

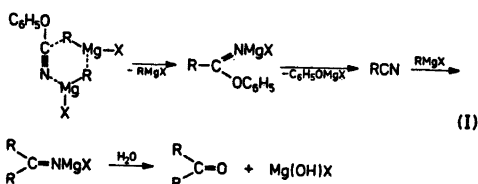
Alkyl Cyanates. XV. Reaction of Alkyl and Aryl Cyanates with Grignard Reagents. Product Formation

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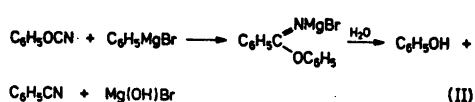
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The reaction between alkyl or aryl cyanates and Grignard reagents has been shown to utilize 1 mol of each reactant and end in formation of a complex of magnesium alcoholate or phenolate, nitrile, and diethyl ether. The same complex is obtained directly by mixing the components. Evidence for imido ester salts as intermediates in the reaction between alkyl or aryl cyanates and Grignard reagents has not been obtained.

The reaction between Grignard reagents and aryl cyanates has been described by Martin and Rackow¹ and by Grigat, Pütter and Mühlbauer.^{2,3} Martin and Rackow found that nitrile was formed and that 2 mol of Grignard reagent to 1 mol of phenyl cyanate were necessary for the reaction to go to completion. The second mol or molecule of Grignard reagent was assumed to act as a Lewis acid facilitating the nucleophilic attack on the cyanate. However, the nitrile formed partly reacts with the excess Grignard reagent yielding a ketone after hydrolysis, according to Martin and Rackow (eqn. I).¹ The experiments were carried out at -20°C .



Grigat *et al.* investigated the reaction at -50°C and isolated benzonitrile in 61% yield using 1 mol of phenylmagnesium bromide to 1 mol of phenyl cyanate. The reaction was formulated as eqn. II.



The magnesium salt of phenyl imidobenzoate was assumed to be an intermediate although no evidence for this was presented. The reaction between phenylmagnesium bromide and 4-methylphenyl cyanate proceeded similarly.

The reaction between ethyl cyanate and Grignard reagents is briefly mentioned by Martin *et al.*⁴ With cyclohexylmagnesium bromide and benzylmagnesium chloride nitrile was formed as described above with the aromatic cyanates. However, ethylcyclohexane and propylbenzene, respectively, were also found to be reaction products. With phenylmagnesium bromide only benzonitrile was identified.

At the time that these results were published we had some unpublished data and now wish to report on a more detailed investigation.

Addition of pentylmagnesium bromide in ether to an equimolar amount of isobutyl cyanate at -80°C gave a white precipitate (*vide infra*). After warming to room temperature the supernatant ether solution was analysed by gas chromatography and found to contain approximately 20% of the theoretical amount of capronitrile. Only traces of isobutyl alcohol were present. After hydrolysis of the reaction mixture the total yields of capronitrile and isobutyl alcohol were 72% and 73%, respectively.

The addition of phenylmagnesium bromide to an equimolar amount of isobutyl cyanate at -80°C proceeded similarly, and benzonitrile

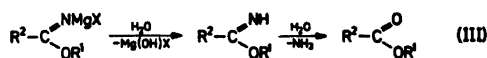
and isobutyl alcohol were isolated in 87 % and 89 % yields, respectively, after hydrolysis. Furthermore, the gas-chromatographic analysis showed that some benzene (8 %) was also formed.

When 2 mol of phenylmagnesium bromide were added to 1 mol of isobutyl cyanate at -80°C and the mixture was warmed to room temperature a further reaction with the benzonitrile formed took place. After hydrolysis diphenylketimine, $(\text{C}_6\text{H}_5)_2\text{C}=\text{NH}$, could be isolated in 70 % yield besides an 84 % yield of isobutyl alcohol, even though diphenylketimine is liable to form benzophenone on further hydrolysis. Benzophenone was the only product isolated by Martin and Rackow and by Grigat *et al.*

To test the generality of these reactions a number of experiments were carried out in which the organic moieties of the cyanate and the Grignard reagent were varied. As shown in Table 1 the yields in most cases were high. The low yields of ethanol isolated in the reactions between ethyl cyanate and Grignard reagents are assumed to be due to the high solubility of ethanol in water from which ethanol

is extracted. Secondary cyanates are known to undergo elimination reactions with basic reagents⁵ and this may explain the low yields of alcohol and nitrile isolated from the reactions of isopropyl cyanate with aliphatic Grignard reagents. In no cases were alkylation products detected in the reaction mixture as found in the investigation of Martin *et al.*⁴

We have most carefully tried to obtain evidence for the intermediacy of the halomagnesium imidate proposed by Martin and Rackow and by Grigat *et al.* (eqns. I and II). On hydrolysis the imidate salt should yield an imido ester or eventually a further hydrolysis product (eqn. III).



