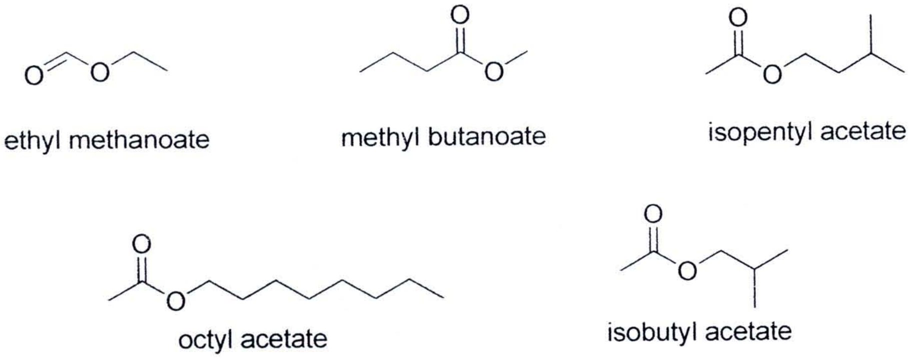
CHAPTER I

INTRODUCTION

1. Esters

Esters, which are widely found in nature, are carboxylic acid derivatives. Esters with low molecular weight are commonly used as fragrances. They are found in essential oils and fruity odors. In most cases, the characteristic flavors and fragrances of fruits are shown below. For example, ethyl methanoate has been isolated from rum truffle of chocolate[1], methyl butanoate is a fragrance of pineapple, isopentyl acetate is a constituent of banana oil[2], octyl acetate is an orange fragrance and isobutyl acetate is the odor of strawberry[3] as shown in Figure 1.1.



ethyl methanoate

methyl butanoate

isopentyl acetate

octyl acetate

isobutyl acetate

Figure 1.1 Esters from fruits

Many natural occurring fats and oils are the fatty acid esters of glycerol such as propane-1,2,3-triyl tripalmitate is a fat of coconut oil. The chemical industry uses esters for a variety of purposes. For example, ethyl acetate is a common solvent for nail-polish remover and dialkyl phthalates are employed as plasticizers which keep plastics from turning brittle[4-5] as shown in Figure 1.2.

propane-1,2,3-triyl tripalmitate

dibutyl phthalate (a plasticizer)

Figure 1.2 Structural of propane-1,2,3-triyl tripalmitate and dibutyl phthalate

2. Preparation of esters

Esters can be prepared by various methods basically from alcohols and carboxylic acids or their derivatives such as acid chlorides, acid anhydrides and esters as shown in Figure 1.3.

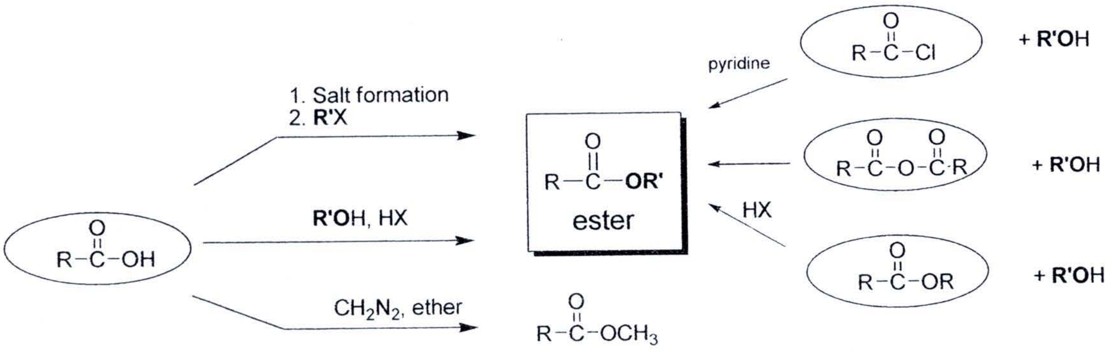


Figure 1.3 Preparation of esters

2.1 Fischer esterification[6-8]

The classical method of ester synthesis is the Fischer esterification which involves treating a carboxylic acid with an alcohol in the presence of a dehydrating agent.

$$\mathrm{RCOOH} + \mathrm{R'OH} \xrightleftharpoons{\text{conc. } H_2SO_4} \mathrm{RCOOR'} + H_2O$$

Strong acids, such as sulfuric acid catalyzes this reaction which is highly reversible. The simple reaction of one equivalent each of acid and alcohol gives a mixture of starting materials and products.

