Appendix 2: Functionalization

App 2.1 Aldehydes

Aromatic aldehydes can be prepared by oxidising an aromatic methyl substituent (Fig. 1).

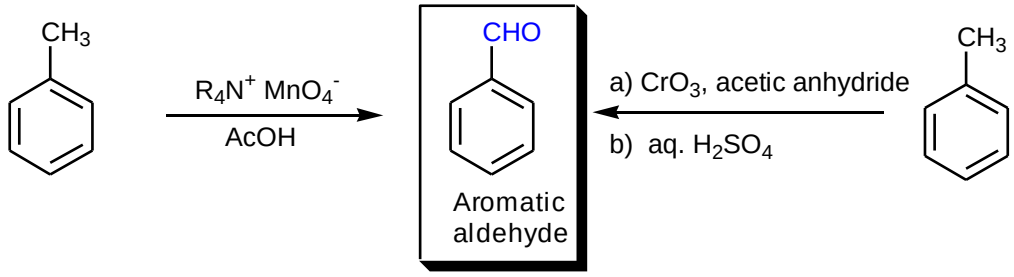

Figure 1 Oxidation of aromatic methyl groups.

App 2.2 Alkyl halides

An aromatic methyl group can be chlorinated to a trichloromethyl substituent (Fig. 2). Further treatment with SbF_5 results in a trfluoromethyl group.

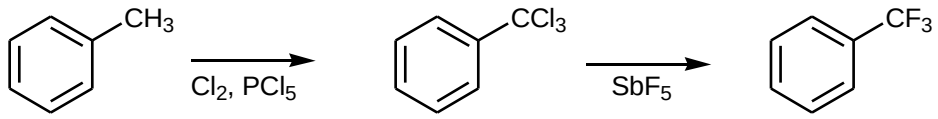

Figure 2 Halogenation of an aromatic methyl substituent.

Benzyl bromides can be prepared by treatment of an alkyl-substituted aromatic ring with *N*-bromosuccinimide (Fig. 3a), but it is important to appreciate that this reagent can also react at the α-positions of alkenes, alkynes and carbonyl groups. Benzyl bromides and benzyl chlorides can also be synthesised using bromine and chlorine in the presence of light or heat (Fig. 3b). There is no halogenation in the aromatic ring under these conditions.

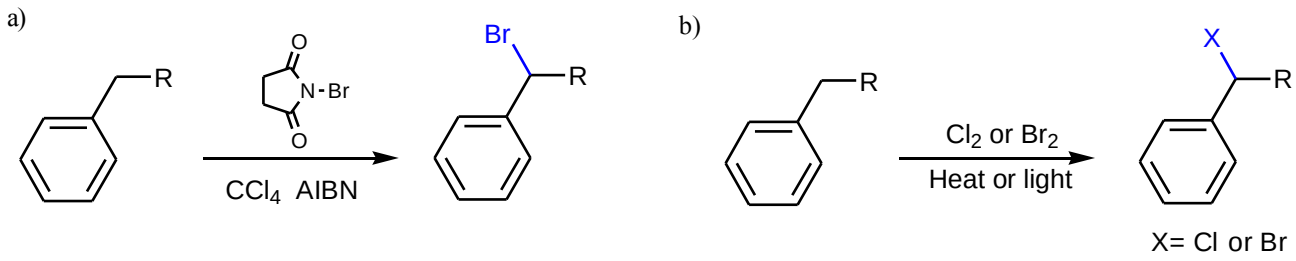

Figure 3 Benzylic halogenation.

App 2.3 Aryl halides

Aromatic halogenations can be carried out in the presence of a Lewis acid such as ferric bromide (Fig. 4a). If a strongly activating group is present in the ring, such as a phenol or amine, then the Lewis acid is not required. Halogenation can take place at both *ortho* positions and the *para* position (Figs 4b and 4c).

