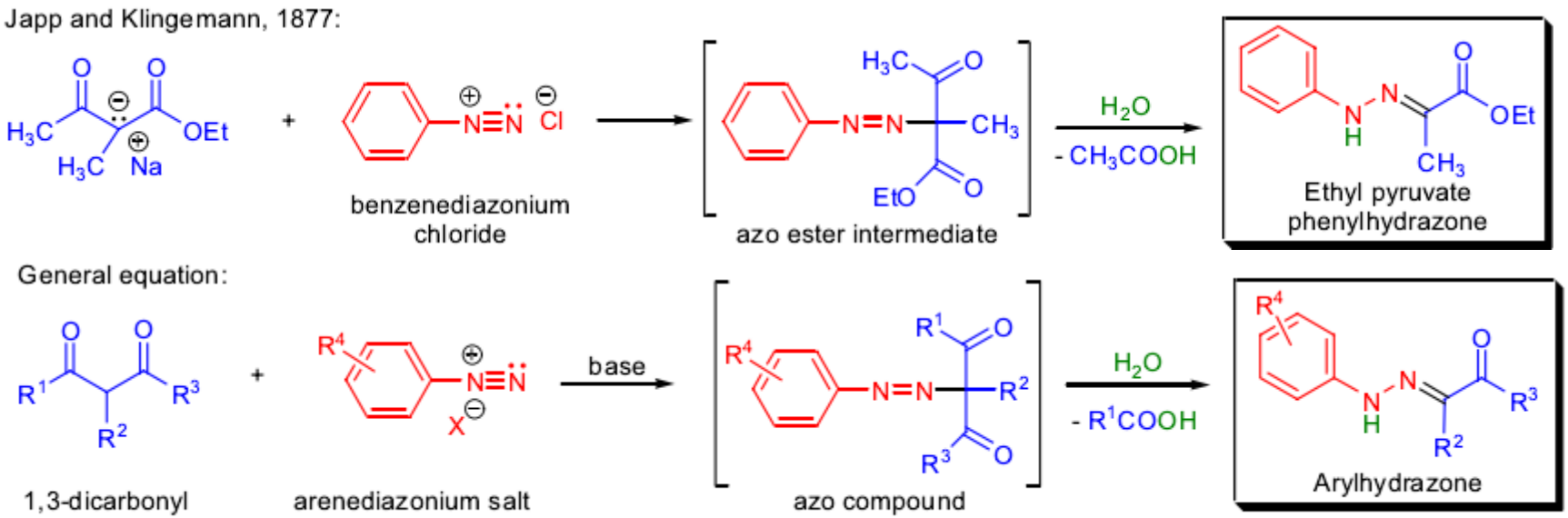
JAPP-KLINGEMANN REACTION

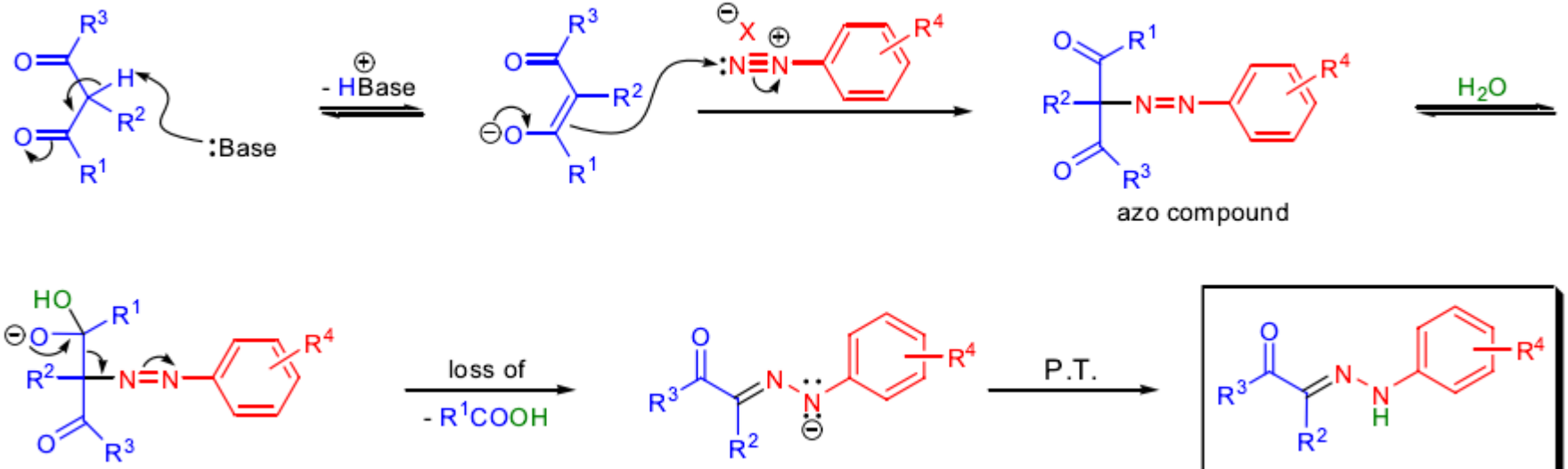
Liangleiming
20151124

In 1887, F.R. Japp and F. Klingemann attempted to prepare an azo ester by coupling benzenediazonium chloride with the sodium salt of ethyl-2-methylacetoacetate.However, the isolated product turned out to be the phenylhydrazone of ethyl pyruvate, which contained two carbon atoms less than the expected azo ester. Subsequent experiments showed that the reaction was general and the initial coupling product was the azo ester, which was unstable under the reaction conditions and it rapidly rearranged to the phenylhydrazone with loss of the aliphatic acyl group. The coupling reaction between aryldiazonium salts and 1,3-dicarbonyl compounds to yield arylhydrazones is known as the Japp-Klingemann reaction.