2.2 Reaction of acyl chlorides or acid anhydrides with alcohols

More efficient method for ester syntheses could be achieved by allowing alcohols to react with acyl chlorides or acid anhydrides.

$$RCOCl + R'OH \longrightarrow RCOOR' + HCl$$

$$(RCO)_2O + R'OH \longrightarrow RCO_2R' + RCO_2H$$

These reactions are rapid and irreversible, thus, simplifying the work-up. However, acyl chlorides and acid anhydrides are so moisture sensitive that anhydrous conditions are required.

2.2.1 Reaction of acyl halide and alcohol

The reaction of an acyl halide with an alcohol is a common reaction that usually is very rapid due to the high reactivity of the acyl halide. It is normally performed at low temperature, but for the same reason it tends to be difficult to control, often resulting in a mixture of low purity products and a high percentage of by-products. A non-nucleophilic weak base can be used to neutralize the produced hydrogen halide in order to prevent side reactions caused by acidity. Synthesis of ethyl benzoate by using benzoyl chloride and ethyl alcohol in the presence of pyridine is shown in Figure 1.4.[9]

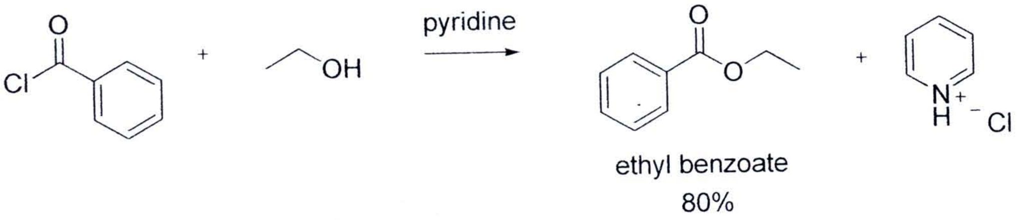


Figure 1.4 Synthesis of ethyl benzoate

2.2.2 Reaction of acid anhydride and alcohol

The reaction of an acid anhydride with an alcohol also gives ester in good yield. This method is suitable for the synthesis of phenyl esters as exemplified by the synthesis of aspirin[10] shown in Figure 1.5. However, it is not a very efficient ester synthetic method with respect to the acid.

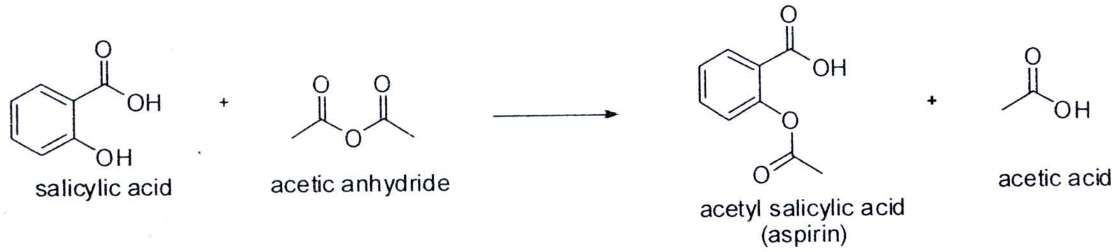


Figure 1.5 The synthesis of aspirin

2.3 Transesterification[11-13]

Transesterification is the process of exchanging the alkoxy group OR' of an ester with the alkoxy group OR" of an alcohol. This reaction is often catalyzed by the addition of an acid. In this procedure, the equilibrium reaction can be shifted to the right by distilling off the low boiling alcohol from the reaction mixture as shown in Figure 1.6.

