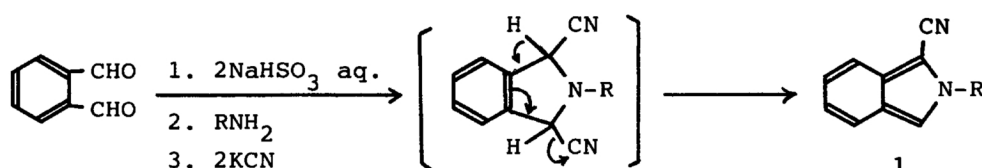


AN EFFICIENT METHOD FOR SYNTHESIS OF 1-CYANO-2-SUBSTITUTED-ISOINDOLES  
BY STRECKER REACTION USING o-PHTHALALDEHYDE AND PRIMARY AMINES

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An efficient sequence proposed here provides a new synthetic method for preparation of 1-cyano-2-substituted-isoindoles by Strecker reaction using o-phthalaldehyde and primary amines.

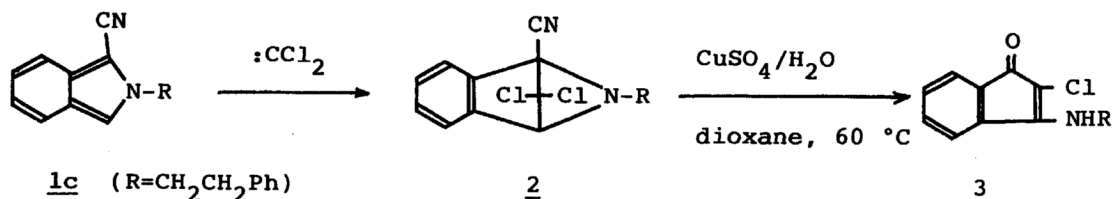
Recently isoindoles have attracted considerable theoretical and synthetic interest, and there has been a considerable expansion in isoindole chemistry as reviewed.<sup>1,2)</sup> There is, however, no information about synthesis of isoindoles by Strecker reaction. We report here the Strecker reaction gives new 1-cyano-2-substituted-isoindoles (1) in good yields.



Scheme 1.

A typical procedure for the synthesis of 1 is as follows: To a mixture of o-phthalaldehyde<sup>3)</sup> (3.35 mmol) and water (60 ml) was added sodium hydrogensulfite (7.1 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h and then primary amine (4.3 mmol) was added. The solution was stirred for successive 40 h at room temperature and then solid potassium cyanide (7.41 mmol) was added. The solution was stirred over 6 h at room temperature and then extracted with dichloromethane. Product 1 was chromatographed on Florisil using benzene-hexane as eluent. Thus, 1-cyano-2-substituted-isoindoles (1a-1e) were obtained in 33-86% yields (Table 1). All reactions for the preparation of 1 were carried out under a nitrogen atmosphere, otherwise the yields decreased. Furthermore, the yield depended on the reaction time after the addition of amine, the highest yields being obtained after 40 h. Structures of the products were confirmed by IR, mass, and <sup>1</sup>H-NMR spectra and microanalyses (see Table 1).

Interestingly, treatment of 1c with dichlorocarbene derived from chloroform in a two-phase system gave new 1-cyano-1,3-dichloromethano-3H-2-phenethylisoindole (2)<sup>4)</sup> in 31% yield. Furthermore, hydrolysis of 2 in the presence of copper sulfate gave 2-chloro-3-(N-phenethylamino)indenone (3)<sup>5)</sup> in 63% yield. Thus, new isoindoles 1 obtained in this work have interesting utility as synthetic reagent. The work about a new 1,4-addition of dichlorocarbene to 1 and the conversion of 2 to 3 is in progress.



Scheme 2.

Table 1. Physical properties of new isoindoles 1

Compound <u>1</u> <sup>a)</sup> R	Yield %	Mp/°C	IR(KBr) $\nu_{\text{CN}}/\text{cm}^{-1}$	<sup>1</sup> H-NMR(CDCl <sub>3</sub> /TMS) $\delta$
a CH <sub>3</sub>	86	93.0-94.5	2220	4.12(s, 3H), 7.00-7.90(m, 5H)
b CH <sub>2</sub> Ph	80	91.5-92.5	2200	5.39(s, 2H), 6.80-7.80(m, 10H)
c CH <sub>2</sub> CH <sub>2</sub> Ph	68	84.0-85.0	2200	3.18(t, 2H, J=7 Hz), 4.49(t, 2H, J=7 Hz), 6.80-7.80(m, 10H)
d C <sub>4</sub> H <sub>9</sub>	59	oil (1f)	2220	0.82(t, 3H, J=6 Hz), 1.00-1.50(m, 2H), 1.80(t-t, 2H, J=7 Hz), 4.12(t, 2H, J=7 Hz), 6.80-7.30(m, 3H), 7.30-7.90(m, 2H)
e p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	33 <sup>b)</sup>	140.0-141.0	2200	3.92(s, 3H), 7.10-7.90(m, 9H)

a) They gave satisfactory microanalysis (C $\pm$ 0.26, H $\pm$ 0.15, N $\pm$ 0.30).

b) Time allowed for cyclization was shorter (16 h) than the others (40 h).

## References

- 1) J. D. White and M. E. Mann, "Advances in Heterocyclic Chemistry," Academic Press, New York and London (1969), Vol. 10, pp. 113-147.
- 2) R. Bonnett and S. A. North, "Advances in Heterocyclic Chemistry," Academic Press, New York and London (1981), Vol. 23, pp. 341-399.
- 3) o-Phthalaldehyde was easily synthesized according to the literature procedure: J. C. Bill and D. S. Tarbell, Org. Synth., Coll. Vol. IV, 807(1963).
- 4) Physical properties of 2 are as follows: viscous oil; IR(1f):  $\nu_{\text{CN}}$  2220 cm<sup>-1</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>/TMS)  $\delta$ : 3.15(t, 2H, J=7 Hz), 4.29(t, 2H, J=7 Hz), 7.25(s, 1H), 7.38(s, 5H), 6.58(s, 3H), 7.83(m, 1H); MS(70 eV): m/e 295.0837(M<sup>+</sup>-Cl, 2%), 293.0860(M<sup>+</sup>-Cl<sup>\*</sup>, 3%). Found: C, 65.30; H, 4.45; N, 8.26%. Calcd for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>Cl<sub>2</sub>: C, 65.67; H, 4.29; N, 8.51%.
- 5) Physical properties of 3a are as follows: mp 118-119.5 °C; IR(KBr):  $\nu_{\text{CO}}$  1660 cm<sup>-1</sup>; <sup>1</sup>H-NMR(CDCl<sub>3</sub>/TMS)  $\delta$ : 2.89-3.15(m, 2H), 4.34-4.60(m, 2H), 6.58(s, 1H), 7.28(s, 5H), 7.35-7.56(m, 4H). Found: C, 71.96; H, 5.15; N, 4.79%. Calcd for C<sub>17</sub>H<sub>14</sub>NOCl: C, 71.78; H, 4.97; N, 4.94%.

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