

### A Simple One-Pot Synthesis of Acylated Cyanohydrins of 3-Indolecarbaldehydes

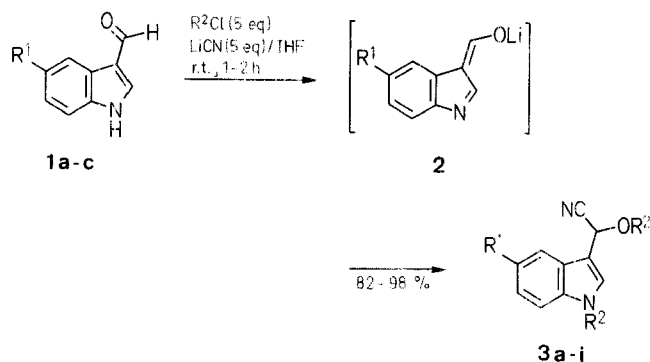
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Reaction of 3-indolecarbaldehydes with a variety of acylchlorides in the presence of lithium cyanide to give 1-acyl-3-( $\alpha$ -acyloxy)indoleacetonitriles is described.

It is well known that benzaldehyde and its analogs are in general converted into acylated cyanohydrins *via* acylation of their cyanohydrins in aqueous or non-aqueous conditions,<sup>1</sup> or by a one-pot reaction of the starting aldehydes with potassium cyanide and acyl chlorides using crown ether as phase-transfer catalysis.<sup>2</sup> Recently we have reported a simple one-pot synthesis of silylated and acylated cyanohydrins of a variety of carbonyl compounds using lithium cyanide.<sup>3</sup> However no attention has been focused on acylcyanation of the heteroaromatic aldehydes such as 3-indolecarbaldehydes.

We now report a simple one-pot process for the conversions of 3-indolecarbaldehydes **1a–c** into the corresponding acylated cyanohydrins (**3a–3i**). These are efficient intermediates for the synthesis of 3-( $\alpha$ -acyloxy)indoleacetic acid derivatives,<sup>4</sup> by treatment with acyl chlorides in the presence of lithium cyanide.<sup>5</sup> The scope of the new acylcyanation procedure is shown in the Table.

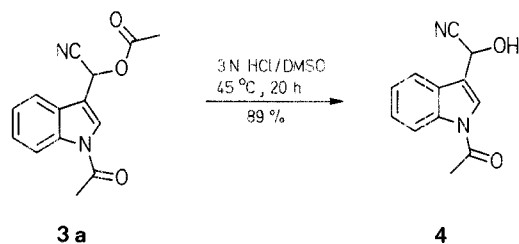


1	R <sup>1</sup>
a	H
b	Br
c	OCH <sub>3</sub>

3	R <sup>1</sup>	R <sup>2</sup>	3	R <sup>1</sup>	R <sup>2</sup>
a	H	COCH <sub>3</sub>	f	Br	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>
b	H	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	g	Br	COC <sub>6</sub> H <sub>5</sub>
c	H	COC <sub>6</sub> H <sub>5</sub>	h	OCH <sub>3</sub>	COCH <sub>3</sub>
d	H	COCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	i	OCH <sub>3</sub>	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>
e	Br	COCH <sub>3</sub>			

The reaction is performed in general by using 5 equivalents of both the acyl chloride and lithium cyanide at room temperature in tetrahydrofuran. The use of limited amounts of these reagents provided **3** in low yields, together with the *N*-acylated aldehydes, which were readily converted into **3** by further treatment with

acylchlorides and lithium cyanide. Since indole itself does not provide any *N*-acylated products, and since *N*-methyl-3-indolecarbaldehyde is unreactive with acyl chlorides and lithium cyanide, this reaction is believed to proceed by the initial formation of the imino lithium enolates (**2**),<sup>6</sup> followed by *N*-acylation and then acylcyanation of the aldehyde group. As is shown in the Table, the reaction is complete within 1–2 h at room temperature, and all of the products are obtained in excellent yields. The procedure described here as acylcyanations offers a convenient method under non-aqueous reaction conditions. Partial hydrolysis of **3a** with 3 normal hydrochloric acid in dimethylsulfoxide at 45°C gave the cyanohydrin **4** in good yield.



