Copper(I) Catalysed Reactions between Hydrazines and Isocyanides

PALLE JAKOBSEN

Medicinsk-Kemisk Institut, University of Copenhagen, Rådmandsgade 71, DK-2200 Copenhagen, Denmark

The reaction between isocyanides and hydrazines, N,N-disubstituted hydrazines, and trisubstituted hydrazine catalysed by copper(I) chloride has been investigated.

Cyclohexyl isocyanide and N,N-disubstituted hydrazines form amidrazones in good yield in a rather slow process. Aromatic isocyanides give formamidrazones in good yield when reacted with trisubstituted hydrazine, while decomposition reactions occur in reactions with N,N-disubstituted hydrazines giving complex mixtures. The components of these mixtures have been identified by GLC or GLC-MS. They consist of amines, amidines and amidrazones. The amines corresponding to the isocyanides are formed in good yields in all reactions between aromatic isocyanides and hydrazine or unsymmetrical disubstituted hydrazines.

The formamidrazones prepared have been identified by means of IR, 1H and 13C NMR spectroscopy.

Results

The reaction between aromatic isocyanides and hydrazines (reactions a–f). The reactions were carried out by refluxing isocyanide, hydrazine and CuCl without solvent, until the infrared spectrum from the reaction mixture showed no absorption around 2100 cm⁻¹. The mixture was subsequently distilled and the components isolated, or the composition was determined by GLC or GLC-MS.

In each reaction with unsubstituted hydrazine or N,N-disubstituted hydrazines, the main product was the amine corresponding to the isocyanide. Scheme 1 represents the identified products (I–VII) from the reactions (a–h). The product distributions found are summarized in Table 1.

The presence of CuCl in the reaction mixture not only influenced the reaction time (the time
Scheme 1. Identified products from the reactions between isocyanide and hydrazines. (Reaction; R,R',R'',R''': (a) Ph,H,H,H; (b) Ph,Me,Me,Me; (c) Ph,Et,Et,H; (d) Ph,Me,Ph,H; (e) p-CH_3C_6H_4, Me,Me,Me,H; (f) Ph,Me,Me,Me; (g) C_6H_5,Me,Me,Me,H; (h) C_8H_11,Me,Me,Ph,H).

required until the isocyanide absorption had disappeared from the IR spectrum of the reaction mixture) but also the product distribution (cf. Table 1).

No obvious dependence on the amount of catalyst was found in the reaction between phenyl isocyanide and N,N-dimethyldihydrazone carried out with CuCl amounts varying from 0.075 to 0.6 mmol (see experimental part).

It is interesting to note that the reaction between N-phenythioformamide and N,N-diethyldihydrazone which was attempted for the preparation of amidrazones (VI c) gave products analogous to those found in the reaction between phenyl isocyanide and N,N-diethyldihydrazone.

PhNHCS + Et_2NNH_2 → PhNH_3 + PhNCHNCHNNEt_2 (IVc) (Vlc)

The evolution of hydrogen sulfide and the formation of elemental sulfur was detected. A similar reaction between O-ethyl thiocarbamoyl and N,N-dimethyldihydrazone has been reported by Walter et al.4

Reaction between aliphatic isocyanides and hydrazines (g–j). The reactions of aliphatic isocyanides and hydrazines differed greatly from those of aromatic isocyanides and hydrazines in reactivity and product distribution. The reaction time was much longer, up to 150 h, and no amine corresponding to the isocyanide was formed. The product arising from α-addition was formed in appreciable yield.

Table 1. Product distribution a from the reaction RNC + R'N'CHNRR'''. Ratio RNC/R''N''H = 1/3 and CuCl/RNC = 1.6/100.

<table>
<thead>
<tr>
<th>Reaction time/h</th>
<th>RNC%</th>
<th>R''N''H%</th>
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<tbody>
<tr>
<td>80</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>20</td>
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<td>65</td>
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<td>5</td>
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<td>1</td>
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<td>0.1</td>
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<tr>
<td>0.01</td>
<td>35</td>
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<tr>
<td>0.001</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>no reaction</td>
<td>0</td>
<td>100</td>
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</table>

Based on gas chromatographic analysis of the distilled mixtures (90-10%); 5. Ratio RNC/R''N''H = 1/11. 6. 5% of (Eh)NCHNCHN(Eh) was identified. Parentheses indicate data without CuCl catalyst.

