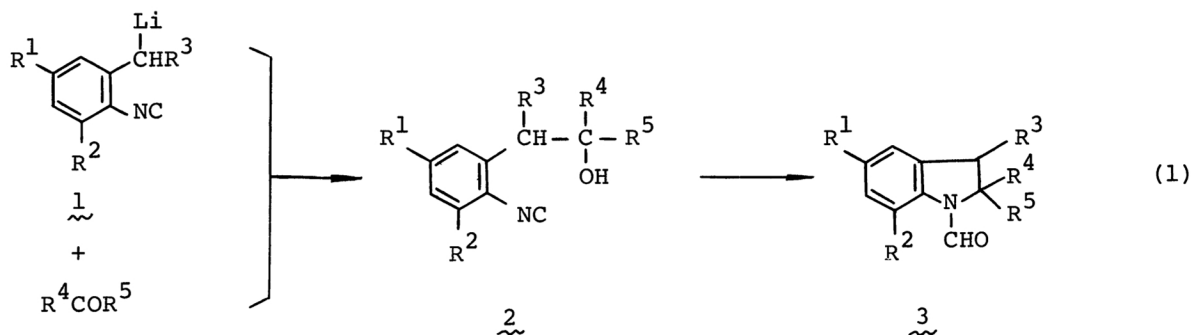


SYNTHESIS OF N-FORMYLINDOLINE DERIVATIVES BY LEWIS ACID
CATALYZED CYCLIZATIONS OF o-(2-HYDROXYALKYL)PHENYL ISOCYANIDES

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o-(2-Hydroxyalkyl)phenyl isocyanides (2), which are prepared by the reaction of o-lithiomethylphenyl isocyanides (1) with ketone and aldehyde are cyclized by Lewis acid catalyst to N-formylindoline derivatives (3).

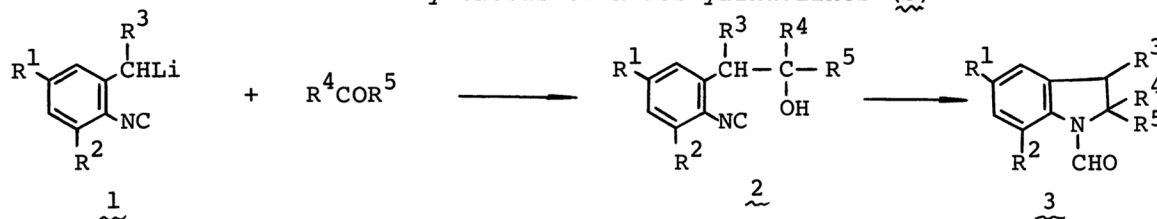
Syntheses of indoles and the related heterocycles¹⁾ have been achieved by the reaction of o-lithiomethylphenyl isocyanide (1a), which is generated in situ at -78°C from o-tolyl isocyanide, with electrophiles followed by intramolecular cycloaddition. It was already reported²⁾ that o-(2-hydroxyalkyl)phenyl isocyanide (2) prepared by the reaction of 1a with ketone and aldehyde were cyclized by Cu₂O catalyst to afford 4,5-dihydro-3,1-benzoxazepines in high yields. Herein, we wish to describe a new synthetic method of N-formylindoline derivatives (3), in which o-(2-hydroxyalkyl)phenyl isocyanide (2) is treated with a Lewis acid such as BF₃·OEt₂, ZnCl₂ and SnCl₄.



As already reported,²⁾ o-lithiomethylphenyl isocyanide (1a) readily reacted with aliphatic and aromatic saturated aldehyde and ketone to furnish o-(2-hydroxyalkyl)phenyl isocyanides (2) in high yields. In the present study, we found that α, β -unsaturated ketones and aldehydes also reacted with 1a in the manner of 1,2-addition³⁾ to afford the corresponding o-(2-hydroxyalkyl)phenyl isocyanides (2). Preparations of a variety of o-(2-hydroxyalkyl)phenyl isocyanides are summarized in Table 1.

