmol) was added. The mixture was stirred at room temperature for 10-180 min (Table 1) and 1M solution of *p*-chlorobenzaldehyde (0.72 ml, 0.72 mmol) in THF was added. The mixture was stirred for 20 min and quenched with H_2O (1 ml). The internal standard (0.60 ml,

0.1 mmol 0,167M solution of 4,4′-di-*tert*-butylbiphenyl or hexamethylbenzene in THF) was added. The solvent was evaporated under reduced pressure and the residue was passed through a layer of SiO_2 (20 × 20 mm) using EtOAc:$CHCl_3$ (1:1) as eluent. The solvent was evaporated at reduced pressure and analyzed by ^{1}H NMR spectroscopy (see Supplementary materials).

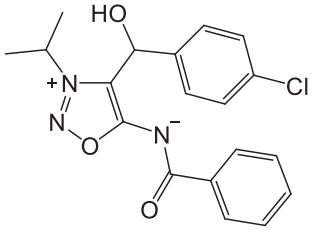
4.3. Preparation of 4-formyl derivatives of sydnone imines (9) (general procedure)

A 1M solution of 1-methoxy-*N,N*-dimethylmethanaminium methylsulphate **8** (0.72 ml, 0.72 mmol) in DMF was added to a solution of the 4-lithio derivative of sydnone imine **4** (0.6 mmol) in THF (20 ml) prepared by one of the methods described above (see Table 1). The reaction mixture was stirred for 20 min and quenched with H_2O (1 ml). The internal standard (0.60 ml, 0.1 mmol, 0,167M solution of 4,4′-di-*tert*-butylbiphenyl or hexamethylbenzene in THF) was added. The solvent was evaporated at reduced pressure. The residue was dissolved in ethyl acetate (20 ml) and washed with water (20 ml). The organic layer was separated and passed through a layer of SiO_2 (20 × 20 mm) using EtOAc:$CHCl_3$ (1:1) as the eluent. The solvent was evaporated at reduced pressure and analyzed by ^{1}H NMR spectroscopy (see Supplementary materials).

The analytical samples of compounds **6a-i, 7, 9a-j** were obtained by column chromatography (SiO_2, 20 × 150 mm, EtOAc:$CHCl_3$ (from 1:9 to 1:1)) followed by crystallization from, unless otherwise indicated, isopropanol/hexanes.

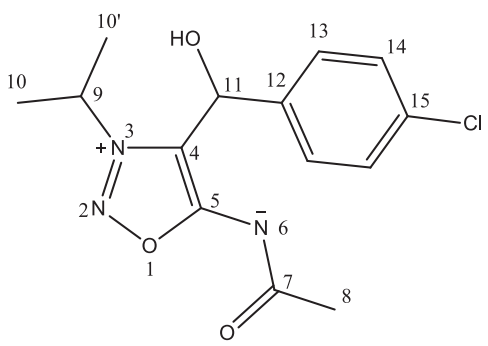
4.4. Analytical data for compounds 6a-i, 7, 9a-j

4-[(4'-Chlorophenyl)-hydroxymethyl]-3-isopropyl-N_6-benzoylsydnone imine (6a).



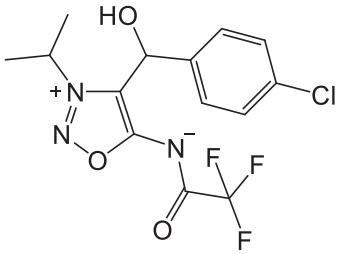
White solid, m. p. 162-163°C. Calculated for $C_{19}H_{18}ClN_3O_3$: C, 61.37; H, 4.88; Cl, 9.54; N, 11.30 %. Found C, 61.40; H, 4.91; N, 11.28 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, 3H, J = 6.7 Hz, CH(C**H$_3$**)$_2$); 1.76 (d, 3H, J = 6.6 Hz, CH(C**H$_3$**)$_2$); 5.14 (hept, 1H, J = 6.4 Hz, C**H**(CH$_3$)$_2$); 6.14 (s, 1H, C**H**-OH); 6.73 (s, 1H, **C**H-O**H**); 7.34-7.37 (m, 5H + 1H, C_6**H$_4$**Cl + *m*-C_6**H$_5$**); 7.45 (t, 1H, J = 7.3 Hz, *p*-C_6**H$_5$**); 8.05 (d, 2H, J = 7.4 Hz, *o*-C_6**H$_5$**). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.7, 22.0, 57.2, 63.5, 119.1, 126.8, 127.9, 128.8, 129.6, 131.5, 133.7, 137.0, 138.0, 168.3, 173.6.