PhNHCS + Et_2NNH_2 → PhNH_3 + PhNCHNCHNNEt_2 (IVc) (Vlc)

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<tr>
<td>1</td>
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<td>65</td>
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<tr>
<td>0.1</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>0.01</td>
<td>35</td>
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<tr>
<td>0.001</td>
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<td>65</td>
</tr>
<tr>
<td>no reaction</td>
<td>0</td>
<td>100</td>
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</tbody>
</table>

Based on gas chromatographic analysis of the distilled mixtures (90-10%); 5. Ratio RNC/R''N''H = 1/11. 6. 5% of (Eh)NCHNCHN(Eh) was identified. Parentheses indicate data without CuCl catalyst.
Reactions with hydrazones. Two reactions were carried out with phenyl isocyanide and hydrazones (benzophenone hydrazone and acetophenone hydrazone). The reaction time was longer than that found for reactions with hydrazines. From the reaction with benzophenone hydrazone $N^2,N^4$-bis-(diphenylmethylene)formohydrazide hydrazone (VIII) was isolated (10 % yield).

$$(\text{Ph})_2\text{CNNH}_2 + \text{PhNC} \rightarrow (\text{Ph})_2\text{CNNHCHNNN(Ph)}_2$$

(VIII)

DISCUSSION

For the reaction between aliphatic isocyanides and hydrazines and the reaction between aromatic isocyanides and trimethylhydrazine, for which the $\alpha$-addition product is formed in good yield, it seems reasonable to propose that the reaction mechanism is analogous to those proposed for reaction between isocyanides and amines or alcohols. The two possibilities are a reaction in the coordination sphere of an isocyanide- hydrazine - copper complex, or a nucleophilic attack of hydrazine on a copper- isocyanide complex.

Very little is reported about complexes with dialkylhydrazines as ligands. From the long reaction time found and from the lack of reaction in cases where reaction with amines proceeds readily, it seems reasonable to conclude that for the reaction with aliphatic isocyanides, dialkylhydrazines are less efficient nucleophiles or less efficient in coordination to copper than amines. The difference in reaction time found for the reaction between aromatic isocyanides with trisubstituted hydrazines compared to that of aliphatic isocyanides with disubstituted hydrazines might be explained by the difference in strength of the copper isocyanide complex. Aromatic isocyanides show weak new IR-isocyanide stretch absorptions while in the case of aliphatic isocyanide the absorption of the Cu-isocyanide complex is medium to strong after short time reflux.

In the reaction between aromatic isocyanides and $N,N$-disubstituted hydrazines new reactions occur, compared to the analogous reactions with aliphatic isocyanides. Only small amounts of amidrazine from simple $\alpha$-addition are found, but amidines, amines and amidrazones from more complex reactions are found.

Hydrazine—Isocyanide Reactions

$$R'R''\text{NNH}_2 + \text{Cu}^+ \rightarrow R'R''\text{NH}$$

(VII)

$$
\begin{align*}
R'R''\text{NH} &\rightarrow R'R''\text{NNH}_2 \\
\text{RNC} &\rightarrow R'R''\text{NNH}_2 \\
\text{RNCHNNR'}^+ &\rightarrow \text{RNCHNNNRR'}^+ \\
\text{R'}R''\text{NNCHNNR'}^+ &\rightarrow \text{R'}R''\text{NNCHNNR'}^+ + \text{RNH}_2 \\
\text{R'}R''\text{NNCHNNR'}^+ + \text{PhNC} &\rightarrow \text{R'}R''\text{NNCHNNR'}^+ + \text{PhNC} \\
\end{align*}
$$

(VIII)

Scheme 2.

This complexity is possibly due to the aromatic isocyanides forming weaker complexes with copper than the aliphatic isocyanides under the conditions used.

In the former case greater amount of metal ion is accessible for the hydrazine, causing cleavage of the NN-bond with formation of secondary amine. The products formed thus arise from two competing $\alpha$-addition reactions of the isocyanide (with amine or hydrazine, respectively) and possible further reactions of the first formed products/complexes. A reaction scheme, including the reaction products found, is presented as Scheme 2.

GLC measurements on reaction b shows that formation of aniline proceeds during the reaction. The lack of $N,N'$-diphenylformamidine formation indicates that the reaction between aromatic isocyanides and aniline proceeds slower than the reactions with secondary amine and $N,N$-disubstituted hydrazine.

Recently Neuhoeffer et al. reported the formation of $N$-unsaturated hydrazines from reactions between amidrazines and hydrazine.

Amine formation from reactions with isocyanides has previously only been reported in reactions between t-butyl isocyanide and aminoalcohols.

The difference in product distribution between reaction with $N$-methyl-$N$-phenylhydrazine and those with $N,N$-dimethylhydrazine (Table 1) can be ascribed to the great lability of the NN-bond in the former, especially when subjected to heating.

