

## Electrochemical Generation of Alkyl and Aryl Isocyanides

Antonio Guirado,<sup>a\*</sup> Andrés Zapata,<sup>a</sup> Jesús L. Gómez,<sup>a</sup>  
Luis Trabalón,<sup>a</sup> and Jesús Gálvez<sup>b</sup>

<sup>a</sup>Departamento de Química Orgánica, <sup>b</sup>Departamento de Química Física, Facultad de Química,  
Universidad de Murcia, Campus de Espinardo, 30071-Murcia, Apartado 4021, Spain

Received 30 March 1999; revised 19 May 1999; accepted 3 June 1999

**Abstract:** An efficient and widely applicable reagent-free method for the synthesis of alkyl and aryl isocyanides has been established. The electrochemical reduction of alkyl and aryl carbonimidoyl dichlorides under constant cathode potential leads to the corresponding isocyanides in almost quantitative yields. The availability of the starting materials, the mildness of the reaction conditions as well as the easy isolation of products are noteworthy, advantageous features of the procedure. © 1999 Elsevier Science Ltd. All rights reserved.

*Keywords:* Isocyanides; Carbonimidoyl dichlorides; Electrochemical reduction

For many years isocyanides<sup>1</sup> have been regarded as unnatural compounds without significant applications. However, they now have a well demonstrated utility as intermediates for the preparation of a wide variety of compounds<sup>1</sup> such as heterocycles, alkaloids, aminoacids and peptides, formamidines, nitriles, steroids, cyclophanes, carboxylic acids, ketones, hydroxy aldehydes, metal complexes, polymers, antibiotics, radiopharmaceuticals, etc. This great synthetic versatility along with the emergent attention to naturally occurring isocyanides,<sup>2</sup> some of them with potential therapeutic activity, has encouraged interest in the research of isocyano group formation.

Although many reactions yielding isocyanides have been described,<sup>1</sup> those that appear to have general application in synthesis are few in number. The experimental difficulties of the early classical preparative methods should be noted. Thus, the alkylation of heavy metal cyanide salts<sup>1b-d,3</sup> followed by treatment with large amounts of potassium cyanide, provides isocyanides in modest to low yields accompanied by the corresponding isomeric nitriles. Moreover, the application of this method involves the generation of highly concentrated aqueous cyanide solutions that are not easily disposable residues. On the other hand, the reaction of primary amines with dichlorocarbene<sup>1b-d,4</sup> generated either by treatment of chloroform<sup>4</sup> with strong bases or thermal decomposition of

---

\* E-mail: [anguir@fcu.um.es](mailto:anguir@fcu.um.es)

sodium trichloroacetate, commonly called the 'carbylamine method', has never enjoyed popularity. It provides isocyanides in moderate to very low yields and frequently they are attended by tarry byproducts.

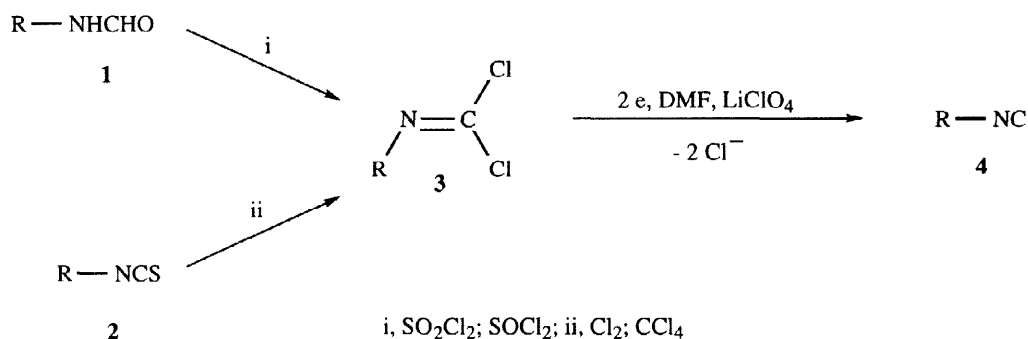
Isocyanides have also been prepared by reduction of isocyanates and isothiocyanates with different reagents.<sup>1c,d</sup> Owing to the high temperatures that are frequently required, isomerizations and polymerizations of the primarily formed isocyanide products are severe limiting factors. 2-Phenyl-3-methyl-1,3,2-oxazaphospholidine,<sup>5</sup> diphenyl-*t*-butylsilyllithium and trichlorosilane-triethylamine<sup>6</sup> seem to be the best low temperature reducing agents.

