Chemistry of Nitrosoimines. XIII.[1] Reactions of 3-Substituted 2-Nitrosoimino-2,3-dihydrobenzothiazoles with Organolithiums

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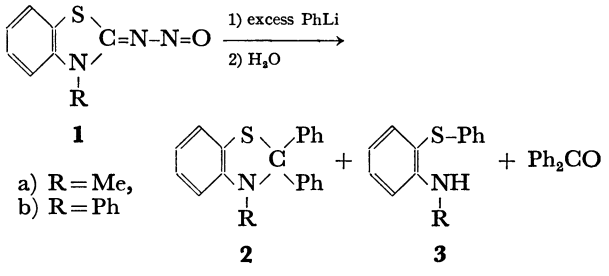
Reactions of 3-substituted 2-nitrosoimino-2,3-dihydrobenzothiazoles (**1**) with phenyl- and *n*-butyllithiums give the corresponding (*N*-substituted *o*-amino)phenyl sulfides as the major product due to direct attack on the sulfur atom of the benzothiazoline ring, while that with benzyllithium gives 2,2-dibenzyl derivatives and bis[*o*-(*N*-substituted amino)phenyl] disulfides. The difference between the reactions of **1** with Grignard reagents and those with organolithiums has been explained by the difference of the coordination site, thiophilicity and the ionic character of the reagents.

The reactions of 3-substituted 2-nitrosoimino-2,3-dihydrobenzothiazoles (**1**) with Grignard reagents give different types of main products depending on the structure of Grignard reagents.[1-3]

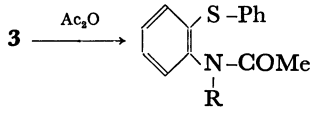
In this paper, the reaction of **1** with organolithiums,[4] which differ from those with Grignard reagents in their main reaction paths, are described in detail. The reason for the apparent difference in reactivity is also discussed.

3-Substituted 2-nitrosoimino-2,3-dihydrobenzothiazoles (**1**) were allowed to react with excess phenyllithium (about five molar equivalents) in ether for 1 hr at 0 °C under nitrogen. 3-Substituted 2,2-diphenyl-2,3-dihydrobenzothiazole (**2**), the main product in the corresponding Grignard reaction,[2] was obtained only in a very low yield. The major product was phenyl *N*-substituted *o*-aminophenyl sulfide (**3**) and benzophenone. Refluxing of **3** in acetic anhydride gave the corresponding acetylated derivative (**4**) in a high yield.



1 **2** **3**

	R	2	3	Ph_2CO
a)	Me	trace	36%	52%
b)	Ph	trace	38%	58%



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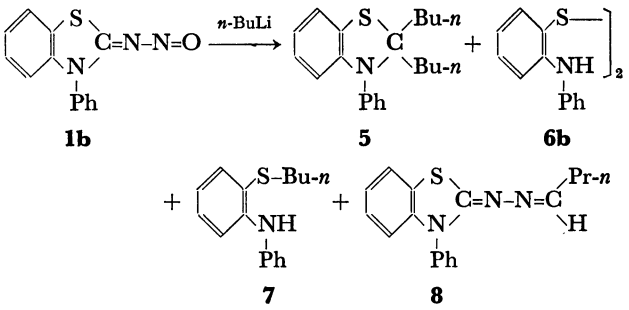
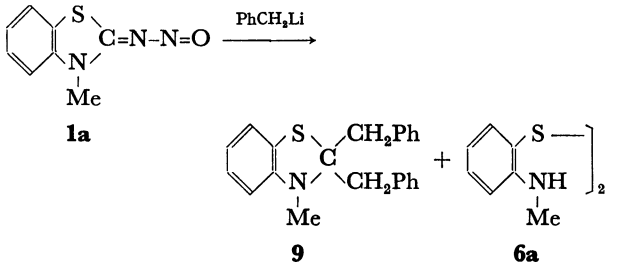
When excess *n*-butyllithium was added to a suspension of **1b** in ether under nitrogen at 0 °C, 2,2-di-*n*-butyl-3-phenyl-2,3-dihydrobenzothiazole (**5**, 10%), bis(*o*-anilinophenyl) disulfide (**6b**, 3%), *o*-anilinophenyl *n*-butyl sulfide (**7**, 43%), and 2-*N'*-*n*-butylidenehydrazono-3-phenyl-2,3-dihydrobenzothiazole (**8**, 10%) were obtained.