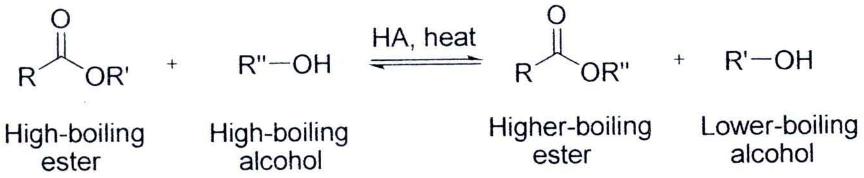


Figure 1.6 Transesterification

2.4 Reaction of carboxylic acid and diazomethane

The reaction of a carboxylic acid with diazomethane usually gives a quantitative yield of the methyl ester. However, diazomethane is a toxic explosive gas which almost always prepared just prior to the time it is needed. The reaction of cyclohexane carboxylic acid with diazomethane shown in Figure 1.7 gives methyl cyclohexanecarboxylate in a quantitative yield.[14]

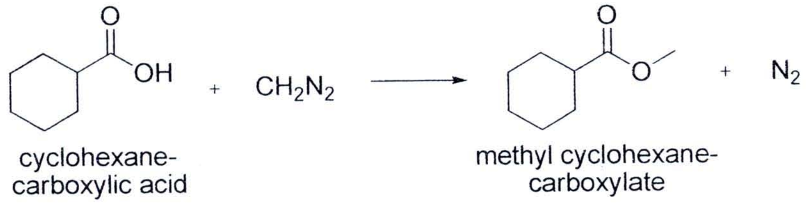


Figure 1.7 The synthesis of methyl cyclohexanecarboxylate

2.5 Alkylation of carboxylate salts[15-17]

The reaction of an alkali carboxylate and an electrophilic alkylating agent such as an alkyl halide gives ester. This is not a reversible reaction and therefore can run to completion naturally. In the case that an alkyl chloride is used, an iodide salt may be added to catalyze the reaction (Finkelstein reaction). The carboxylate salt may be generated *in situ* or prior to the reaction. In difficult cases, the silver carboxylate may be used, since the silver ion coordinates to the halide aiding its departure and improving the reaction rate. This reaction can suffer from anion availability problems and therefore can benefit from the addition of phase transfer catalysts or highly polar aprotic solvents such as DMF. As an example, the reaction of potassium 2,4,6-trimethylbenzoate with ethyl iodide is shown in Figure 1.8.[16]

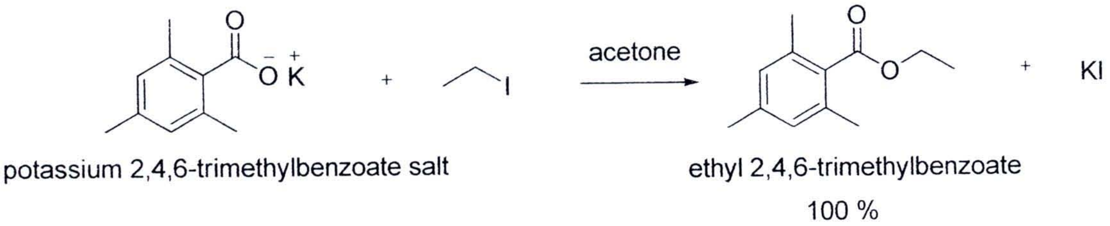


Figure 1.8 The synthesis of ethyl-2,4,6-trimethyl benzoate

2.6 Steglich esterification[18-19]

The Steglich esterification is the method of forming esters under mild conditions. It is especially popular in peptide synthesis, where the substrates are sensitive to harsh conditions like high heat. DCC is used to activate the carboxylic acid to further reaction. DMAP is used catalytically as an acyl-transfer agent as shown in Figure 1.9.

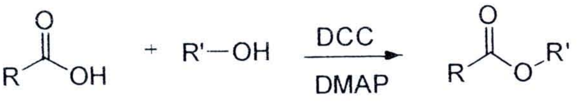


Figure 1.9 Steglich esterification

The well established and very common route for ester preparation is now the treatment of carboxylic acid derivatives such as acid chlorides or acid anhydrides with alcohols. Good to excellent yield of the products could be obtained from these methods although the handling of those reagents can cause problems due to the highly reactive nature of the compounds which usually are sensitive to the moisture and sometime commence violent reactions. In order to avoid such drawbacks, new catalysts for Fischer esterification have been developed.[20-24] All give excellent yields of esters but the reactions are usually performed in rather acidic condition and take a very long time to completion as shown in Figure 1.10.

