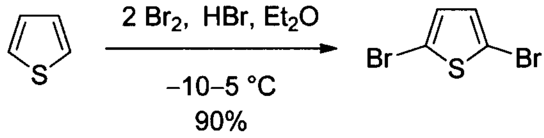
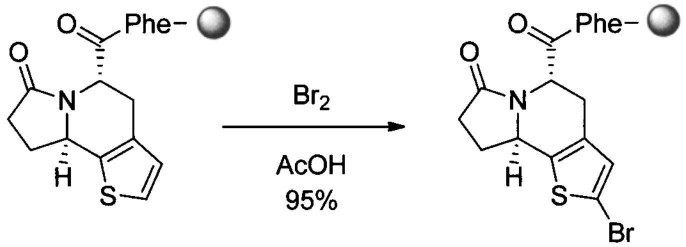
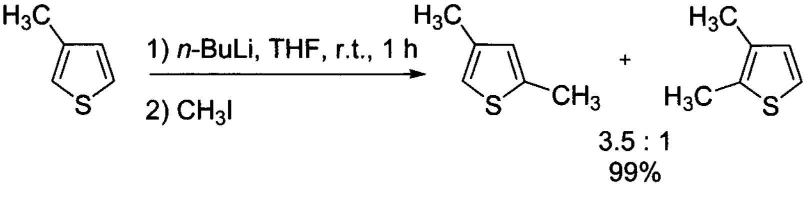


As seen throughout this chapter, halogenation produces functionalized thiophenes that are valuable intermediates in metal–halogen exchange reactions, perfluoroalkylation, and cross-coupling reactions, among others. One such example is the solid-phase bromination of thiophene at the *C2* position in greater than 95% yield. The bromination product can then be exploited further through various cross-coupling reactions.[76]



Lithiation/Methylation

Lithiation of 3-methylthiophene and subsequent addition of an electrophile, in this case methyl iodide, produces a mixture of products at the *C2* or *C5* positions, with the 2,4-disubstituted thiophene predominating. However, a strong electron-withdrawing or sterically hindered *C3*-substituent will direct the formation of the *C5* methylated thiophene to the more sterically favorable position.[77]



The selection of the lithiation reagent also has a strong influence over the regioselectivity of the electrophilic substitution; the bulkier the base, the more favorable the reaction at the *C5* position. For example, lithium 2,2,6,6-tetramethylpiperidine (LiTMP) directs the formation of the *C5*-substituted product at a 79:1 ratio to the *C2*-substituted thiophene. A variety of electrophiles can be substituted after lithiation by LiTMP.[77]