Attack on the C-2 position of the benzothiazoline ring became the main path, when **1a** and benzyllithium were allowed to react in tetrahydrofuran (THF) under almost the same conditions, giving **9** and **6a** in 16 and 38% yields, respectively.



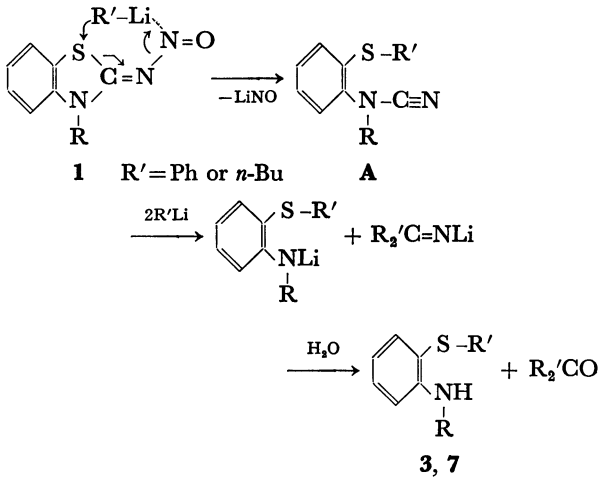
1b **5** **6b**

7 **8**



1a **9** **6a**

Mechanism of Formation. The formation of products other than **3** and **7** can be explained by a mechanism analogous to that for the reactions with Grignard reagents.[1-3] The path of formation of **3** and **7** is explained as shown in Scheme 1.



1 R'=Ph or *n*-Bu **A**

3, 7

Scheme 1.

Phenyl- and *n*-butyllithium directly attack the sulfur atom of the benzothiazoline ring *via* lithium–nitrogen coordination and cleavage of the carbon–sulfur linkage followed by loss of NO^- anion to give the corresponding phenyl and *n*-butyl *N*-substituted *o*-cyanaminophenyl sulfides (**A**) as a primary product. **A** reacts further with excess organolithium to produce **3** or **7** and benzophenone after hydrolysis.

The cyano group in **A** behaves as a pseudo-halogen, undergoing nucleophilic displacement or metal-cyanide exchange. In fact, the cyano group is transferred from *N*,*N*-diphenylcyanamide to phenylmagnesium bromide[5] and from *N*-methyl-*N*-phenylcyanamide to phenyllithium.[6] These results support the second step of Scheme 1.

The formation of **6** is ascribable to the intermediacy of ring-opened nitrosoimine (**C**) (Scheme 2), which is similar to that of Grignard reagent.[1]

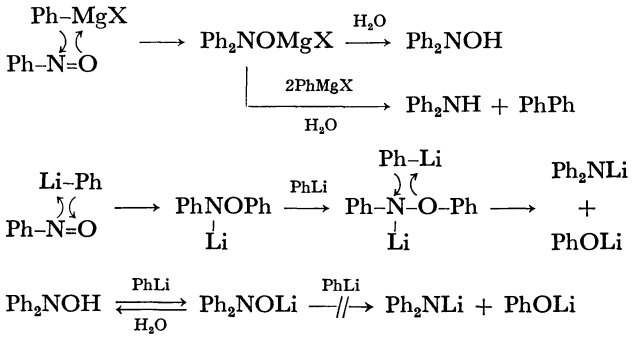
Path a-iii is assumed to be another route for **6**, due to the large ionic character of the –O–Li bond in contrast to the –O–MgX bond. The same kind of difference was observed in the reaction of **1** with lithium and Grignard reagents of the corresponding 2-iminobenzothiazolines.[7]

Direct attack on the sulfur atom of the benzothiazoline ring, which was the main path in the case of phenyl- and *n*-butyl–lithium, was observed neither in the case of benzyllithium nor in the reactions with Grignard reagents.

