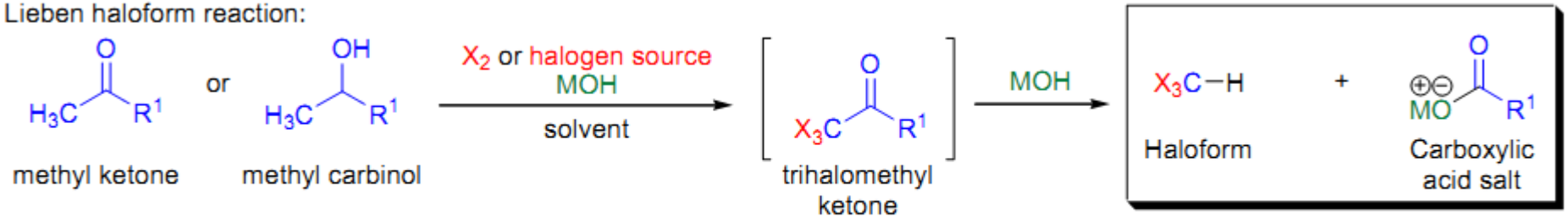
LIEBEN HALOFORM REACTION

Lieben haloform reaction:



methyl ketone | methyl carbinol | trihalomethyl ketone | Haloform | Carboxylic acid salt

R^1 = H, alkyl, aryl; X_2 = Cl_2, Br_2, I_2; halogen source: NaOCl, NaOBr, NaOI, ICN; X_3C = F_3C, Cl_3C,Br_3C, I_3C; MOH = NaOH, KOH; solvent: H_2O, dioxane/H_2O, THF/MeOH

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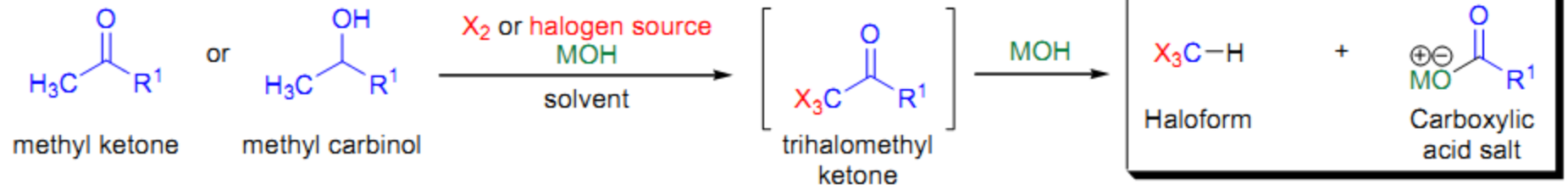

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- Compounds containing the methyl ketone (CH_3-CO) functional group or compounds that get oxidized under the reaction conditions to methyl ketones will undergo the transformation;

- In addition to methyl ketones and methyl carbinols, mono-, di-, and trihalogenated methyl ketones also give rise to haloforms;

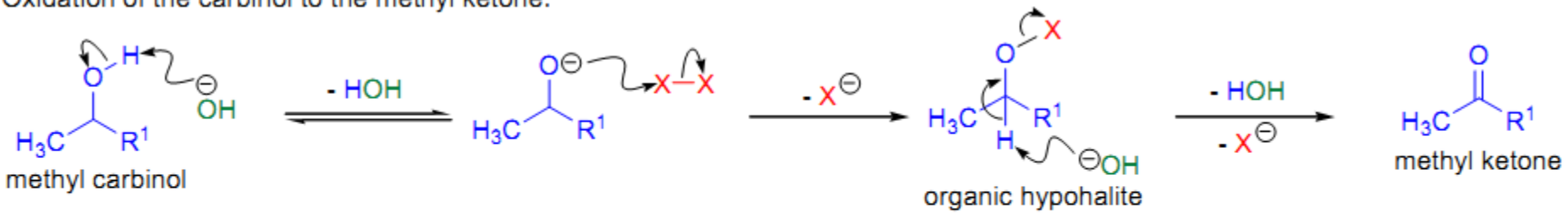
- The reaction is usually conducted in aqueous alkali, but for compounds that are insoluble in water the addition of a co-solvent such as dioxane or THF is necessary;

- The reaction is sensitive to steric hindrance, so when the R1 group is bulky, the hydrolysis of the trihalomethyl ketone usually does not take place, and the reaction stops;

