[Contribution from the Department of Chemistry, University of Tennessee]

Ortho-Substitution of Benzyl-Type Grignard Reagents by Cyanogen and Thiocyanogen

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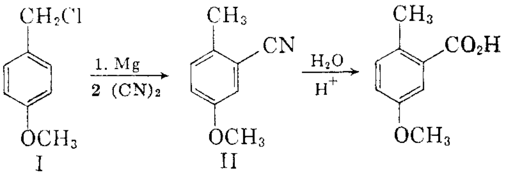
Reactions of the Grignard reagents from 4-methoxybenzyl chloride, 2-chlorobenzyl chloride, and β-chloromethylnaphthalene with cyanogen proceed with *ortho*-substitution, which yields, respectively, 2-methyl-5-methoxybenzonitrile, 2-methyl-3-chlorobenzonitrile, and 2-methyl-1-naphthonitrile. Reaction of benzylmagnesium chloride with thiocyanogen proceeds with both direct and *ortho*-substitution which yields, respectively, benzyl mercaptan and *o*-tolyl thiocyanate. Possible mechanisms for the two thiocyanogen reactions are briefly discussed.

Recently it was found that benzylmagnesium chloride and cyanogen react to give *o*-tolunitrile and that this new *ortho*-substitution reaction occurs also with cyanogen and certain other benzyl-type Grignard reagents.[1] Reported in this paper is a further study of the scope of this reaction. Additional benzyl-type Grignard reagents and benzyllithium have been treated with cyanogen, and benzylmagnesium chloride itself has been treated with cyanogen bromide and with thiocyanogen.

When cyanogen was treated with the Grignard reagents from 4-methoxybenzyl chloride (I), 2-chlorobenzyl chloride, and β-chloromethylnaphthalene, there were produced, respectively, 2-methyl-5-methoxybenzonitrile (II), 2-methyl-3-chlorobenzonitrile, and 2-methyl-1-naphthonitrile. Each nitrile was hydrolyzed to the corresponding carboxylic acid for the purpose of identification. The reactions are illustrated (1) for 2-methoxybenzyl chloride.



(1)

The Grignard reagent in each of the above cases was prepared in the usual way and added to ethereal cyanogen. A more careful preparation of the Grignard reagents, to avoid coupling, would almost certainly improve the yield of nitrile, which was about 40% in this work. For example, from the reaction which gave 39% of nitrile from 4-methoxybenzyl chloride, there was also isolated a 42% yield of the coupled product, 1,2-bis(4-methoxyphenyl)ethane. When β-bromomethylnaphthalene (instead of the corresponding chloromethyl compound) was used, the yield of naphthonitrile was very low, probably as a consequence of the greater extent of coupling of the bromo compound.

Benzyllithium (III) was prepared from benzyl methyl ether and treated with cyanogen. In this case no *ortho*-substitution product was obtained but phenylacetonitrile was. The over-all yield of

$$C_6H_5CH_2OCH_3 \xrightarrow{Li} \underset{III}{C_6H_5CH_2Li} \xrightarrow{(CN)_2} C_6H_5CH_2CN \quad (2)$$

nitrile was poor, but this can be accounted for primarily as a consequence of the poor yield of benzyllithium. In our hands the cleavage of benzyl methyl ether by lithium could not be accomplished nearly so well (see Experimental) as has been reported.[2]

There are a number of compounds related to cyanogen, "pseudohalogens," whose reactions with the benzyl-type Grignard reagent might be of interest. The first two of these we have studied are thiocyanogen (NCSSCN) and cyanogen bromide (BrCN). The latter compound with benzylmagnesium chloride gives benzyl bromide in good yield. Cyanogen bromide is known to react with other Grignard reagents in a similar manner.[3]

