Synthesis of *N*-Substituted 5-Hydroxyindoles

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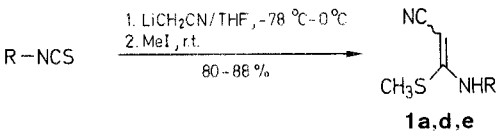
α-Methylthio-β-cyanoenamines are found to be useful starting compounds for the synthesis of *N*-substituted 5-hydroxyindoles. In connection with the preparation of the starting compounds, a novel decarboxyamidation is presented.

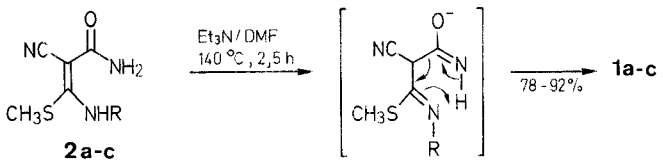
The Nenitzescu reaction has been well known as an important synthetic method of 5-hydroxyindoles.[1] The reaction involves the condensation of 1,4-benzoquinones with enamines which have mainly α-alkyl and β-carbethoxy groups. However the yield reported are generally low due to the side reactions.[2] In order to increase the yield of the physiologically important 5-hydroxyindoles, we have now used α-methylthio-β-cyanoenamines which can act as effective enamines in this reaction owing to the electronic effect of cyano and methylthio groups.

α-Methylthio-β-cyanoenamines [3-(*N*-substituted) 3-(methylthio)acrylonitriles] **1** were prepared by two procedures:

1. The reaction of some appropriate isothiocyanates with acetonitrile lithium anion followed by methylation; and
2. Decarboxyamidation of 3-(*N*-aryl substituted amino)-2-carbamoyl-3-(methylthio)acrylonitriles **2**.

Although there are several reports[3] on decarboxyamidation, the reaction given under 2 is unprecedented. The reaction can be reasonably interpreted by the formation of a six-membered chelate intermediate involving 3-(*N*-substituted) imino group followed by loss of cyanate.

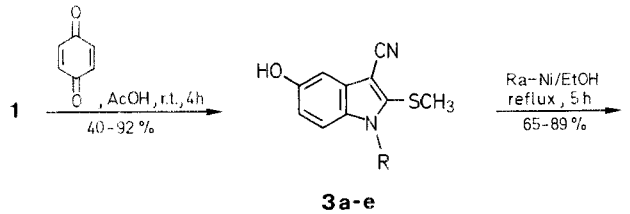


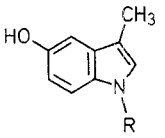


As the reaction medium acetic acid gave the best result even though an effective use of nitromethane had been reported.[4]

Compounds **1** thus obtained (a mixture of *E*-, *Z*-, and imino forms) were allowed to react with 1,4-benzoquinone in acetic acid at room temperature for 4 h to afford *N*-substituted 3-cyano-5-hydroxy-2-(methylthio)indoles **3** in good yield, except **3e** (Table 2). In the preparation of **3e**, 3-cyano-5-hydroxy-2-(methylamino)benzofuran **(5e)** was accompanied in 10% yield as a by-product.

The reaction of **3** with Raney nickel gave *N*-substituted 5-hydroxy-3-methylindoles **4** in moderate yield. Although the direct transformation cyano into methyl groups by means of catalytic hydrogenation has appeared in the literature,[5] the present reaction accompanied by desulfurization is noteworthy.





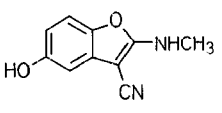


Table 1. Acrylonitriles **1** Prepared

Product	R	Yield (%)	*E*/*Z*/Imino Form[a]	Molecular Formula[b]	MS *m/e*	IR (KBr) ν(cm^{-1})
1a	C_6H_5	92[c], 88[d]	1:1:1	$C_{10}H_{10}N_2S$ (190.3)	190, 143	3250, 3220, 2180
1b	4-ClC_6H_4	91[c]	1:1:3	$C_{10}H_9ClN_2S$ (224.7)	226, 224	3280, 3070, 2180
1c	4-$CH_3OC_6H_4$	78[c]	1:1:1	$C_{11}H_{12}N_2OS$ (220.3)	220, 173	3210, 2950, 2200
1d	$C_6H_5CH_2$	80[d]	2:1	$C_{11}H_{12}N_2S$ (204.3)	204, 91	3320, 3010, 2900, 2180
1e	CH_3	86[d]	6:1	$C_5H_8N_2S$ (128.2)	128, 81	3300, 3040, 2980, 2180