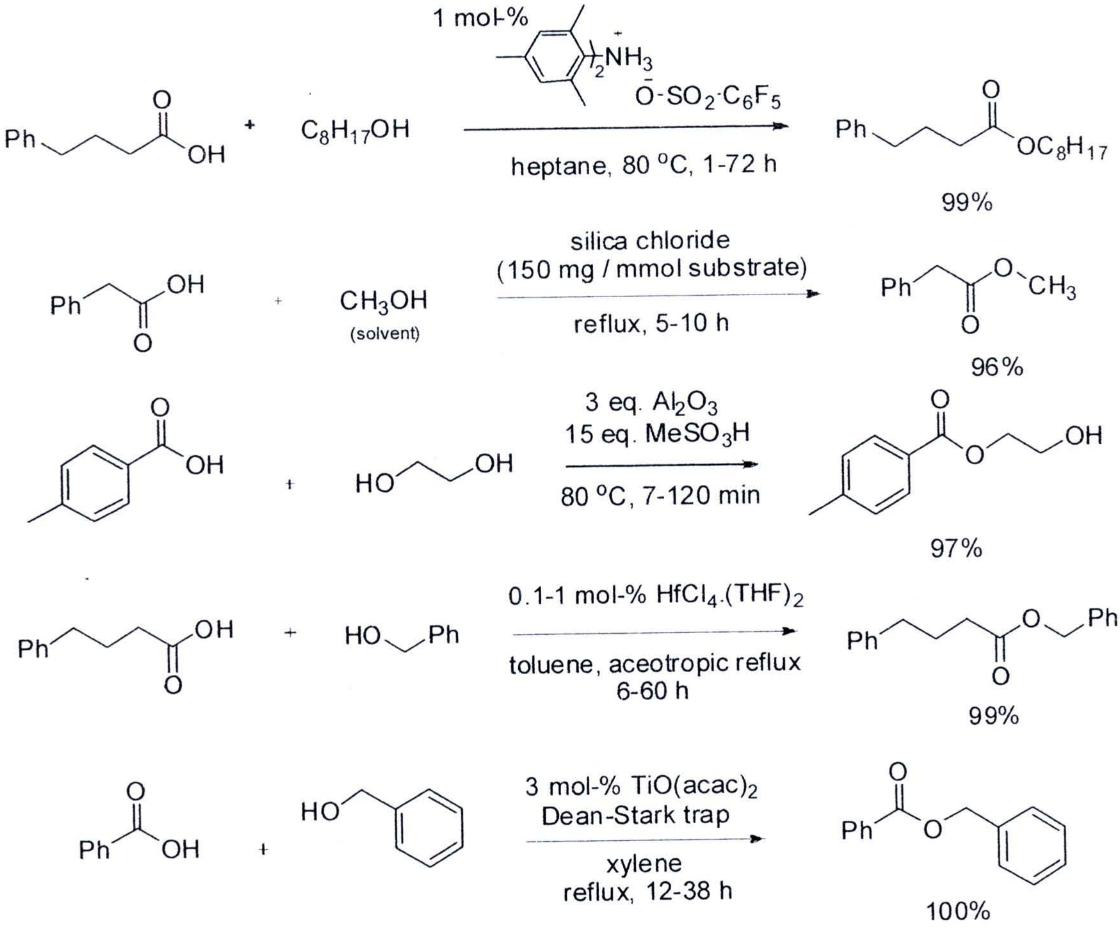


Figure 1.10 Modified Fischer esterifications employing newly developed catalysts

Apparently, it was found that esterification could possibly be carried out under neutral or basic condition by using benzotriazole as an acyl transfer reagent.[25] The advantage of this methodology is due to the fact that benzotriazole ring is very stable and acts as a good leaving group which expands the scope of acylation to a great extent.