Discussion on the Difference between the Reactions with Grignard Reagents and Those with Organolithiums. Based on the results of the spectral study on **1**,[8] the reactions of **1** with nucleophiles are expected to take place on three possible reaction centers, *i.e.*, the C-2 position of the benzothiazoline ring (*a*), the nitrogen atom of the nitroso group (*b*) and the sulfur atom of the ring (*c*).

The difference between the reactions of **1** with Grignard reagents and those with organolithiums can primarily be attributed to the difference in the coordination position of organomagnesium and organolithium compounds to the nitrosoimino group of **1**.

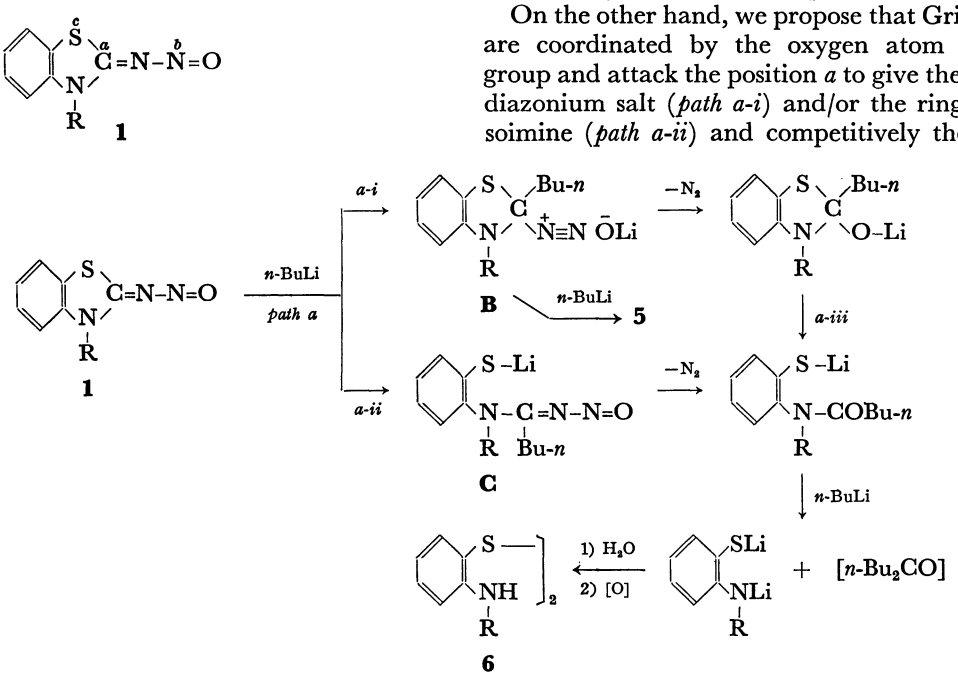
This postulate is supported by the reactions of nitrosobenzene with Grignard reagents[9–12] and phenyllithium.[13] The reaction with an equimolar amount of phenylmagnesium bromide has been shown to give the corresponding hydroxylamine,[9,11,12] which reacts successively with excess Grignard reagent to give diphenylamine and biphenyl.[11] On the other hand, nitrosobenzene reacts with excess phenyllithium to give diphenylamine and phenol, but the reaction of *N*,*N*-diphenylhydroxylamine with excess phenyllithium does not produce diphenylamine and phenol, recovering the hydroxylamine.[13]



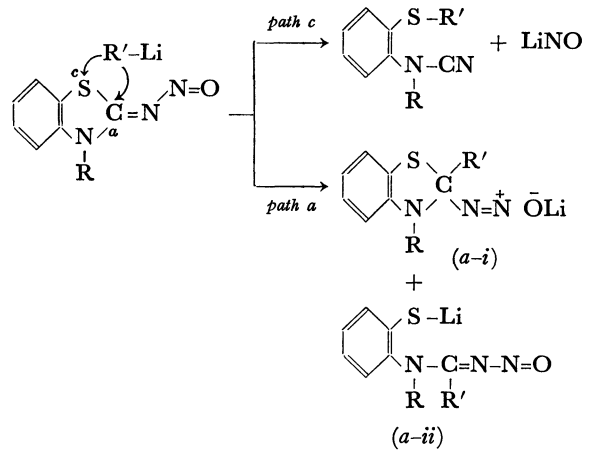
It was proposed from the results that the reaction of nitrosobenzene with phenyllithium initially gives not *O*-lithio compound but *N*-lithio compound, which is then attacked by another phenyllithium to give diphenylamine and phenol.[13]

