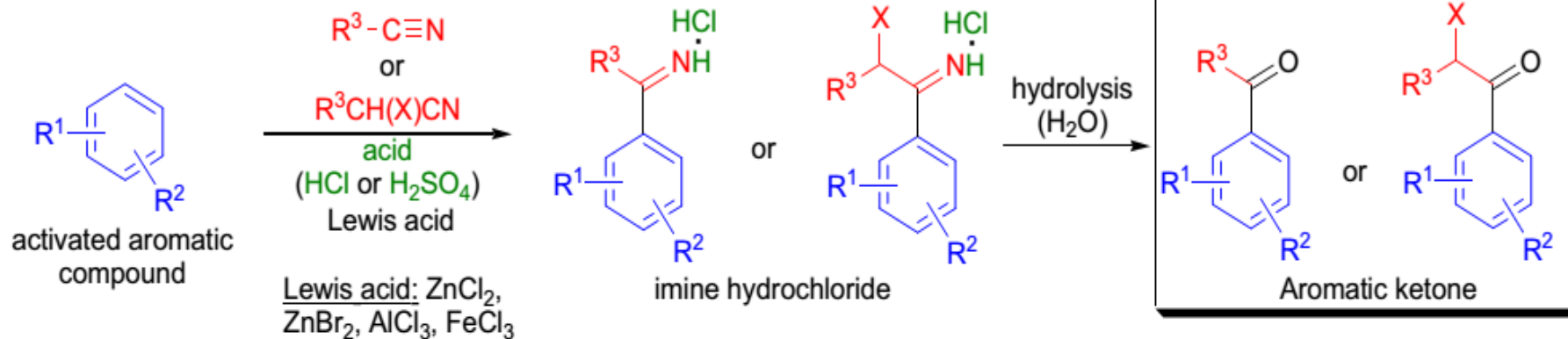


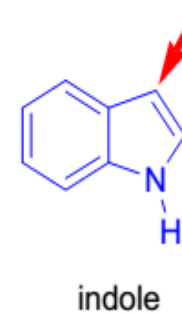
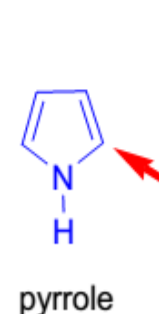
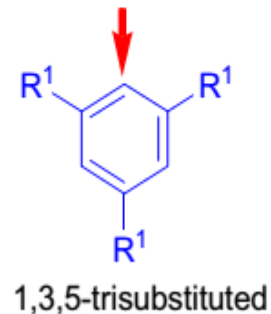
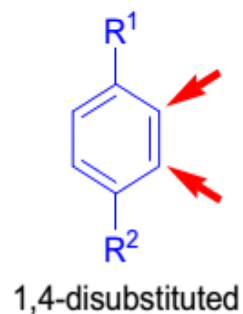
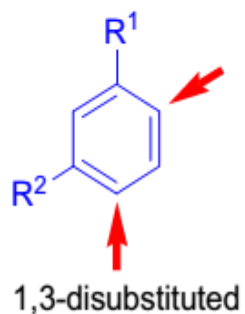
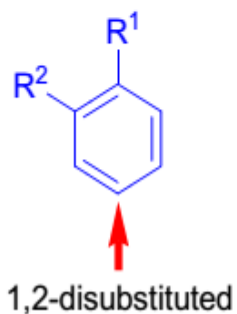
Houben-Hoesch Reaction / Synthesis

Wangtao

By the early 1900s the Friedel-Crafts acylation and the Gattermann formylation were widely used to prepare aromatic ketones and aldehydes, respectively. The preparation of monoacylated derivatives of highly activated (electron rich) substrates (e.g., polyphenols) was not possible, since usually more than one acyl group was introduced using the standard Friedel-Crafts acylation conditions. In 1915, K. Hoesch reported the extension of the Gattermann reaction for the preparation of aromatic ketones by using nitriles instead of hydrogen cyanide and replaced the aluminum chloride with the milder zinc chloride.^{1,2} A decade later the scope and the limitation of this novel ketone synthesis was examined in great detail by J. Houben, who showed that the procedure principally worked for polyphenols or polyphenolic ethers.³ The condensation of nitriles with polyhydroxy- or polyalkoxyphenols to prepare the corresponding polyhydroxy- or polyalkoxyacyloxyphenones is known as the Houben-Hoesch reaction.