3. Benzotriazoles and their derivatives in organic synthesis

Benzotriazole mediated synthetic methodology has been developed rapidly and has now become an important synthetic tool for many chemical processes, including multistep preparations of drugs, biologically active compounds and synthetic analogs of natural products.[26-28] Much of its attractiveness lies in its ability to be readily introduced and easy to remove or displace during syntheses, as well as its ability to activate other parts of the molecule. Benzotriazole and many of its derivatives are obtained from diazotized *o*-phenylenediamine or an appropriately substituted derivative. The third triazole nitrogen may be supplied by a diazonium salt instead of nitrous acid as shown in Figure 1.11.

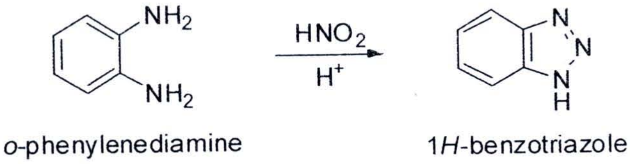


Figure 1.11 Diazotization of *o*-phenylenediamine

The multifaced nature of benzotriazole intermediates is embeded in their versatile electronic character, in many cases the benzotriazole heteroring can act as an electron-donating or electron-withdrawing moiety, depending on the type of substituent that is attached to nitrogen. Many applications of benzotriazoles depend both on the good leaving ability of the benzotriazole moiety upon displacement with nucleophiles, and on the α-proton acidity enhancement[29] as shown in Figure 1.12.

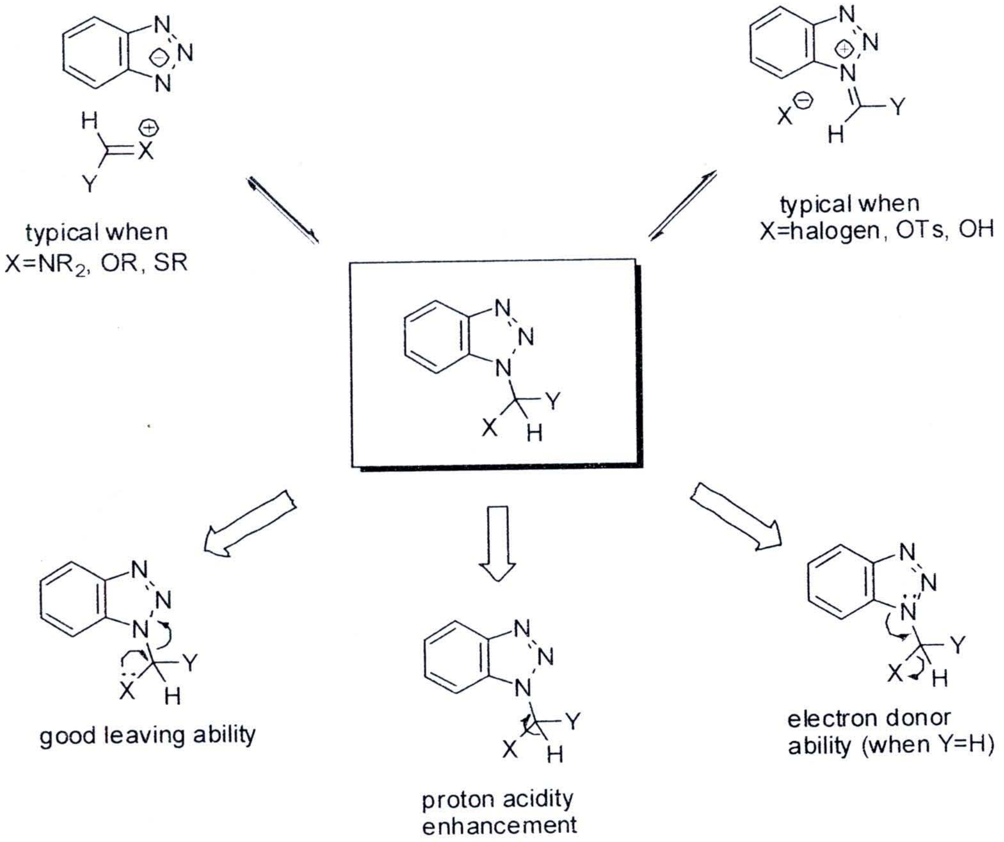


Figure 1.12 Synthetic tool of benzotriazole for many chemical processes

Furthermore, benzotriazole substitution has been reported. 4(7)-Nitrobenzotriazole could be obtained in 30 % yield[30] by treating benzotriazole with a mixture of HNO_3 and H_2SO_4 as shown in Figure 1.13.

