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A NEW SYNTHESIS OF 4,5-DIHYDRO-3,1-BENZOXAZEPINE AND 4H-5,6-DIHYDRO-3,1-BENZOXAZOCINE DERIVATIVES

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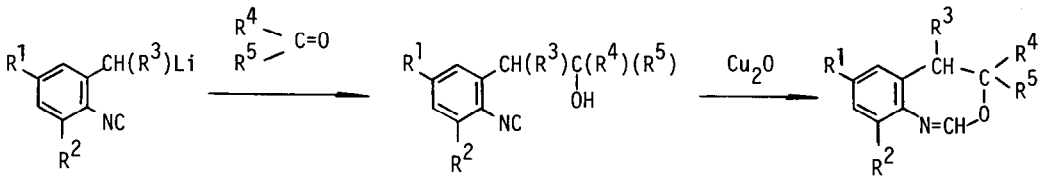
In a previous paper[1] we described the generation of o-lithiomethylphenyl isocyanide, which was a versatile reagent for syntheses of indole derivatives. Herein, we wish to report an elaboration of the lithiomethylphenyl isocyanide to lead to heterocycles such as 4,5-dihydro-3,1-benzoxazepine (3) and 4H-5,6-dihydro-3,1-benzoxazocine (5) derivatives.

o-(β-Hydroxyalkyl)phenyl isocyanides (2), which were prepared by the reactions of o-lithiomethylphenyl isocyanide with aldehydes or ketones, were heated with a catalytic amount of Cu_2O in benzene to produce 4,5-dihydro-3,1-benzoxazepine derivatives (3) in excellent yields.

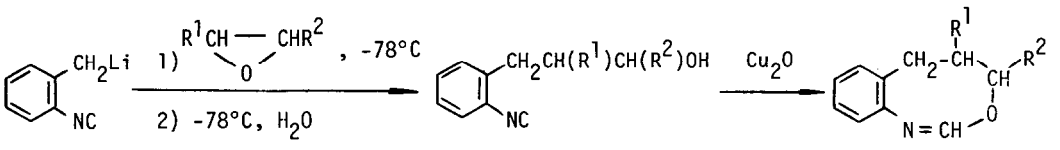


1 2 3

The intramolecular cyclization reaction is based upon the copper catalyzed insertion reaction of isonitriles into the oxygen-hydrogen bond of alcohols which was found by us.[2] A sample procedure is illustrated as follows. To o-lithiomethylphenyl isocyanide, which was generated in situ at -78°C by treating 176 mg (1.5 mmol) of o-tolyl isocyanide with lithium diisopropylamide (LDA) (3.0 mmol) in 4 ml of diglyme according to the reported procedure,[1] was dropwise added 174 mg (3.0 mmol) of propionaldehyde. The red color characteristic of the lithiomethylphenyl isocyanide disappeared immediately. The reaction mixture was quenched at -78°C with aq NH_4Cl, extracted with ether, dried over Na_2SO_4 and evaporated. The residue was distilled

using Kugelrohr to afford a 93% yield of o-(β-hydroxybutyl)phenyl isocyanide (2b) (bp 98°C/0.6 mmHg) contaminated with a trace amount of 4-ethyl-4,5-dihydro-3,1-benzoxazepine (3b) as judged by the IR spectrum. [2b : IR (neat) 3400, 2115 cm^{-1}; NMR (CCl_4 with TMS) δ 0.98 (t, 3H), 1.5 (m, 2H), 1.7 (broad s, 1H), 2.65 (d, 2H), 3.6 (m, 1H), 7.08 (s, 4H)]. On injection of 2b into a glpc instrument at 200°C, 2b was converted to 3b to the extent of more than 80%. A suspension of 240 mg (1.37 mmol) of 2b and 40 mg (0.28 mmol) of Cu_2O in 3 ml of benzene was heated at reflux for 20 min to give 4-ethyl-4,5-dihydro-3,1-benzoxazepine (3b) (bp 82°C/0.6 mmHg) in almost quantitative yield. [3b : IR (neat) 1646 cm^{-1} ; NMR ($CDCl_3$ with TMS) δ 0.93 (t, 3H), 1.52 (q, 2H), 2.96 (d, 2H), 4.40 (m, 1H), 6.9∼7.3 (m, 5H)]. Compound 3 was not stable to moisture, decomposing gradually in air. The progress of the cyclization of 2 was monitored by the IR absorption band at about 2100 cm^{-1} due to the N≡C group of the starting material (2). As illustrated by entries in Table 1, the present method for the preparation of 4,5-dihydro-3,1-benzoxazepine (3) is readily extended to various o-alkylphenyl isocyanides and aldehydes or ketones.[3] Following the above procedure, 2,4-xylyl isocyanide and 2,6-xylyl isocyanide were converted to the corresponding 4,5-dihydro-3,1-benzoxazepines (3) via selective lithiation at the ortho methyl group followed by reaction with aldehydes or ketones (Run No. 7 and 8). Moreover, o-ethylphenyl isocyanide, of which selective lithiation at the benzylic carbon can be achieved by treatment with lithium 2,2,6,6-tetramethylpiperidide, was successfully used for the synthesis of 4,5-dihydro-3,1-benzoxazepine derivatives (Run No. 10).

