BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 48(10), 2981—2982 (1975)

A Convenient Method for the Preparation of Aryl and Alkyl Isothiocyanates Using Amines, Carbon Disulfide, and a Grignard Reagent

Shizuyoshi Sakai, Tatsuo Fujinami, and Toshiyuki Aizawa

Department of Industrial Chemistry, Faculty of Engineering, Shizuoka University, Hamamatsu 432

(Received January 7, 1975)

Synopsis. The thermal decomposition of bromomagnesium *N*-aryl- or *N*-alkyl-*N*-bromomagnesio-dithiocarbamate (**3**), prepared *in situ* from amines, carbon disulfide, and a Grignard reagent, is a new and convenient method for the preparation of aryl or alkyl isothiocyanate.

The reported methods for the preparation of isothiocyanates from amines have usually involved the decomposition reactions of dithiocarbamate derivatives.[1–4] However, these methods are inconvenient, because a poisonous reagent, such as a heavy metal or a phosgene derivative, is used as the starting material. In view of this, we have already described a new method, which consists of the decomposition reaction of lithium *N*-lithio-dithiocarbamate prepared *in situ* using butyllithium. Grignard reagent appears also to have an interesting synthetic potential in isothiocyanate preparation. In this report, we will describe a more convenient and alternative approach for isothiocyanate synthesis using a Grignard reagent, and will compare this new method with that using an organolithium compound.

Aromatic amines were treated with two equivalents of ethylmagnesium bromide in tetrahydrofuran under a nitrogen atmosphere to form bis(bromomagnesio)-aniline (**2**; R=Aryl); then excess amounts to carbon disulfide were added below room temperature to give bromomagnesium *N*-aryl-*N*-bromomagnesio-dithiocarbamate (**3**; R=Aryl) *in situ*. The characteristic band of the ν_{NCS} of isothiocyanate could not be detected after the reaction mixture had been refluxed for 1 hr. After the evaporation of the mixture of tetrahydrofuran and excess carbon disulfide, the distillation residue was heated at 120—140 °C to decompose (**3**), thus affording aryl isothiocyanate (**4**; R=Aryl). The results for other amines are designated by 'Direct Method' in Table 1.

$$\underset{\mathbf{1}}{\mathrm{RNH_2}} \xrightarrow[-2\mathrm{EtH}]{+2\mathrm{EtMgBr}} \underset{\mathbf{2}}{\mathrm{RN(MgBr)_2}} \xrightarrow{+\mathrm{CS_2}} \underset{\mathbf{3}}{\mathrm{RN(MgBr)CS_2MgBr}}$$

$$\xrightarrow[-(\mathrm{BrMg})_2\mathrm{S}]{} \underset{\mathbf{4}}{\mathrm{RNCS}} \qquad (1)$$

The by-product, '$(BrMg)_2S$', could not be characterized, but it reacted violently with water to evolve hydrogen sulfide gas.

Bis(bromomagnesio)anilines are well known to be formed by the reaction of aromatic amines with a Grignard reagent.[6] However, the dimetallation reaction of primary aliphatic amines by organomagnesium is difficult to complete; therefore, the yields of alkyl isothiocyanates by the 'Direct Method' are rather low, except for cyclohexylamine (Table 1). To improve the yield of alkyl isothiocyanate, an alternative approach was tried; in it we treated alkylamine with the Grignard reagent and carbon disulfide, step-by-step, in the way described in Eq. (2) ('Step-by-step Method' in Table 1).

$$\underset{\mathbf{1}}{\mathrm{RNH_2}} \xrightarrow[-\mathrm{EtH}]{+\mathrm{EtMgBr}} \underset{\mathbf{5}}{\mathrm{RNHMgBr}} \xrightarrow{+\mathrm{CS_2}} \underset{\mathbf{6}}{\mathrm{RNHCS_2MgBr}}$$

$$\xrightarrow[-\mathrm{EtH}]{+\mathrm{EtMgBr}} \mathbf{3} \xrightarrow[-(\mathrm{BrMg})_2\mathrm{S}]{} \mathbf{4} \qquad (2)$$

The temperature required to decompose the *N*-alkyl-*N*-bromomagnesio-dithiocarbamate (**3**; R=