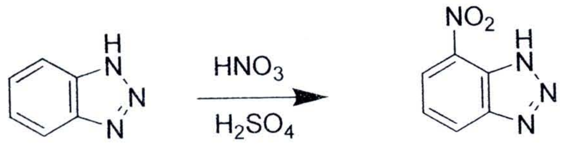


Figure 1.13 Preparation of 4(7)-nitrobenzotriazole

The iodination of benzotriazole can be done by using butyl lithium in tetrahydrofuran in the presence of tetraglyme, follow by lithium-cerium exchange with cerium(III)chloride, subsequent iodination using 1,2-diiodoethane leads to the 7-iodo derivative in 95 %yield[31] as shown in Figure 1.14.

Figure 1.14 Iodination of benzotriazole

4. *N*-Acylbenzotriazoles as acylating agents

4.1 Synthesis of *N*-acylbenzotriazoles

Alan R. Katritzky[32] had extensively studied several methods for the preparation of *N*-acylbenzotriazoles from benzotriazole and carboxylic acids or acid chlorides to give *N*-acylbenzotriazoles as shown in Figure 1.15 and Table 1.1.

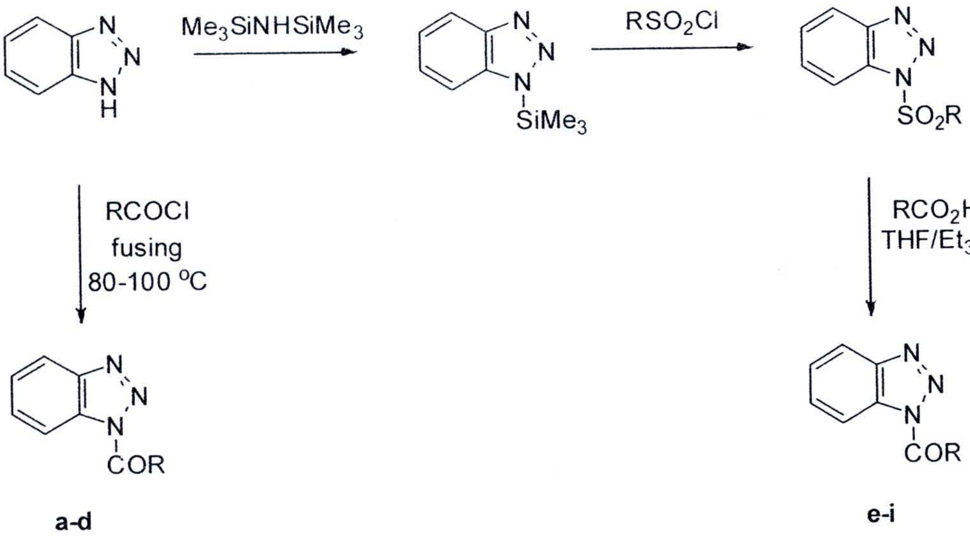


Figure 1.15 Preparation of *N*-acylbenzotriazoles

Table 1.1 Acylbenzotriazoles prepared by Katritzky's methods

	R	yield (%)	mp (°C)	recryst.sovent
a	Me	70	51-52	aq.MeOH
b	Et	90	80-82	EtOH
c	n-Bu	79	42-44	MeOH
d	Ph	90	112-113	MeOH
e	2-Py	90	97-100	$CHCl_3$/hexane
f	3-Py	92	86-89	$CHCl_3$/hexane
g	4-Py	80	148-150	$CHCl_3$/hexane
h	2-pyrrolyl	80	161-162	MeOH
i	2-furanyl	95	172-174	MeOH

It should be noted that Katritzky did not get esters from acylbenzotriazoles even though alcohols were used as recrystallizing solvents.