4-[(4'-Chlorophenyl)hydroxymethyl]-3-isopropyl–N_6-acetylsydnone imine (6b).



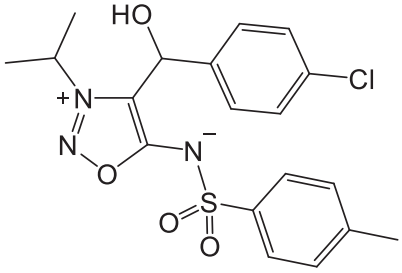
White solid, m. p. 142-143°C. Calculated for $C_{14}H_{16}ClN_3O_3$: C, 54.29; H, 5.21; Cl, 11.45; N, 13.57 %. Found C, 54.41; H, 5.33; N, 13.68 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, 3H, J = 6.7 Hz, CH(C**H$_3$**)$_2$); 1.67 (d, 3H, J = 6.6 Hz, CH(C**H$_3$**)$_2$); 2.11 (s, 3H, C**H$_3$**CO); 4.99 (hept, 1H, J = 6.6 Hz, C**H**(CH$_3$)$_2$); 6.27 (s, 1H, C**H**-OH); 7.06 (s_{br}, 1H, CH-O**H**), 7.32-7.39 (m, 4H, C_6**H$_4$**). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.6 (C_{10}, $C_{10'}$), 22.0 (C_{10}, $C_{10'}$), 26.8 (C_{11}), 57.6 (C_9), 63.3 (C_{11}), 118.7 (C_4), 126.9 (C_{13}), 128.8 (C_{14}), 133.8 (C_{15}), 137.9 (C_{12}), 169.0 (C_5), 179.4 (C_7). (2D ^{1}H^{13}C-HMQC and 2D ^{1}H^{13}C-HMBC correlation of **6b** – See Supplementary materials)

4-[(4'-Chlorophenyl)hydroxymethyl]-3-isopropyl–N_6-trifluoroacetylsydnone imine (6c).



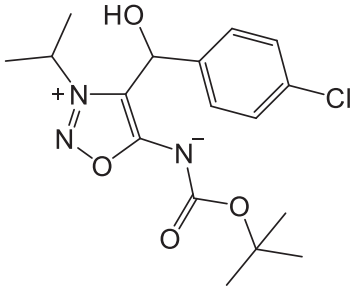
White solid, m. p. 134-135°C. Calculated for $C_{14}H_{13}ClF_3N_3O_3$: C, 46.23; H, 3.60; Cl, 9.75; F, 15.67; N, 11.55 %. Found C, 46.36; H, 3.73; N, 11.62 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, 3H J = 6.6 Hz, CH(C**H$_3$**)$_2$); 1.74 (d, 3H, J = 6.6 Hz, CH(C**H$_3$**)$_2$); 5.10 (hept, 1H, J = 6.5 Hz, C**H**(CH$_3$)$_2$), 6.40 (s, 1H, C**H**-OH), 7.32-7.41 (m, 4H, C_6**H$_4$**). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.7, 22.1, 58.9, 63.3, 118.3 (q, J = 285.9 Hz), 121.3, 126.7, 129.1, 134.3, 136.7, 142.5, 162.6 (q, J = 36.3 Hz), 170.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.57.

4-[(4'-Chlorophenyl)hydroxymethyl]-3-isopropyl-N_6-tosylsydnone imine (6d).



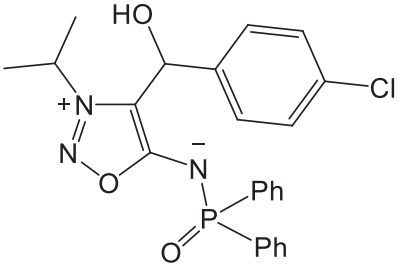
White solid, m. p. 183-184°C. Calculated for $C_{19}H_{20}ClN_3O_4S$: C, 54.09; H, 4.78; Cl, 8.40; N, 9.96; S, 7.60 %. Found C, 54.17; H, 4.85; N, 10.07 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.22 (d, 3H, J = 6.7 Hz, CH(C**H$_3$**)$_2$); 1.55 (d, 3H, J = 6.6 Hz, CH(C**H$_3$**)$_2$); 2.37 (s, 3H, C**H$_3$**-C_6H_4); 5.09 (hept, 1H, J = 6.6 Hz, C**H**(CH$_3$)$_2$); 5.95 (d, 1H, J = 4.3 Hz, CH-O**H**); 6.87 (d, 1H, J = 4.3 Hz, C**H**-OH); 7.35 (d, 2H, J = 8.1 Hz, C_6**H$_4$**-CH$_3$); 7.40 (d, 2H, J = 8.6 Hz, C_6**H$_4$**-Cl); 7.45 (d, 2H, J = 8.6 Hz, C_6**H$_4$**-Cl); 7.74 (d, 2H, J = 8.2 Hz, C_6**H$_4$**-CH$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 21.4, 21.8, 22.0, 58.0, 62.9, 116.3, 126.8, 127.8, 128.9, 129.8, 132.9, 138.9, 140.7, 142.6, 163.2.