A more general and efficient access to isocyanides results from dehydration of *N*-monosubstituted formamides. Phosgene provides by far the best results generally,<sup>1a-c</sup> but the application of this reagent is limited by its extreme toxicity and cumbersome handling.<sup>7</sup> Numerous efforts devoted to circumventing the use of phosgene as well as overcoming some limitations of this reagent have been reported.<sup>7,8</sup>

It should also be noticed that due to the extremely distressing odour of isocyanides the application of the usual techniques of purification is especially difficult since the exposure to isocyanide vapours, even at very low levels, must be rigorously avoided. Loss of yield due to the formation of secondary products during the formation reaction or during purification are other frequent obstacles to be overcome in the preparative work of isocyanides. Given the above, it is apparent that non-thermal and reagent-free transformations are of particular interest in isocyanide synthesis. However, the application of the electrochemical preparative techniques have scarcely been exploited. 5-Aminotetrazoles have been anodically oxidized to 5-iminotetrazoles which give isocyanides (39 - 48% yields) and nitrogen by cycloreversion.<sup>9</sup> An interesting synthesis of isocyanides involving an electrochemical reduction step has been recently reported.<sup>10</sup> However, the reaction is not used to generate the isocyano function but to remove the activating tosyl group. As was reported in a preliminary communication, the electrochemical reduction of carbonimidoyl dichlorides provides a highly efficient and easy method for the generation of isocyanides.<sup>11</sup> In this paper we describe full details of the previous communication as well as additional new results derived from exploring the scope and limitations of the reported reaction.

Carbonimidoyl dichlorides **3** are inexpensive and easily available reagents<sup>12</sup> bearing a geminally dichlorinated active centre which suggests an attractive entry to isocyanides. Reported reactions, however, have been mainly focused on nucleophilic attack with displacement of chlorine atoms and retention of the carbon - nitrogen double bond. In connection with this reaction mode we have also reported almost quantitative electrochemical syntheses of 2-arylimino-4,5-diaryl-1,3-dioxoles and 3,4,5-triaryl-2-aryliminooxazolines by electrochemical reduction of diaryl-1,2-diketones<sup>13</sup> or benzilmonoimines<sup>14</sup> in the presence of carbonimidoyl dichlorides.

Through the electrochemical method reported here isocyanides are cleanly and quantitatively generated in a normal organic solvent which additionally contains inorganic lithium perchlorate and lithium chloride salts, exclusively (Scheme 1). Therefore this solution has direct utility for many synthetic purposes. However, if isolated isocyanides are required they can be easily obtained in a high purity state<sup>15</sup> by addition of water to dissolve the inorganic salts and simple extraction with ether. Therefore, difficult purification processes can be fully avoided.



Scheme 1

Cathodic reductions of solutions of carbonimidoyl dichlorides **3** in DMF-LiClO<sub>4</sub> at a mercury pool cathode were carried out under constant potential. The electricity consumption was 2 F/ mol of **3**. After electrolyses, the catholyte solutions were checked by TLC and GC showing a total transformation of starting materials to single products which were easily isolated by mixing the catholyte solution with cold brine and simple filtration or extraction. Highly pure isocyanides **4** were isolated and were identified by IR, CG/MS, high field NMR spectroscopy and microanalyses. Yields were almost quantitative. The results of a number of reactions are summarized in Table 1.

With few exceptions, the electrochemical reductions of aryl and alkyl carbonimidoyl dichlorides led to the corresponding isocyanides **4**. The reductions permit the selective generation of the isocyanide without altering other reducible functional groups present in the starting materials. Anomalous reactions were found when the reductions of nitrocarbonimidoyl dichlorides **3p** - **r** were attempted, which gave a complex mixture of products that could not be identified. Since nitrocompounds are easily reduced electrochemically, the failure of these electrolyses can be reasonably attributed to unclear processes promoted by initial electron transfer to the nitro groups. 2,4,6-Trichlorophenylcarbonimidoyl dichloride **3j** was also unselectively reduced. In this case a mixture of 2,4,6-trichlorophenylisocyanide **4j** and 2,4-dichlorophenylisocyanide **4g** (2 : 1) was formed. This points towards attributing the lack of selectivity of this reaction to the accumulation of electronegative groups in the aromatic ring which makes the cleavage of carbon - chlorine bonds on the ring as feasible as at the imidoyl centre.

In conclusion, a simple, effective and general procedure for the synthesis of alkyl and arylisocyanides is reported. The availability of starting materials, the mildness of the reaction conditions as well as its efficiency are relevant advantages of the method. Owing to the general adversity of work with isocyanides, the possibility of a direct use of the catholyte solutions as well as the trivial isolation of highly pure products are also very valuable features of the procedure.

**Table 1.** Preparation of isocyanides **4** by cathodic reduction of carbonimidoyl dichlorides **3**

Entry	R	Cathode potential V vs SCE	Yield (%) <sup>a</sup>
a	C <sub>6</sub> H <sub>5</sub>	-1.90	91
b	3-ClC <sub>6</sub> H <sub>4</sub>	-1.55	92
c	4-ClC <sub>6</sub> H <sub>4</sub>	-1.40	94
d	2-Cl-4-MeC <sub>6</sub> H <sub>3</sub>	-1.45	82
e	4-Cl-2-MeC <sub>6</sub> H <sub>3</sub>	-1.55	87
f	2,3-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	-1.40	98
g	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	-1.25	95
h	2,5-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	-1.45	90
i	2,6-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	-1.50	86
j	2,4,6-Cl <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	-1.15	58 <sup>b</sup>
k	4-BrC <sub>6</sub> H <sub>4</sub>	-1.45	88
l	4-FC <sub>6</sub> H <sub>4</sub>	-1.50	87
m	4-NCC <sub>6</sub> H <sub>4</sub>	-1.10	89
n	4-EtOOC <sub>6</sub> H <sub>4</sub>	-1.50	90
o	4-CNC <sub>6</sub> H <sub>4</sub>	-1.25	94
p	2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	-0.80	-
q	3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	-0.85	-
r	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	-0.80	-
s	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	-1.75	96
t	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>	-1.82	97
u	C <sub>6</sub> H <sub>11</sub>	-1.85	90
v	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> CH <sub>2</sub>	-1.88	92
w	CH <sub>3</sub> CH <sub>2</sub> CH(CH <sub>3</sub> )CH <sub>2</sub>	-1.90	83
x	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub>	-1.86	95