4.2 Acylation using *N*-acylbenzotriazoles

Benzotriazole has been commonly employed as a leaving group and used extensively as a novel synthetic auxiliary.[33] Generally, *N*-acylbenzotriazoles are more stable than acid chlorides and can be used in many acylation reactions, often without diacylation or other side reactions that may complicate the traditional methods. These mild, regioselective and regiospecific reagents provide excellent alternatives to Friedel-Crafts and Vilsmeier-Haack acylation methodologies, and can be employed when the corresponding acid chlorides are not readily available. Recent facile acylations achieved with *N*-acylbenzotriazoles have led to the synthesis of 3-acylindoles and 2- or 3-acylpyrroles[34], α-substituted β-ketonitriles[35], β-oxo-sulfones[36], primary, secondary or tertiary amides[37-39], oxazolines and thiazolines[40], β-keto esters and β-diketones[41], and α-nitroketones[42] as shown in Figure 1.16.

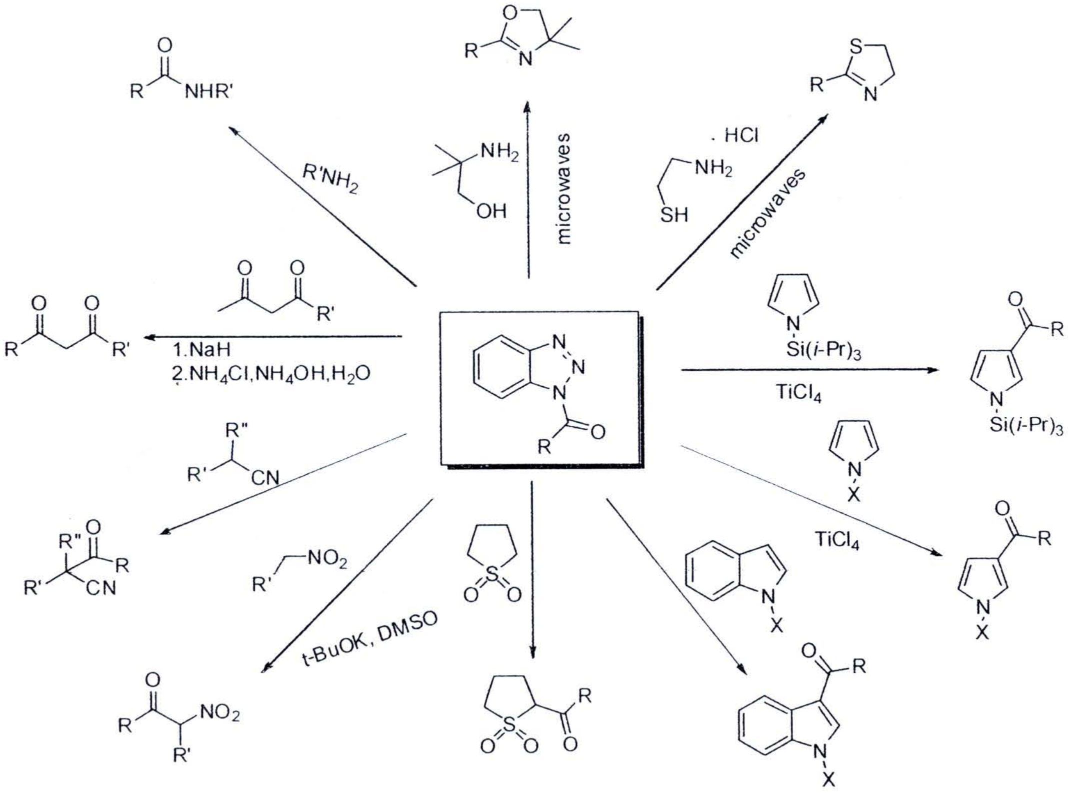


Figure 1.16 *N*-Acylbenzotriazoles in organic synthesis

Furthermore, 1,2-diketones can be synthesized in moderate to excellent yields when *N*-acylbenzotriazoles are treated with SmI_2 in THF. If acetonitrile is used as the solvent instead, a ring-opening reaction occurs, resulting in the formation of 1-acylamido-2-alkyl-(or aryl-)benzimidazoles[43] as shown in Figure 1.17.