4-[(4'-Chlorophenyl)hydroxymethyl]-3-isopropyl-N_6-*tert*-butoxycarbonylsydnone imine (6e).



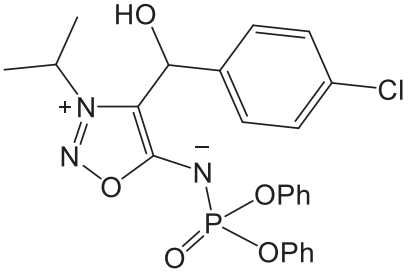
White solid, m. p. 159-160°C. Calculated for $C_{17}H_{22}ClN_3O_4$: C, 55.51; H, 6.03; Cl, 9.64; N, 11.42 %. Found C, 55.58; H, 6.09; N, 11.46 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, 3H J = 6.7 Hz, CH(C**H$_3$**)$_2$); 1.49 (s, 9H, C(**CH$_3$**)$_3$); 1.62 (d, 3H, J = 6.6 Hz, CH(C**H$_3$**)$_2$); 4.96 (hept, 1H, J = 6.3 Hz, C**H**(CH$_3$)$_2$); 6.32 (s$_{br}$, 1H, CH-O**H**); 6.17 (s, 1H, C**H**-OH); 7.28-7.35 (m, 4H, C$_6$**H$_4$**). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.5, 22.1, 28.2, 57.3, 62.9, 79.8, 117.2, 126.9, 128.8, 133.7, 138.4, 158.6, 167.4.

4-[(4'-Chlorophenyl)hydroxymethyl]-3-isopropyl-*N*$_6$-diphenylphosphinylsydnone imine (6f).



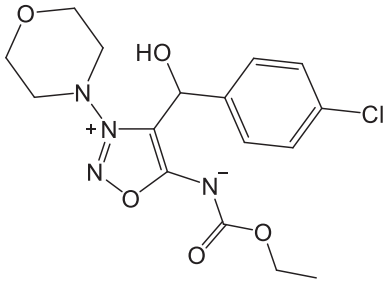
White solid, m. p. 202-203°C. Calculated for $C_{24}H_{23}ClN_3O_3P$: C, 61.61; H, 4.95; Cl, 7.58; N, 8.98; P, 6.62 %. Found C, 61.74; H, 5.07; N, 9.14 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, 3H, J = 6.7 Hz, CH(C**H$_3$**)**$_2$**); 1.62 (d, 3H, J = 6.6 Hz, CH(C**H$_3$**)**$_2$**); 5.20 (hept, 1H, J = 6.6 Hz, C**H**(CH$_3$)$_2$); 6.15 (s, 1H, C**H**-OH); 7.20-7.42 (m, 10H, C$_6$**H$_4$** + C$_6$**H$_5$**); 7.72-7.77 (m, 2H, C$_6$**H$_5$**); 7.83-7.88 (m, 2H, C$_6$**H$_5$**). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.7, 21.9, 56.8, 63.3, 116.4 (d, J = 12.9 Hz), 126.8, 128.1 (d, J = 5.1 Hz), 128.3 (d, J = 5.5 Hz), 128.5, 130.9 (d, J = 2.4 Hz), 131.0 (d, J = 2.7 Hz), 131.22 (d, J = 10.0 Hz), 131.48 (d, J = 9.8 Hz), 133.2, 135.2 (d, J = 139.7 Hz), 135.4 (d, J = 126.2 Hz), 139.5, 165.22 (d, J = 3.1 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.8.

4-[(4'-Chlorophenyl)hydroxymethyl]-3-isopropyl-*N*$_6$-diphenylphosphorylsydnone imine (6g).