Treatment of o-(2-hydroxyalkyl)phenyl isocyanides (2) thus prepared with Lewis acid catalyst gave N-formylindoline derivatives (3) as listed in Table 1. When o-(2-hydroxyalkyl)phenyl isocyanides (2a-i~2a-iii and 2b), prepared from 1 and α, β -unsaturated ketones, were treated with a catalytic amount of BF₃·OEt₂

Table 1. Synthesis of N-Formylindolines (3)



Entry	Isocyanides	Carbonyl Compounds	2 (%) ^a	3 (%) ^{a,b}	Method ^c (2 → 3)
1	1a (R ¹ =R ² =R ³ =H)		93 (2a-i)	80 (3a-i)	A
2			67 (2a-ii)	68 (3a-ii)	A
3			98 (2a-iii)	62 (3a-iii)	A
4			~ 100 (2a-iv)	77 (3a-iv)	B
5			86 (2a-v)	76 (3a-v)	B
6			77 (2a-vi)	81 (3a-vi)	B
7			~ 100 (2a-vii)	70 (3a-vii)	B
8			78 (2a-viii)	75 (3a-viii)	C
9			91 (2a-ix)	48 (3a-ix)	C
10			97 (2a-x)	32 (3a-x)	D
11	1b (R ¹ =Me, R ² =R ³ =H)		94 (2b)	63 (3b)	A
12	1c (R ¹ =R ³ =H, R ² =Me)		82 (2c)	66 (3c)	C
13	1d (R ¹ =R ² =H, R ³ =Me)		87 (2d)	73 (3d)	B
14	1e (R ¹ =R ² =H, R ³ =MeS)		80 (2e-i)	70 (3e-i)	C
15			80 (2e-ii)	60 (3e-ii)	C

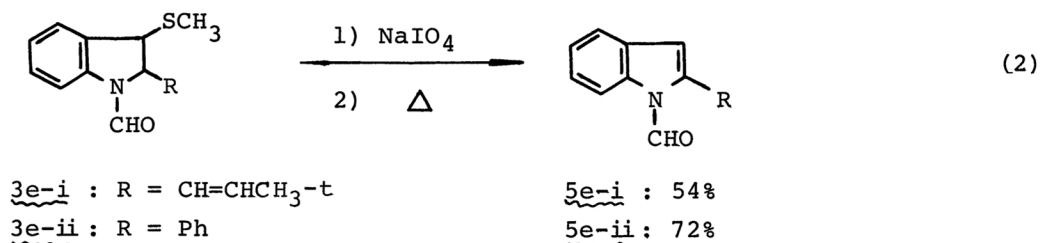
a) Isolated Yields. b) Reference 7. c) Method A : 0.1 equiv BF₃·OEt₂, 0°C, 1 h; Method B : 0.1 equiv BF₃·OEt₂, room temp., overnight; Method C : 1 equiv ZnCl₂, room temp., overnight; Method D : 1 equiv SnCl₄, room temp., overnight.

(-78°C to 0°C; 1hr), the cyclization took place to furnish N-formylindoline derivatives (3a-i ~ 3a-iii and 3b) in good yields.⁴⁾ o-(2-Hydroxyalkyl)phenyl isocyanides (2a-iv ~ 2a-vii and 2d), prepared from 1 and aromatic ketones, were also cyclized to the corresponding N-formylindolines by treatment with BF₃·OEt₂ catalyst (room temperature; overnight). The cyclizations of o-(2-hydroxyalkyl)-phenyl isocyanides (2a-viii, 2a-ix, 2c, 2e-i and 2e-ii), prepared from 1 and α,β-unsaturated aldehydes or aromatic aldehydes, were more efficiently

catalyzed by one equivalent of ZnCl_2 than by $\text{BF}_3 \cdot \text{OEt}_2$. Moreover, o-(2-hydroxyalkyl)phenyl isocyanides prepared from 1 and aliphatic ketone were not cyclized by $\text{BF}_3 \cdot \text{OEt}_2$, but cyclized by SnCl_4 catalyst. For instance, the cyclization of o-(2-hydroxy-2-methylpropyl)phenyl isocyanide (2a-x) was induced by one equivalent of SnCl_4 to afford N-formyl-2,2-dimethylindoline (3a-x) in a 32% yield.