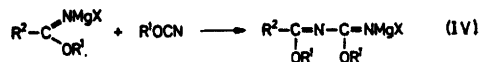
However, despite careful scrutiny we have not observed any of these products, either in the final reaction mixture or when the reaction was interrupted before completion. We have furthermore not observed reaction products of the possible imidate salt and a second mol of cyanate, which would be similar to those

Table 1. Yields of reaction products in the reaction between alkyl and aryl cyanates and Grignard reagents.

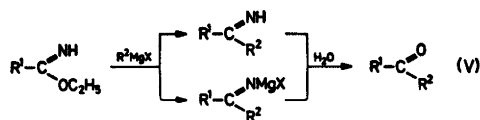
R ¹ OCN	R ² MgX	Molar ratio R ¹ OCN/R ² MgX	Yield ^a		
			R ¹ OH %	R ² CN %	R ² ₂ C=NH %
C ₂ H ₅ OCN	CH ₃ MgBr	1:1	48	62	—
»	C ₄ H ₉ MgBr	1:1	51	71	—
(CH ₃) ₂ CHO CN	CH ₃ MgBr	1:1	46	38	—
»	C ₄ H ₉ MgBr	1:1	58	57	—
»	<i>t</i> -C ₄ H ₉ MgCl	1:1	45	34	—
»	C ₆ H ₅ MgBr	1:1	90	79	—
(CH ₃) ₂ CHCH ₂ OCN	CH ₃ MgBr	1:1	79	61	—
»	C ₄ H ₉ MgCl	1:1	87	92	—
»	C ₆ H ₅ MgBr	1:1	90	87	—
»	<i>t</i> -C ₄ H ₉ MgCl	1:1	72	68	—
»	C ₆ H ₁₁ MgBr	1:1	73 ^b	72 ^b	—
»	C ₆ H ₅ MgBr	1:1	89 ^b	87 ^b	—
»	»	1:2	84 ^b	~0 ^b	70 ^b
C ₆ H ₅ OCN	CH ₃ MgBr	1:1	86	71	—
»	C ₄ H ₉ MgBr	1:1	100	86	—
»	<i>t</i> -C ₄ H ₉ MgCl	1:1	87	92	—
»	C ₆ H ₅ MgBr	1:1	92	81	—

^a The yields are calculated from the amount of cyanate employed and were obtained from gas chromatograms by electronic integration unless another means is indicated. ^b Yields determined by conventional work-up.

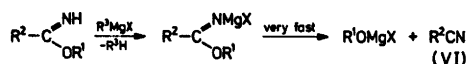
obtained in reactions between some nitriles and Grignard reagents (eqn. IV).^{6,7}



It seems evident that the halomagnesium imidate should be formed in a reaction between an alkyl imido ester and a Grignard reagent. This reaction has been commented on only briefly, but general reaction schemes (eqn. V) were proposed.^{8,9}



In a reinvestigation we have found, however, that nitrile is the isolable reaction product (eqn. VI).¹⁰



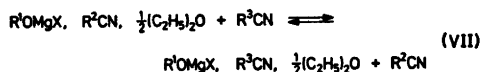
Obviously combination of the nitrile with excess Grignard reagent followed by hydrolysis will lead to the observed ketone.

Thus the reaction between alkyl imido ester and Grignard reagent in fact yields the same products as are obtained from cyanates and Grignard reagents. It is also important to note that we have not been able to isolate the halomagnesium salt that obviously should be first formed, which again parallels the reaction between cyanate and Grignard reagent.

