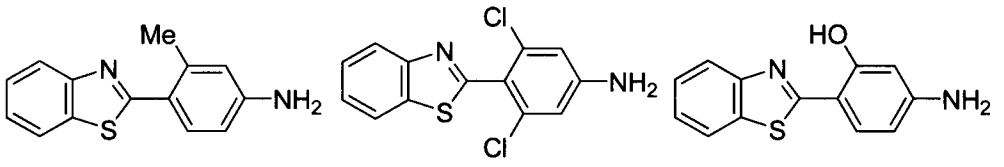
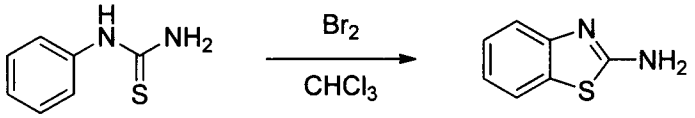


a b c

7.5.2 *Hugerschoff Synthesis*

The Hugerschoff reaction is a classical method to convert arylthioureas into aminobenzothiazoles under oxidative conditions. It was discovered by Hugerschoff in the early 1900s, who found that an arylthiourea can be cyclized with liquid bromine in chloroform to form a 2-aminobenzothiazole.[94] Solvents such as carbon tetrachloride and carbon disulfide can also be used. This transformation is aided by thiophilic bromine or its equivalent and requires an intramolecular aromatic electrophilic substitution reaction of the aryl ring to the thiocarbonyl group of thiourea. Attempts have been made to avoid the use of bromine due to the handling concerns it poses. For example, Jordan and coworkers have used benzyltrimethylammonium tribromide.[95,96]



A side product possessing a thioamido guanidine moiety presumably forming *via* a disulfide intermediate is often observed along with the desired 2-aminobenzothiazole. Yella and co-workers have observed that for the Hugerschoff product to form, the aryl ring has to be sufficiently activated.[97] An application of this method is illustrated below where treatment of arylthiourea with bromine in dichloromethane provided 4-methoxybenzothiazol-2ylamine in > 95% yield.[98] The Medicinal Chemistry team at Amgen had identified AMG 628 as a highly efficacious vanilloid receptor-1 antagonist, the large-scale synthesis of which required the ready availability of the benzothiazole raw material. The Process Research team developed a scalable process for 4-methoxybenzothiazol-2ylamine, a commercially available yet expensive intermediate. The original cyclization conditions involved bromine in dichloromethane yielding 60% product. Optimization efforts led to the identification of bromine with lithium bromide in acetic acid.