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Reactions of 2-Hydroxyimino-3-methyl-2,3-dihydrobenzothiazole Derivatives with Grignard Reagents and Organolithiums

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Synopsis. Reactions of 2-hydroxyimino-3-methyl-2,3-dihydrobenzothiazole derivatives (**1**) with Grignard reagents gave 2-hydroxyimino (**1e**) and 2-(substituted imino)-3-methyl-2,3-dihydrobenzothiazoles as major products, where **1e** was reduced by excess Grignard reagents to 2-imino derivative. On the other hand, reactions of **1** with organolithiums afforded *o*-(methylamino)phenyl sulfides as a major product.

As reported previously, reactions of 3-substituted 2-nitrosoimino-2,3-dihydrobenzothiazoles with Grignard reagents[1] and organolithiums[2] give products through attacks on the C-2 and the sulfur atom in the ring and the nitrogen atom of the nitroso group, depending on the type of nucleophiles.[3] Therefore, it is interesting to examine reactions of 2-hydroxyimino-3-methyl-2,3-hydrobenzothiazole derivatives (**1**) with the same kind of nucleophiles, expecting to see whether these can be controlled to effect ring-expansion[4,5] by changing the nature of leaving groups.

Reactions of 2-hydroxyimino-3-methyl-2,3-dihydrobenzothiazole derivatives (**1**) with Grignard reagents gave 2-hydroxyimino- (**1e**), 2-imino- (**2**), and 2-(substituted imino)-3-methyl-2,3-dihydrobenzothiazoles (**3**), bis[*o*-(*N*-cyanomethylamino)phenyl] disulfide (**4**), bis[*o*-(methylamino)phenyl] disulfide (**5**), and *o*-(methylamino)phenyl sulfide (**6**), depending on the substituent of **1** and reaction conditions. The results are summarized in Table 1.

The tosyloxyimino (**1a**) and benzoyloxyimino derivatives (**1b**) reacted easily in ether–benzene at room temperature, whereas the trimethylsilyloxyimino (**1c**), methoxyimino (**1d**), and hydroxyimino derivatives (**1e**) reacted only in refluxing benzene.

Table 1. Reactions of **1** with Grignard reagents

1	R	Condition	**1e**(%)	**2**(%)	**3**(%)	**4**(%)	**5**(%)	**6**(%)
1a	*p*-MeC_6H_4	Et_2O-PhH, r. t.	—	—	69	—	—	—
1a	Et	Et_2O-PhH, r. t.	—	—	72	12	—	—
1b	*p*-MeC_6H_4	Et_2O-PhH, r. t.	78	—	—	—	—	—
1c	Et	PhH, reflux	—	78	4	—	3	—
1d	Et	PhH, reflux	—	72	—	—	—	—
1e	Et	PhH, reflux	—	85	—	—	6	6

The possible reaction centers in **1** are a) the nitrogen atom in the imino group, b) the α-atom in the X group, c) the sulfur atom, d) the C-2 atom on the ring.

The formation of **2** is due to *in situ* reduction of **1e** by excess Grignard reagent, which is formed through an attack on the X group (path b). The formation of **4** and **5** is attributable to the presence of ring-opening equilibrium of Grignard type reagent of **2**, which was established in a previous paper.[4] The sulfide **6** is formed through an attack on the sulfur atom in the ring (path c).

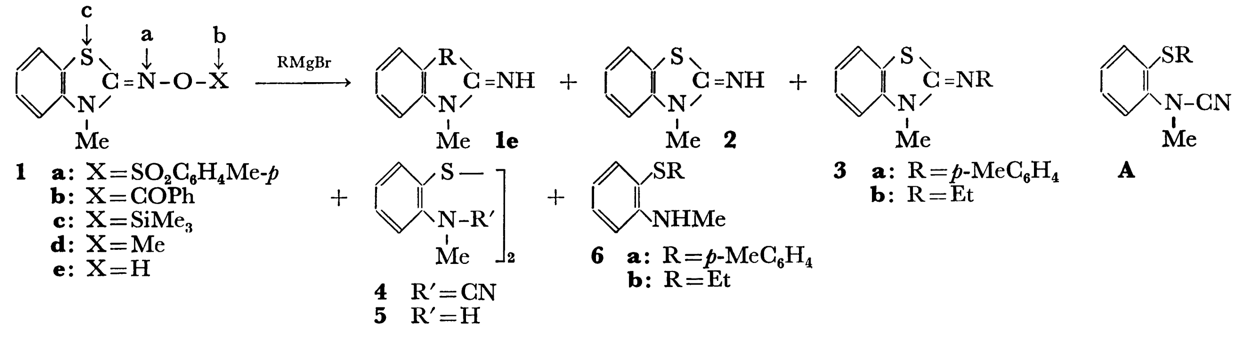
Thus, **1a** reacts mainly by path a showing high ability of *p*-toluenesulfonate as a leaving group,[6] **1b**, **1c**, and **1d** do almost exclusively by path b producing Grignard type reagent of **1e** *in situ*.

