



Online Resources for Medical Student Neurosurgery Education

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Description

In InCl_3 -catalyzed three-component aza-Friedel-Crafts reactions of Aldehydes, 4-Aminofluorescein, and indoles in methanol have been developed. The aza-Friedel-Crafts products could be easily transformed into various 3-substituted indoles including biologically active compounds. This system offers a novel efficient method for the synthesis of 3-substituted indole derivatives in good yields. Further, the molecules are predicted to bind with Induced myeloid leukemia cell differentiation protein Mcl-1 using Extended Connectivity fingerprint ECfp4 NN (ECfp4)+NB (ECfp4). Molecular docking studies with Mcl-1 showed a docking score of -7.8kcal/mol with two hydrogen bonds and nine hydrophobic contacts by interaction with the R263 hot-spots implying a potential inhibitor against Mcl-1.

The Aza-Friedel-Crafts Reactions (AFCR) have attracted much attention as a synthetically outstanding carbon-carbon bond-forming process that leads to functionalized amines in a green transformation and completely atom-economic way. However, in spite of its significance, many potential problems related to arena nucleophile, electrophilic substrate, or functional group tolerance still remain for this transformation. For example, the aza-Friedel-Crafts reaction seems to be restricted to highly electrophilic substrates, such as trifluoromethyl imines and highly nucleophile substrates, such as in doles, electron-rich arenas due to the low reactivity of imines. In addition, the one-pot Multicomponent Coupling Reactions (MCRs), which introduce several elements of diversity into a molecule in a single step. For a long time, the transition metal-catalyzed Multi-Component Reactions (MCRs) have attracted much interest because of their capability of offering many challenging transformations using one-pot method. Particularly those metal catalysts, which are derived from the group VIII-X metals, display remarkable efficiency for the

formation of carbon-carbon and carbon-heteroatom bonds are shown in Furthermore, Piersanti and co-workers reported the reaction using enamines derived from α -ketoesters with indoles to give products with moderate enantioselectivities. The recently reported the highly enantioselective aza-Friedel-Crafts reaction of 2-substituted-3H-indol-3-one derivatives with pyrroles using novel chiral imidazole-phosphoric acid catalysts.

In addition, Indoles are important structural units in many natural products and their derivatives are known to possess various biological properties, such as antibacterial, ant oxidative, and insecticidal activities, and some in dole derivatives have been used as antibiotics in pharmaceuticals. Among in dole derivatives, bis-indolylalkanes, 3-alkyl in doles, and 3-diarylmethyl in doles are an important class of bioactive metabolite, which can be synthesized by Lewis acid catalysis and much attention has been paid to the synthesis of them for a long while. Although the synthesis of 3-alkyl in doles has been studied extensively, the synthesis of other unsymmetrical indole derivatives is still highly desirable in the synthetic community due of it needs more practical procedures and mild reaction conditions. As part of our ongoing efforts devoted to InCl_3 -catalyzed organic reactions, herein we wish to report the first genuinely and highly efficient InCl_3 as Lewis acid-catalyzed one-pot three-component aza-Friedel-Crafts reactions of indoles, Aldehyde, and Amine. The reactions generated the corresponding 3-substituted indole derivatives in good yields under mild reaction conditions.

Experimental Section

Aldehydes, 4-Amino fluorescein, Indole, Indium (III) Chloride, and other alcohols/solvents are obtained from SRL, Chennai, Tamil Nadu, and India. Column chromatography was performed on Silica Gel (100-200 mesh). NMR spectra were recorded on Bruker DRX 300 MHz in CDCl_3 or DMSO-d_6 at the University of Madras (Chennai, Tamil Nadu, and India). TMS was used as the internal standard ($\delta=0.00$ ppm) and all the J values are given in hertz. Optical rotation was performed by using Rudolph-Autopol II digital polarimeter. Elemental analyses were performed using Perkin-Elmer 2400 elemental analyzer.

To a solution of the aldehydes 1a-e (1 mmol), 4-aminofluorescein 2 (1 mmol), Indole 3 (1 mmol), Indium trichloride (1 mmol, 0.22 g) as a catalyst, and dry MeOH (25 ml) were added. After stirring at 120°C oil bath reflux temperature for a given period of time, the reaction mixture was evaporated under reduced pressure and extracted by chloroform-water. The chloroform layer was dried over anhyd. Na_2SO_4 and concentrated to dryness. The product was further purified by flash column chromatography.