Reactions between organometallics and the thiocyano group have received very little attention, and the specific reaction of thiocyanogen with a Grignard reagent does not appear to have been studied at all. Reactions of thiocyanogen with certain other organometallics yield organothiocyanates, *e.g.*, IV in Equation 3.[4] Reactions of organothiocyanates with Grignard reagents yield thiols and thioethers, *e.g.*, Equation 4.[5] For the latter reaction an attractive hypothesis for the intermediate yielding the thioether is structure V. Rearrangement of this complex could proceed as indicated (Equation 5) for the five-membered quasi-ring. Such an intramolecular rearrangement (rather than bimolecular attack involving a second molecule of Grignard reagent) should be favored by addition of the organometallic to the thiocyanate, and it was found that the formation of thioether is enhanced by this inverse addition.[5]

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[1] J. F. Eastham and V. F. Raaen, *Proc. Chem. Soc.*, 149 (1958); V. F. Raaen and J. F. Eastham, *J. Am. Chem. Soc.*, **82**, 1349 (1960).

[2] H. Gilman, H. A. McNinch, and D. W. Henberg, *J. Org. Chem.*, **23**, 2044 (1958).

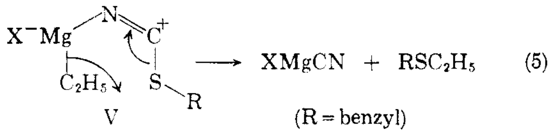
[3] V. Grignard and O. Kaschichi, *Bull. soc. chim.*, (4) **39**, 1589 (1926).

[4] E. Soderback, *Ann.*, **419**, 217 (1919).

[5] R. Adams, H. B. Bramlet, and F. H. Tendick, *J. Am. Chem. Soc.*, **42**, 2369 (1920).

$$(C_6H_5)_2Hg \xrightarrow{(SCN)_2} \underset{IV}{C_6H_5SCN} + C_6H_5HgSCN \quad (3)$$

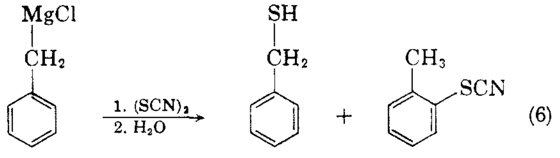
$$C_6H_5CH_2SCN \xrightarrow[2)\ H_2O]{1)\ C_2H_5MgCl} C_6H_5CH_2SH + C_6H_5CH_2SC_2H_5 \quad (4)$$



(5)

V (R = benzyl)

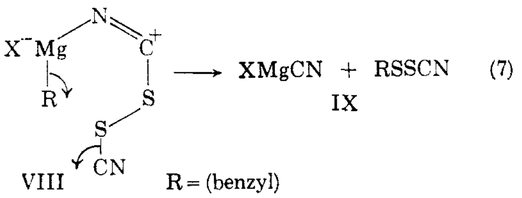
After treatment of thiocyanogen with benzylmagnesium chloride, hydrolysis yields two products of interest: benzyl mercaptan (VI, 30% yield) and *o*-tolyl thiocyanate (VII, 10% yield). The Grignard reagent was added to the thiocyanogen, which was freshly prepared by the action of bromine on lead thiocyanate. Each product was characterized by its physical properties and by conversion to known derivatives.



(6)

VI VII

Formation of the major product, benzyl mercaptan (VI), may be rationalized with the intermediate VIII, whose rearrangement in the indicated manner (Equation 7) would yield benzyl thiothiocyanate (IX). Subsequent hydrolysis would convert the thiothiocyanate to a thiol (Equation 8).[6] Hypothesis of the rearrangement of V is comparable to that of VIII, except that the quasi-ring involved in this latter example is six-membered; in the former it is five-membered.

