Isocyanide Synthesis with Phosphoryl Chloride and Diisopropylamine

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The standard procedure[1] for the preparation of isocyanides **2** is the dehydration of the corresponding formamides **1**.

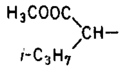
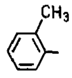
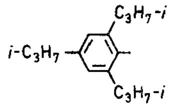
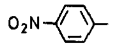
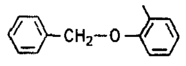
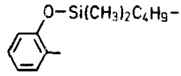
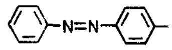
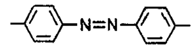
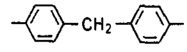
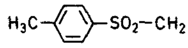
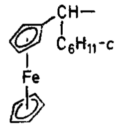
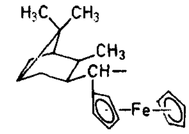
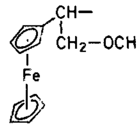
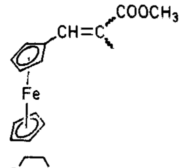
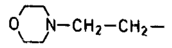
$$\underset{\mathbf{1}}{\mathrm{R{-}NH{-}CH{=}O}} \xrightarrow[-\,H_2O]{} \underset{\mathbf{2}}{\mathrm{R{-}NC}}$$

A variety of reagents has been used for this reaction, including phosgene[2], diphosgene (trichloromethyl carbonochloridate)[3] and phosphoryl chloride[4-10] in combination with bases, in most cases tertiary amines. Although phosgene and diphosgene generally give the highest yields, their application is limited to laboratory scale work due to extreme toxicity and cumbersome handling in the case of phosgene and high costs in the case of diphosgene. We therefore felt the necessity to improve the phosphoryl chloride method to give yields comparable to those obtained with phosgene and diphosgene.

Triethylamine has been mostly used as base for the dehydration of formamides with phosphoryl chloride[5-10]. We have found that simple replacement of triethylamine by diisopropylamine enhances the average yields of the phosphoryl chloride method to the levels of the phosgene or diphosgene procedures in many cases. In addition, the isocyanides are often obtained in higher purity; thus chromatographic purification is avoidable. The yields are well reproducible (± 5 %).

This unique behaviour of the above secondary amine is probably due to the steric bulk of the isopropyl groups. Less bulky secondary amines, e. g. diethylamine, do not give any trace of the isocyanide. The present method seems to be considerably milder than the diphosgene method. In the cases of the ferrocenylalkyl isocyanides **2m** and **2n** which are prepared in fair yields (see Table), diphosgene/triethylamine leads to a mixture of cyanide and isocyanide (compound **2n**), or to elimination to form cyclohexylidenemethylferrocene (from compound **2m**).

Table. Isocyanides **2a–q** from Formamides **1a–q** by the Diisopropylamine/Phosphoryl Chloride Method

Isocyanide **2** R	Yield [%] found	Yield [%] reported	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[a] or Lit. Data	I.R. (state) ν_{NC} [cm^{-1}]
a $C_2H_5OOC-CH_2-$	84	76[7]; 77[2]	36–38°/0.8	80–82°/12[7]	(film) 2150
b $H_3COOC-CH_2-$	75	83[3]; 58[14]	34–36°/0.8	77–79°/2.5[14]	(film) 2150
c  $(H_3COOC)(i\text{-}C_3H_7)CH-$	70	76[2]	37–38°/0.4	37–38°/0.5[2]	(film) 2140
d 	53	54[4]; 83[2]	36–38°/0.5	36–38°/0.6[2]	(film) 2115
e 	60	–	80–83°/0.005	$C_{16}H_{23}N$ (229.4)	(film) 2110
f 	77	68[2]	115–118°	119–120°[2]	(KBr) 2130
g 	79	64[11]; 86[11]	51–53°	oil	(KBr) 2130
h 	56[b]	35[c 12]	47–48°/0.01	oil[12]	(film) 2125
i 	68	73[2]	102–104°	102–104°[2]	(KBr) 2120
j 	64	35[2]	193° (decomp.)	195° (decomp)[2]	(KBr) 2120
k 	89	83[2]	131–133°	131–132°[2]	(KBr) 2120
l 	68	76–84[9]	112–114°	116–117°[9]; 110°[15]	(Nujol) 2150
m 	51	–	78–80°	$C_{18}H_{21}FeN$ (307.2)	(KBr) 2130
n 	49	–	oil	$C_{22}H_{27}FeN$ (361.3)	(film) 2130
o 	77	–	oil	$C_{14}H_{15}FeNO$ (269.1)	(film) 2140
p 	60	–	99–102°	$C_{15}H_{13}FeNO_2$ (295.1)	(KBr) 2110
q 	68	79[16]	63–64°/0.2	70°/0.05[16]	(film) 2150

[a] Satisfactory microanalyses obtained for the new compounds: C ±0.35, H ±0.28, N ±0.16.

