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HETEROCYCLE SYNTHESIS USING o-METHYLPHENYL ISOCYANIDE

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It has already been reported that o-tolyl isocyanide is treated with 2 equiv of lithium diisopropylamide (LDA) in diglyme at -78° to generate o-lithiomethylphenyl isocyanide (1) in an almost quantitative yield and that o-lithiomethylphenyl isocyanide is a versatile intermediate for preparation of indole derivatives. This paper describes some other elaborations of 1 leading to indole derivatives and related heterocycles. The o-lithiomethylphenyl isocyanide (1) was treated with isocyanate and isothiocyanate at -78° to produce N-substituted o-isocyanophenylacetamide (2) and o-isocyanophenylacetothioamide (3) in good yields, respectively [e.g., N-n-butyl o-isocyanophenylacetamide (70%): N-phenyl o-isocyanophenylacetothioamide (82%)] . Isocyanides 2 and 3 thus obtained were treated with 2 equiv of LDA at -78° and than allowed to warm up to room temperature to afford indole-3-carboxamide (4) and indole-3-thiocarboxamide (5) in moderate yields, after H_2O work up [e.g., indole-3-(N-tert-butylcarboxamide) (57%) : indole-3-(N-cyclohexyl thiocarboxamide)(60%)]. On the other hand, isocyanide (2) was heated with a catalytic amount of Cu_2O in benzene to afford 4 together with dihydrobenzodiazepinone (6), the ratio of 4 to 6 depending upon the substituent on amide nitrogen.

The o-lithiomethylphenyl isocyanide (1) was reacted with allyl carboxylate at -78° to produce o-(acylmethyl)phenyl isocyanide (7) in moderate yields [e.g., o-(acetylmethyl)phenyl isocyanide (48%) : o-(benzoylmethyl)phenyl isocyanide (95%)]. o-(Acylmethyl)phenyl isocyanide (7) was treated with a catalytic amount of Cu_2O to afford 3-acylindoles in good yields [e.g., 3-butyrylindole (71%) : 3-benzoylindole (80%)].

Selective lithiations at the methyl groups of 2.4-xylyl isocyanide and 2,6-xylyl isocyanide and their elaboration to synthesize 3,5-disubstituted indole and 3,7-disubstituted indole will be also mentioned.