EXPERIMENTAL

Microanalyses were carried out in the micro-analysis department of the Chemical Laboratory II, the H. C. Ørsted Institute. $^1$H NMR spectra
were obtained on a JEOL JNM MH 60/II instrument with TMS as internal reference. IR spectra were recorded on a Perkin-Elmer model 225 grating spectograph. Mass spectra were taken on a Finnigan 1015 S/L or an AEI-902 instrument operating at 70 eV. 13C NMR spectra were recorded on a Bruker WH 90 instrument. Melting points were taken on a Büchi melting point apparatus and are uncorrected.

GLC-analyses were carried out on a Perkin-Elmer F 11 gas chromatograph. Columns: Chromosorb 103 or 2% neopentyl glycol succinate on Chromosorb G (80–100 mesh). GLC-MS analyses were carried out on the Finnigan column. Columns: 10% SE 30 on Chromosorb W HMDS (100–120 mesh) or 10% neopentyl glycol succinate on Diatomite CQ (100–120 mesh).

Isoycanides were prepared according to the literature.

Reaction a. Phenyl isocyanide (0.1 mol), N,N-dimethylhydrazine (0.3 mol) and CuCl (1.5 mmol) were mixed with external cooling; when the exothermic reaction ceased the mixture was refluxed for 1 h. Distillation in vacuo resulted in 3.6 g of aniline identified by IR, 1H NMR and GLC.

Reaction b. (1) Phenyl isocyanide (0.1 mol), N,N-dimethylhydrazine (0.3 mol) and CuCl (1.5 mmol) were refluxed for 1.5 h. The mixture was subsequently distilled. Fraction (1) b.p. 20–100 °C, 760 mmHg, fraction (2) b.p. 68–108 °C, 10–1.2 mmHg. The composition of the fractions was determined by GLC on a Chromosorb 103 column using authentic samples as reference compounds (see below); ca. 50% of the N,N-dimethylhydrazine was recovered. The product distribution of the other compounds can be seen from Table 1.

(2) Phenyl isocyanide (0.01 mol), N,N-dimethylhydrazine (0.03 mol) and CuCl (see below) were mixed as described under (1); the products were identified by GLC on a neopentyl glycol succinate column using authentic samples as reference compounds.

The alteration in product distribution between aniline, N,N,N′-dimethyl-N,N′-phenylenformamide hydrazone and N,N,N′-dimethyl-N,N′-phenylenformamidime are summarized below.

<table>
<thead>
<tr>
<th>Compound</th>
<th>mmol CuCl</th>
<th>% aniline</th>
<th>% amine</th>
<th>% amidrazo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(IV b)</td>
<td>0.075</td>
<td>0.15</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>(IV)</td>
<td>0.12</td>
<td>0.17</td>
<td>0.2</td>
<td>0.3</td>
</tr>
</tbody>
</table>

N,N,N′-Dimethyl-N,N′-phenylenformamide hydrazone (VI b). (1) Phenyl isocyanide (0.2 mol), N,N,N′-dimethylhydrazine (0.6 mol) and CuCl (0.3 mmol) were refluxed for 1.5 h. The mixture was filtered and distilled twice in vacuo, b.p. 77–78 °C/0.5 mmHg. The distillate crystallised on standing at 0 °C, m.p. 49–50 °C, yield 2.1 g (6%). The spectroscopic data are in accordance with those of an authentic sample.

(2) N-Phenyliothioformamide (0.05 mol) and N,N,N′-dimethylhydrazine (0.05 mol) were refluxed in abs. ethanol (60 ml) for 8 h. After cooling the solvent was evaporated and the residue was distilled in vacuo yielding 4.2 g (52%) liquid (b.p. 71–72 °C, 0.15 mmHg) which crystallized on cooling. Recrystallization from hexane, m.p. 49–50 °C. Anal. C10H8N4S: C, H, N. MS m/e (% of base peak): 164(11), 163(100)M+*, 119(13), 106(27), 104(20), 93(67), 77(24), 65(14), 60(67), 58(17), 45(12), 44(23), 42(14). 14C NMR (CDCl3): δ 145.8, 139.8, 129.6, 122.1, 115.5, 46.9. 1H NMR data are in accordance with literature.

N,N,N′,N′′-Tetramethylformimidazidrione (II b). N,N-Dimethylformamide dimethyl acetal (0.1 mol) was dissolved in methanol (10 ml), N,N-dimethylhydrazine (0.1 mol) was added, and the mixture stirred at room temperature for 0.5 h and at reflux temperature for 1 h. B.p. 141–143 °C, 760 mmHg, yield 51%. 1H NMR (CDCl3): δ 7.6 (1 H, s), 2.79 (6 H, s), 2.42 (6 H, s).