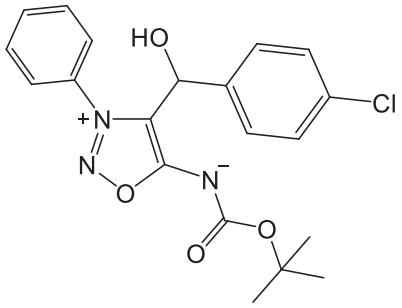
White solid, m. p. 132-133°C. Calculated for $C_{24}H_{23}ClN_3O_5P$: C, 57.66; H, 4.64; Cl, 7.09; N, 8.41; P, 6.20 %. Found C, 57.71; H, 4.68; N, 8.47 %. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 1.21 (d, 3H J = 6.0 Hz, CH(C**H$_3$**)$_2$); 1.58 (d, 3H, J = 5.9 Hz, CH(C**H$_3$**)$_2$); 5.00-5.18 (m, 1H, C**H**(CH$_3$)$_2$); 5.97 (s$_{br}$, 1H, O**H**); 6.85 (d, J = 2.3 Hz, 1H, CH); 7.11-7.26 (m, 6H, C$_6$**H$_5$** + C$_6$**H$_4$**); 7.27-7.48 (m, 8H, C$_6$**H$_5$**+ C$_6$**H$_4$**). ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 21.7, 22.0, 57.6, 63.0, 115.6, 115.8, 120.6 (d, J = 4.7 Hz), 120.7 (d, J = 4.7 Hz), 124.8 (d, J = 4.4), 127.7, 128.9, 130.1, 132.8, 139.3, 151.7 (d, J = 7.2 Hz), 151.8 (d, J = 7.4 Hz), 164.8. ^{31}P NMR (162 MHz, $CDCl_3$) δ 7.6.

4-[(4'-Chlorophenyl)hydroxymethyl]-3-morpholyl-*N*$_6$-ethoxycarbonylsydnone imine (6h).



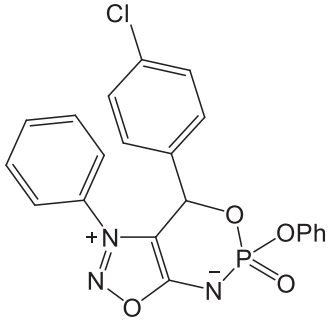
White solid, m. p. 155.5-156.5°C. Calculated for $C_{16}H_{19}ClN_4O_5$: C, 50.20; H, 5.00; Cl, 9.26; N, 14.64 %. Found C, 50.33; H, 5.11; N, 14.71 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, 3H, J = 7.1 Hz, C**H$_3$**-CH$_2$); 3.46-3.47 (m, 4H, C**H$_2$**-CH$_2$); 3.82 (m, 4H, C**H$_2$**-CH$_2$); 3.89-3.99 (m, 2H, CH$_3$-C**H$_2$**); 6.08 (s$_{br}$, 2H, CH-O**H** + C**H**-OH); 7.22-7.43 (m, 4H, C$_6$**H$_4$**). ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.3, 55.9, 61.7, 64.1, 66.0, 114.3, 126.9, 128.6, 133.7, 137.5, 160.7, 169.5.

4-[(4'-Chlorophenyl)hydroxymethyl]-3-phenyl-*N*$_6$-*tert*-butoxycarbonylsydnone imine (6i).



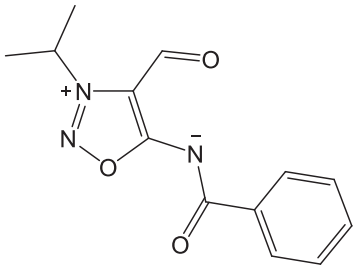
White solid, m. p. 163-164°C. Calculated for $C_{20}H_{20}ClN_3O_4$: C, 59.78; H, 5.02; Cl, 8.82; N, 10.46 %. Found C, 59.89; H, 5.20; N, 10.51 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 9H, C(**CH$_3$**)$_3$); 5.80 (s, 1H, C**H**-OH); 6.55 (s$_{br}$, 1H, CH-O**H**); 7.12 (d, 2H, J = 8.3 Hz, C$_6$**H$_4$**); 7.21 (d, 2H, J = 8.4 Hz, C$_6$**H$_4$**); 7.53-7.77 (m, 5H, C$_6$**H$_5$**). ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.0, 64.8, 79.7, 117.5, 125.2, 126.8, 128.7, 130.2, 132.5, 132.9, 133.6, 137.5, 159.8, 169.7.

9-(4-Chlorophenyl)-8-oxa-7-oxo-7-phenoxy-3-phenyl-7-phospha-6,4-propanosydnone imine (7).