Let us propose that organolithiums are coordinated by the nitrogen atom of the nitroso group and attack the sulfur atom of the benzothiazoline ring (*path c*) and competitively the C-2 position of the ring (*path a*). *Path c* may be a process of higher energy than *path a*, since benzyllithium follows *path a* exclusively.

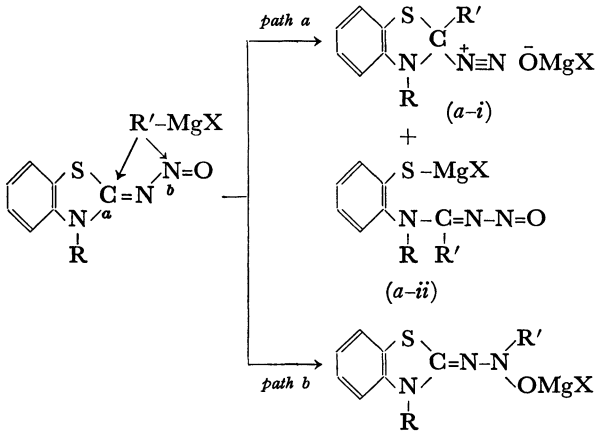
On the other hand, we propose that Grignard reagents are coordinated by the oxygen atom of the nitroso group and attack the position *a* to give the corresponding diazonium salt (*path a-i*) and/or the ring-opened nitrosoimine (*path a-ii*) and competitively the position *b* to



Scheme 2.



produce the magnesium salt of the corresponding hydrazono derivative (*path b*). Contribution of these paths to the reaction depends on the nature of Grignard reagents.[1]



It should be kept in mind that addition of Grignard reagents and organolithiums occurs exclusively on the carbon atom of Schiff's base[14] and that organolithiums are usually more reactive than Grignard reagents as shown by the addition of methyllithium to *N*-benzylidene-*t*-butylamine which is inert to methylmagnesium bromide.[15]

There may be another factor contributing to the difference in reactivity of Grignard reagents and organolithiums, *viz.*, thiophilicity.

Organometallics have been shown to attack the sulfur of thioketones[16] and thioketenes,[17] generating the corresponding carbanions. There is no definite comparison of thiophilicity of organolithiums and Grignard reagents. However, the fact that the yield of benzhydryl phenyl sulfide was 70% (isolated yield) and 37% (glc yield), respectively, when thiobenzophenone reacted with phenyllithium and phenylmagnesium bromide[17] shows greater thiophilicity of phenyllithium than that of phenylmagnesium bromide.

Thus, the difference in reactivity between organolithiums and Grignard reagents can be ascribed to three factors, *i.e.*, i) coordination site, ii) thiophilicity, and iii) ionic character of both reagents.[18]

Experimental

Materials. Benzyl methyl ether was prepared from benzyl chloride, methanol, and sodium hydroxide,[19] bp 48—49 °C/10 mmHg (lit,[19] 170.5 °C). Commercial *n*-butyllithium in *n*-hexane was used. Phenyllithium was prepared from lithium and bromobenzene in ether under nitrogen by the method of Jones and Gilman.[20] Excess lithium was filtered off before use. Benzyllithium was prepared from benzyl methyl ether and lithium in THF at −27——5 °C according to the method of Gilman and McNinch.[21] Excess lithium was filtered off before use. 3-Methyl- (**1a**, mp 143 °C (dec.))[22] and 3-phenyl-2-nitrosoimino-2,3-dihydrobenzothiazoles (**1b**, mp 140 °C (dec.))[23] were prepared by the reported methods.

All the reactions were carried out under nitrogen.