<sup>a</sup>yields of isolated products; <sup>b</sup>product **4g** (29%) was also generated

## Experimental

Carbonimidoyldichlorides **3** were prepared by standard procedures<sup>12,16</sup>. DMF was taken from a freshly opened bottle and dried with molecular sieves. LiClO<sub>4</sub> was anhydrous. Both were purchased from Fluka, and were directly used without further purification. NMR spectra were determined on Bruker AC-200 or Varian AC-300 Unity instruments with tetramethylsilane as internal reference. Electron-impact mass spectra (70 eV) were obtained on a Hewlett-Packard 5995 GC/MS spectrometer. IR spectra (Nujol emulsions) were recorded on

Nicolet 5DX or Impact 400 spectrophotometers. Gas chromatography was carried out with OV-101 capillary column (12 m). Microanalyses were performed on a Carlo Erba EA-1108 analyzer. Melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. Electrochemical experiments were performed with a preparative Amel 557 potentiostat (200 V, 1 A) coupled to an Amel 558 integrator.

### General Electrolysis Procedure

Preparative electrolyses were carried out under a constant cathodic potential in a concentric cylindrical cell with two compartments separated by a circular glass frit (medium) diaphragm. A mercury pool (diameter 5 cm) was used as the cathode and a platinum plate as the anode. The catholyte was magnetically stirred. The temperature was kept at approximately 15 °C by external cooling. The reductions were performed in DMF-LiClO<sub>4</sub>, 0.2 M. Approximately 50 mL and 20 mL of this solution were placed in the cathodic and the anodic compartments, respectively. Anhydrous sodium carbonate (3 g) was placed in the anode compartment to prevent accumulation of electrogenerated acid. Solutions of the carbonimidoyl dichlorides (1) (5 mmol) were electrolyzed under the appropriate cathodic potentials which are shown in Table 1. GC/MS analyses with capillary column of the catholyte solutions showed a single peak of the corresponding isocyanides. Highly pure products were isolated by dropping the catholyte solution onto cold brine (200 mL) and filtering or extracting the mixture with ether which was washed with cold water and dried (Na<sub>2</sub>SO<sub>4</sub>). Products **4c**, **e - i**, **k**, **m - o** were collected by filtration. Products **4a**, **b**, **d**, **j**, **l**, **s - w** were extracted with ether. Product **4x** was extracted with petroleum ether (30 - 40 °C). The directly collected solid products and those liquid compounds obtained after removing solvent under reduced pressure<sup>17</sup> gave satisfactory IR, MS, <sup>1</sup>H NMR, <sup>13</sup>C NMR spectra and microanalyses.

### Phenyl isocyanide (4a)

Pale yellow oil<sup>1b</sup>; (Found: C, 81.37; H, 5.01; N, 13.64. C<sub>7</sub>H<sub>5</sub>N requires: C, 81.53; H, 4.89; N, 13.58); <sup>1</sup>H n.m.r.  $\delta$  (CDCl<sub>3</sub>, 200 MHz): 7.37 (br s, 5H); <sup>13</sup>C n.m.r.  $\delta$  (CDCl<sub>3</sub>, 50.3 MHz): 126.17 (CH), 126.45 (t, C, J = 13.3 Hz), 129.17 (CH), 129.24 (CH), 164.04 (t, NC, J = 5.7 Hz); m.s., m/z (%): 103 (M<sup>+</sup>, 100), 76 (59), 50 (26); i.r.: 2128, 1589, 1487, 1456, 756, 685 cm<sup>-1</sup>.

### 3-Chlorophenyl isocyanide (4b)

Pale yellow oil<sup>18</sup>; (Found: C, 60.94; H, 2.86; N, 10.03. C<sub>7</sub>H<sub>4</sub>ClN requires: C, 61.12; H, 2.93; N, 10.18); <sup>1</sup>H n.m.r.  $\delta$  (CDCl<sub>3</sub>, 300 MHz): 7.25-7.42 (m, 4H); <sup>13</sup>C n.m.r.  $\delta$  (CDCl<sub>3</sub>, 75.4 MHz): 124.60 (CH), 126.55 (CH), 129.79 (CH), 130.43 (CH), 135.07 (C), 165.83 (NC); m.s., m/z (%): 139 (M<sup>+</sup>+2, 31), 137 (M<sup>+</sup>, 100), 102 (68), 75 (39), 50 (43); i.r.: 2129, 1594, 1584, 1575, 1472, 852, 784, 675 cm<sup>-1</sup>.