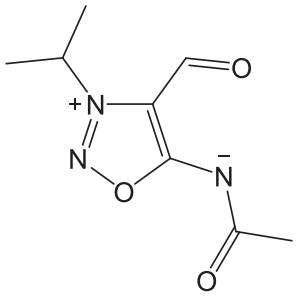
White solid, m. p. 136-137°C (dec.). Calculated for $C_{21}H_{15}ClN_3O_4P$: C, 57.35; H, 3.44; Cl, 8.06; N, 9.55; P, 7.04 %. Found C, 57.43; H, 3.50; N, 9.62 %. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 6.85 (s, 1H, C**H**); 7.20 (m, 3H); 7.30-7.47 (m, 8H); 7.48-7.59 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 74.2 (d, J = 7.9 Hz), 110.0 (d, J = 14.5 Hz), 121.0 (d, J = 4.5 Hz), 125.11, 125.34, 128.76, 129.93, 130.21, 131.40, 132.33, 132.83, 133.2 (d, J = 7.5 Hz), 134.88, 151.1 (d, J = 7.7 Hz), 172.1 (d, J = 12.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.51.

4-Formyl-3-isopropyl-N_6-benzoylsydnone imine (9a).



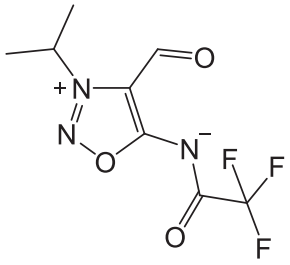
White solid, m. p. 117-118°C. Calculated for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21 %. Found C, 60.32; H, 5.16; N, 16.29 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (d, 6H, J = 6.6 Hz, CH(C**H$_3$**)**$_2$**); 5.76 (hept, 1H, J = 6.6 Hz, C**H**(CH$_3$)$_2$); 7.46 (t, 2H, J = 7.6 Hz, *m*-C$_6$**H$_5$**); 7.54 (t, 1H, J = 7.2 Hz, *p*-C$_6$**H$_5$**); 8.27 (d, 2H, J = 7.5 Hz, *o*-C$_6$**H$_5$**); 10.13 (s, 1H, C**H**O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.4, 51.1, 54.5, 60.1, 110.9, 128.2, 129.9, 132.3, 136.1, 167.2, 173.4, 177.7.

4-Formyl-3-isopropyl-N_6-acetylsydnone imine (9b).



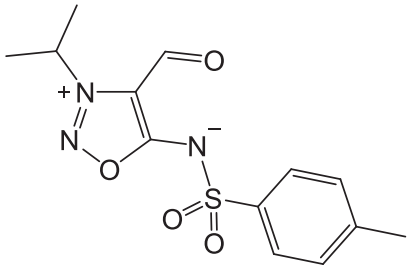
Pale yellow oil. Calculated for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31 %. Found C, 48.99; H, 5.43; N, 21.11 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 (d, 6H, J = 6.6 Hz, CH(C**H$_3$**)**$_2$**); 2.28 (s, 3H, C**H$_3$**CO); 5.74 (hept, 1H, J = 6.6 Hz, C**H**(CH$_3$)$_2$); 9.99 (s, 1H, C**H**O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.4, 27.5, 60.1, 110.3, 165.5, 177.6, 179.9.

4-Formyl-3-isopropyl-N_6-trifluoroacetylsydnone imine (9c).



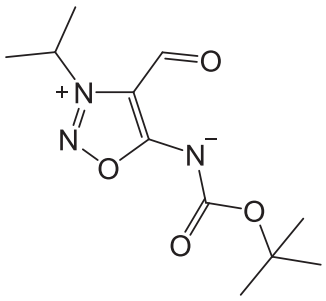
White solid, m. p. 73-74°C. Calculated for $C_8H_8F_3N_3O_3$: C, 38.26; H, 3.21; F, 22.69; N, 16.73 %. Found C, 38.28; H, 3.26; N, 16.80 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (d, 6H, J = 6.6 Hz, CH(C**H$_3$**)**$_2$**); 5.81 (hept, 1H, J = 6.5 Hz, C**H**(CH$_3$)$_2$); 10.16 (s, 1H, C**H**O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.4, 61.4, 112.8, 116.4 (q, J = 287.8 Hz), 163.2 (q, J = 37.7 Hz), 170.9, 177.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.21.

4-Formyl-3-isopropyl-N_6-tosylsydnone imine (9d).