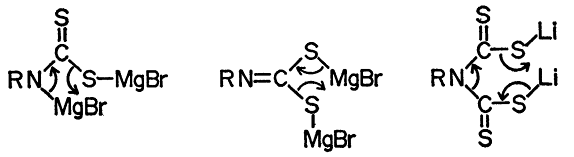
Table 1. Yields of isothiocyanates in the decomposition reactions of bromomagnesium *N*-bromomagnesio-dithiocarbamates (**3**)

Amine used (RNH_2)	Direct Method (1) Yield (%)[a]	Step-by-step Method (2) Temp (°C[b])	Step-by-step Method (2) Yield (%)	Bp of RNCS (°C/mmHg)	ν_{NCS} (cm^{-1})
$EtNH_2$	—	c)	68	53—55/50	2090
n-$PrNH_2$	28	c)	93	71—72/45	2090
i-$PrNH_2$	—	c)	80	55—58/50	2090
n-$BuNH_2$	20	c)	85	83—85/50	2090
t-$BuNH_2$	21	c)	24	93—95/85	2090
Cyclo-$C_6H_{11}NH_2$	70	c)	90	104—105/10	2090
$PhNH_2$	82	~130	82	105—107/20	2070
p-$CH_3C_6H_4NH_2$	81	~130	87	106—109/10	2070
o-$CH_3C_6H_4NH_2$	71	~130	83	105—108/10	2070
α-Naphthyl-NH_2	30	—	—	125—127/0.5	2090
β-Naphthyl-NH_2	40	—	—	118—119/0.1	2110

a) Two mol of CS_2 and EtMgBr were used per one mol of amine through the reaction (1), and the reaction mixture prepared *in situ* was decomposed at 120—140 °C. b) The temperature where the carbamate (**3**) began to decompose. c) Refluxing temperature of tetrahydrofuran solution.

Alkyl) thus prepared was substantially lower than that needed for the corresponding *N*-aryl derivative (**3**; R=Aryl). The dithiocarbamate (**3**; R=Alkyl) was decomposed for 1 hr at the refluxing temperature in tetrahydrofuran, thus affording a good yield of **4**.

Contrary to the case of isothiocyanate synthesis using butyllithium, where two equivalents of carbon disulfide per mole of amine were essentially required,[5] the 'direct' and 'step-by-step' methods using the Grignard reagent needed only one equivalent of carbon disulfide. Although mechanistic comparisons of these reactions are now in progress, a four-centered scheme (**7a** or **7b** in Fig. 1) for the reaction using the Grignard reagent and a six-centered scheme (**8**) *via* a lithium intermediate can tentatively be suggested to explain the different amounts of carbon disulfide needed.



7a **7b** **8**

Fig. 1. Tentative schemes for isothiocyanate formation.

In conclusion, the Grignard reagent is superior to butyllithium both in purity and in yield of isothiocyanate obtained, except for the lower yield of isothiocyanate from sterically hindered amines such as *tert*-butylamine and α-naphthylamine.

Experimental

All the boiling points are uncorrected. The IR and NMR spectra were determined with a JASCO Model IRA-1 spectrometer and a Hitachi Perkin-Elmer Model R-24 spectrometer respectively. The tetrahydrofuran, carbon disulfide, and amines were dried using metallic sodium, diphosphorous pentoxide, and pellets of sodium hydroxide respectively, and were distilled before use. Some standard examples of the preparation of aryl and alkyl isothiocyanates are given below.