[a] Estimated by ^{1}H-NMR spectra.
[b] Satisfactory microanalyses obtained: C ±0.27, H ±0.21, N ±0.18.
[c] Prepared from compound **2**.
[d] Prepared from alkyl isothiocyanate.

Table 2. ^{1}H-NMR Data of **1a–e**

Compound	^{1}H-NMR ($CDCl_3$) δ, J(Hz)
1a	2.10 (s, 1H); 2.34 (s, 1H); 2.36 (s, 1H); 3.22 (br, $\frac{2}{3}$H); 4.00 (s, $\frac{1}{3}$H); 4.44 (s, $\frac{1}{3}$H); 6.60 (br, $\frac{2}{3}$H); 7.00 (m, 5H)
1b	2.36 (s, $\frac{3}{5}$H); 2.56 (s, $\frac{9}{5}$H); 2.64 (s, $\frac{3}{5}$H); 3.44 (br, $\frac{6}{5}$H); 4.20 (s, $\frac{1}{5}$H); 4.75 (s, $\frac{1}{5}$H); 6.00 (br, $\frac{1}{5}$H); 6.60–7.40 (m, 2$\frac{1}{5}$H)
1c	2.16 (s, 1H); 2.40 (s, 1H); 2.48 (s, 1H); 3.28 (s, $\frac{2}{3}$H); 3.68 (s, $\frac{10}{3}$H); 3.84 (s, $\frac{1}{3}$H); 4.30 (s, $\frac{1}{3}$H); 5.96 (br, $\frac{1}{3}$H); 6.44–7.08 (m, 4H)
1d	2.28 (s, 1H); 2.44 (s, 2H); 3.70 (s, $\frac{1}{3}$H); 4.10 (d, $\frac{4}{3}$H, J = 6); 4.16 (s, $\frac{2}{3}$H); 4.44 (d, $\frac{2}{3}$H, J = 6); 4.85 (br, $\frac{2}{3}$H); 5.30 (br, $\frac{1}{3}$H); 7.20 (s, 5H)
1e	2.25 (s, $\frac{3}{7}$H); 2.36 (s, $\frac{18}{7}$H); 2.68 (d, $\frac{18}{7}$H, J = 5); 2.92 (d, $\frac{3}{7}$H, J = 5); 3.54 (s, $\frac{1}{7}$H); 3.80 (s, $\frac{6}{7}$H); 5.50 (br, 1H)

Table 3. 5-Hydroxyindoles **3** and **4** Prepared

Product	R	Yield (%)[a]	m.p. (°C) or b.p. (°C)/mbar	Molecular Formula[b]	MS *m/e*
3a	C_6H_5	79	231–232	$C_{16}H_{12}N_2OS$ (280.3)	280, 265
3b	4-ClC_6H_4	92	187–188	$C_{16}H_{11}ClN_2O$ (314.8)	316, 314, 264
3c	4-$CH_3OC_6H_4$	87	204–205	$C_{17}H_{14}N_2O_2S$ (310.4)	310, 295
3d	$C_6H_5CH_2$	89	221–222	$C_{17}H_{14}N_2OS$ (294.4)	294, 279
3e	CH_3	40	163–164	$C_{11}H_{10}N_2OS$ (218.3)	218, 203
4a	C_6H_5	89	oil, 175/0.07	$C_{15}H_{13}NO$ (223.3)	223
4b	4-ClC_6H_4	83	oil, 200/0.2	$C_{15}H_{12}ClNO$ (257.7)	258, 256, 221
4c	4-$CH_3OC_6H_4$	85	oil, 250/0.05	$C_{16}H_{15}NO_2$ (253.3)	253, 238
4d	$C_6H_5CH_2$	65	142–143	$C_{16}H_{15}NO$ (237.3)	237, 146

[a] Yields of compounds **3** and **4** are isolated yields, based on compounds **1** and **3**, respectively.
[b] Satisfactory microanalyses obtained: C ±0.23, H ±0.09, N ±0.11.