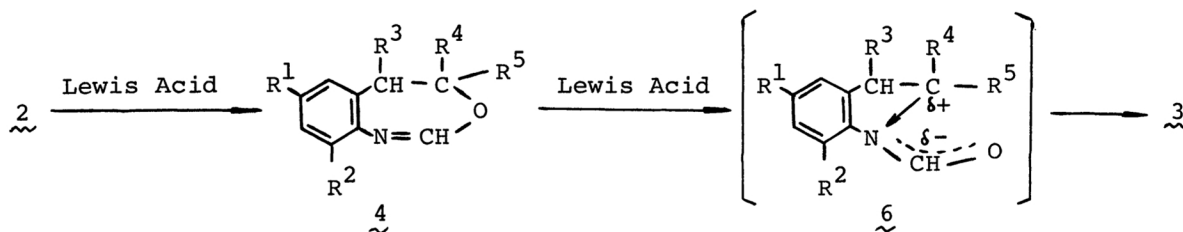
A typical experimental procedure for the preparation of N-formylindoline is exemplified as follows. To a stirred solution of 3.0 mmol of 1a¹⁾ in 8 mL of diglyme at -78°C was dropwise added 588 mg (6 mmol) of mesityl oxide. The red color characteristic of 1a disappeared immediately. The reaction mixture was quenched at -78°C with aq NH_4Cl , extracted with ether, and distilled to give o-(2-hydroxy-2,4-dimethyl-3-pentenyl)phenyl isocyanide (2a-i) (93%) (bp $105^\circ\text{C}/0.2$ mmHg) [IR (neat) $3450, 2120\text{ cm}^{-1}$; NMR (CCl_4 with Me_4Si) δ 1.2 (broad 1H), 1.29 (s, 3H), 1.62 (d, 6H), 2.84 (s, 2H), 5.15 (m, 1H), 7.1-7.4 (m, 4H)]. Next, to a solution of 603 mg (2.8 mmol) of 2a-i in 28 mL of CH_2Cl_2 at -78°C was added 40 mg (0.28 mmol) of $\text{BF}_3 \cdot \text{OEt}_2$. After stirring at -78°C for 10 min, the mixture was warmed up to 0°C and then stirred for additional 1 hr.⁵⁾ The reaction mixture was washed with water and distilled to furnish N-formyl-2-methyl-2-(2-methyl-1-propenyl)indoline (3a-i) (80%) (bp $120^\circ\text{C}/0.2$ mmHg) [IR (neat) 1670 cm^{-1} ; NMR (CDCl_3 with Me_4Si) δ 1.47 (s, 6H), 1.68 (s, 3H), 2.88 (d, 1H), 3.22 (d, 1H), 5.47 (m, 1H), 6.9-7.2 (m, 3H), 7.9-8.3 (m, 1H), 8.33 (s, 1H)].

The benzylic carbanions (1b ~ 1e) generated in situ from 2,4-xylyl isocyanide, 2,6-xylyl isocyanide, o-ethylphenyl isocyanide and o-(methylthiomethyl)phenyl isocyanide can enter to the present indoline syntheses, according to the equation (1). N-Formyl-3-methylthioindolines (3e-i and 3e-ii) thus prepared were converted to indole derivatives (5e-i and 5e-ii) by oxidation with NaIO_4 and the subsequent elimination reaction.⁶⁾



Finally, attempts to cyclize o-(3-hydroxyalkyl)phenyl isocyanides,^{1),2)} which are prepared by the reaction of 1 with epoxide, gave rise to N-formyl-1,2,3,4-tetrahydroquinolines only in low yields. Treatment of o-(3-hydroxy-3-methylbutyl)phenyl isocyanide with SnCl_4 afforded 11% of N-formyl-2,2-dimethyl-1,2,3,4-tetrahydroquinoline.