Thermal Decomposition of Bromomagnesium N-*Bromomagnesio*-N-*Phenyldithiocarbamate (**3**; R=Ph) (Direct Method).* In a flask equipped with a mechanical stirrer, a condenser, a dropping funnel, and a nitrogen inlet, ethylmagnesium bromide (110 mmol) was prepared in the usual manner from a magnesium ribbon (2.68 g; 110 mmol) and bromoethane (*ca.* 115 mmol) in dry tetrahydrofuran (80 ml) under a dry nitrogen atmosphere. To the solution we then slowly added aniline (4.66 g; 50 mmol) in dry tetrahydrofuran (5 ml), followed by 4 hrs' refluxing to form bis(bromomagnesio)aniline. The resulting suspension was treated slowly with excess amounts of carbon disulfide (7.61 g; 100 mmol) in tetrahydrofuran (5 ml) below room temperature. A violent heat evolution was observed in the reaction at room temperature; therefore, the mixture had to be cooled by mean of a water bath. The solution of the reaction mixture was heated for 1 hr and was then transferred into a distillation apparatus. After the solvent and excess carbon disulfide had then been recovered by distillation, the residue[7] was heated for 1 hr at 120—140 °C to decompose the bromomagnesium *N*-bromomagnesio-*N*-phenyldithiocarbamate (**3**; R=Ph), thus affording phenyl isothiocyanate (**4**; R=Ph). The product was redistilled *in vacuo* to separate **4** (R=Ph); yield 5.54 g (82% based on the aniline used); bp 105—107 °C/20 mmHg (Ref,[5] 96—98 °C/15 mmHg); IR(neat) ν_{NCS} 2070 cm^{-1}. The NMR and IR spectra were in good agreement with those of the authentic sample prepared by the published method.[5]

Even when an equivalent amount of carbon disulfide (3.81 g; 50 mmol) was used in the reaction with bis(bromomagnesio)aniline, phenyl isothiocyanate was obtained in a slightly lower yield (75%). However, excess amounts (two equivalents) of carbon disulfide were used in most cases; the results are summarized in Table 1.

Hydrogen sulfide was violently evolved by the addition of water to the distillation residue.

Thermal Decomposition of Bromomagnesium N-*Bromomagnesio*-N-*butyldithiocarbamate (**3**; R=Bu) (Step-by-step Method).* A solution of *n*-butylamine (3.66 g; 50 mmol) in tetrahydrofuran (5 ml) was added, drop-by-drop, to a solution of ethylmagnesium bromide (55 mmol) in tetrahydrofuran (50 ml) under dry nitrogen in the apparatus described above. After refulxing for 1 hr, the solution of **5** (R=Bu) was treated with an equivalent amount of carbon disulfide (3.81 g; 50 mmol) in tetrahydrofuran (5 ml) under cooling by water, to form the *N*-butyl-dithiocarbamate salt (**6**; R=Bu). Heat evolution was observed during this procedure at room temperature. The solution thus prepared *in situ* was treated again with ethylmagnesium bromide (55 mmol) to give bromomagnesium *N*-bromomagnesio-*N*-butyldithiocarbamate (**3**; R=Bu) and ethane. After the reaction mixture had then been heated with stirring for 1 hr under reflux, the characteristic band of isothiocyanate at 2090 cm^{-1} appeared in the IR spectrum of the product mixture. The tetrahydrofuran was recovered by distillation, and the residue was heated for 1 hr at 120—140 °C. Butyl isothiocyanate was obtained by distillation *in vacuo*; yield 4.89 g (85%); bp 64—66 °C/20 mmHg (lit,[5] 47—48 °C/10 mmHg); IR(neat) ν_{NCS} 2090 cm^{-1}.

In separate experiments, an additional amount of carbon disulfide (3.81 g; 50 mmol) was added to the solution of **3** (R=Bu), but no heat evolution was ever observed. The treatment of the reaction mixture in the same manner as has been described above afforded an 86% yield of BuNCS.

References

1) J. E. Hodgkins, W. P. Reeves, and M. G. Ettlinger, *J. Org. Chem.*, **21**, 404 (1956); **29**, 3098 (1964).

2) T. Wagner-Jauregg, H. Arnold, and H. Rausen, *Ber.*, **74**, 1372 (1941).

3) K. Itoh, I. K. Lee, I. Matsuda, S. Sakai, and Y. Ishii, *Tetrahedron Lett.*, 2667 (1967).

4) F. B. Dains, R. Q. Brewster, and C. P. Olander, "Organic Syntheses," Coll. Vol. I, p. 71 (1956).

5) S. Sakai, T. Aizawa, and T. Fujinami, *J. Org. Chem.*, **39**, 1970 (1974).

6) E. W. Abel and G. R. Willey, *J. Chem. Soc.*, **1964**, 1528.

7) Solid at room temperature but melted at the beginning of the distillation.