R^1 = alkyl, aryl; R^2 = H, alkyl, aryl, acyl, CN, Cl, Br; R^3 = *O*-alkyl, *O*-aryl, OH; R^4 = electron-withdrawing or electron-donating groups

Mechanism: [12-21]



Features:

1 :The substituted arenediazonium salts are prepared from the corresponding o-, m-, and p-substituted anilines via diazotization (treatment with HNO2);

2: the reaction works for compounds having an acidic C-H bond between two or three electron-withdrawing groups (e.g., substituted β-diketones, β-keto esters, malonic esters, cyanoacetic esters, or alkali salts of their corresponding acids);

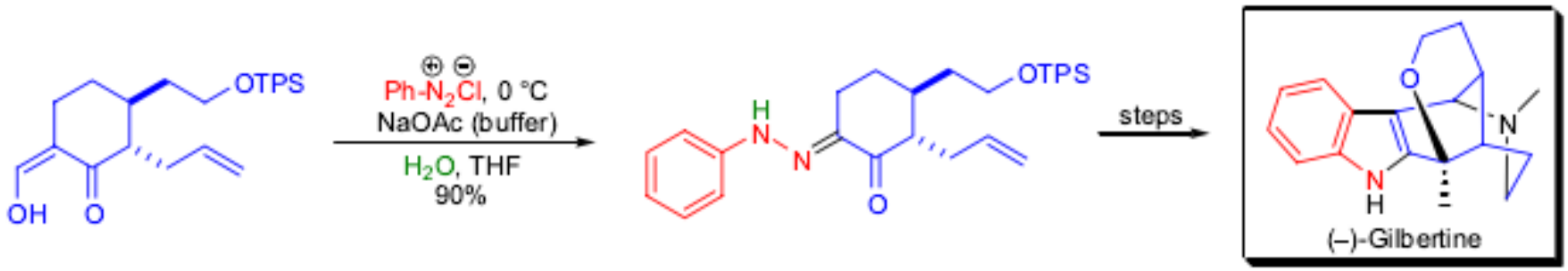
3: if the coupling is carried out with the alkali metal salt of a β-keto acid, the carboxylate anion will undergo decarboxylation (CO2 is lost) to give the arylhydrazone of the corresponding 1,2- diketone;