Redistillation b.p. 67 °C, 3–8 mmHg yielded a mixture of liquid and crystals. The crystals were isolated and recrystallized from pentane and ether, m.p. 49 °C. These crystals were identified as N,N,N′,N′-tetraethylformyldrazide hydrazide (III c). (Found: C 57.61; H 10.89; N 29.52. Calc. for C15H14N4: C 58.02; H 11.90; N 30.07. MS m/e (% of base peak): 187(11), 186(95)M+*, 157(11), 116(10).) 1H NMR (CDCl3): δ 1.05 (6 H, t); 1.13 (6 H, t); 2.68 (4 H, q); 2.77 (4 H, q); 6–7 (1 H, broad); 7.02 (1 H, s).

N,N′-Diethyl-N,N′-phenylenformamide hydrazone (VI c) was prepared by stirring ethyl N-phenylenformimidate (0.02 mol) and N,N-dimethylhydrazine (0.02 mol) for 20 h at room temperature. The mixture was distilled in vacuo. B.p. 110 °C, 3 mmHg, yield 60%. Anal. C10H12N4: C, H, N. MS m/e (% of base peak): 186(11), 185(100)M+*, 139(13), 124(27), 107(20), 95(67), 88(49), 87(31), 86(29), 74(19), 73(97), 72(71), 71(36), 70(24), 69(12), 68(55), 59(31), 58(100), 57(29), 56(97), 55(14), 45(29), 44(88), 43(21), 42(86), 41(24), 40(12). 1H NMR (CDCl3): δ 1.05 (6 H, t); 1.13 (6 H, t); 2.68 (4 H, q); 2.77 (4 H, q); 6–7 (1 H, broad); 7.02 (1 H, s).

the broad singlet at δ 7.78 to a sharp singlet.
IR (CCl₃ in cm⁻¹): 3400s, 3420s, 3350m, 3190w broad, 3052w, 2978m, 2938m, 2875m, 2839m, 1690m, 1635s, 1600s, 1502s, 1444m, 1400m, 1375m, 1360m, 1338m, 1330m, 689s, 1250w, 1192w, 1178w, 1138w, 1075m, 1058w, 698s. MS m/e (% of base peak): 192(15), 191(100)M⁺, 177(12), 176(50), 147(10), 146(42), 137(15), 119(35), 118(15), 106(54), 104(38), 93(44), 92(22), 78(24), 77(57), 73(15), 65(38), 63(11), 56(10), 52(11), 51(31), 50(13), 44(13), 42(21). ¹³C NMR (CDCl₃): δ 148.1, 139.2, 129.0, 121.5, 114.5, 51.7, 16.2.

Attempted preparation of N,N'-diethyl-N'-phenylformamidine hydrozone. N-Phenyliothioformamide (0.04 mol) and N,N'-dimethylhydrazine (0.04 mol) were refluxed in abs. ethanol (60 ml) for 8 h. H₂S evolution was detected. On cooling small amounts of precipitate were formed (sulfur). These were filtered off and the filtrate evaporated in vacuo and subsequently distilled, b.p. 46–82 °C, 3–1 mmHg. The composition of the distillate was determined by GLC on a neopentyl glycol succinate column as: aniline 10 % N,N'-diethyl-N'-phenylformamidine 10 % and N,N'-diethyl-N'-phenylformamide hydrozone 70 %.

N,N'-Diethyl-N'-phenylformamide (IV) was prepared by dropping N,N'-diethylformamide (0.1 mol) and aniline (0.1 mol) in CHCl₃ (20 ml) to a solution of PCl₅ (30 g) in CHCl₃ (80 ml). The mixtures were refluxed for 3 h. After standing overnight at room temperature, ether was added until the phases separated. The ether phase was washed with water, the combined water extracts made alkaline with NaOH, and subsequently extracted with ether. The ether layer was dried over MgSO₄, and the ether was evaporated. Distillation of the residue gave 88 % of a yellowish liquid, b.p. 87 °C, 3 mmHg. ¹H NMR (CDCl₃): δ 1.17 (6 H, t), 3.33 (4 H, q), 6.6–7.3 (5 H, m), 7.46 (1 H, s). ¹³C NMR (CDCl₃): δ 13.6, 24.0, 120.1, 122.1, 128.8, 151.2, 152.0. MS m/e (% of base peak): 176(4)M⁺, 175(3), 147(9), 104(27), 93(55), 85(11), 77(100), 72(48), 68(95), 56(33), 51(78).

