HETEROCYCLE SYNTHESIS USING o-TOLYL ISOCYANIDE

SYNTHESES OF INDOLE AND DIHYDROXAZEPINE DERIVATIVES

Yoshihiko Ito, Kazuhiro Kobayashi and Takeo Saegusa
Department of Synthetic Chemistry, Faculty of Engineering
Kyoto University, Yoshida, Kyoto

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.