4: when a mixed β-diketone (having both an aliphatic and an aromatic acyl group) is used, the aliphatic acyl group will be cleaved preferentially;

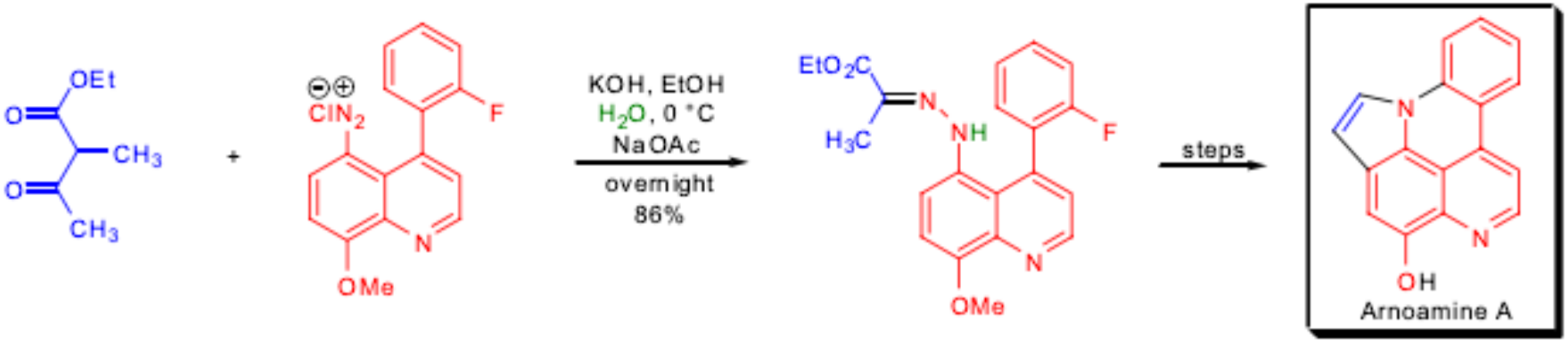
5: when acyl derivatives of acetoacetic esters are used (R2=acyl), the products are the monoarylhydrazones of α,β-diketo esters;
6: cyclic β-keto esters undergo ring-opening in the second stage of the reaction;
7: alkali metal salts of cyclic β-keto acids are not opened, but rather they undergo decarboxylation to give 1,2-diketone monoarylhydrazones;
8: the coupling is usually carried out in acidic or basic aqueous medium at 0° C and if solubility of the substrate is poor, ethanol or methanol is added;
9:under basic conditions both stages of the reaction take place, whereas under acidic conditions the azo compound can be isolated, and it has to be treated with a mild base to bring about the rearrangement;
10: the rate of the reaction depends on the C-H acidity of the 1,3- dicarbonyl compound and the more activated compounds tend to react faster;
11: excess diazonium salt leads to numerous decomposition products, so the use of one equivalent is advised;
12: the reaction is easy to monitor visually, since the intermediate azo compounds are more highly colored than the product arylhydrazones;
13: themain use of arylhydrazones is as substrates for the Fischer indole synthesis as well as for the synthesis of enantiopure amino acids.

Synthetic Applications:

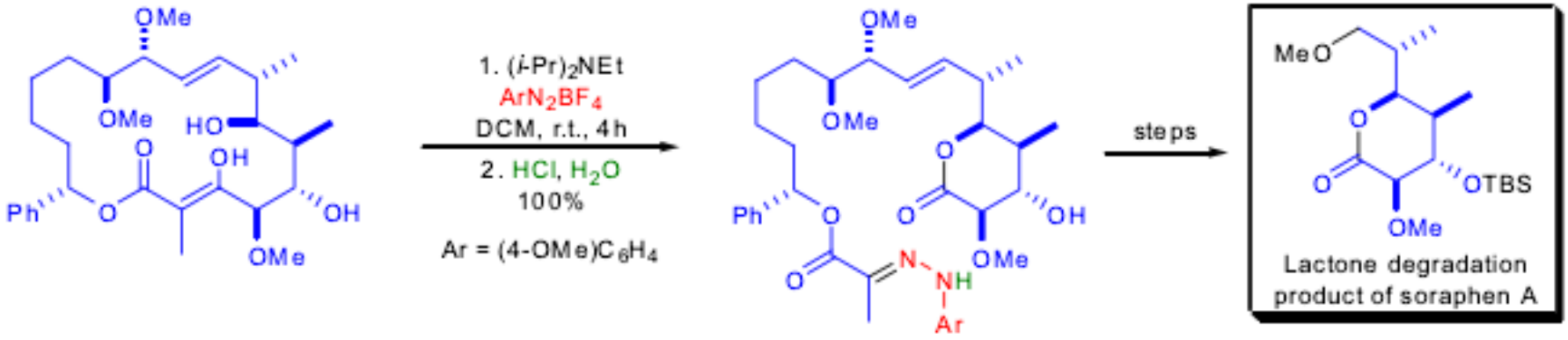
The first enantioselective total synthesis of (–)-gilbertine was accomplished by S. Blechert and co-workers using a *cationic cascade cyclization* as the key step.[22] The indole moiety was introduced by first applying the *modified Japp-Klingemann reaction* on a substituted formylcyclohexanone precursor followed by the *Fischer indole synthesis* of the resulting phenylhydrazone. The benzenediazonium chloride was prepared prior to the reaction by treating aniline with concentrated HCl/ aqueous $NaNO_2$. Then the strongly acidic solution was buffered by the addition of NaOAc before the formylcyclohexanone derivative was added. The buffering increased the yield of the phenylhydrazone from 10% to 90%!



The *Japp-Klingemann reaction* was the key step during the first synthesis of the pentacyclic pyridoacridine marine cytotoxic alkaloid arnoamine A by E. Delfourne et al.[23] The diazonium salt was added to a vigorously stirred solution of ethyl-2-methyl-3-oxobutyrate in ethanol containing KOH, NaOAc and water. The resulting hydrazone was exposed to polyphosphoric acid to form the indole ring.



The macrolide soraphen A was shown to exhibit potent fungicidal activity against a variety of plant pathogenic fungi. In the laboratory of J.-L. Sinnes, a new approach was undertaken in which the natural product was degraded to a key lactone, which was used to build several simplified analogs of soraphen A.[24] The key degradation step was the *Japp-Klingemann reaction* of the macrocyclic β-keto ester in its enol form. Treatment of this enol with 4-(methoxyphenyl)diazonium tetrafluoroborate under mildly basic conditions resulted in the quantitative cleavage of the C-C bond of the macrocycle. Since the natural product was very sensitive to strong acids and bases, this approach was a mild alternative to a *retro-Claisen reaction*, which would have required the use of strongly acidic or basic conditions.



A new heterocyclic ring system, 5*H*,12*H*-[1]Benzoxepino[4,3-*b*]indol-6-one, was prepared by the *Fischer indole cyclization* of a substituted benzoxepin-5b-one phenylhydrazone by G. Primofiore and co-workers.[25] The phenylhydrazone precursor was prepared *via* the *Japp-Klingemann reaction* of the corresponding 3,4-dihydro-4-hydroxymethylene[1]benzoxepin-5(2*H*)-one.

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Practical Methodologies for the Synthesis of Indoles

Guy R. Humphrey* and Jeffrey T. Kuethe*

Department of Process Research, Merck & Co., Inc., Rahway, New Jersey 07065

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2.3. Via Japp–Klingemann Reaction

The Japp-Klingemann reaction provides a very useful alternative route to a number of arylhydrazones employedin the Fischer indolization process (Scheme20).36When aryldiazonium salts 101 are treated directly with –ketoesters 102, deacylation is followed by indole formation to giveindole-2-carboxylate esters 106.37

Alternatively, if a -ke-toacid 103 is used, decarboxylation occurs and a 2-acylindole 107 is formed.38The Japp-Klingemann procedure avoids the formation and use of arylhydrazines, which can be difficult to prepare and handle in some cases.