Reaction e. 4-Methylphenyl isocyanide (0.1 mol), N,N-dimethylhydrazine (0.3 mol) and CuCl (1.5 mmol) were refluxed for 2 h and subsequently stirred overnight at room temperature. The mixture was distilled (I) b.p. 30–80 °C, 760 mmHg, (11 g), consisting mainly of N,N-dimethylhydrazine, and (II) b.p. 40–100 °C (12 g). The last fraction was redistilled in vacuo, the composition of the fractions was determined by GLC and GLC-MS using a neopentyl glycol succinate column (see Table 1).

MS of N,N-dimethyl-N'-(4-methylphenyl)formamidine (IV). m/e (% of base peak): 177(9)M⁺, 120(14), 118(14), 107(45), 106(82), 91(56), 60(100).

Reaction f. Phenyl isocyanide (0.095 mol), N,N'-trimethylhydrazine (0.1 mol) and CuCl (1.5 mmol) were refluxed for 2 h. The mixture was then distilled twice in vacuo, b.p. 70–73 °C, 0.04 mmHg, yield 42 % of N,N'-dimethyl-N'-phenylformylhydrazide phenylformimide (Vf). Anal. C₈H₈N₃O : C, H, N. IR (CCl₃ in cm⁻¹): 3060w, 3028w, 2920w, 2955m, 2780w, 1690w, 1650b, 1500s, 1490m, 1452m, 1328w, 1281m, 1150m, 692s. ¹³C NMR (CDCl₃): δ 154.7, 151.8, 128.9, 122.6, 121.3, 43.5, 24.1. ¹H NMR (CDCl₃): δ 7.92 (1 H, s), 6.8–7.5 (5 H, m), 3.00 (3 H, s), 2.57 (6 H, s). MS m/e (% of base peak): 177(13)M⁺, 134(19), 119(10), 104(13), 93(56), 77(48), 74(28), 73(18), 59(100), 51(22), 44(14), 43(13), 42(44).

Reaction g. N,N'-Dimethyl-N'-cyclohexylformamidine hydrozone (VI). Cyclohexyl isocyanide (0.1 mol), N,N-dimethylhydrazine (0.3 mol) and CuCl (1.5 mmol) were refluxed for 6 days. After cooling the mixture was distilled in vacuo, b.p. 64–65 °C, 0.3 mmHg, it crystallized on cooling, m.p. 45 °C (from hexane), yield 20 %. Anal. C₇H₈N₃O : C, H, N. MS m/e (% of base peak): 170(12), 168(100)M⁺, 125(19), 124(2), 123(3), 110(7), 98(21), 96(12), 95(10), 87(23), 86(14), 83(13), 67(11), 60(35), 59(23), 56(21), 55(28), 54(17), 46(28), 45(74), 44(63), 43(32), 42(28), 41(35). IR (CCl₃ in cm⁻¹): 3450w, 3365m, 3260w broad, 3015m, 2940s, 2860s, 2820s, 1635s, 1465s, 1448s, 1425m, 1405m, 1365m, 1345m, 1338m, 1265m, 1228m, 1150m, 1148m, 1016m, 958s, 880m, 1H NMR (CDCl₃): δ 6.85 (1 H, d), 5.6–5.0 (1 H, broad), 3.3–2.8 (1 H, broad), 2.40 (6 H, s), 2.1–1.0 (10 H, m broad). ¹³C NMR (CDCl₃): δ 24.1, 24.8, 34.1, 46.0, 52.6, 149.5.

Reaction h. Cyclohexyl isocyanide (0.013 mol), N-methyl-N-phenylhydrazine (0.040 mol) and CuCl (0.2 mmol) were refluxed for 3 h. The mixture was distilled in vacuo; some products were identified by GLC on a chromosorb 103 column, using authentic samples as reference compounds (Table 1).


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Reaction with hydrazones. Phenyl isocyanide (0.08 mol), benzophenone hydrazone (0.26 mol) and CuCl (1.5 mmol) were refluxed in 400 ml of benzene for 240 h. The isocyanide absorption in the IR spectrum had not completely disappeared. The mixture was cooled and the precipitate filtered off. Recrystallization from methanol gave 90% unreacted benzophenone hydrazone and 10% of N,N'-bis(diphenylmethylene) formohydrazone hydrazone (VIII), identified by comparison with authentic sample.

Phenyl isocyanide (0.05 mol), acetophenone hydrazone (0.1 mol) and CuCl (0.2 mmol) were refluxed in 25 ml CCl₄ for 24 h. The isocyanide absorption in IR did not disappear completely. Cooling the solution caused the precipitation of yellow crystals, which were isolated and identified as acetophenone azine by comparison with an authentic sample.

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REFERENCES


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