CHEMISTRY LETTERS, pp. 1563-1566, 1980.

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

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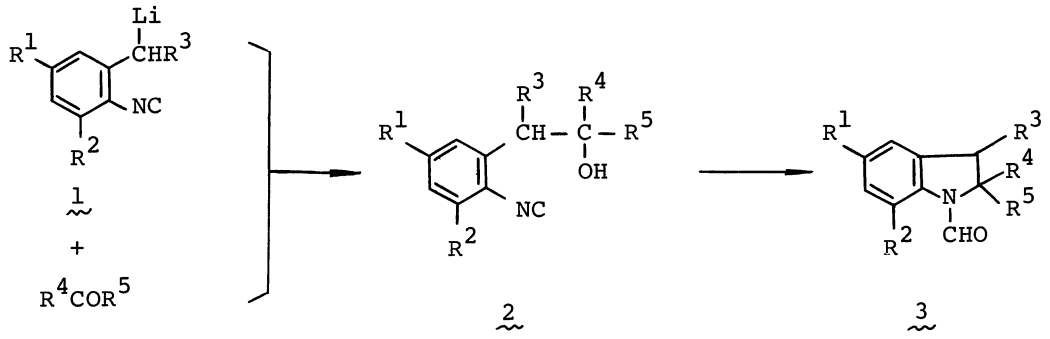
o-(2-Hydroxyalkyl)phenyl isocyanides (2), which are prepared by the reaction of o-lithiomethylphenyl isocyanides (1) with ketone and aldehyde are cyclized by Lewis acid catalyst to N-formylindoline derivatives (3).

Syntheses of indoles and the related heterocycles[1] 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 reported[2] that o-(2-hydroxyalkyl)phenyl isocyanide (2) prepared by the reaction of 1a with ketone and aldehyde were cyclized by Cu_2O 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 $BF_3 \cdot OEt_2$, $ZnCl_2$ and $SnCl_4$.

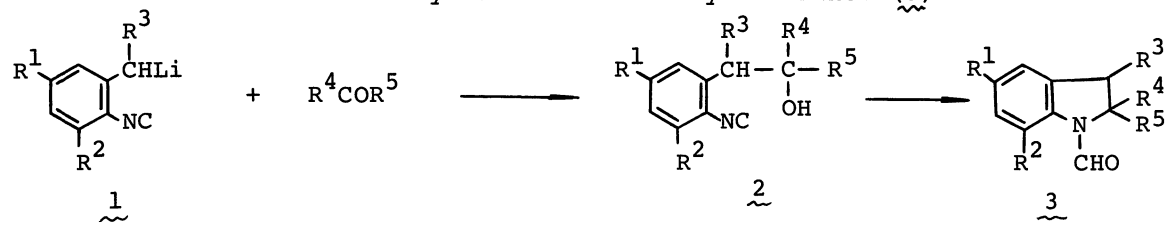


(1)

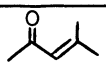
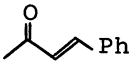
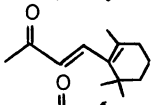
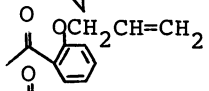
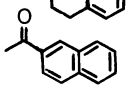
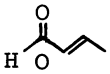
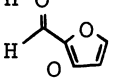
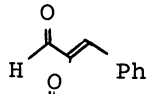
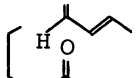
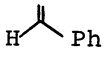
As already reported,[2] o-lithiomethylphenyl isocyanide (1a) readily reacted with aliphatic and aromatic saturated aldehyde and ketone to furnish o-(2-hydroxyalkyl)phenyl isocyanides (2) in high yields. In the present study, we found that α,β-unsaturated ketones and aldehydes also reacted with 1a in the manner of 1,2-addition[3] 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 $BF_3 \cdot OEt_2$

Table 1. Synthesis of N-Formylindolines (3)



1 2 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

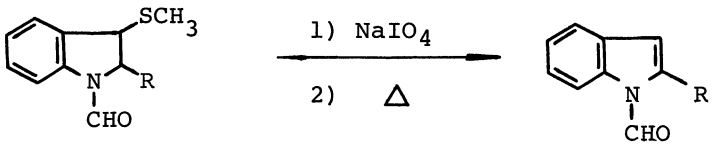
a) Isolated Yields. b) Reference 7. c) Method A : 0.1 equiv $BF_3 \cdot OEt_2$, 0°C, 1 h; Method B : 0.1 equiv $BF_3 \cdot OEt_2$, room tempt., overnight; Method C : 1 equiv $ZnCl_2$, room tempt., overnight; Method D : 1 equiv $SnCl_4$, room tempt., overnight.

(-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 $BF_3 \cdot OEt_2$ 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 $BF_3 \cdot OEt_2$. Moreover, o-(2-hydroxyalkyl)phenyl isocyanides prepared from 1 and aliphatic ketone were not cyclized by $BF_3 \cdot OEt_2$, 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 1a[1] 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°C/0.2 mmHg) [IR (neat) 3450, 2120 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 $BF_3 \cdot OEt_2$. 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°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]



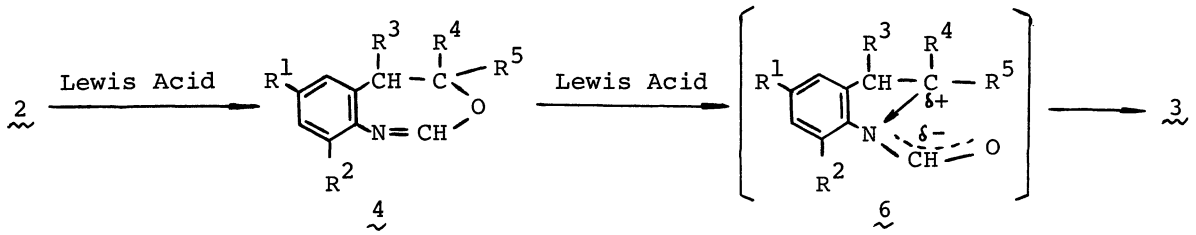
(2)

3e-i : R = $CH{=}CHCH_3$-t — 5e-i : 54%

3e-ii : R = Ph — 5e-ii : 72%

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 independently[2] 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 C_2 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-alkylarylazides[8] 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 $BF_3 \cdot OEt_2$ 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 ($CHCl_3$)] : IR (neat) 1667 cm^{-1}; NMR ($CDCl_3$) 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 $CHCl_3$-AcOEt)]: IR (neat) 1666 cm^{-1}; NMR ($CDCl_3$) 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 ($CDCl_3$) 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 $CHCl_3$-AcOEt)]: IR (neat) 1665 cm^{-1}; NMR (CCl_4) 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 $CHCl_3$-AcOEt)]: IR (neat) 1670 cm^{-1}; NMR ($CDCl_3$) 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).
8) G. Somolinsky and B. I. Feuer, J. Am. Chem. Soc., 83, 2489 (1961).
9) R. J. Sundberg, J. Am. Chem. Soc., 88, 3781 (1966).

(Received September 29, 1980)