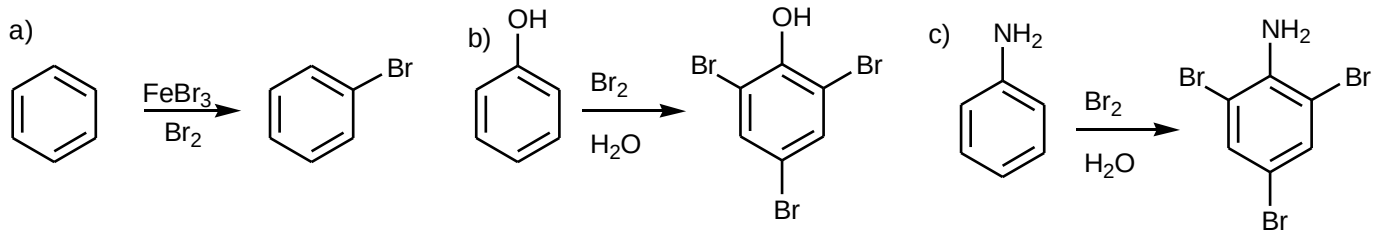

Figure 4 Halogenation of aromatic rings.

App 2.4 Aryl sulphonic acids

Sulphonic acid substituents can be added to aromatic rings by electrophilic substitution. Sulphonation involves a strong electrophile and does not need the presence of a Lewis acid as catalyst (Fig. 5).

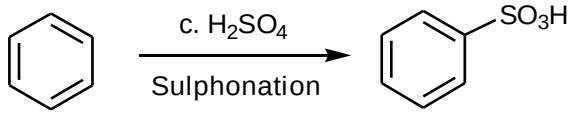

Figure 5 Sulphonation.

App 2.5 Carboxylic acids

Alkyl-substituted aromatic rings can be oxidised to aromatic carboxylic acids with potassium permanganate as long as the benzylic position contains protons (Fig. 6).

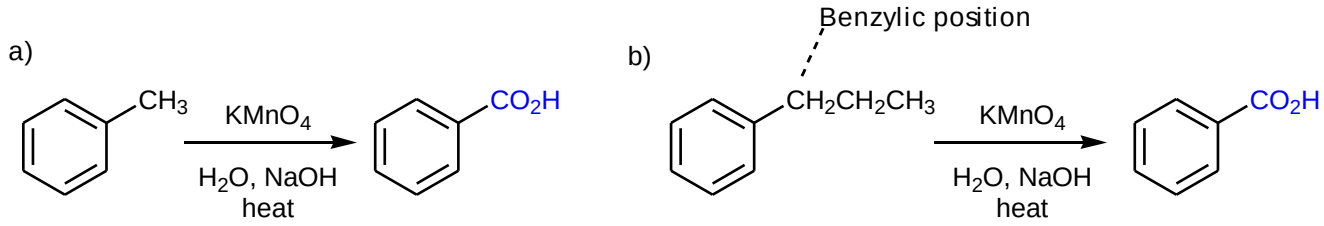

Figure 6 Oxidation of alkyl-substituted aromatic rings to aromatic carboxylic acids.

App 2.6 Nitroaryls

Aromatic nitro groups are relatively uncommon in drugs because they are often associated with toxic side effects. However the antibiotic chloramphenicol contains an aromatic nitro group, as does the

anti-protozoal drug oxamniquine. The antibacterial agent metronidazole has a nitro substituent on an imidazole ring.

Nitro substituents can be added to aromatic rings by electrophilic substitution. A strong electrophile is involved and so the reaction does not need the presence of a Lewis acid as catalyst (Fig. 7). The addition of an aromatic nitro group can be useful in synthetic strategy as it is generally unreactive, but can be reduced to an amine when required. The presence of a strongly deactivating nitro group can also promote nucleophilic substitutions of aryl halides.

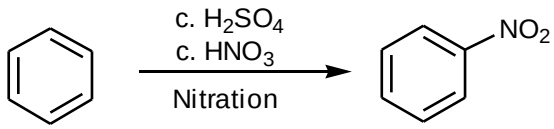

Figure 7 Nitration.