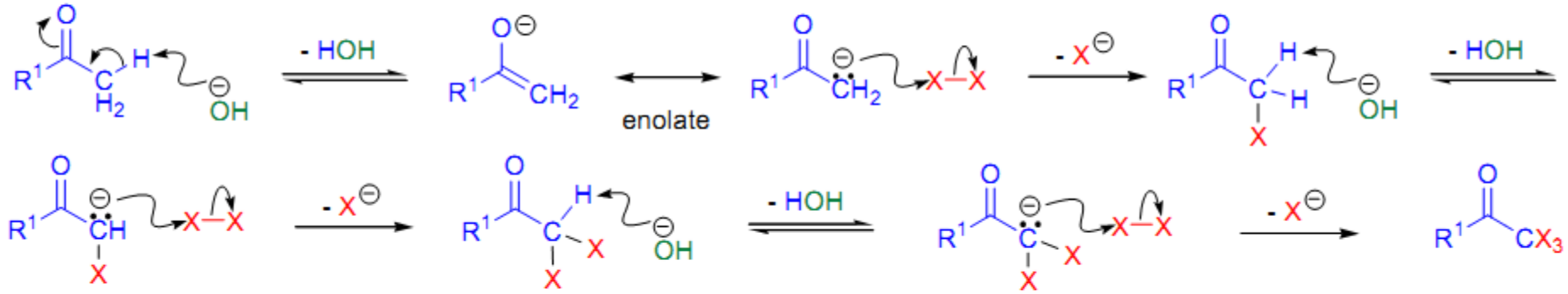
- Certain side reactions such as the α-halogenation and subsequent cleavage of the other alkyl group is possible.

Mechanism

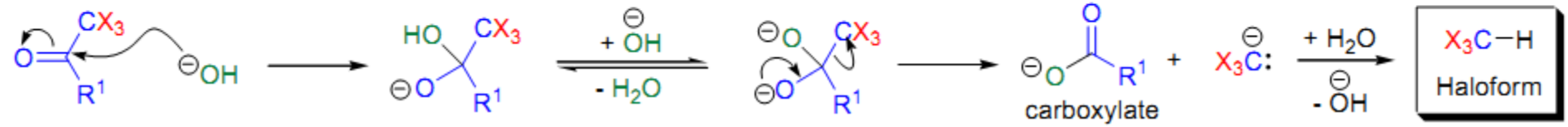
Oxidation of the carbinol to the methyl ketone:



Sequential halogenation of the methyl group:



Hydrolysis of the trihalomethyl ketone:



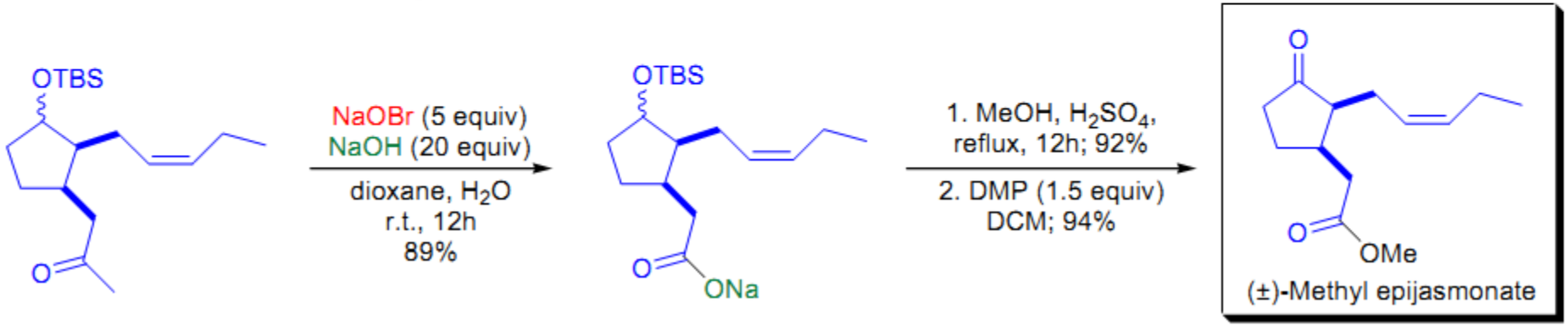
Iodoform test

When iodine and sodium hydroxide are used as the reagents, a positive reaction gives iodoform. Iodoform (CHI_3) is a pale-yellow substance. Due to its high molar mass caused by the three iodine atoms, it is solid at room temperature. It is insoluble in water and has an antiseptic smell. A visible precipitate of this compound will form from a sample only when either a methyl ketone, ethanal, ethanol, or a methyl secondary alcohol is present.

