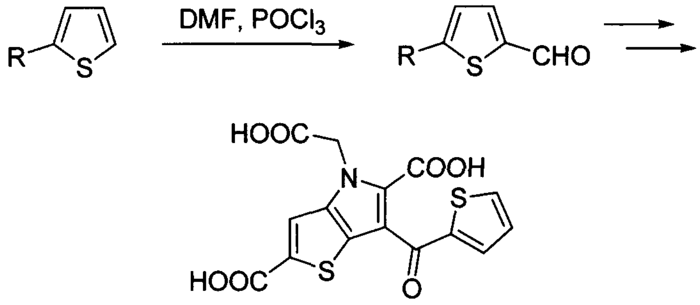
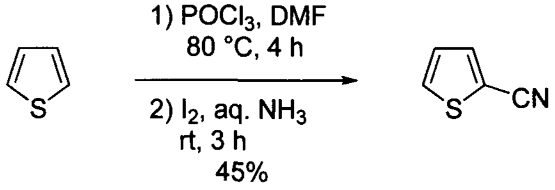
formylation reaction. Treatment of thiophene or a thiophene derivative with DMF and phosphorus oxychloride generates the corresponding aldehyde which can be further functionalized. For example, additional synthetic transformations on the Vilsmeier–Haack product of a 2-substituted thiophene produced an anti-inflammatory agent that displayed limited desired biological activity.[82]

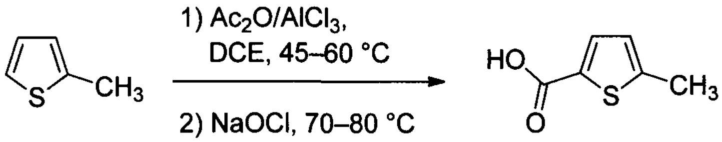


Aromatic nitriles, including thiophenes, can be accessed through a Vilsmeier–Haack protocol followed by the addition of iodine and aqueous ammonia. Benzothiophene (not shown) was found to be unreactive in this system. The authors theorized that this was possibly due to insufficient electron density.[83]



Carboxylation

Carboxylation of the thiophene ring may occur in a variety of ways. A classic method involves a Friedel–Crafts acylation followed by oxidation.[82]



Other methods of carboxylation include the use of palladium(II) acetate in the presence of carbon dioxide. Carboxylation is favored predominately at the *C2* position (or *C5* if *C2* is substituted). Interestingly, when a thiophene containing a *C3* methyl substituent was subjected to