Reaction of 2-Nitrosoimino-3-phenyl-2,3-dihydrobenzothiazole (1b) with Phenyllithium. **1b** (4.91 g, 19.2 mmol) was added portionwise over a period of 0.5 hr at 0 °C to a stirred solution of phenyllithium prepared from lithium (1.71 g, 0.25 mol) and bromobenzene (15.87 g, 0.10 mol) in ether (100 ml). Stirring was continued for further 0.5 hr after the addition. The reaction mixture was treated with 100 ml of 17% aqueous ammonium chloride, and extracted with ether. The extracts were washed with water and dried over anhydrous magnesium sulfate. After evaporation of ether, the residue was chromatographed on silica gel. A trace amount of 2,2,3-triphenyl-2,3-dihydrobenzothiazole (**2b**) was eluted with *n*-hexane, mp 191.5—192.5 °C (from benzene–ethanol) (lit,[2] 191.5—192.5 °C). *o*-Anilinophenyl phenyl sulfide (**3b**) was eluted with *n*-hexane–benzene (1 : 1) and recrystallized from benzene–ethanol as pale yellow crystals, yield 1.83 g, (38%), mp 93.0—94.5 °C. IR (KBr): 3350 (NH) and 1585 cm^{-1}; NMR ($CDCl_3$): δ 6.35—7.65 (m, ArH). A signal due to N–H proton was obscure. Mass: *m/e* 277 (M^+, 100).

Found: C, 78.15; H, 5.22; N, 5.12; S, 11.53%. Calcd for $C_{18}H_{15}NS$: C, 77.94; H, 5.45; N, 5.05; S, 11.56%.

Compound **3b** (0.19 g, 0.7 mmol) was refluxed in acetic anhydride (5 ml) for 1.5 hr to give *N*-acetylated derivative (**4b**, 0.18 g, 80%), mp 107.0—107.5 °C (from ethanol). IR (KBr): 1670 cm^{-1} (CO); NMR ($CDCl_3$): δ 2.08 (s, 3H, CH_3) and 7.0—7.5 (m, 14H, ArH); Mass: *m/e* 319 (M^+, 8.9%), 277 (M^+–$H_2C{=}C{=}O$, 65), and 210 (M^+–PhS, 100).

Found: C, 75.37; H, 5.12; N, 4.30; S; 9.80%. Calcd for $C_{20}H_{17}NOS$: C, 75.21; H, 5.36; N, 4.39; S, 10.04%.

Benzophenone (1.81 g, 58%) was also eluted with *n*-hexane–benzene (1:1), benzene and benzene–dichloromethane (1:1), bp 123 °C/4 mmHg (lit,[24] 187—190 °C/15 mmHg). The spectral data (NMR and IR) were in agreement with those of an authentic sample.

Reaction of 3-Methyl-2-nitrosoimino-2,3-dihydrobenzothiazole (1a) with Phenyllithium. In a manner similar to run a), **1a** (4.91 g, 17.2 mmol) was allowed to react with phenyllithium (0.10 mol) in ether (100 ml). The reaction mixture was chromatographed on silica gel after the usual work-up. A trace amount of 2,2-diphenyl-3-methyl-2,3-dihydrobenzothiazole (**2a**, 0.11 g, 0.35 mmol) was eluted with *n*-hexane, mp 142—143 °C (from chloroform) (lit,[2] 142—143 °C). *o*-Methylaminophenyl phenyl sulfide (**3a**, 1.97 g, 36%) was eluted with *n*-hexane–benzene (1: 1) as an oil. The structure of **3a** was confirmed by the following spectral data: IR (neat): 3400 cm^{-1} (NH); NMR ($CDCl_3$): δ 2.75 (s, 3H, CH_3–N), 4.82 (broad s, 1H, N–H), and 6.5—7.6 (m, 9H, ArH); Mass: *m/e* 215 (M^+, 100%). Compound **3a** (0.57 g, 2.66 mmol) was refluxed in acetic anhydride (6 ml) for 1.5 hr to afford the *N*-acetyl derivative (**4a**, 0.47 g, 68%) as an oil, which was chromatographed on silica gel (dry column method) to give an analytically pure sample of **4a**. IR (neat): 1670 cm^{-1} (CO); NMR ($CDCl_3$): δ 1.85 (s, 3H, $COCH_3$), 3.23 (s, 3H CH_3–N), and 7.03—7.69 (m, 9H, ArH); Mass: *m/e* 257 (M^+, 4.1%), 215 (M^+–$CH_2{=}C{=}O$, 11), and 148 (M^+–PhS,

100).