The white precipitate formed on mixing cyanate with Grignard reagent (*vide supra*) appears to be a complex with the composition $\text{R}^1\text{OMgX} \cdot \text{R}^2\text{CN} \cdot \frac{1}{2}(\text{C}_2\text{H}_5)_2\text{O}$. This composition was obtained from the integrals of the nuclear magnetic resonance spectrum of the complex ($\text{R}^1 = \text{R}^2 = \text{C}_6\text{H}_5$) dissolved in $(\text{CD}_3)_2\text{SO}$. In the infrared spectrum obtained in paraffin oil an absorption is observed at 2263 cm^{-1} which is assigned to benzonitrile coordinated to the magnesium atom. In infrared spectra of the complexes $\text{C}_6\text{H}_5\text{CN} \rightarrow \text{AlCl}_3$ and $\text{C}_6\text{H}_5\text{CN} \rightarrow \text{SnCl}_4$ the absorptions are observed at 2280 cm^{-1} and 2258 cm^{-1} , respectively.^{11,12} Uncoordinated benzonitrile absorbs at 2235 cm^{-1} in paraffin oil. The product obtained on mixing phenoxy-magnesium bromide and benzonitrile in diethyl

ether had the same characteristics as those described for the complex formed from phenyl cyanate and phenylmagnesium bromide.

Further evidence for the composition of the complex was obtained by adding a different nitrile to the reaction mixture before hydrolysis. It could be shown by means of GLC that an exchange of nitrile in the complex with the nitrile added had taken place (eqn. VII).



It has not been possible to obtain a satisfactory elemental analysis of the white complex owing to its hygroscopic nature.

In conclusion, the reaction between alkyl or aryl cyanates and Grignard reagents has been shown to proceed with 1 mol of each reactant despite the statement of Martin and Rackow.¹ The presence of a halomagnesium imidate on the route to the final products has not been shown, but on the other hand the data obtained do not exclude this intermediate. The final reaction product is in all cases a complex between magnesium alcoholate or phenolate, nitrile, and diethyl ether, which can also be made directly by mixing the components.

The further details of these reactions can be ascertained only from kinetic experiments, the results of which are presented in following papers.^{13,14}

EXPERIMENTAL

All Grignard reagents were prepared in diethyl ether distilled from lithium aluminum hydride directly into the glass apparatus. This solvent was used in all reactions. The glass apparatus had been flamed and filled with argon. The magnesium used (monosublimed, Dow Chemical Corp.) was washed with anhydrous diethyl ether. Every precaution was taken against oxygen and moisture. The halides used in the preparations of the Grignard reagents were distilled and their purity checked gas-chromatographically. The molarity of the Grignard reagents was determined by titration with standard acid and the content of halogen by titration with standard silver nitrate. The content of halogen was never more than 4% higher than the content of Grignard reagent. The different concentrations were obtained by dilution of *ca.* 2 M standard solution.

Alkyl cyanates were prepared from 5-alkoxy-1,2,3,4-thiazoles^{5,15} and aryl cyanates from

phenols and cyanogen chloride in the presence of triethylamine.¹⁶ The purity of the cyanates was checked by infrared and nuclear magnetic resonance spectroscopy and elemental analysis.

Infrared spectra were obtained on a Perkin-Elmer 337 grating spectrometer and nuclear magnetic resonance spectra on a Varian A-60 A instrument.

A. The reaction between isobutyl cyanate and pentylmagnesium bromide. To 50 ml of 2 M isobutyl cyanate cooled in an acetone/dry ice bath was added 50 ml of 2 M pentylmagnesium bromide with stirring over a 30 min period. After approximately 10 % of the Grignard solution had been added a white precipitate was formed. After the addition was finished the reaction mixture was allowed slowly to reach room temperature (30 min), which caused transformation of the solid into a very viscous liquid. A sample of the supernatant ether solution was analysed by means of gas chromatography and found to contain capronitrile corresponding to approximately 20 % of the theoretical amount, but only traces of isobutyl alcohol. After hydrolysis with 50 ml of 4 M hydrochloric acid saturated with sodium chloride a sample of the ether phase was again analysed gas-chromatographically and now found to contain capronitrile and isobutyl alcohol, both in approximately 75 % yield based on isobutyl cyanate. The water phase was extracted twice with 20 ml of ether, the combined extracts dried over magnesium sulfate and the ether partially removed by evaporation *in vacuo* at 10 °C. Distillation at atmospheric pressure yielded 3 fractions: 1. 80–103 °C, 0.7 g; 2. 103–108 °C, 5.0 g (68 %); 3. 160–163 °C, 6.5 g (73 %); residue 1.0 g. The first fraction was found on gas chromatography to contain ether and isobutyl alcohol; the second was almost

pure isobutyl alcohol and the third almost pure capronitrile. The products were identified by comparison of their infrared spectra with those of authentic samples. The residue was a tar of unknown composition.