#### 1-Ethoxycarbonyl-3-(z-ethoxycarbonyloxy)indoleacetonitrile (**3b**); Typical Procedure:

Lithium cyanide (165 mg, 5 mmol) is added to a magnetically stirred solution of 3-indolecarbaldehyde (145 mg, 1 mmol) in dry tetrahydrofuran (10 ml) at room temperature. After being stirred for 5 min, a solution of ethyl chloroformate (540 mg, 5 mmol) in tetrahydrofuran (5 ml) is added, and the mixture is stirred for 10 min at room temperature. The solvent is removed by evaporation *in vacuo*, and the residue is dissolved in water (10 ml) and ethyl acetate (30 ml). The organic layer is separated, washed with water (2 × 10 ml) and dried with anhydrous

Table. Compounds **3a–i** Prepared

Product	Reaction Time (min)	Yield (%)	m. p. (°C) (Solvent)	Molecular Formula <sup>a</sup>	IR (KBr) ν <sub>C=O</sub> (cm <sup>-1</sup> )	<sup>1</sup> H-NMR (CDCl <sub>3</sub> ) δ (ppm)
<b>3a</b>	120	88	115–116 (benzene)	C <sub>14</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub> (256.3)	1750, 1710	2.18 (s, 3H); 2.69 (s, 3H); 6.94 (s, 1H); 7.40 (m, 2H); 7.78 (d, 1H, <i>J</i> = 7.9 Hz); 8.17 (s, 1H); 8.39 (d, 1H, <i>J</i> = 7.9 Hz)
<b>3b</b>	15	97	83–84 (benzene)	C <sub>16</sub> H <sub>15</sub> N <sub>2</sub> O <sub>5</sub> (316.3)	1750, 1735	see experimental
<b>3c</b>	60	95	112–113 ( <i>i</i> -C <sub>3</sub> H <sub>7</sub> OH)	C <sub>24</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> (380.4)	1740, 1690	6.90 (s, 1H); 7.4–7.8 (m, 13H); 8.04 (d, 1H, <i>J</i> = 7.2 Hz); 8.40 (d, 1H, <i>J</i> = 7.9 Hz)
<b>3d</b>	120	95	139–141 (CH <sub>3</sub> CN)	C <sub>26</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> (408.5)	1740, 1720	3.72 (d, 1H, <i>J</i> = 3.6 Hz); 4.22 (s, 2H); 6.65 (s, 1H); 7.29 (m, 8H); 7.74 (s, 1H); 8.50 (d, 1H, <i>J</i> = 7.0 Hz)
<b>3e</b>	30	86	154–155 (benzene)	C <sub>14</sub> H <sub>11</sub> BrN <sub>2</sub> O <sub>3</sub> (335.2)	1750, 1720	2.19 (s, 3H); 2.67 (s, 3H); 6.63 (s, 1H); 7.53 (dd, 1H, <i>J</i> = 9.1, 2 Hz); 7.71 (s, 1H); 7.79 (d, 1H, <i>J</i> = 2 Hz); 8.34 (d, 1H, <i>J</i> = 9.1 Hz)
<b>3f</b>	15	98	106–107 (C <sub>2</sub> H <sub>5</sub> OH)	C <sub>16</sub> H <sub>15</sub> BrN <sub>2</sub> O <sub>5</sub> (395.2)	1755, 1725	1.36 (t, 3H, <i>J</i> = 7.4 Hz); 1.49 (t, 3H, <i>J</i> = 7.3 Hz); 4.25–4.60 (m, 4H); 6.48 (s, 1H); 7.52 (dd, 1H, <i>J</i> = 8.9, 2 Hz); 7.84 (d, 1H, <i>J</i> = 2 Hz); 7.94 (s, 1H); 8.10 (d, 1H, <i>J</i> = 8.9 Hz)
<b>3g</b>	60	82	179–181 (DMF + H <sub>2</sub> O)	C <sub>24</sub> H <sub>15</sub> BrN <sub>2</sub> O <sub>3</sub> (459.3)	1725, 1695	6.84 (s, 1H); 7.40–8.10 (m, 13H); 8.30 (d, <i>J</i> = 8.4 Hz)
<b>3h</b>	60	97	166–168 (benzene)	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub> (286.3)	1750, 1705	2.18 (s, 3H); 2.65 (s, 3H); 3.88 (s, 3H); 6.67 (s, 1H); 7.03 (dd, 1H, <i>J</i> = 8.6, 2 Hz); 7.08 (d, 1H, <i>J</i> = 2 Hz); 7.68 (s, 1H); 8.35 (d, 1H, <i>J</i> = 8.6 Hz)
<b>3i</b>	15	98	95–97 (benzene)	C <sub>17</sub> H <sub>18</sub> N <sub>2</sub> O <sub>6</sub> (346.4)	1760, 1735	1.34 (t, 3H, <i>J</i> = 7.3 Hz); 1.48 (t, 3H, <i>J</i> = 7.3 Hz); 3.88 (s, 3H); 4.2–4.6 (m, 4H); 6.51 (s, 1H); 7.02 (dd, 1H, <i>J</i> = 9.2, 2.2 Hz); 7.14 (d, 1H, <i>J</i> = 2.2 Hz); 7.91 (s, 1H); 8.10 (d, 1H, <i>J</i> = 9.2 Hz)