$\text{R}^1 = \text{OH, O-alkyl}; \text{R}^2 = \text{OH, O-alkyl, alkyl, Cl, Br, I}; \text{R}^3 = \text{alkyl, aryl, substituted alkyl or aryl}; \text{X} = \text{H, OH, O-alkyl, Cl, Br, I}$



The general features of this reaction are:

- 1) only highly activated disubstituted aromatic compounds undergo the transformation (at least one of the substituents should be a hydroxy or an alkoxy group);
- 2) the aromatic compound can be heterocyclic so pyrroles, indoles, and furans are also substrates of this transformation;
- 3) the structure of the nitrile is freely variable: alkyl, aryl, and substituted alkyl groups (e.g., α -halogenonitriles, α -hydroxynitriles, and their ethers and esters) are all compatible with the reaction conditions;
- 4) aliphatic nitriles tend to give higher yields than aromatic nitriles;
- 5) the aromatic nitrile cannot have a strongly electron-withdrawing group in its ortho-position (no reaction is observed), but these groups in the meta-position have no effect on the reactivity of the aromatic nitrile;
- 6) the nitriles are often introduced as their hydrochloride salts;
- 7) zinc chloride is the most widely used Lewis acid but for very electron rich substrates (e.g., phloroglucinol) no Lewis acid is needed;
- 8) the initial product of the reaction is the imine hydrochloride that is hydrolyzed to afford the final product aromatic ketone.

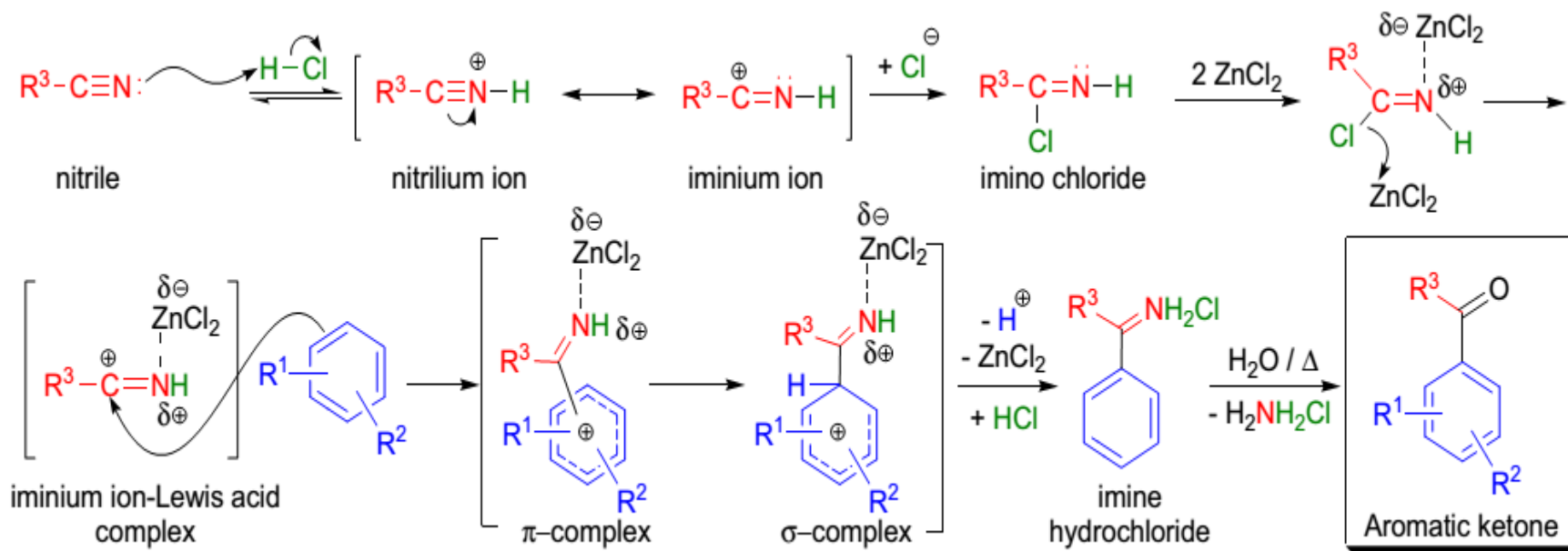
The most important modifications of the Houben-Hoesch reaction are:

- 1) by using trichloroacetonitrile, even non-activated aromatics can be acylated; and
 - 2) switching the Lewis acid to BCl_3 the acylation of aromatic amines can be realized with high ortho regioselectivity.¹³
-