### 4-Chlorophenyl isocyanide (4c)

Colourless needles mp 73-75 °C. (Lit<sup>19</sup>, mp 71-73 °C); (Found: C, 61.17; H, 3.00; N, 10.01. C<sub>7</sub>H<sub>4</sub>ClN requires: C, 61.12; H, 2.93; N, 10.18); <sup>1</sup>H n.m.r.  $\delta$  (CDCl<sub>3</sub>, 200 MHz): 7.32 (d, 2H, J = 8.9 Hz), 7.35 (d, 2H, J = 8.9 Hz); <sup>13</sup>C n.m.r.  $\delta$  (CDCl<sub>3</sub>, 50.3 MHz): 124.89 (t, C, J = 14.1 Hz), 127.49 (CH), 129.59 (CH), 135.22

(C), 165.68 (NC); m.s., m/z (%): 139 ( $M^{+2}$ , 34), 137 ( $M^{+}$ , 100), 102 (59), 75 (25), 50 (20); i.r. (Nujol): 2126, 1487, 1092, 1017, 829  $\text{cm}^{-1}$ .

#### 2-Chloro-4-methylphenyl isocyanide (4d)

Pale yellow oil; (Found: C, 63.11; H, 3.91; N, 9.32.  $\text{C}_8\text{H}_6\text{ClN}$  requires: C, 63.38; H, 3.99; N, 9.24);  $^1\text{H}$  n.m.r.  $\delta$  ( $\text{CDCl}_3$ , 200 MHz): 2.36 (s, 3H), 7.08 (d, 1H,  $J = 8.1$  Hz), 7.25–7.33 (m, 2H);  $^{13}\text{C}$  n.m.r.  $\delta$  ( $\text{CDCl}_3$ , 50.3 MHz): 21.04 ( $\text{CH}_3$ ), 122.77 (t, C,  $J = 15.3$  Hz), 127.44 (CH), 128.12 (CH), 130.19 (C), 130.33 (CH), 141.07 (C), 168.28 (NC); m.s., m/z (%): 153 ( $M^{+2}$ , 8), 151 ( $M^{+}$ , 26), 116 (100), 89 (31), 63 (17), 50 (11); i.r.: 2126, 1597, 1489, 1464, 1059, 883, 818, 718, 687  $\text{cm}^{-1}$ .

#### 4-Chloro-2-methylphenyl isocyanide (4e)

White needles mp 46–48 °C; (Found: C, 63.46; H, 3.94; N, 9.15.  $\text{C}_8\text{H}_6\text{ClN}$  requires: C, 63.38; H, 3.99; N, 9.24);  $^1\text{H}$  n.m.r.  $\delta$  ( $\text{CDCl}_3$ , 300 MHz): 2.41 (s, 3H), 7.15–7.21 (m, 1H), 7.24–7.29 (m, 2H);  $^{13}\text{C}$  n.m.r.  $\delta$  ( $\text{CDCl}_3$ , 75.4 MHz): 18.50 ( $\text{CH}_3$ ), 125.08 (t, C,  $J = 13.7$  Hz), 126.97 (CH), 127.61 (CH), 130.57 (CH), 135.00 (C), 136.78 (C), 167.28 (t, NC,  $J = 5.0$  Hz); m.s., m/z (%): 153 ( $M^{+2}$ , 11), 151 ( $M^{+}$ , 34), 116 (100), 89 (48), 63 (19), 50 (11); i.r. (Nujol): 2121, 1486, 1178, 1118, 890, 874, 832  $\text{cm}^{-1}$ .

#### 2,3-Dichlorophenyl isocyanide (4f)

Pale yellow needles mp 43–45 °C; (Found: C, 49.11; H, 1.81; N, 8.01.  $\text{C}_7\text{H}_3\text{Cl}_2\text{N}$  requires: C, 48.88; H, 1.76; N, 8.14);  $^1\text{H}$  n.m.r.  $\delta$  ( $\text{CDCl}_3$ , 300 MHz): 7.25 (t, 1H,  $J = 8.1$  Hz), 7.38 (dd, 1H,  $J = 8.1$  Hz,  $J = 1.8$  Hz), 7.51 (dd, 1H,  $J = 8.1$  Hz,  $J = 1.8$  Hz);  $^{13}\text{C}$  n.m.r.  $\delta$  ( $\text{CDCl}_3$ , 75.4 MHz): 126.12 (CH), 127.60 (CH), 129.92 (C), 131.07 (CH), 134.32 (C), 170.28 (NC); m.s., m/z (%): 173 ( $M^{+2}$ , 46), 171 ( $M^{+}$ , 77), 136 (76), 109 (22), 100 (100), 84 (26), 75 (68), 61 (22), 50 (53); i.r. (Nujol): 2129, 1449, 1429, 1190, 861, 781, 700  $\text{cm}^{-1}$ .

