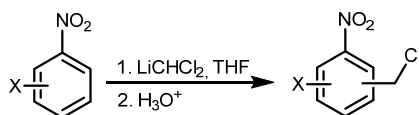


# VICARIOUS NUCLEOPHILIC CHLOROMETHYLATION OF NITROAROMATICS

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The key nucleophilic reagent for direct VNS chloromethylation used in this study is dichloromethylithium ( $\text{LiCHCl}_2$ ) prepared by deprotonation of dichloromethane with *n*-butyllithium at low temperature (ca.  $-100^\circ\text{C}$ ). [1, 2] Although dichloromethylithium is rather unstable, its nucleophilicity should be higher than that of deprotonated chloroform or bromoform, which are also known to undergo VNS (to form dihalomethylnitrobenzenes) despite their limited stability at low temperature. [3] Furthermore, the synthetic use of dichloromethylithium as nucleophilic species was previously demonstrated on homologation of boronic esters  $\text{R-B(OR')}_2$  to form  $\alpha$ -chloro boronic esters  $\text{R-CHCl-B(OR')}_2$ . [4, 5]



In this study a novel methodology for regioselective vicarious nucleophilic chloromethylation of nitroaromatics using a lithium salt of dichloromethane is disclosed. The reaction requires low temperature ( $< -100^\circ\text{C}$ ) and is very fast for nitrobenzenes substituted with electron-acceptor groups. For less reactive substrates, boosting nucleophilicity of  $\text{LiCHCl}_2$  with TMEDA and longer reaction times proved to be beneficial. Protected formyl, carboxylic acid or hydroxyl functional groups showed good compatibility. The chlorine atom in products was efficiently substituted in situ with various nucleophiles, providing benzylic compounds of previously inaccessible substitution pattern. Finally, a mild oxidation of the chloromethyl group was developed to access substituted nitrobenzaldehydes.

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