Negative and positive iodoform test

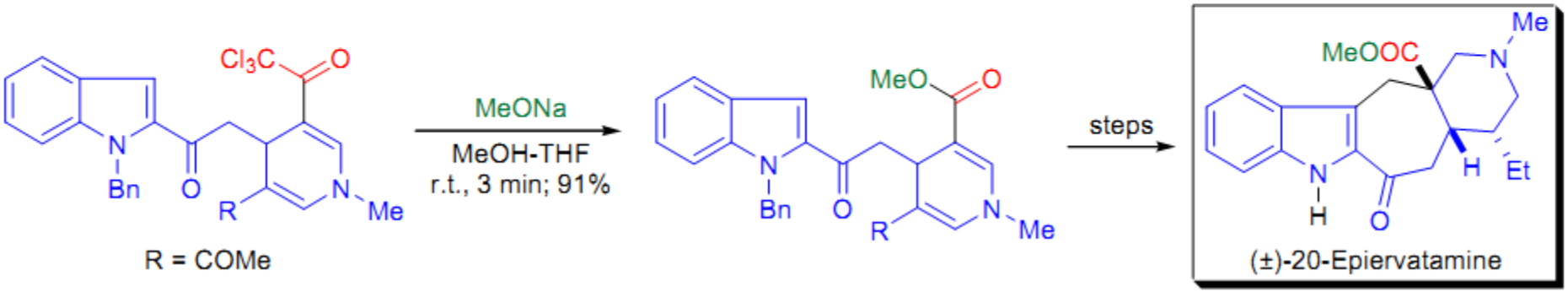
Synthetic Applications

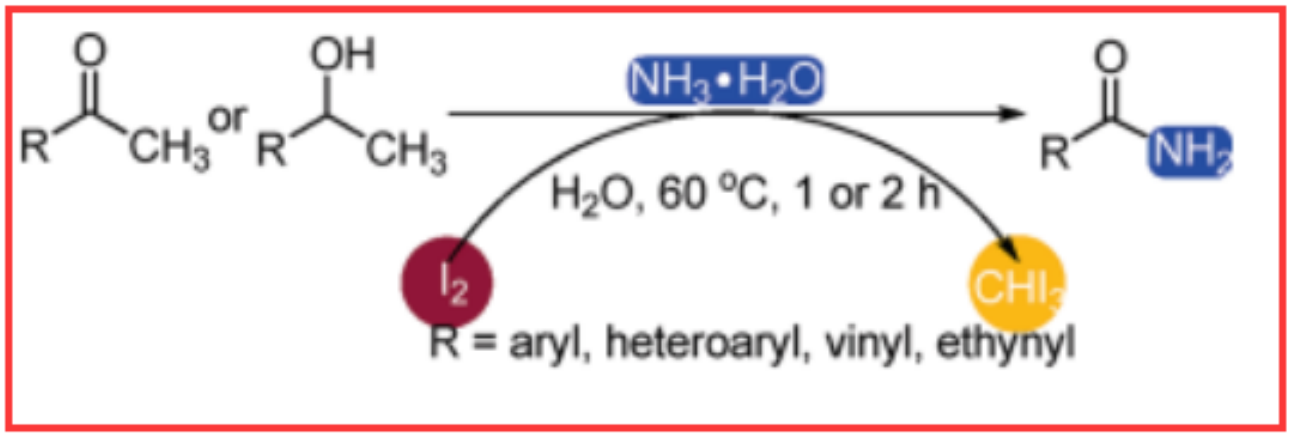
The blossoms of many flowers contain methyl jasmonates that are frequently used as ingredients in perfumes. It is noteworthy that the methyl epi-isomers have greater biological activity, and they play a role in inducing gene expression, mediate plant defense mechanisms, and signal transmission. The total synthesis of (±)-methyl epijasmonate was undertaken by H.C. Hailes and co-workers, who used a highly regioselective *Diels-Alder reaction* to install the required 2,3-*cis* stereochemistry.[18] After the ozonolysis of the cyclohexene double bond, the resulting methyl ketone moiety had to be transformed to a methyl ester, which was accomplished by using the *Lieben haloform reaction*. The aqueous solution of sodium hypobromite (prepared by adding Br_2 to sodium hydroxide) was slowly added to the solution of substrate in dioxane. The resulting carboxylate salt was converted to the methyl ester using *Fischer esterification* conditions under which the silyl protecting group was also removed. A final *Dess-Martin oxidation* furnished the natural product.



Synthetic Applications

The biomimetic total synthesis of (±)-20-epiervatamine was accomplished by J. Bosch et al.[20] The authors used the addition of 2-acetylindole enolate to a 3-acylpyridinium salt as akey step to connect the two main fragments. The *in situ* formed 1,4-dihydropyridine was trapped with trichloroacetic anhydride to afford the corresponding trichloroacetyl-substituted 1,4-dihydropyridine derivative. The conversion of the trichloroacetyl group to a methyl ester was achieved by treatment with sodium methoxide. This transformation can be regarded as the second step of the *haloform reaction*.





Org. Lett., 2009, 11, 3810-3813.