#### 2,4-Dichlorophenyl isocyanide (4g)

Pale yellow needles mp 36–37 °C; (Found: C, 48.94; H, 1.71; N, 7.97.  $\text{C}_7\text{H}_3\text{Cl}_2\text{N}$  requires: C, 48.88; H, 1.76; N, 8.14);  $^1\text{H}$  n.m.r.  $\delta$  ( $\text{CDCl}_3$ , 200 MHz): 7.30 (dd, 1H,  $J = 8.6$  Hz,  $J = 1.9$  Hz), 7.39 (d, 1H,  $J = 8.6$  Hz), 7.51 (d, 1H,  $J = 1.9$  Hz);  $^{13}\text{C}$  n.m.r.  $\delta$  ( $\text{CDCl}_3$ , 50.3 MHz): 124.01 (C), 127.87 (CH), 128.49 (CH), 129.99 (CH), 131.66 (C), 135.71 (C), 170.67 (NC); m.s., m/z (%): 175 ( $M^{+} + 4$ , 10), 173 ( $M^{+2}$ , 61), 171 ( $M^{+}$ , 100), 136 (37), 100 (27), 75 (12), 50 (13); i.r. (Nujol): 2128, 1660, 1584, 1476, 1106, 1059, 839, 818, 700, 621  $\text{cm}^{-1}$ .

#### 2,5-Dichlorophenyl isocyanide (4h)

White needles mp 91–93 °C; (Found: C, 48.66; H, 1.79; N, 8.22.  $\text{C}_7\text{H}_3\text{Cl}_2\text{N}$  requires: C, 48.88; H, 1.76; N, 8.14);  $^1\text{H}$  n.m.r.  $\delta$  ( $\text{CDCl}_3$ , 200 MHz): 7.30–7.47 (m, 3H);  $^{13}\text{C}$  n.m.r.  $\delta$  ( $\text{CDCl}_3$ , 50.3 MHz): 127.88 (CH), 129.37 (C), 130.60 (CH), 131.00 (CH), 133.20 (C), 170.91 (t, NC,  $J = 3.0$  Hz); m.s., m/z (%): 173 ( $M^{+2}$ , 62), 171 ( $M^{+}$ , 100), 136 (52), 100 (56), 75 (29), 50 (40); i.r. (Nujol): 2136, 1102, 1060, 875, 820, 606  $\text{cm}^{-1}$ .

**2,6-Dichlorophenyl isocyanide (4i)**

White needles mp 114–115 °C. (Lit<sup>20</sup>, mp 111 °C); (Found: C, 48.94; H, 1.73; N, 8.10. C<sub>7</sub>H<sub>3</sub>Cl<sub>2</sub>N requires: C, 48.88; H, 1.76; N, 8.14); <sup>1</sup>H n.m.r. δ (CDCl<sub>3</sub>, 200 MHz): 7.25–7.50 (m, 3H); <sup>13</sup>C n.m.r. δ (CDCl<sub>3</sub>, 50.3 MHz): 128.33 (CH), 130.06 (CH), 132.35 (C), 174.08 (NC); m.s., m/z (%): 173 (M<sup>+</sup>+2, 63), 171 (M<sup>+</sup>, 100), 136 (55), 100 (67), 75 (47), 50 (49); i.r. (Nujol): 2123, 1439, 802, 778, 711 cm<sup>-1</sup>.

**2,4,6-Trichlorophenyl isocyanide (4j)**

m.s., m/z (%): 207 (M<sup>+</sup>+2, 23), 205 (M<sup>+</sup>, 26), 197 (84) 195 (100) 124 (79) 97 (42) 62 (45). An authentic sample<sup>1b</sup> gave coincident results on gas chromatography-mass spectrometry.

**4-Bromophenyl isocyanide (4k)**

Colourless needles mp 98–99 °C. (Lit<sup>19</sup>, mp 98–99 °C); (Found: C, 45.98; H, 2.26; N, 7.77. C<sub>7</sub>H<sub>4</sub>BrN requires: C, 46.19; H, 2.22; N, 7.70); <sup>1</sup>H n.m.r. δ (CDCl<sub>3</sub>, 200 MHz): 7.25 (d, 2H, J = 8.6 Hz), 7.53 (d, 2H, J = 8.6 Hz); <sup>13</sup>C n.m.r. δ (CDCl<sub>3</sub>, 50.3 MHz): 123.39 (C), 125.46 (t, C, J = 13.7 Hz), 127.83 (CH), 132.69 (CH), 165.86 (t, NC, J = 5.3 Hz); m.s., m/z (%): 183 (M<sup>+</sup>+2, 29), 181 (M<sup>+</sup>, 30), 102 (100), 75 (49), 50 (53); i.r. (Nujol): 2121, 1482, 1071, 1014, 824 cm<sup>-1</sup>.

**4-Fluorophenyl isocyanide (4l)**

Pale green oil<sup>19</sup>; (Found: C, 69.21; H, 3.36; N, 11.63. C<sub>7</sub>H<sub>4</sub>FN requires: C, 69.42; H, 3.33; N, 11.56); <sup>1</sup>H n.m.r. δ (CDCl<sub>3</sub>, 300 MHz): 7.09 (dd, 2H, J = 9.0 Hz, J = 8.1 Hz), 7.38 (dd, 2H, J = 8.7 Hz, J = 4.5 Hz). <sup>13</sup>C n.m.r. δ (CDCl<sub>3</sub>, 75.4 MHz): 116.70 (d, CH, J = 23.5 Hz), 123.01 (d, C, J = 18.8 Hz), 128.44 (d, CH, J = 9.2 Hz), 162.39 (d, C, J = 251.8 Hz), 164.52 (t, NC, J = 5.2 Hz); m.s., m/z (%): 122 (M<sup>+</sup>+1, 7), 121 (M<sup>+</sup>, 100), 95 (9), 94 (48), 75 (11), 70 (8), 57 (8), 50 (18); i.r.: 2128, 1605, 1505, 1236, 1187, 1155, 1096, 842, 709 cm<sup>-1</sup>.