A possible reaction mechanism for the Lewis-acid catalyzed cyclizations of o-(2-hydroxyalkyl)phenyl isocyanide to N-formylindolines may involve a cationic 1,3-rearrangement of dihydro-3,1-benzoxazepines (4), which may be initially produced by the intramolecular insertion of the isocyanide carbon into the O-H linkage of 2. The finding that dihydro-3,1-benzoxazepines (4) prepared independently²⁾ underwent 1,3-rearrangement to produce the corresponding N-formylindolines (3) under the same reaction conditions is taken to support the reaction mechanism.



A cationic character of the 1,3-rearrangement is consistent with an observation that the cyclizations of 2 with aryl and vinyl substituents at C₂ of the alkyl side chain proceeded well to give 3 in high yields. The aryl and vinyl substituents may be expected to stabilize the assumed cationic species (6) in the 1,3-rearrangement.

No general method for synthesis of indoline derivatives has not been known to our best knowledge. Some preparations of indoline skeletons have been hitherto achieved by the thermolysis of o-alkylarylazides⁸⁾ and the deoxygenation of o-alkylnitrobenzenes.⁹⁾ The present reactions provide a convenient preparative method of indoline derivatives, especially 2-aryl and 2-vinyl substituted indolines.

References and Notes

- 1) Y. Ito, K. Kobayashi and T. Saegusa, *J. Am. Chem. Soc.*, **99**, 3532 (1977).
- 2) Y. Ito, K. Kobayashi and T. Saegusa, *Tetrahedron Lett.*, 2087 (1978).
- 3) Benzylideneacetophenone and cyclohexenone reacted with 1a to give the corresponding 1,4-adducts in 97 and 80% yields, respectively. 3-Penten-2-one reacted with 1a to give a mixture of 1,2-adduct (57%) and 1,4-adduct (38%).
- 4) A minor by-product is N-[o-(1-alkenyl)phenyl]formamide.
- 5) Higher reaction temperature and prolonged reaction time led to somewhat decreased yield in the cases with BF₃·OEt₂ catalyst.
- 6) B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976).
- 7) 3a-ii [Tlc on silica gel, R_f=0.44 (CHCl₃)] : IR (neat) 1667 cm⁻¹; NMR (CDCl₃) δ 1.68 and 1.71 (s, 3H), 2.95 (d, 1H), 3.27 (d, 1H), 6.22 (d, 1H), 6.56 (d, 1H), 7.0-7.4 (m, 8H), 8.0-8.3 (m, 1H), 8.37 and 8.96 (s, 1H).
3-iv [Tlc on silica gel, R_f=0.68 (10:1 CHCl₃-AcOEt)] : IR (neat) 1666 cm⁻¹; NMR (CDCl₃) δ 0.3-0.7 (m, 4H), 0.9-1.3 (m, 1H), 1.28 and 1.57 (s, 3H), 2.6-3.2 (m, 2H), 6.9-7.2 (m, 3H), 7.9-8.2 (m, 1H), 8.57 and 8.93 (s, 1H).
3a-viii (bp 110°C/0.1 mmHg) : IR (neat) 1674 cm⁻¹; NMR (CDCl₃) δ 1.64 and 1.73 (d, 3H), 2.6-3.6 (m, 2H), 4.4-5.2 (m, 1H), 5.3-5.7 (m, 2H), 6.6-7.2 (m, 3H), 7.8-8.0 (m, 1H), 8.14 and 8.65 (s, 1H).
3a-x [Tlc on silica gel, R_f=0.61 (10:1 CHCl₃-AcOEt)] : IR (neat) 1665 cm⁻¹; NMR (CCl₄) δ 1.68 (s, 3H), 1.74 (s, 3H), 2.97 (d, 2H), 6.8-7.2 (m, 3H), 8.0-8.3 (m, 1H), 8.47 and 8.99 (s, 1H).
3d [A mixture of diastereoisomers; Tlc on silica gel, R_f=0.62 (100:1 CHCl₃-AcOEt)] : IR (neat) 1670 cm⁻¹; NMR (CDCl₃) δ 0.82 and 1.27 (d, 3H), 1.70 (s) and 2.00 (d) (3H), 3.3-3.8 (m, 1H), 7.0-7.6 (m, 9H), 8.1-8.4 (m, 1H).
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(Received September 29, 1980)