The gas-chromatographic analyses were performed on a Perkin-Elmer 116 E gas chromatograph; column SE 30; column temperature 117 °C; injection temperature 200 °C; detector temperature 100 °C; carrier gas helium; flow rate approximately 100 ml/min.

B. The reaction between isobutyl cyanate and phenylmagnesium bromide (molar ratio 1:1). This experiment was carried out analogously to the reaction between isobutyl cyanate and pentylmagnesium bromide. After drying the combined ether extracts and evaporation of the ether, the remaining liquid was shown by gas chromatography to contain benzene in an amount corresponding to 8 % of the phenylmagnesium bromide used. The following fractions were obtained by distillation: 1. 10 mmHg, bath temperature 40 °C, 6.6 g (89 %); 2. 1 mmHg, bath temperature 80 °C, 9.0 g (87 %); residue 0.2 g (black tar). Fractions 1 and 2 were found to consist, of isobutyl alcohol and benzonitrile, respectively, by gas chromatography and infrared spectroscopy.

C. The reaction between isobutyl cyanate and phenylmagnesium bromide (molar ratio 1:2). To 50 ml of 2 M isobutyl cyanate cooled in an acetone/dry ice bath was added 100 ml of 2 M phenylmagnesium bromide with stirring during 30 min. The reaction mixture was then warmed to room temperature and stirred for additional 24 h. Water (100 ml) was added, the phases separated and the water phase extracted twice with 30 ml of ether. After drying ether was removed *in vacuo* and the residue distilled: 1. 1 mmHg, bath temperature 30

Table 2. Conditions for the gas-chromatographic analysis for determining yields of the reaction between cyanates and Grignard reagents.

Column	Column temp. °C	Determination of yield of
Carbowax 1500	59	Ethanol and acetonitrile
Polypropylene glycol	59	Ethanol and valeronitrile
Carbowax 1500	59	2-Propanol and acetonitrile
Polypropylene glycol	55	2-Propanol and valeronitrile
»	57	2-Propanol and pivalonitrile
»	95	2-Propanol and benzonitrile
»	85	2-Methyl-1-propanol and acetonitrile
»	90	2-Methyl-1-propanol and valeronitrile
»	50	2-Methyl-1-propanol and pivalonitrile
»	50→120 ^a	Phenol and acetonitrile
»	50→120 ^a	Phenol and valeronitrile
»	50→120 ^a	Phenol and pivalonitrile
»	135	Phenol and benzonitrile

^a Temperature programming (5 min at 50 °C and increase of the temperature to 120 °C at 10 °C per min).

°C, 6.2 g (84 %); 2. 1 mmHg, bath temperature 125 °C, 12.6 g (70 %); residue 0.5 g (black tar). Fraction 1 was identified as isobutyl alcohol by infrared spectroscopy and fraction 2 as diphenylketimine by infrared spectroscopy and elemental analysis (Found: C 85.91; H 6.22; N 7.29. Calc. for $(C_6H_5)_2C=NH$: C 86.20; H 6.08; N 7.74).

D. Determination of yields by electronic integration of gas chromatograms in reactions of cyanates with Grignard reagents. 40 ml of 1 M cyanate was mixed with 40 ml of 1 M Grignard reagent by flowing the two solutions together in a stainless steel T-tube of diameter 0.6 mm. After mixing the reaction mixture was sprayed into a glass bulb cooled in ice/water. The reagents were cooled to -50 °C before mixing. The reaction mixture was hydrolysed with 20 ml of 4 M hydrochloric acid saturated with sodium chloride and the ether and water phases separated. The water was extracted 3 times with 30 ml of ether and the combined ether phases were dried over magnesium sulfate. A known amount of *o*-xylene (internal standard) was added to the filtered ether solution and the mixture diluted to 200 ml in a graduated flask. The gas chromatograms (conditions are given in Table 2) of these solutions were integrated electronically and yields of alcohol, phenol, and nitrile determined from standard curves (g_x plotted against $g_s A_x/A_s^*$). Gas chromatographic analyses were performed on a Pye Unicam 104 chromatograph in connection with a Varian aerograph 477 integrator and a Victor digital recorder. The flow rate was 45 ml/min.