The interesting point in the reaction of **1** with organolithiums is that path c is observed in a comparable extent with paths a and b, respectively, in the cases of **1a** and **1c**, which was not the case with Grignard reagents.[2] Moreover, **1d** reacts exclusively by path c in dramatic contrast to the result with ethylmagnesium bromide which followed path b almost exclusively. The results are summarized in Table 2.

The high thiophilicity of organolithiums compared with Grignared reagents has been observed in the reaction of the nitrosoimino derivatives with these organometalloids[2] and also in that of thioketones.[7] Conversion of an intermediate, *o*-(*N*-cyanomethylamino)phenyl sulfide (**A**), in to **6** was confirmed by the formation of benzophenone of the corresponding amount in the reaction with phenyllithium.

Table 2. Reactions of **1** with organolithiums

1	R	**1e**(%)	**3**(%)	**5**(%)	**6**(%)	Ph_2CO(%)
1a	Bu	12	16	12	34	—
1c	Ph	42	—	—	36	32
1d	Bu	—	—	—	90	—
1d	Ph	—	—	—	91	89



1 **a**: $X=SO_2C_6H_4Me$-*p*
b: X=COPh
c: $X=SiMe_3$
d: X=Me
e: X=H

4 R′=CN
5 R′=H

6 **a**: R=*p*-MeC_6H_4
b: R=Et

3 **a**: R=*p*-MeC_6H_4
b: R=Et

A

Experimental

2-Hydroxyimino-3-methyl-2,3-dihydrobenzothiazole (**1e**) was prepared by the reported method,[9] mp 203—204 °C (lit, 202—203 °C).

3-Methyl-2-tosyloxyimino- (**1a**), 2-benzoyloxyimino-3-methyl- (**1b**), 3-methyl-2-trimethylsilyloxyimino- (**1c**), and 3-methyl-2-methoxyimino-2,3-dihydrobenzothiazole (**1d**) were prepared from **1e** and the corresponding halides with base (triethylamine or sodium methoxide) in yields of 80, 69, 87, and 59%, respectively, with correct elemental analyses.

1a: mp 167—169 °C (from benzene–hexane). NMR ($CDCl_3$): δ 2.44 (s, 3H), 3.34 (s, 3H), 6.65—7.95 (m, 8H).

1b: mp 140—142 °C (from methanol). NMR ($CDCl_3$): δ 3.55 (s, 3H), 6.90—7.55 (m, 7H), 8.10—8.25 (m, 2H).

1c: bp 152 °C/3.5 mmHg, mp 49—50 °C. NMR ($CDCl_3$): δ 0.15 (s, 9H), 3.39 (s, 3H), 7.4—7.6 (m, 4H).

1d: bp 125—127 °C/115 mmHg, mp 47—48 °C (from hexane). NMR (CCl_4): δ 3.30 (s, 3H), 3.82 (s, 3H), 6.62—7.30 (m, 4H).

The following reactions were carried out under nitrogen.

Reaction of Tosyloxyimino Derivative (1a). 1) With p-Tolylmagnesium Bromide: *p*-Tolylmagnesium bromide (4.5 mmol) in ether (15 ml) was added dropwise to a solution of **1a** (1.00 g, 3.0 mmol) in benzene (15 ml) at room temperature, and the mixture was stirred for 0.5 h. The reaction mixture was treated with 10% aq ammonium chloride (25 ml), extracted with dichloromethane and the dried extract was evaporated. The residue was submitted to dry column chromatography (DCC) (SiO_2, hexane: CH_2Cl_2=1:1) to afford 3-methyl-2-*p*-tolylimino-2,3-dihydrobenzothiazole (**3a**), yield 523 mg, (69%), mp 92—93 °C (from MeOH). NMR ($CDCl_3$): δ 2.34 (s, 3H), 3.55 (s, 3H), and 6.80—7.42 (m, 8H); MS: *m/e* 254 (M^+, 100%).

The compound (**3a**) was identical in every data with the authentic sample prepared from p-toludine and 3-methyl-2-methylthiobenzothiazolium iodide.[10]

2) With Ethylmagnesium Bromide: Ethylmagnesium bromide (3.9 mmol) in ether (15 ml) was added dropwise to **1a** (1.00 g, 3 mmol) in benzene (30 ml) and the mixture was stirred for 1 h. After usual work-up and DCC (SiO_2, CH_2Cl_2:AcOEt-4:1), 274 mg of **1a** was recovered, and oily 2-ethylimino-3-methyl-2,3-dihydrobenzothiazole (**3b**) (302 mg, 72%) and bis[*o*-(*N*-cyanomethylamino)phenyl] disulfide (**4**) (42 mg, 12%), mp 141 °C (lit,[11] 140—141 °C), were isolated.