Table 4. Spectral Data of **3a–e** and **4a–d**

Compound	IR (KBr or neat) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$-DMSO-d_6/TMS) δ, J(Hz)
3a	3300, 2220, 1615, 1490	2.28 (s, 3H); 6.40 (s, 1H); 6.76 (d, 1H, J = 8); 7.20–7.60 (m, 7H)
3b	3300, 2210, 1620, 1490	2.36 (s, 1H); 6.48 (s, 1H); 6.84 (d, 1H, J = 8); 7.28 (d, 2H, A part of AB system, J = 8); 7.40–7.56 (m, 3H)
3c	3300, 2210, 1615, 1510, 1490	2.30 (s, 3H); 3.80 (s, 3H); 6.38 (s, 1H); 6.72 (d, 1H, J = 8); 6.90 (d, 2H, B part of AB system, J = 8); 7.12 (d, 2H, A part of AB system, J = 8); 7.25 (d, 1H, J = 4)
3d	3250, 2210, 1610, 1490	2.32 (s, 3H); 5.28 (s, 2H); 7.00 (s, 5H); 6.40–7.40 (m, 3H)
3e	3310, 2220, 1630, 1580	2.40 (s, 1H); 3.62 (s, 3H); 6.60 (s, 1H); 6.64 (d, 1H, J = 8); 7.20 (d, 1H, J = 8)
4a	3300, 2900, 1700, 1610, 1590	2.28 (s, 3H); 5.40 (br, 1H); 6.68 (d, 1H, J = 8); 6.80–7.20 (m, 3H); 7.28 (s, 5H)
4b	3300, 2900, 1620, 1595	2.20 (s, 3H); 6.40–7.30 (m, 8H)
4c	3350, 2900, 1620	2.26 (s, 3H); 3.78 (s, 3H); 6.40–7.30 (m, 8H)
4d	3350, 2900, 1620	2.16 (s, 3H); 4.92 (s, 2H); 6.50 (m, 2H); 6.80–7.15 (m, 6H)

3-(Benzylamino)-3-(methylthio)acrylonitrile (1d); Typical Procedure:
To a stirred mixture of CH_3CN (1.23 g, 30 mmol) and THF, (40 mL) is added an 1.65 molar hexane solution of BuLi (17 mL, 28 mmol) at −78 °C. After stirring for 0.5 h at the same temperature benzyl isothiocyanate (1.49 g, 10 mmol) is added to the mixture. The resulting mixture is stirred for 0.5 h at 0 °C and then extracted with water (3 × 40 mL). The extract is washed with benzene (50 mL) and then treated with CH_3I (4.26 g, 30 mmol). The mixture is stirred at room temperature for 1 h and then extracted with EtOAc (3 × 50 mL). The extract is concentrated *in vacuo* to give a yellow material. Recrystallization from ethanol gives white prisms of **1d**; yield: 4.9 g (80%) (Table 1).

(*E*)-3-(Phenylamino)-2-cyano-3-(methylthio)acrylamide (2a); Typical Procedure:
A mixture of 2-cyano-3,3-bis(methylthio)acrylamide[6] (3.8 g, 20 mmol), aniline (2 mL, 22 mmol), and ethanol (40 mL) is refluxed for 15 h. The white crystals formed are collected, washed with ethanol, and recrystallized from ethanol to give **2a** as white needles; yield: 4.6 g (99%); m.p. 147–149 °C (Lit.[7] m.p. 147–149 °C). By the same method as mentioned above compounds **2b** and **2c** were prepared starting from 4-chloroaniline and 4-methoxyaniline, respectively.

2b: White prisms; yield: 98%; m.p. 198–199 °C.