**4-Isocyanobenzonitrile (4m)**

Colourless needles mp 175 °C decomp. (Lit<sup>1b</sup>, mp 130 °C decomp.); (Found: C, 75.18; H, 3.16; N, 21.94. C<sub>8</sub>H<sub>4</sub>N<sub>2</sub> requires: C, 74.99; H, 3.15; N, 21.86); <sup>1</sup>H n.m.r. δ (DMF-d<sub>6</sub>, 200 MHz): 7.86 (dt, 2H, J = 8.5 Hz, J = 1.8 Hz), 8.07 (dt, 2H, J = 8.5 Hz, J = 1.8 Hz); <sup>13</sup>C n.m.r. δ (DMF-d<sub>6</sub>, 50.3 MHz): 112.60 (C), 117.14 (CN), 127.31 (CH), 129.06 (C), 133.69 (CH), 167.87 (NC); m.s., m/z (%): 129 (M<sup>+</sup>+1, 10), 128 (M<sup>+</sup>, 100) 101 (20), 75 (5), 50 (5); i.r. (Nujol): 2234, 2138, 1700, 1610, 1504, 1284, 847 cm<sup>-1</sup>.

**Ethyl 4-Isocyanobenzoate (4n)**

Pale brown needles mp 101–105 °C. (Lit<sup>1b</sup>, mp 95–103 °C); (Found: C, 68.38; H, 5.13; N, 7.97. C<sub>10</sub>H<sub>9</sub>NO<sub>2</sub> requires: C, 68.56; H, 5.18; N, 8.00); <sup>1</sup>H n.m.r. δ (CDCl<sub>3</sub>, 200 MHz): 1.41 (t, 3H, J = 7.2 Hz), 4.40 (c, 2H, J = 7.2 Hz), 7.45 (d, 2H, J = 8.5 Hz), 8.09 (d, 2H, J = 8.5 Hz); <sup>13</sup>C n.m.r. δ (CDCl<sub>3</sub>, 50.3 MHz): 14.23 (CH<sub>3</sub>), 61.58 (CH<sub>2</sub>), 126.39 (CH), 130.78 (CH), 131.25 (C), 131.50 (C), 164.97 (COO), 166.92 (t, NC, J =

2.5 Hz); m.s., m/z (%): 175 (M<sup>+</sup>, 13), 147 (39), 130 (100), 102 (70), 75 (22), 51 (16); i.r. (Nujol): 2125, 1724, 1610, 1370, 1277, 1107, 1020, 865, 770, 691 cm<sup>-1</sup>.

#### 1,4-Diisocyanobenzene (4o)

Pale brown needles mp 103–105 °C. (Lit<sup>1b</sup>, mp 100 °C); (Found: C, 74.73; H, 3.10; N, 21.97. C<sub>8</sub>H<sub>4</sub>N<sub>2</sub> requires: C, 74.99; H, 3.15; N, 21.86); <sup>1</sup>H n.m.r. δ (CDCl<sub>3</sub>, 200 MHz): 7.45 (s, 4H); <sup>13</sup>C n.m.r. δ (CDCl<sub>3</sub>, 50.3 MHz): 126.45 (t, C, J = 11.3 Hz), 127.68 (CH), 167.45 (NC); m.s., m/z (%): 129 (M<sup>+</sup>+1, 9), 128 (M<sup>+</sup>, 100), 101 (44), 75 (18), 64 (11), 50 (32); i.r. (Nujol): 2134, 1499, 1282, 1183, 842, 727, 718, 512 cm<sup>-1</sup>.

#### Benzyl isocyanide (4s)

Colourless oil<sup>1b</sup>; (Found: C, 82.21; H, 6.10; N, 12.05. C<sub>8</sub>H<sub>7</sub>N requires: C, 82.02; H, 6.02; N, 11.96); <sup>1</sup>H n.m.r. δ (CDCl<sub>3</sub>, 200 MHz): 4.56 (t, 2H, J = 1.9 Hz), 7.32–7.36 (m, 5H); <sup>13</sup>C n.m.r. δ (CDCl<sub>3</sub>, 50.3 MHz): 45.23 (t, CH<sub>2</sub>, J = 7.2 Hz), 126.37 (CH), 128.13 (CH), 128.71 (CH), 132.18 (C), 157.62 (t, NC, J = 5.2 Hz); m.s., m/z (%): 118 (M<sup>+</sup>+1, 9), 117 (M<sup>+</sup>, 100), 116 (48), 91 (57), 90 (72), 89 (43), 63 (18), 51 (22); i.r.: 2153, 1499, 1456, 1443, 1354, 1030, 950, 905 cm<sup>-1</sup>.