3b: NMR ($CDCl_3$): δ 1.30 (t, J=7 Hz, 3H), 3.25 (q, J=7 Hz, 2H), 3.40 (s, 3H), and 6.79—7.40 (m, 4H).

Reaction of Benzoyloxyimino Derivative (1b) with p-*Tolylmagnesium Bromide* in benzene at room temperature afforded, after usual work-up, **1e** in 78% yield.

Reaction of Hydroxyimino Derivative (1e) with Ethylmagnesium Bromide. Ethylmagnesium bromide (17 mmol) in ether (15 ml) was added to **1e** (500 mg, 2.8 mmol) in warm benzene (30 ml) and the mixture was refluxed for 3 h. After usual work-up and DCC (SiO_2, CH_2Cl_2:AcOEt=4 : 1) followed by preparative thin-layer chromatography (PTLC) (SiO_2, CH_2Cl_2:hexane=1:1), 40 mg of **1e** was recovered, and 2-imino-3-methyl-2,3-dihydrobenzothiazole (**2**) (357 mg, 85%) mp 122—123 °C (lit,[12] 123 °C), bis[*o*-(methylamino)phenyl] disulfide (**5**) (22 mg, 6%), mp 66—67 °C (lit,[13] 67—68 °C), and ethyl *o*-(methylamino)phenyl sulfide (**6b**) (24 mg, 6%) were obtained.

6b: IR (neat): 3350 cm^{-1}; NMR ($CDCl_3$): δ 1.18 (t, J=7 Hz, 3H), 2.72 (q, J=7 Hz, 2H), 2.85 (s, 3H), and 6.5—7.5 (m, 4H); MS: *m/e* 167 (M^+, 100%).

Reaction of Trimethylsilyloxyimino Derivative (1c) with Ethylmagnesium Bromide in refluxing benzene (1.5 h) gave, after the same procedure as the preceding one, **2** (78%), **3b** (4%), and **5** (3%).

Reaction of Methoxyimino Derivative (1d) with Ethylmagnesium Bromide in refluxing benzene (3 h) gave, after usual work-up, **2** (72%).

Reaction of 1a with Butyllithium. Butyllithium (10 mmol) in hexane (6 ml) was added to **1a** (836 mg, 2.5 mmol) in benzene (35 ml) and the mixture was stirred for 2 h. After usual work-up, the residue was submitted to DCC (SiO_2, CH_2Cl_2) and then PTLC (SiO_2, CH_2Cl_2: AcOEt=10:1 and then CH_2Cl_2:hexane=1:1) to give **1e** (53 mg, 12%), butyl *o*-(methylamino)phenyl sulfide (**6d**) (165 mg, 34%), 2-butylimino-3-methyl-2,3-dihydrobenzothiazole (**3d**) (86 mg, 16%), and bis[*o*-(methylamino)phenyl] disulfide (**5**) (42 mg, 12%).

3d: oily material; NMR ($CDCl_3$): δ 0.8—1.8 (m, 7H), 3.20 (t, J=7 Hz, 2H), 3.39 (s, 3H), and 6.7—7.4 (m, 4H).

6d: oily material; IR (neat): 3360 cm^{-1}; NMR ($CDCl_3$): δ 0.7—1.0 (m, 3H), 1.2—1.7 (m, 4H), 2.71 (t, J=7 Hz, 2H), 2.89 (s, 3H), 4.80 (bs, 1H), and 6.5—7.5 (m, 4H).

Reaction of 1c with Phenyllithium. Phenyllithium (36 mmol) in ether (20 ml) was added to **1c** (756 mg, 3.0 mmol) in benzene (30 ml) and the mixture was stirred for 1 h. After usual work-up, **1e** (225 mg, 42% after recrystallization from methanol) precipitated from the residue. DCC of the filtrate gave benzophenone (173 mg, 32%), mp 47 °C, and *o*-(methylamino)phenyl phenyl sulfide (**6c**)[2] (233 mg, 36%) (by IR and NMR[2]).

Reaction of 1d with Butyllithium in benzene afforded, after usual work-up and DCC (SiO_2, CH_2Cl_2:hexane=1:4), butyl *o*-(methylamino)phenyl sulfide (**6d**) (90%).

Reaction of 1d with Phenyllithium in benzene afforded, after usual work-up, benzophenone (89%) and **6c** (91%).

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