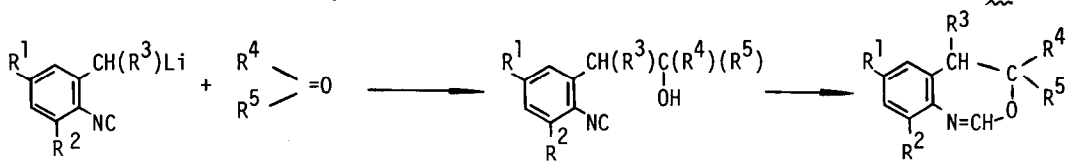
As already reported,[1] o-(γ-hydroxyalkyl)phenyl isocyanides (4), which are prepared in fairly good yields by the reaction of o-lithiomethylphenyl isocyanide with alkylene oxides, may be converted to tryptophol derivatives. Now it is found that o-(γ-hydroxylakyl)phenyl isocyanides (4) subjected to the Cu_2O-catalyzed cyclization produce 4H-5,6-dihydro-3,1-benzoxazocine derivatives (5) in low to moderate yields.



4 5

To a solution of o-lithiomethylphenyl isocyanide (1.5 mmol) in 4 ml of diglyme at -78°C, propylene oxide (3 mmol) was added dropwise, and the mixture was stirred at this temperature for 3 hr. During this time, the characteristic red color of o-lithiomethylphenyl isocyanide turned

Table 1. Synthesis of 4,5-Dihydro-3,1-benzoxazepine Derivatives (3)



1 2 3

Run No.	3 a)	R^1	R^2	R^3	R^4	R^5	% (overall yield for 1→3)	Reaction Time (min) (Conversion 2→3)
1	3a :	H	H	H	H	CH_3	90	20
2	3b :	H	H	H	H	C_2H_5	93	20
3	3c :	H	H	H	H	C_6H_5	93	30
4	3d :	H	H	H	H	Furyl b)	89	30
5	3e :	H	H	H	CH_3	CH_3	96	60
6	3f :	H	H	H	— $(CH_2)_4$ —		93	180
7	3g :	CH_3	H	H	CH_3	CH_3	87	60
8	3h :	H	CH_3	H	H	C_2H_5	90	180
9	3i :	Cl	H	H	CH_3	CH_3	95	60
10	3j :	H	H	CH_3	CH_3	CH_3	93	30

a) All products of 3 [4] showed satisfactory elemental analyses and mass spectra (M^+).

b) Fury : 

gradually to violet. The reaction mixture at -78°C was quenched with aq NH_4Cl, extracted with ether, dried over Na_2SO_4 and evaporated. o-(γ-Hydroxybutyl)phenyl isocyanide (4a) (bp 140°C/2 mmHg) was obtained in 91% yield. [4a : IR (neat) 3400, 2115 cm^{-1} ; NMR ($CDCl_3$ with TMS)δ 1.25 (d, 3H), 1.8 (m, 2H), 2.7 (m, 3H), 3.80 (m, 1H), 7.0~7.2 (m, 4H)]. A suspension of 260 mg (1.5 mmol) of 4a and 55 mg (0.38 mmol) of Cu_2O in 3 ml of benzene was heated at reflux for 10 hr. The product 4-methyl-4H-5,6-dihydro-3,1-benzoxazocine (5a) was isolated by Kugelrohr distillation(bp 75°C/10^{-3}mmHg). [5a : IR (neat) 1655 cm^{-1} ; NMR ($CDCl_3$ with TMS)δ 1.15 (d, 3H), 1.5 (m, 2H), 2.72 (t, 2H), 4.4 (m, 1H), 6.9~7.1 (m, 5H)]. Similarly, the corresponding 4H-5,6-dihydro-3,1-benzoxazocine derivatives (5b) was prepared by the reaction of o-lithiomethylphenyl isocyanide with 1-butene oxide in 42% isolated yield.[5)]

References and Notes

1) Y. Ito, K. Kobayashi and T. Saegusa, J. Am. Chem. Soc., 99, 3532 (1977).

2) a) T. Saegusa and Y. Ito, Synthesis, 291 (1975).

b) T. Saegusa, Y. Ito, N. Takeda and K. Hirota, Tetrahedron Lett., 1273 (1967)

c) D. Hoppe, Angew. Chem., 86, 878 (1974).

3) α,β-Unsaturated Ketones reacted with o-lithiomethylphenyl isocyanide via conjugate addition under the reaction conditions.

4) 3c : bp 160°C/1 mmHg ; IR (neat) 1640 cm^{-1} ; NMR ($CDCl_3$ with TMS)δ 3.2 (m, 2H), 5.30 (dd, 1H), 6.9~7.3 (m, 10H).

3f : bp 110°C/0.6 mmHg ; IR (neat) 1642 cm^{-1} ; NMR (CCl_4 with TMS)δ 1.5~2.0 (m, 8H), 3.00 (s, 2H), 6.8~7.2 (m, 5H).

3h : bp 95°C/0.6 mmHg ; IR (neat) 1649 cm^{-1} ; NMR (CCl_4 with TMS) ε 0.95 (t, 3H), 1.43 (q, 2H), 2.27 (s, 3H), 2.80 (d, 2H), 4.3 (m, 1H), 6.6~7.0 (m, 4H).

3j : bp 90°C/0.6 mmHg ; IR (neat) 1645 cm^{-1} ; NMR (CCl_4 with TMS)ε 1.06 (s, 3H), 1.17 (d, 3H), 1.39 (s, 3H), 2.75 (q, 1H), 6.8~7.2 (m, 5H).

5) 5b : bp 83°C/10^{-3} mmHg ; IR (neat) 1656 cm^{-1} ; NMR ($CDCl_3$ with TMS)ε 0.80 (t, 3H), 1.4 (m, 4H), 2.73 (t, 2H), 4.3 (m, 1H), 7.0~7.2 (m, 5H).