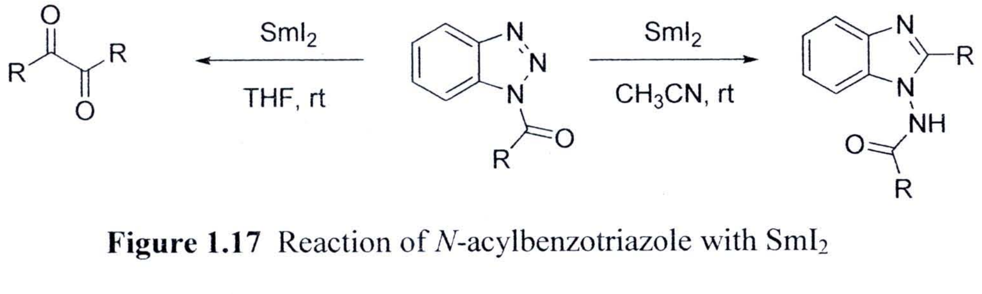


Figure 1.17 Reaction of *N*-acylbenzotriazole with SmI_2

C-Acylation of acetoacetic esters, followed by spontaneous deacetylation, lead to useful preparative methods for homologated acetic esters. Similar treatment of acetonyl ketones affords a variety of *β*-diketones[44] as shown in Figure 1.18.

Figure 1.18 *C*-Acylation of acetoacetic ester

Common route for ester synthesis is the treatment of a carboxylic acid with alcohol in the presence of an acid catalyst such as concentrated sulfuric acid. However, the reaction takes a long period of time to reach its equilibrium and large excess of reagent is unavoidable in order to get an ester in high yield. Although activation of carboxylic acids such as acid chlorides or acid anhydrides gives better results, they suffer from the problems of reagent handling and manipulating the reaction due to the highly reactive nature of the reagents. Exothermic reactions are always encountered and anhydrous conditions are required. Eventhough Katritzky's ester synthesis via *N*-acylbenzotriazole[45] shows very promising results, it also suffers from the highly basic condition which also required an inert atmosphere during the course of reaction. Acylation under neutral condition was possible only under the influence of microwave radiation and using large excess of alcohols as shown in Figure 1.19.

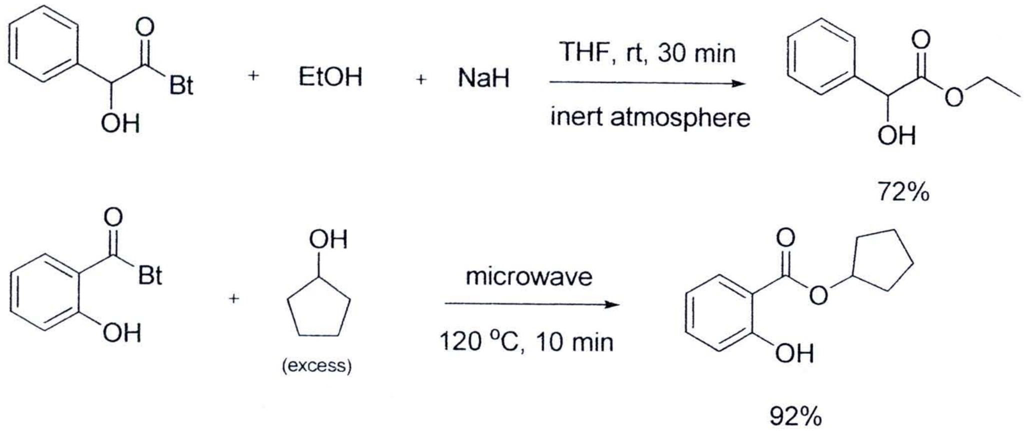


Figure 1.19 Katritzky's ester synthesis via *N*-acylbenzotriazole

In order to overcome these difficulties we have developed a much milder and simple method for ester synthesis using *N*-acylbenzotriazoles and their derivatives as acylating agents which are stable solids that can easily be stored, handled and manipulated as will be shown in the next section.