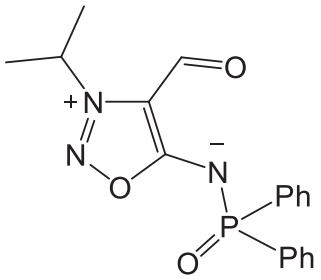
White solid, m. p. 139-140°C. Calculated for $C_{13}H_{15}N_3O_4S$: C, 50.47; H, 4.89; N, 13.58; S, 10.37 %. Found C, 50.51; H, 4.93; N, 13.61 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (d, 6H, J = 6.6 Hz, CH(C**H$_3$**)**$_2$**); 2.42 (s, 3H, C**H$_3$**-C$_6$H$_4$); 5.65 (hept, 1H, J = 6.6 Hz, C**H**(CH$_3$)$_2$); 7.31 (d, 2H, J = 8.2 Hz, C$_6$**H$_4$**); 7.94 (d, 2H, J = 8.2 Hz, C$_6$**H$_4$**); 9.65 (s, 1H, C**H**O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.2, 21.6, 60.6, 109.7, 127.2, 129.5, 138.5, 143.4, 163.6, 176.1.

4-Formyl-3-isopropyl-N_6-*tert*-butoxycarbonylsydnone imine (9e).



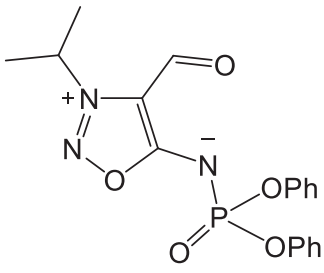
White solid, m. p. 63-64°C. Calculated for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46 %. Found C, 51.88; H, 6.83; N, 16.54 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 9H, C(**CH$_3$**)**$_3$**); 1.67 (d, 6H, J = 6.6 Hz, CH(C**H$_3$**)**$_2$**); 5.69 (hept, 1H, J = 6.5 Hz, C**H**(CH$_3$)$_2$); 9.81 (s, 1H, C**H**O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.3, 28.0, 59.8, 80.5, 109.5, 157.8, 165.7, 176.8.

4-Formyl-3-isopropyl-N_6-diphenylphosphinylsydnone imine (9f).



White solid, m. p. 121-122.5°C. Calculated for $C_{18}H_{18}N_3O_3P$: C, 60.84; H, 5.11; N, 11.83; P, 8.72 %. Found C, 60.91; H, 5.22; N, 11.91 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (d, 6H, J = 6.6 Hz, CH(C**H$_3$**)**$_2$**); 5.63 (hept, 1H, J = 6.5 Hz, C**H**(CH$_3$)$_2$); 7.42-7.46 (m, 6H, C$_6$**H$_5$**); 7.89-7.95 (m, 4H, C$_6$**H$_5$**); 9.93 (s, 1H, C**H**O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.1, 59.7, 109.5 (d, J = 9.9 Hz), 128.3 (d, J = 12.9 Hz), 131.3 (d, J = 9.9 Hz), 131.3 (d, J = 2.8 Hz), 135.0 (d, J = 131.6 Hz), 164.3, 177.4. ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.1.

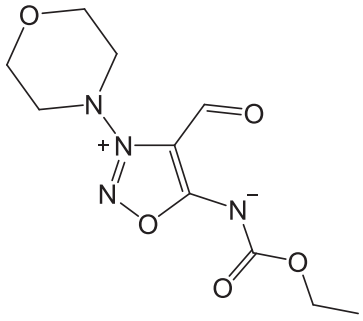
4-Formyl-3-isopropyl-N_6-diphenylphosphorylsydnone imine (9g).



Pale yellow oil. Calculated for $C_{18}H_{18}N_3O_5P$: C, 55.82; H, 4.68; N, 10.85; P, 8.00 %. Found C, 55.92; H, 4.83; N, 10.98 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (d, 6H, J = 6.6 Hz, CH(C**H$_3$**)**$_2$**); 5.63 (hept, 1H, J = 6.6 Hz, C**H**(CH$_3$)$_2$); 7.14-7.17 (m, 2H, C$_6$**H$_5$**); 7.29-7.37 (m, 8H, C$_6$**H$_5$**); 9.68 (s, 1H, C**H**O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.2,

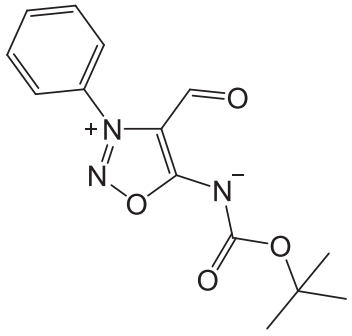
60.2, 109.5, 109.7, 120.5, 120.5, 124.8, 129.6, 151.1, 151.2, 165.2, 165.2, 176.7. ^{31}P NMR (162 MHz, $CDCl_3$) δ -9.1.