E. The reaction of phenyl cyanate with phenylmagnesium bromide. To 20 ml of 0.2 M phenyl cyanate was added slowly 2.4 ml of 1.67 M phenylmagnesium bromide with stirring at room temperature. The ether solvent was evaporated and the residue washed 3 times with 5 ml of anhydrous ether and kept at 1 mmHg and 35 °C for 1 h.

The nuclear magnetic resonance spectrum of the white product dissolved in $(CD_3)_2SO$ indicated a content of phenolate, benzonitrile, and diethyl ether in the ratio 2:2:1.

The infrared spectrum of the product in paraffin oil had a characteristic band at 2263 cm^{-1} . Benzonitrile dissolved in paraffin oil absorbs at 2235 cm^{-1} .

F. The reaction of phenoxymagnesium bromide with benzonitrile. 0.02 mol (1.88 g) of phenol and 0.02 mol (2.06 g) of benzonitrile were dissolved in 50 ml of diethyl ether. To this solution was added at room temperature 9.72 ml of 2.057 M methylmagnesium bromide. A white precipitate was formed at once. The ether was evaporated *in vacuo* and the residue

washed 3 times with 5 ml of anhydrous ether and kept at 1 mmHg and 35 °C for 1 h.

The nuclear magnetic resonance spectrum of the product in $(CD_3)_2SO$ showed a content of phenolate, benzonitrile and diethyl ether in ratio 2:2:1.

The infrared spectrum of the product dissolved in paraffin oil had an absorption band at 2263 cm^{-1} .

G. Exchange of nitrile formed in the reaction of a cyanate with a Grignard reagent with a different nitrile. 50 ml of 2 M isobutyl cyanate and 50 ml of 2 M pentylmagnesium bromide were allowed to react as described above. After warming to room temperature 20 % of the theoretical amount of capronitrile was shown to be present in the supernatant ether by means of GLC. Valeronitrile (0.1 mol, 8.3 g) was added to the reaction mixture, and after 10 min with stirring the contents of caponitrile and valeronitrile in the ether phase were 36 % and 76 %, respectively, of the theoretical. After hydrolysis with 4 M hydrochloric acid saturated with sodium chloride the contents of caponitrile, valeronitrile and isobutyl alcohol in the ether phase were 75 %, 100 %, and 75 %, respectively, of the theoretical. The conditions for the gas-chromatographic analysis are described in A.

A similar experiment was carried out on the mixture from the reaction between phenyl cyanate and phenylmagnesium bromide. The benzonitrile formed was exchanged with *p*-tolunitrile.

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REFERENCES

1. Martin, D. and Rackow, S. *Chem. Ber.* 98 (1965) 3662.
2. Grigat, E., Pütter, R. and Mühlbauer, E. *Chem. Ber.* 98 (1965) 3777.
3. Grigat, E. and Pütter, R. *Angew. Chem.* 79 (1967) 219.
4. Martin, D., Weise, A., Niclas, H.-J. and Rackow, S. *Chem. Ber.* 100 (1967) 3756.
5. Jensen, K. A., Due, M. and Holm, A. *Acta Chem. Scand.* 19 (1965) 438.
6. Moore, L. O. *J. Org. Chem.* 31 (1966) 3910.
7. Marxer, A. *Helv. Chim. Acta* 55 (1972) 430.
8. Roger, R. and Neilson, D. G. *Chem. Rev.* 61 (1961) 179.
9. Kaji, K. and Nagashima, N. *J. Pharm. Soc. Jap.* 76 (1956) 1250.
10. Hüge-Jensen, E. *To be published.*
11. Martin, D. and Weise, A. *Chem. Ber.* 100 (1967) 3747.
12. Brown, T. L. and Kubota, M. *J. Amer. Chem. Soc.* 83 (1961) 4175.

* g_x grams of alcohol, phenol or nitrile; g_s grams of internal standard. A_x and A_s are the corresponding areas found by integration.

13. Høge-Jensen, E. and Holm, A. *Acta Chem. Scand. B* 28 (1974) 757.
14. Holm, A., Holm, T. and Høge-Jensen, E. *Acta Chem. Scand. B* 28 (1974) 781.
15. Jensen, K. A. and Holm, A. *Acta Chem. Scand.* 18 (1964) 826.
16. Grigat, E. and Pütter, R. *Chem. Ber.* 97 (1964) 3012.

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