HETEROCYCLE SYNTHESIS USING o-TOLYL ISOCYANIDE
SYNTHESES OF INDOLE AND DIHYDROXAZEPINE DERIVATIVES

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Selective lithiation at the methyl group of o-tolyl isocyanide (1) was successfully performed by treatment of 1 with 2 equiv of lithium diisopropylamide (LDA) in diglyme at -78°C. The resulting o-lithiomethylphenyl isocyanide (2) in diglyme at -78°C was allowed to warm up to room temperature to produce, after H_2O workup, indole in an almost quantitative yield. The lithiomethylphenyl isocyanide (2) at -78°C was reacted with 2 equiv of alkyl halides to give o-substituted phenyl isocyanides (3) in high yields [e.g., CH_3I : o-ethylphenyl isocyanide (95%), iso-C_4H_9Br : o-(3-methylbutyl)phenyl isocyanide (78%).]. o-Alkylphenyl isocyanides (3) thus obtained were cyclized to 3-substituted indoles (4) in fairly good yields via the ortho-lithiation of the alkyl group in 3 using 2 equiv of lithium 2,2,6,6-tetramethylpiperidide (LTMP) [e.g., 3-methylindole (95%), 3-iso-butylindole (78%)]. A mixture of the lithiomethylphenyl isocyanide (2) and 2 equiv of alkylene oxide which had been stirred at -78°C for 2∼5 hr was subsequently treated with 2 equiv of LDA at the same temperature and allowed to warm up to room temperature to give 3-(β-hydroxyalkyl)-indole (6) in moderate yield [e.g., iso-Butene oxide : 3-(β-hydroxy-β-methylpropyl)indole (68%), Propylene oxide : 3-(β-hydroxypropyl)indole (65%)]. Next, 2 generated at -78°C was allowed to warm up to above -25°C, and then reacted with alkyl halides and alkylene oxides producing 1-substituted indoles (10) in good yields [e.g., 1-n-butylindole (82%), 1-(β-hydroxybutyl)indole (84%)]. Finally, o-(β-hydroxyalkyl)phenyl isocyanides (8), which were prepared by the reaction of 2 in diglyme at -78°C with 2 equiv of ketones or aldehydes, were heated with a catalytic amount of Cu_2O in benzene to afford dihydrobenzoxazepine derivatives (9) in high yields. Similarly, Cu_2O-catalyzed cyclizations of o-(γ-hydroxyalkyl)phenyl isocyanides (5) , which were prepared from 2 and alkylene oxides, gave tetrahydrobenzoxazocine derivatives (7) in moderate yields.