$C_{11}H_{10}ClN_3OS$ (267.7) calc. C 49.35 H 3.76 N 15.69
found 49.05 3.75 15.67

IR (KBr): ν = 3360, 3310, 3250, 2200, 1680, 1640, 1600, 1580, 1560 cm^{-1}.

^{1}H-NMR ($CDCl_3$/DMSO-d_6): δ = 2.15 (s, 3H); 6.0 (br, 2H); 7.28 (s, 4H); 12.44 (br, 1H).

IR (KBr): ν = 3360, 3310, 3250, 2200, 1680, 1640, 1600, 1580, 1560 cm^{-1}.

^{1}H-NMR ($CDCl_3$/DMSO-d_6): δ = 2.15 (s, 3H); 6.0 (br, 2H); 7.28 (s, 4H); 12.44 (br, 1H).

MS: m/e = 267 (M^+).

2c: White prisms; yield 99%; m.p. 159–160°C.

$C_{12}H_{13}N_3O_2S$	calc.	C 54.74	H 4.98	N 15.96
(263.3)	found	54.72	4.99	15.93

IR (KBr): ν = 3390, 3300, 3180, 3000, 2950, 2200, 1640, 1600, 1540 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.80 (s, 3H); 3.76 (s, 3H); 5.70 (br, 2H); 6.80 (d, 2H, J = 8 Hz, B part of AB system); 7.08 (d, 2H, J = 8 Hz, A part of AB system); 12.15 (br, 1H).

MS: m/e = 263 (M^+).

Decarboxyamidation of 2a: Typical Procedure:
A mixture of **2a** (233 mg, 1 mmol), triethylamine (323 mg, 3.2 mmol), and DMF (3 mL) is stirred at 140°C under nitrogen for 2.5 h. The mixture is quenched with aqueous NH_4Cl solution and then extracted with benzene (3 × 25 mL). The benzene extract is washed with water (30 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give a yellow oil, which is subjected to preparative TLC on silica gel (EtOAc/hexane, 1:2) to give **1a** in 92% yield as white needles (recrystallization from ether or hexane).

3-Cyano-5-hydroxy-2-methylthio-1-phenylindole (3a); Typical Procedure:
A mixture of **1a** (1.9 g, 10 mmol), 1,4-benzoquinone (1.1 g, 10 mmol), and acetic acid (30 mL) is stirred at room temperature for 4 h. The resulting precipitate is collected and washed with ethanol. Recrystallization from ethanol gives white needles; yield: 2.2 g (79%); m.p. 231–232°C.

In the case of **3e**, it did not precipitate after the reaction is completed. The reaction mixture is chromatographed on silica gel column using EtOAc/hexane (1:1) as eluent and then purified by preparative TLC on silica gel using $CHCl_3$/EtOAc (9:1) as eluent (**3e** moves faster than **5e**).

5e: White crystals; m.p. 165°C (dec).

$C_{10}H_8N_2O_2$	calc.	C 63.83	H 4.28	N 14.89
(188.2)	found	63.80	4.27	14.90

IR (KBr): ν = 3350, 3300, 2200, 1640 cm^{-1}.

^{1}H-NMR ($CDCl_3$/DMSO-d_6): δ = 3.0 (s, 3H); 4.44 (br, 1H, appears together with H_2O peak); 6.3–6.8 (m, 3H); 7.08 (br, 1H).

MS: m/e = 188 (M^+).

5-Hydroxy-3-methyl-1-phenylindole (4a); Typical Procedure:
A mixture of **3a** (1.4 g, 5 mmol), activated Raney nickel[8] (ca 10 g), and ethanol (80 mL) is refluxed for 5 h. The mixture is separated from nickel by decantation and centrifugation. The nickel is washed with ethanol and the washings are also centrifuged. The combined alcoholic solution is concentrated *in vacuo* to give a yellow oil, which is purified by preparative TLC on silica gel (EtOAc); colorless oil; yield: 0.99 g (89%); b.p. 175°/0.07 mbar.

Received: 5 January 1987; revised: 17 March 1987

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