<sup>a</sup> The microanalyses were in satisfactory agreement with the calculated values: C, H, N ± 0.3.

sodium sulfate. After concentrating the ethyl acetate layer, the residue is chromatographed on silica gel using benzene/*n*-hexane (10:1) as eluent to give **3b** as a solid; yield: 307 mg (97%).

$C_{16}H_{16}N_2O_5$  calc. C 60.75 H 5.10 N 8.86  
(316.3) found 60.78 5.14 8.69

IR (KBr):  $\nu = 1750$  (OC=O);  $1735\text{ cm}^{-1}$  (C=O)

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta = 1.34$  (t, 3 H,  $J = 7.3$  Hz,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ); 1.49 (t, 3 H,  $J = 7.3$  Hz,  $\text{CO}_2\text{CH}_2\text{CH}_3$ ); 4.30–4.60 (m, 4 H,  $2 \times \text{CO}_2\text{CH}_2\text{CH}_3$ ); 6.55 (s, 1 H, CHCN); 7.43 (m, 2 H, 5-H, 6-H); 7.71 (d, 1 H,  $J = 7.9$  Hz, 4-H); 7.95 (s, 1 H, 2-H); 8.24 ppm (d,  $J = 8.2$  Hz, 7-H).

**1-Acetyl-3-( $\alpha$ -hydroxy)indoleacetonitrile (4):**

A solution of the acetate (**3a**) (256 mg, 1 mmol) in dimethylsulfoxide (5 ml) and 3 normal hydrochloric acid (4 ml) is heated at  $45^\circ\text{C}$  for 20 h. The mixture is diluted with water (50 ml) and extracted with benzene ( $2 \times 30$  ml). The benzene solution is washed with water ( $2 \times 10$  ml), dried with anhydrous sodium sulfate and concentrated *in vacuo*. The residue is recrystallized from benzene/ligroin to give **4** as colorless crystals; yield: 178 mg (89%).

$C_{12}H_{10}N_2O_3$  calc. C 67.28 H 4.71 N 13.08  
(200.2) found 67.44 4.69 12.95

IR (KBr):  $\nu = 3350$  (OH);  $1700\text{ cm}^{-1}$  (C=O).

$^1\text{H-NMR}$  ( $\text{DMSO-}d_6$ ):  $\delta = 2.67$  (s, 3 H,  $\text{CH}_3$ ); 6.0 (d, 1 H,  $J = 6.0$  Hz, OH); 7.08 (d, 1 H,  $J = 6.0$  Hz, CHCN); 7.37 (m, 2 H, 5-H, 6-H); 7.76 (d,  $J = 7.6$  Hz, 4-H), 7.93 (s, 1 H, 2-H); 8.34 ppm (d,  $J = 8.2$  Hz, 7-H).

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