Found: C, 69.72; H, 6.14; N, 5.24%. Calcd for $C_{15}H_{15}NOS$: C, 70.01; H, 5.87; N, 5.44%.

Benzophenone (1.624 g, 52%) was eluted with *n*-hexane–benzene (1:1).

Reaction of ***1b*** *with* n-*Butyllithium.* *n*-Butyllithium (68 mmol) in *n*-hexane was added dropwise to a suspension of **1b** (4.90 g, 19.2 mmol) in ether (70 ml) over a period of 1 hr with stirring at 0 °C. Stirring was continued for 3 hr after the addition. After the usual work-up, the reaction mixture was chromatographed on silica gel. 2,3-Di-*n*-butyl-3-phenyl-2,3-dihydrobenzothiazole (**5**, 0.65 g, 10%) was eluted with *n*-hexane as an oil and the structure of **5** was confirmed by the following spectral data: NMR ($CDCl_3$): δ 0.5—2.2 (m, 18H, $2CH_3CH_2CH_2CH_2$) and 6.0—7.5 (m, 9H, ArH); Mass: *m/e* 325 (M^+, 12%) and 268 (M^+–*n*-Bu, 100). Bis(*o*-anilinophenyl) disulfide (**6b**, 0.13 g, 3%) was eluted with *n*-hexane–benzene (1:1) as an oil. IR (neat): 3350 cm^{-1} (NH); MS: *m/e* 400 (M^+). The structure of **6b** was confirmed by comparing its spectral data (IR and NMR) with those of an authentic sample prepared from 3-phenyl-2,3-dihydrobenzothiazol-2-one and potassium hydroxide in ethanol.[25] *o*-Anilinophenyl *n*-butyl sulfide (**7**, 2.12 g, 43%) was eluted with *n*-hexane–benzene (1:1) as an oil. The structure of **7** was confirmed by the following spectral data: IR (neat): 3350 cm^{-1} (NH); NMR ($CDCl_3$): δ 0.6—1.8 (m, 7H, $CH_3CH_2CH_2$), 2.7 (t, 2H, $-CH_2-S$), and 6.4—7.7 (m, 9H, ArH); Mass: *m/e* 257 (M^+, 97) and 201 ($M^+-CH_2=CHCH_2CH_3$, 100). 2-*N'*-*n*-Butylidenehydrazono-3-phenyl-2,3-dihydrobenzothiazole (**8**, 0.59 g, 10%) was eluted with benzene–dichloromethane (1:1) as pale yellow crystals, mp 112—113 °C. The structure of **8** was confirmed by the following spectral data: IR (KBr): 1615, 1580, 1560, and 1550 cm^{-1}; Mass: *m/e* 295 (M^+, 55%) and 225 (M^+–*n*-PrCH=N, 100).

Reaction of ***1a*** *with Benzyllithium.* **1a** (3.44 g, 17.8 mmol) was added portionwise over a period of 0.5 hr at room temperature to a stirred solution of benzyllithium prepared from lithium (3.27 g, 0.47 mol) and benzyl methyl ether (14.07 g, 0.12 mol) in THF (320 ml). Stirring was continued for an additional 3 hr. After the usual work-up, the reaction mixture was chromatographed on silica gel. 2,2-Dibenzyl-3-methyl-2,3-dihydrobenzothiazole (**9**, 0.96 g, 16%) was eluted with *n*-hexane–benzene (1:1), mp 86.5—87.5 °C (from chloroform–ethanol) (lit,[3] 86.5—87.5 °C). Bis(*o*-methylaminophenyl) disulfide (**6a**, 0.95 g, 38%) was eluted with *n*-hexane–benzene (1:1) and benzene, mp 66.5—67.0 °C (from chloroform–ethanol) (lit,[2] 66.5—67.0 °C).

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