- Mechanism:

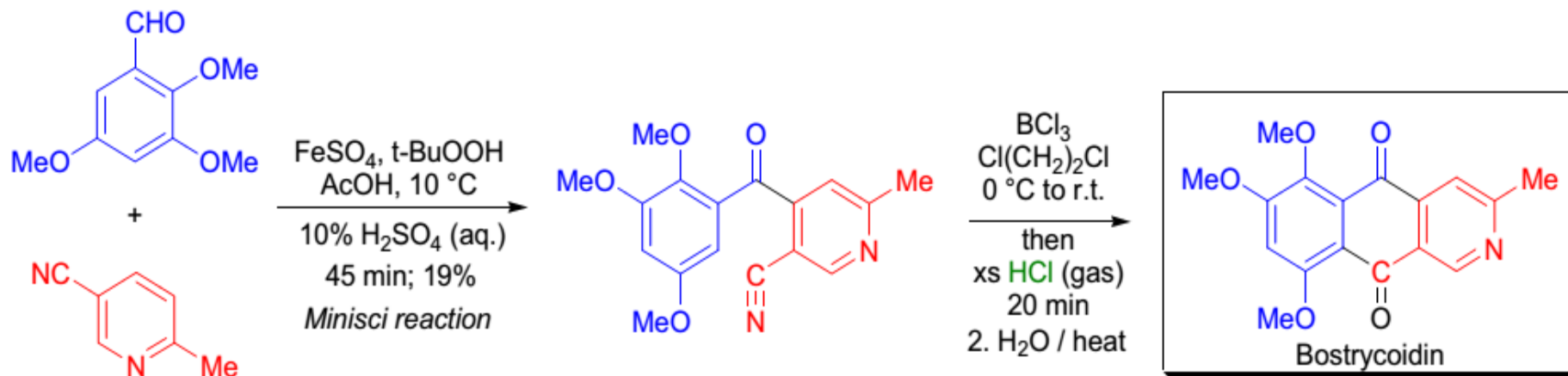
The mechanism is not fully understood, but it is very similar to the mechanism of the Gattermann-Koch formylation.

The first step is the formation of a nitrilium chloride that is subsequently transformed to an imino chloride from which the reactive species, the iminium ion is generated.

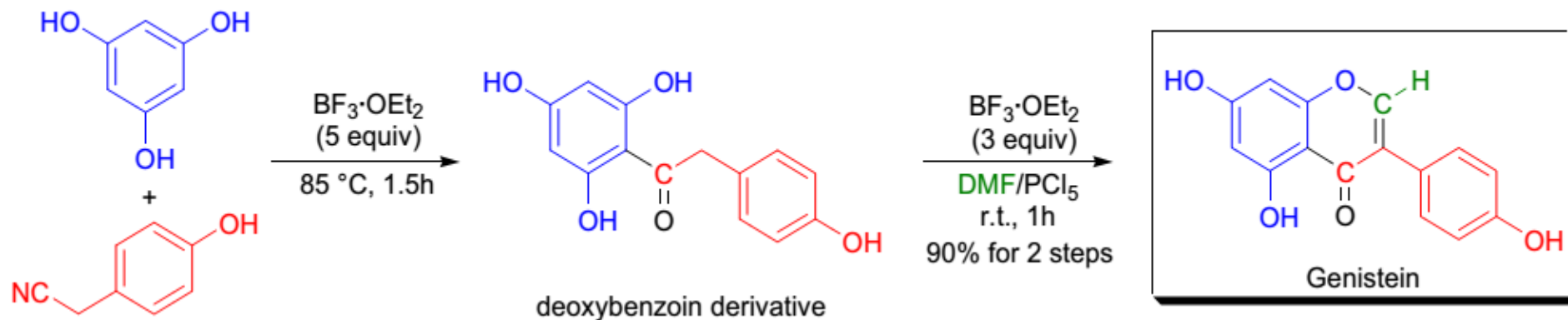


- Synthetic Applications:

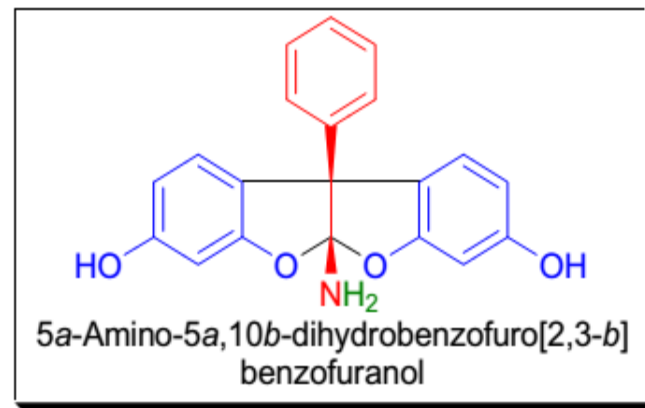
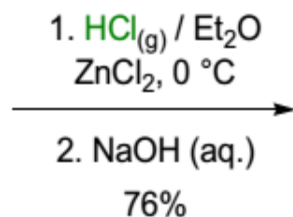
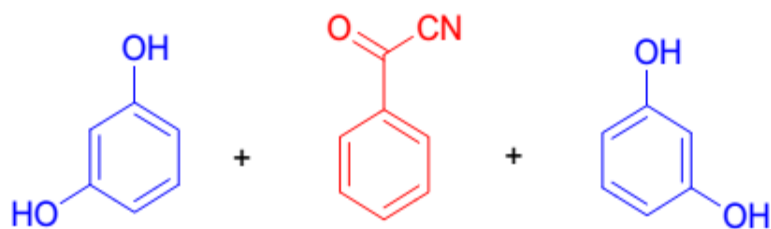
In the laboratory of D.W. Cameron the total synthesis of the azaanthraquinone natural product bostrycoidin was undertaken using the Minisci reaction and the intramolecular Houben-Hoesch reaction as the key steps.²² It is worth noting that the synthesis of specific di- and trihydroxyazaanthraquinones by the Friedel-Crafts acylation is very limited due to the lack of orientational specificity and the lack of reactivity of pyridine derivatives in acylation reactions.



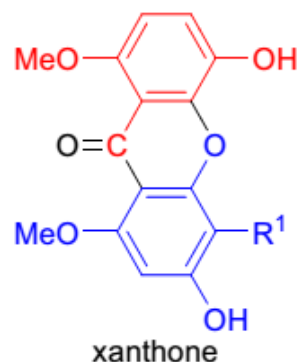
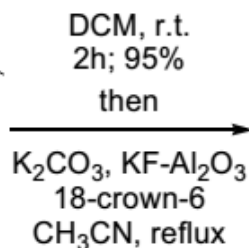
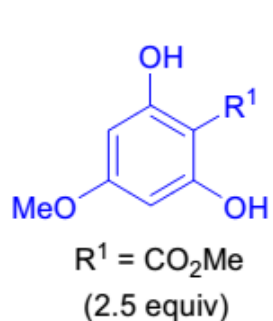
- Genistein (4',5,7-trihydroxyflavone) is an important nutraceutical molecule found in soybean seeds, and it has a wide range of pharmacological effects.²³ The two-step total synthesis of genistein was achieved by M.G. Nair et al. using the Houben-Hoesch reaction to acylate phloroglucinol with p-hydroxyacetonitrile.²⁴ The resulting deoxybenzoin was treated with DMF/PCl₅ in the presence of BF₃·OEt₂ to give genistein in 90% yield. The DMF/PCl₅ mixture was the source of the [(Me₂N=CHCl)⁺Cl⁻] reagent. This synthetic sequence was suitable for the large scale (~1 metric ton) one-pot preparation of the natural product.



- Nitriles having electrophilic or leaving groups in their - or -positions often lead to so-called “abnormal” HoubenHoesch products besides the expected “normal” acylation products. Especially notorious is the reaction of -oxonitriles with phenols that afford exclusively 2H-1-benzopyran-2-one derivatives instead of the expected 1,2-diketones. -Halogenonitriles react with phenols to give the expected 3-benzofuranone and also the abnormal 2-benzofuranone. R. Kawecki and co-workers found that the condensation of phenols with aromatic -hydroxyiminonitriles or -oxonitriles under the Hoesch conditions leads to benzofuro[2,3-b]benzofuran derivatives.²⁵



- The synthesis of 11-hydroxy O-methylsterigmatocystin (HOMST) was carried out in the laboratory of C.A. Townsend by utilizing the alkylnitrilium ion variant of the Houben-Hoesch reaction.¹⁷ The alkylnitrilium salt was prepared by reacting the aryl nitrile with 2-chloropropene in the presence of SbCl_5 . Next, the phenol was added in a 2.5:1 excess. Alkaline hydrolysis then afforded the xanthone, which was subsequently converted to HOMST in few more steps.



steps