[b] One-step procedure from 2-formylaminophenol.

[c] One-step procedure using diphosgene as dehydrating agent.

Completely racemic methyl 2-isocyanopropanoate (**2c**) is obtained from chiral methyl *N*-formylvalinate (**1c**), which indicates that chiral isocyanides derived from amino acids cannot be prepared by this method.

Surprisingly, simple alkylformamides like *N*-*t*-butylformamide fail to yield substantial amounts of isocyanides. This is not due to a reaction between the phosphoryl chloride and the amine, as can be shown by combining the components in reverse order: Addition of methyl *N*-formylaminoacetate to a mixture of phosphoryl chloride and diisopropylamine, stirred for 30 minutes at 0 °C, followed by customary workup, yields 58 % of methyl isocyanoacetate (**2b**).

Moreover, the combination of *O*-silylation and dehydration, with the same base (diisopropylamine), affords an elegant one-pot preparation of the 2-siloxyphenyl isocyanide **2h**.

Dry reagents and solvents have been used for all operations. The formamides have been prepared by reaction of the corresponding amines with ethyl formate (**1a–c**, **1m–o**, and **1g**) or formic acid (**2d–k**). Toluenesulfonylmethylformamide (**1l**) was obtained as described[9].

Methyl 1-Formylamino-3-ferrocenylpropenoate (1p):
This compound is prepared from ferrocenecarboxaldehyde and methyl isocyanoacetate as a ~ 9 : 1 (E/Z)-mixture (by ^{1}H-N.M.R.) according to the known method[13]; yield: 65%, m.p. 125–127 °C (from hexane).

$C_{15}H_{15}FeNO_3$	calc.	C 60.63	H 5.09	N 4.70
(313.1)	found	60.53	4.91	4.60

Isocyanides 2 from Formamides 1; General Procedure:
To a solution or suspension of the formamide (0.1 mol; or 0.045 mol of bisformamide) in dichloromethane (100 ml) and diisopropylamine (0.27 mol), phosphoryl chloride (0.11 mol) is added dropwise with stirring at 0 °C. Stirring is continued for 1 h at 0 °C and, in the case of sparingly soluble formamides, for 8 h at room temperature. A solution of sodium carbonate (20 g) in water (100 ml) is added at a sufficiently slow rate in order to maintain 25–30 °C. After stirring for 1 h at room temperature, more water (100 ml) and dichloromethane (50 ml) are added and the organic layer is washed with water (3 × 50 ml), dried with sodium sulfate, and evaporated. The residue is either distilled in vacuo (**2a–e, h, g**), or recrystallized from hexane (**2f, m, p**), dichloromethane/hexane (**2l**), ethyl acetate (**2i, j**), ethanol (**2g**), or toluene (**2k**). Products **2n** and **2o** are purified by extraction with pentane and evaporation of the solvent.

2-(*t*-Butyldimethylsiloxy)-phenyl Isocyanide (2h):
To a suspension of 2-formylaminophenol (13.7 g, 0.1 mol) in dichloromethane (200 ml) and diisopropylamine (53 ml, 0.37 mol), *t*-butyldimethylchlorosilane (15.1 g, 0.1 mol) is added at room temperature and the mixture is heated to reflux for 3 h. After cooling to 0 °C, phosphoryl chloride (0.11 mol) is added dropwise with stirring. After stirring for 1 h at 0 °C, a solution of sodium carbonate (20 g) in water (100 ml) is added and the mixture is worked up as described above. After evaporation of the solvent, the crude product is distilled in vacuo to give **2h** as a colourless liquid; yield: 12.9 g (56%); b.p. 47–48 °C/0.1 torr (Ref.[12], oil).

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