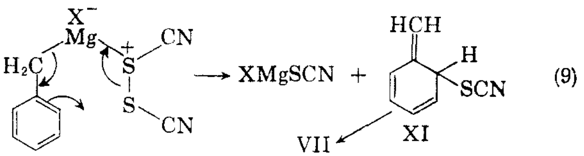


(7)

VIII R = (benzyl)

$$IX + H_2O \rightarrow VI + HOSCN \quad (8)$$

Formation of *o*-tolyl thiocyanate (VII) from benzyl magnesium chloride and thiocyanogen is a new *ortho*-substitution reaction, the first to involve reaction (rupture) of the sulfur-sulfur bond. Possibly the key intermediate for this reaction involves complexing of the Grignard reagent with sulfur, as in X. Rearrangement (Equation 9) of such a complex through a six-membered quasi-ring would produce an intermediate triene (XI), whose subsequent tautomerization would yield the isolable *o*-tolyl thiocyanate. This proposed mechanism is comparable to that substantiated for the reaction of cyanogen with benzyl-type Grignard reagents.[1]



(9)

X

The suggestion that thiocyanogen reacts by two different paths, Equations 9 and 10, requires additional evidence, which is being sought. It would in fact be of interest to learn more about the reactions between thiocyanogen and Grignard reagents in general, and between other sulfur-containing compounds and the benzyl-type Grignard reagent specifically. Apparently not even the reaction between sulfur itself and benzylmagnesium chloride has been studied.

EXPERIMENTAL[7]

Cyanogen. Cyanogen was prepared by treating a warm aqueous solution of copper sulfate with an aqueous solution of potassium cyanide. The gas liberated from the aqueous solution was passed through a calcium chloride drying tube and delivered into dry ether at 0° in a three-necked flask equipped with a stirrer and a Dry Ice reflux condenser. The cyanogen thus obtained, which was measured by the increase in weight of the ether solution, could be stored in the ether at 0° for several hours without appreciable loss.

2-Methyl-5-methoxybenzonitrile from 4-methoxybenzylmagnesium chloride. The Grignard reagent was prepared by the slow addition (2 hr.) of 29.2 g. of *p*-chloromethylanisole in 100 ml. of ether to 24 g. of magnesium turnings in 400 ml. of ether under a nitrogen atmosphere. The resultant solution was slowly added at 0° to 19.1 g. of cyanogen in 250 ml. of ether. The reaction mixture was refluxed for 1 hr. and allowed to stand overnight before hydrolysis with aqueous ammonium chloride. The ether layer was separated, washed with water, and dried over magnesium sulfate, and the ether was distilled at reduced pressure. The residue was distilled *in vacuo* to yield 10.5 g. (39% yield) of 2-methyl-5-methoxybenzonitrile, b.p. 104–108°/10 mm., n_D^{28} 1.5345 (lit. value[8] n_D^{20} 1.5368), λ_{max} 234 and 302 mμ (log ε 4.09 and 3.59, respectively). A brown crystalline material which was recovered from the distillation residue was recrystallized from methanol to yield 9.4 g. of cream-colored 1,2-bis(4-methoxyphenyl)ethane, m.p. 124–126° (lit.,[9] m.p. 125°).

A sample of the 2-methyl-5-methoxybenzonitrile was hydrolyzed with 60% sulfuric acid. The acid which precipitated was recrystallized from methanol-water to give 5-methoxy-2-methylbenzoic acid, m.p. 145–146° (lit.,[10] m.p. 146°).

2-Methyl-3-chlorobenzonitrile from 2-chlorobenzylmagnesium chloride. The Grignard reagent was prepared from 24.5 g. of 2-chlorobenzyl chloride and added in 500 ml. of ether to 12.2 g. of cyanogen in 250 ml. of dry ether at 0°; a yellow precipitate formed during addition. This mixture was re-

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[6] Such thiothiocyanates as IX have been previously reported and are known to be about as easily hydrolyzed as an acid chloride, *cf.* H. Lecher and M. Wittmer, *Ber.*, **55**, 1474 (1922).

[7] Melting points are reported uncorrected. Ultraviolet absorption measurements were made using 95% alcohol solutions in a Beckman Model DU spectrophotometer.

[8] M. S. Carpenter and W. M. Easter, *J. Org. Chem.*, **20**, 401 (1955).