4-Formyl-3-morpholino-N_6-ethoxycarbonylsydnone imine (9h).



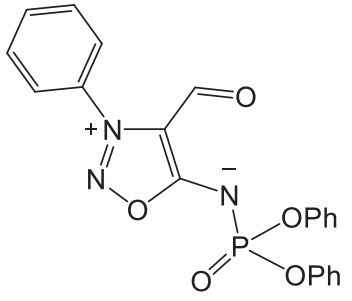
White solid, m. p. 145-146°C. Calculated for $C_{10}H_{14}N_4O_5$: C, 44.44; H, 5.22; N, 20.73 %. Found C, 44.55; H, 5.32; N, 20.86 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, 3H, J = 7.1 Hz, C**H$_3$**-CH_2); 3.58 (m, 4H, C**H$_2$**-CH_2); 3.87-4.07 (m, 4H, C**H$_2$**-CH_2); 4.24 (q, 2H, J = 7.1 Hz, CH_3-C**H$_2$**); 9.76 (s, 1H, C**H**O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 55.5, 62.1, 65.6, 106.9, 158.6, 165.8, 174.2.

4-Formyl-3-phenyl-N_6-*tert*-butoxycarbonylsydnone imine (9i).



White solid, m. p. 170-171°C (dec.). Calculated for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53 %. Found C, 58.23; H, 5.30; N, 14.62 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 9H, C(**CH$_3$**)**$_3$**); 7.50-7.82 (m, 5H, C_6**H$_5$**); 9.81 (s, 1H, C**H**O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.1, 80.8, 110.7, 124.9, 129.9, 132.7, 133.3, 164.9, 175.2, 189.6.

4-Formyl-3-phenyl-N_6-diphenylphosphorylsydnone imine (9j).

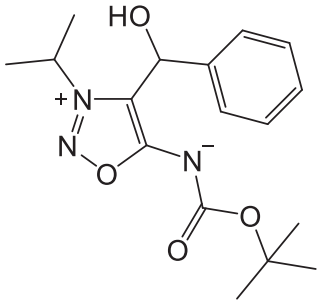


White solid, m. p. 128-128.5°C. Calculated for $C_{21}H_{16}N_3O_5P$: C, 59.86; H, 3.83; N, 9.97; P, 7.35 %. Found C, 59.93; H, 3.94; N, 10.07 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13-7.21 (m, 2H); 7.35 (m, 8H); 7.54-7.78 (m, 5H); 9.70 (s, 1H, C**H**O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 110.6 (d, J = 16.2 Hz), 120.6 (d, J = 5.0 Hz), 124.76, 124.88, 129.65, 129.88, 132.66, 133.44, 151.2 (d, J = 7.8 Hz), 164.6 (d, J = 1.2 Hz), 175.10. ^{31}P NMR (162 MHz, $CDCl_3$) δ -9.24.

4.5. Preparation of sydnone imine derivatives for biological studies

Compounds **10b-e, 11b,c** were prepared according to the reported methods [28].

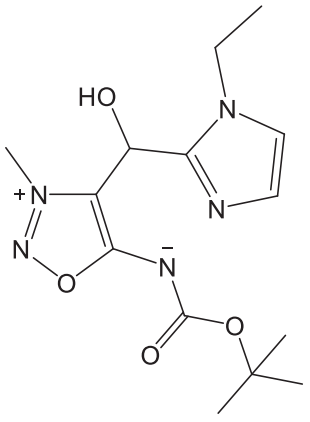
3-Isopropyl-4-[(phenyl)hydroxymethyl]-N_6-*tert*-butoxycarbonylsydnone imine (10a).



A 1.6 M solution of *n*-BuLi in hexane (2.06 ml, 3.3 mmol) was added at -80°C to a solution of 3-isopropyl-N_6-*tert*-butoxycarbonyl sydnone imine(0.68 g, 3.0 mmol) in THF (50 mL). The mixture was stirred at -80°C for 10 min and benzaldehyde (0.34 ml, 3.3 mmol) was added. The mixture was warmed to room temperature and water (1 ml) was added. The solvent was removed under reduced pressure and the products were separated by column chromatography on silica gel ($CHCl_3$:EtOAc [5:1]).