#### 2-Phenylethyl isocyanide (4t)

Colourless oil<sup>1b</sup>; (Found: C, 82.23; H, 6.87; N, 10.55. C<sub>9</sub>H<sub>9</sub>N requires: C, 82.41; H, 6.92; N, 10.68); <sup>1</sup>H n.m.r. δ (CDCl<sub>3</sub>, 200 MHz): 2.91–3.01 (m, 2H), 3.58 (tt, 2H, J = 7.1 Hz, J = 1.5 Hz), 7.16–7.38 (m, 5H); <sup>13</sup>C n.m.r. δ (CDCl<sub>3</sub>, 50.3 MHz): 35.62 (CH<sub>2</sub>), 42.93 (t, CH<sub>2</sub>, J = 6.7 Hz), 127.21 (CH), 128.65 (CH), 128.74 (CH), 136.63 (C), 156.57 (t, NC, J = 5.5 Hz); m.s., m/z (%): 131 (M<sup>+</sup>, 22), 103 (7), 91 (100), 77 (6), 65 (14), 51 (12); i.r.: 2149, 1498, 1455, 1355, 750, 700 cm<sup>-1</sup>.

#### Cyclohexyl isocyanide (4u)

Colourless oil<sup>1b</sup>; <sup>1</sup>H n.m.r. δ (CDCl<sub>3</sub>, 200 MHz): 1.38–1.49 (m, 4H), 1.61–1.89 (m, 6H), 3.58–3.64 (m, 1H); <sup>13</sup>C n.m.r. δ (CDCl<sub>3</sub>, 50.3 MHz): 22.54 (CH<sub>2</sub>), 24.76 (CH<sub>2</sub>), 32.44 (CH<sub>2</sub>), 51.43 (t, CH, J = 5.6 Hz), 153.83 (t, NC, J = 5.3 Hz); m.s., m/z (%): 109 (M<sup>+</sup>, 2), 81 (14), 67 (100), 54 (49); i.r.: 2940, 2858, 2141, 1453, 1367, 1042, 933, 913, 893 cm<sup>-1</sup>. A commercial sample showed identical spectral properties.

#### n-Octyl isocyanide (4v)

Colourless oil<sup>21</sup>; (Found: C, 77.41; H, 12.27; N, 10.15. C<sub>9</sub>H<sub>17</sub>N requires: C, 77.63; H, 12.31; N, 10.06); <sup>1</sup>H n.m.r. δ (CDCl<sub>3</sub>, 200 MHz): 0.84–0.93 (m, 3H), 1.24–1.50 (m, 10H), 1.60–1.75 (m, 2H), 3.38 (tt, 2H, J = 6.6 Hz, J = 1.9 Hz); <sup>13</sup>C n.m.r. δ (CDCl<sub>3</sub>, 50.3 MHz): 13.91 (CH<sub>3</sub>), 22.48 (CH<sub>2</sub>), 26.20 (CH<sub>2</sub>), 28.55 (CH<sub>2</sub>), 28.92 (CH<sub>2</sub>), 29.01 (CH<sub>2</sub>), 31.59 (CH<sub>2</sub>), 41.43 (t, CH<sub>2</sub>, J = 6.3 Hz), 155.63 (t, NC, J = 5.5 Hz); m.s., m/z (%): 139 (M<sup>+</sup>, 0.4), 138 (4), 124 (13), 110 (27), 96 (35), 82 (42), 69 (35), 55 (100); i.r.: 2930, 2857, 2149, 1467, 1455, 1379, 1350, 725 cm<sup>-1</sup>.



**2-Methylbutyl isocyanide (4w)**

Colourless oil<sup>22</sup>; (Found: C, 74.02; H, 11.46; N, 14.38. C<sub>6</sub>H<sub>11</sub>N requires: C, 74.17; H, 11.41; N, 14.42); <sup>1</sup>H n.m.r. δ (CDCl<sub>3</sub>, 300 MHz): 0.88 (t, 3H, J = 7.5 Hz), 0.97 (d, 3H, J = 6.6 Hz), 1.17–1.32 (m, 1H), 1.36–1.50 (m, 1H), 1.61–1.74 (m, 1H), 3.20–3.27 (m, 2H); <sup>13</sup>C n.m.r. δ (CDCl<sub>3</sub>, 75.4 MHz): 10.93 (CH<sub>3</sub>), 16.77 (CH<sub>3</sub>), 26.14 (CH<sub>2</sub>), 34.31 (CH), 47.13 (t, CH<sub>2</sub>, J = 6.3 Hz), 156.07 (t, NC, J = 5.7 Hz); m.s., m/z (%): 98 (M<sup>+</sup>+1, 0.3), 96 (1.5), 82 (10), 69 (10), 68 (11), 57 (100), 55 (37); i.r.: 2966, 2148, 1463, 1385, 1262, 1096, 1016, 797 cm<sup>-1</sup>.