[9] M. Freund and H. H. Reitz, *Ber.*, **39**, 2235 (1906).

[10] O. Jacobsen, *Ber.*, **16**, 1964 (1883).

fluxed for 1 hr. and then hydrolyzed with cold aqueous ammonium chloride. The ether layer was separated, washed with water, dried, and evaporated. Distillation of the residue yielded two fractions. The first was 7.6 g. of 2-methyl-3-chlorobenzonitrile, b.p. 105–109°/25 mm. (lit.,[11] b.p. 107°/28 mm.), n_D^{28} 1.5480, λ_{max} 230 and 292 mμ (log ϵ 3.98 and 3.21, respectively). The second fraction, 4.2 g., was a pungent brownish oil, b.p. 115–120°/25 mm., which decomposed upon standing at room temperature to form a thick reddish liquid and which has not been identified.

Hydrolysis of a sample of the 2-methyl-3-chlorobenzonitrile with 60% sulfuric acid yielded 2-methyl-3-chlorobenzoic acid, m.p. 155–157° (lit.,[12] m.p. 156°).

2-Methyl-1-naphthonitrile from β-chloromethylnaphthalene. The Grignard reagent was prepared in 300 ml. of ether from 10.5 g. of β-chloromethylnaphthalene and added to 8.4 g. of cyanogen in 150 ml. of ether at 0°; a yellow precipitate formed. This mixture was refluxed for 30 min. and then was allowed to stand at room temperature overnight before it was hydrolyzed, first with aqueous ammonium chloride solution and then with dilute hydrochloric acid. The ether layer was treated in the usual manner and the product was distilled at reduced pressure to yield a clear liquid, b.p. 128–131°/1.25 mm., which crystallized. Recrystallization from ethanol yielded 8 g. of 2-methyl-1-naphthonitrile as white rhombic crystals, m.p. 85–87° (lit.,[13] m.p. 87–88°), λ_{max} 226 and 297 mμ (log ϵ 4.69 and 3.89, respectively).

Hydrolysis of a sample of the 2-methyl-1-naphthonitrile by refluxing it 1 hr. with 75% sulfuric acid yielded 2-methyl-1-naphthoamide, m.p. 141–142° (lit.,[13] m.p. 143°).

Benzyllithium from benzyl methyl ether. Benzyllithium was prepared by adding dropwise, over a 2-hr. period with vigorous stirring, 24.4 g. (0.2 mole) of benzyl methyl ether (in enough tetrahydrofuran to make up 100 ml. of solution) to 3.47 g. (0.5 mole) of powdered lithium metal in 400 ml. of tetrahydrofuran at −5 to −15° under a nitrogen atmosphere.[2] At the end of the addition and at 1-hr. intervals, 20-ml. aliquots were removed and shaken with 1.5 g. (0.008 mole) of benzophenone. Each sample was then hydrolyzed with aqueous ammonium chloride and extracted with ether. Evaporation of the ether and recrystallization of any solid material from ligroin (b.p. 60–90°) yielded colorless 1,1,2-triphenylethanol, m.p. 87–88° (lit.,[14] m.p. 89°). The yield of triphenylethanol from the aliquots increased slowly up to about 10 hr. after the benzyl methyl ether and lithium were mixed. The yield was then about 11% and did not exceed that after 13 hr.

Phenylacetonitrile from benzyllithium. Benzyllithium was prepared as in the previous section from 12.2 g. of benzyl methyl ether and 1.74 g. of powdered lithium metal in 500 ml. tetrahydrofuran. The benzyllithium solution was added at 0° to 14.8 g. of cyanogen in 250 ml. of dry ether; a brown precipitate formed immediately. The reaction mixture was hydrolyzed using aqueous ammonium chloride and the ether layer was separated. The aqueous layer was further extracted with three 50-ml. portions of ether and the ethereal solutions were combined, dried, and evaporated. Vacuum distillation of the residue yielded two main fractions. The first was 7.6 g. (62% unchanged) of benzyl methyl ether. The second fraction, 1.6 g. (36% yield based on unrecovered starting benzyl methyl ether) was phenylacetonitrile, b.p. 108–112°/14 mm. and 231–232°/745 mm. (lit.,[15] b.p. 107°/12 mm. and 223–234°/760 mm.). Hydrolysis of this nitrile with 65% sulfuric acid in the usual manner yielded an acid giving no melting point depression with authentic phenylacetic acid.