The product was obtained as a white solid in 85% (0.85 g) yield. M. p. 119-120°C. Calculated for $C_{17}H_{23}N_3O_4$: C, 61.25; H, 6.95; N, 12.60 %. Found C, 61.30; H, 6.99; N, 12.63 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, 3H, J = 6.7 Hz, CH(C**H$_3$**)$_2$); 1.50 (s, 9H, C(C**H$_3$**)**$_3$**); 1.58 (d, 3H, J = 6.6 Hz, CH(C**H$_3$**)$_2$); 4.91 (hept, 1H, J = 6.2 Hz, C**H**$(CH_3)_2$); 6.31 (s, 1H, C**H**-OH); 7.23-7.27 (m, 1H, C_6**H$_5$**); 7.30-7.33 (m, 2H, C_6**H$_5$**); 7.39 (d, 2H, J = 7.5 Hz, *o*-C_6**H$_5$**). ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.25, 22.11, 28.26, 56.95, 63.31, 79.17, 117.12, 125.36, 127.77, 128.57, 139.99, 159.35, 167.88.

3-Methyl-4-[(1-ethyl-1H-imidazole-2-yl)hydroxymethyl]-N_6-*tert*-butoxycarbonylsydnone imine (10f).

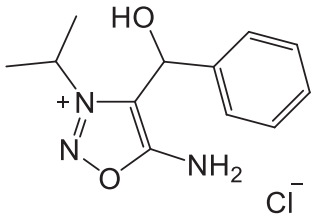


To a solution of 3-methyl-N_6-*tert*-butoxycarbonylsydnone imine (0.5 g, 2.5 mmol) in THF (20 ml) was added 2M solution of *n*-BuLi (1.38 ml, 2.75 mmol) in hexane at -80°C. The mixture was stirred at -80°C for 10 min and then 1-ethyl-2-formylimidazole (0.34 g, 2.75 mmol) was added. The mixture was warmed to room temperature and H_2O (1 mL) was added. The solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel ($CHCl_3$:CH_3OH [9:1]) and recrystallized from toluene.

The product was obtained as a white solid in 45% (0.36 g) yield. M. p. 169-170°C (dec.). Calculated for $C_{14}H_{21}N_5O_4$: C, 52.00; H, 6.55; N, 21.66 %. Found C, 52.17; H, 6.63; N, 21.72 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (m, 3H, C**H$_3$**-CH_2); 1.48 (s, 9H, C(**CH$_3$**)**$_3$**); 3.81

(dq, 1H, J = 14.3, 7.2 Hz, CH_3-C**H**$_2$); 4.09 (dq, 1H, J = 14.4, 7.2 Hz, CH_3-C**H**$_2$); 4.40 (s, 3H, C**H**$_3$-N); 6.49 (s, 1H, C**H**-OH); 6.80 (s_{br}, 1H, CH-O**H**); 6.88 (d, 2H, J = 9.3 Hz, C**H**=C**H**). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.08, 28.21, 39.60, 40.80, 58.64, 76.73, 77.05, 77.37, 79.34, 116.21, 120.37, 127.22, 144.06, 159.20, 166.84.

3-Isopropyl-4-[(phenyl)hydroxymethyl] sydnone imine hydrochloride (11a).



A solution of **10a**(1 g, 3.0 mmol) and 4N HCl in dioxane (2.25 ml, 9.0 mmol) in methanol (20 mL) was heated at reflux for 2-3 h. After cooling to room temperature the solvent was evaporated under reduced pressure. The residue was recrystallized from a mixture of isopropanol and MTBE.

The product was obtained as a white solid in 82% (0.66 g) yield. M. p. 146-147°C. Calculated for $C_{12}H_{16}ClN_3O_2$: C, 53.43; H, 5.98; Cl, 13.14; N, 15.58 %. Found C, 53.56; H, 6.12; N, 15.64 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.19 (d, 3H, J = 6.4 Hz, CH(C**H**$_3$)$_2$); 1.53 (d, 3H, J = 6.4 Hz, CH(C**H**$_3$)$_2$); 5.07-5.13 (m, 1H, C**H**(CH$_3$)$_2$); 6.51 (s, 1H, C**H**-OH); 7.38-7.22 (m, 2H, C_6**H**$_5$); 7.46-7.38 (m, 2H, C_6**H**$_5$); 7.55-7.46 (m, 2H, C_6**H**$_5$); 9.96 (s, 2H, NH_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 21.58, 22.03, 58.78, 62.81, 115.22, 126.30, 128.52, 129.06, 139.79, 167.39.

Data availability statement

Data available in article supplementary material.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by RFBR (grant No. 19-03-00972). NMR studies were performed with the financial support from Ministry of Science and Higher Education of the Russian Federation using the equipment of Center for molecular composition studies of INEOS RAS.

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