**n-Butyl isocyanide (4x)**

Colourless oil<sup>1b</sup>; <sup>1</sup>H n.m.r. δ (CDCl<sub>3</sub>, 300 MHz): 0.96 (t, 3H, J = 7.2 Hz), 1.48 (sext., 2H, J = 7.2 Hz), 1.60–1.73 (m, 2H), 3.39 (tt, 2H, J = 6.4 Hz, J = 2.1 Hz); <sup>13</sup>C n.m.r. δ (CDCl<sub>3</sub>, 75.4 MHz): 12.97 (CH<sub>3</sub>), 19.36 (CH<sub>2</sub>), 30.89 (CH<sub>2</sub>), 41.12 (t, CH<sub>2</sub>, J = 6.3 Hz), 155.60 (t, NC, J = 5.5 Hz); m.s., m/z (%): 83 (M<sup>+</sup>, 0.3), 82 (4), 68 (3), 56 (35), 55 (100), 54 (16); i.r.: 2964, 2878, 2149, 1464, 924, 822, 738 cm<sup>-1</sup>. A commercial sample showed identical spectral properties.

**Acknowledgements:** We gratefully acknowledge the financial support of the Dirección General de Investigación Científica y Técnica.

**References and notes**

1. The chemistry of isocyanides has been excellently reviewed: (a) Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1962**, 1, 8; (b) Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, H. *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 472; (c) *Isonitrile Chemistry*; Ugi, I. Ed.; Academic Press: New York, 1971 (d) Millich, F. *Chem. Rev.* **1972**, 72, 101; (e) Periasamy, M.P.; Walborsky, H.M. *Org. Prep. Proced. Int.* **1979**, 11, 295; (f) Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 810; (g) Walborsky, H.M.; Periasamy, M.P. in *The Chemistry of the Amino Group, Supplement C*; Patai, S.; Rappoport, Z. Eds.; John Wiley & Sons: New York, 1983; Chap. 4. (h) Rüchardt, C.; Meier, M.; Haaf, K.; Pakusch, J.; Wolber, E.; Müller, B. *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 893; (i) Marcaccini, S.; Torroba, T. *Org. Prep. Proced. Int.* **1993**, 25, 141. (j) Arshady, R.; Zecca, M.; Corain, B. *React. Polym.* **1993**, 20, 147.
2. (a) Edenborough, M.S.; Herbert, R.B. *Natural Product Reports*, **1988**, 229; (b) Scheuer, P.J. *Acc. Chem. Res.* **1992**, 25, 433.
3. McKusick, B.B. in *Org. Syntheses*; Rabjohn, N. Ed.; John Wiley & Sons: New York, 1963; Coll. Vol. IV; p. 438.
4. Baker, R.H.; Stanonis, J. *J. Am. Chem. Soc.* **1951**, 73, 699; Smith, P.; Kalenda, N. *J. Org. Chem.* **1958**, 23, 1599.
5. Mukaiyama, T.; Yokota, Y. *Bull. Chem. Soc. Jpn.*, **1965**, 38, 858.
6. Baldwin, J.E.; Bottaro, J.C.; Riordan, P.D.; Derome, A.E. *J. Chem. Soc., Chem. Commun.* **1982**, 942; Baldwin, J.E.; Derome, A.E.; Riordan, P.D. *Tetrahedron* **1983**, 39, 2989.

7. Skorna, G.; Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 259; Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* **1985**, 400.
8. See for example: Walborsky, H.M.; Niznik, G.E. *J. Org. Chem.* **1971**, 37, 187; Kim, S.; Yi, K.Y. *Tetrahedron Lett.* **1986**, 27, 1925; Baldwin, J.E.; O'Neil, I.A. *Synlett* **1990**, 603.
9. Höfle, G.; Lange, B. *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 113.
10. Heß, U.; Brosig, H.; Fehlhammer, W.P. *Tetrahedron Lett.* **1991**, 32, 5539.
11. Guirado, A.; Zapata, A.; Fenor, M. *Tetrahedron Lett.* **1992**, 33, 4779.
12. For general reviews, see: Kühle, E. *Angew. Chem. Int. Ed. Engl.* **1962**, 1, 647; Kühle, E.; Anders, B.; Zumach, G. *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 649; Ulrich, H. *The Chemistry of Imidoyl Halides*, Plenum Press: New York, 1968; Chap. 2.
13. Guirado, A.; Zapata, A.; Gálvez, J. *Tetrahedron Lett.* **1994**, 35, 2365; Guirado, A.; Zapata, A.; Jones, P.G. *Tetrahedron* **1995**, 51, 3641.
14. Guirado, A.; Zapata, A.; Jones, P.G. *Tetrahedron* **1995**, 51, 10375.
15. GC/MS (capillary column), IR and high field  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for crude products were recorded showing negligible differences with those recorded for high purity specimens.
16. Kauer, J.C.; Sheppard, W.A. *J. Org. Chem.* **1967**, 32, 3580.
17. Owing to their high volatility isolation of products **4w** and **4x** requires distillation (vigreux column) under atmospheric pressure.
18. Katritzky, A.R.; Keogh, H.J.; Ohlenrott, S.; Topsom, R.D. *J. Am. Chem. Soc.* **1970**, 92, 6855.
19. Becker, C.A.L. *Inorg. Chim. Acta* **1966**, 31, 3473.
20. N.V. Philips' Gloeilampenfabrieken. Fr. 1,341,781; C.A. **1964**, 60, 5402h.
21. Feuer, H.; Rubinstein, H.; Nielsen, A.T. *J. Org. Chem.* **1958**, 23, 1107.
22. Rupe, H.; Glenz, K. *Justus Liebigs Ann. Chem.* **1924**, 436, 184.