Benzyl bromide from benzylmagnesium chloride and cyanogen bromide. To the Grignard reagent prepared from 63 g. of benzyl chloride in 500 ml. of ether there was added dropwise at 0° with vigorous stirring 53 g. of cyanogen bromide in 100 ml. of ether. The reaction mixture was hydrolyzed with aqueous ammonium chloride and the ether layer separated, dried, and evaporated, and the residue distilled at reduced pressure. The first fraction, 3.0 g., b.p. 40–45°/17 mm., was identified as toluene. The second fraction was 26 g. of benzyl bromide, b.p. 107–112°/17 mm., n_D^{20} 1.5224. The third fraction, isolated from the distillation residue and recrystallized from 95% ethanol, was 18 g. of bibenzyl, m.p. 50–51°.

Preparation of anhydrous thiocyanogen in benzene solution.[16] Lead thiocyanate was precipitated from a lead nitrate solution with sodium thiocyanate at 0°. The product was collected by filtration, washed with ice water, and allowed to dry over phosphorus pentoxide at reduced pressure in the dark. If the product did not remain perfectly white it was not used. One part by weight in grams of lead thiocyanate was suspended in 5 to 10 parts in milliliters of dry benzene in a glass-stoppered flask and cooled to ice bath temperature. A solution of 10% bromine in the same solvent was then added in small portions with vigorous shaking until lead thiocyanate remained in about 10% excess. The solids were allowed to settle and the colorless thiocyanogen solution was decanted. Any pink coloration indicated the presence of moisture, which must be avoided.

Reaction of benzylmagnesium chloride with thiocyanogen. The Grignard reagent prepared from 25.3 g. of benzyl chloride in 500 ml. of ether was added slowly to 31.4 g. of thiocyanogen in 500 ml. of benzene at 0°; a bright yellow precipitate immediately formed. The resulting mixture was allowed to stand at 5° overnight before hydrolysis with aqueous ammonium chloride. The organic layer was separated, washed with water, dried, and evaporated. The residue was distilled under reduced pressure to obtain three fractions. The first was 7.3 g. of benzyl mercaptan, b.p. 85–90°/15 mm., 193°/748 mm. (lit.,[17] b.p. 194°/760 mm.). With 2,4-dinitrochlorobenzene, the mercaptan yielded a sulfide, m.p. 128–129° (lit.,[17] m.p. 130°) and the sulfide formed a sulfone, m.p. 179–180° (lit.,[17] m.p. 182°) on oxidation with permanganate. The second fraction was 3.6 g. of *o*-tolylthiocyanate, b.p. 120–125°/15 mm. (lit.,[18] b.p. 122.5°/15 mm.). With alkaline lead tartrate, this fraction gave a positive test for an organothiocyanate.[16] Treatment of the *o*-tolylthiocyanate with 95% sulfuric acid at 0–5° for 20 hr. yielded *o*-tolyl thiocarbamate, m.p. 136–138° (lit.,[18] m.p. 139°), which gave a precipitate with alcoholic silver nitrate.[18] *o*-Tolyl thiocarbamate also formed when the *o*-tolyl thiocyanate was allowed to stand in air at room temperature for several days. The third fraction was recovered from the distillation residue and recrystallized from 95% ethanol to yield 3.4 g. of bibenzyl, m.p. 49–50°.

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[16] J. L. Wood, *Org. Reactions*, **3**, 254 (1946).

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