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N-Acylation in non-aqueous and aqueous medium- method of amide synthesis in non-peptide compounds

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ABSTRACT

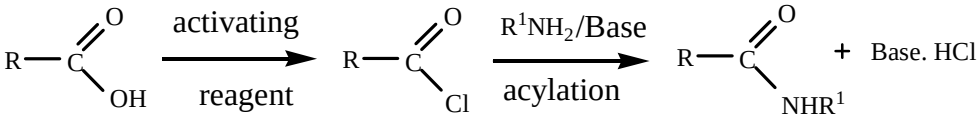
N-acylation in non-aqueous and aqueous medium i.e. Schotten-Baumann method of amide synthesis with carboxylic acid activating reagent such as thionyl chloride and Phosphine-halogen reagents have been discussed. Limitations, alternatives and applications of these reagents are illustrated.

Key words: Activating reagents, N-acylation, Appel's salt, 4-picoline, steric effect.

INTRODUCTION

In recent years with the introduction of new peptide coupling reagent in organic synthesis, the methods of amide synthesis have been significantly advanced. But the two step acylation, activation of carboxylic acid and reaction with amines have been often used in non-peptide chemistry. Acid chlorides are generally recognized as key intermediate for acylation, for conversion into many other functional groups along with amides such as anhydrides, esters and ketones.

N-acylation is the technique of protecting group in multi-step synthetic processes, important synthetic routes for many bioactive compounds such as Vitamins, agrochemicals, Xanthenes, and in combinatorial peptide synthesis. Literature survey reveals that various drugs e.g., *Penicillin* (antibacterial), *pyrazineamide* (anti tubercular) possesses their specific activities due to the amide linkage in their structure [1].
In a typical N-acylation reaction, the carboxylic acid is first activated by converting into acid chloride and then reacted with amine (Scheme 1).



Scheme 1

Since acid halides are moisture sensitive they are immediately converted to more stable and inert organic compounds [2] , amides and need not necessary to purify, so when amines are added in situ amides are formed by a 'one pot' exothermic reaction. Although amide synthesis has been continuously studied, convenient reaction conditions have not yet been achieved, may be due to molecular diversity and complexity.

This review focuses on acid chloride intermediate, evaluates its advantages and disadvantages, acylation in non-aqueous medium and aqueous acylation i.e., Schotten-Baumann method of amide synthesis.

DISCUSSION

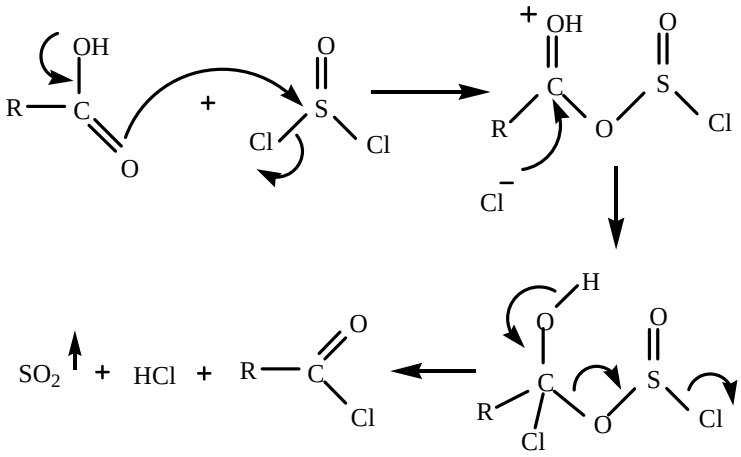
1. Intermediate acid halides

Carboxylic acid halides are generally prepared from various starting compounds by using common and recently introduced reagents such as $SOCl_2$[3-12], $COCl_2$[13,14], $(COCl)_2$[15], PCl_3[16], PCl_5[17], $POCl_3$[18], $PhCCl_3/FeCl_3$, $SOCl_2$-TPPO [19], $Cl_3CCOCCl_3$/ PPh_3[20], Cl_3CCN/PPh_3 [21-23], PPh_3/trichloroisocyanuric acid [24], carboxylic acid esters, Cl_3CCONH_2/ PPh_3, CCl_4/PPh_3, 1-halo N,N-2-trimethylpropenylamine and cyanuric chloride (some reagents are illustrated with references in text).

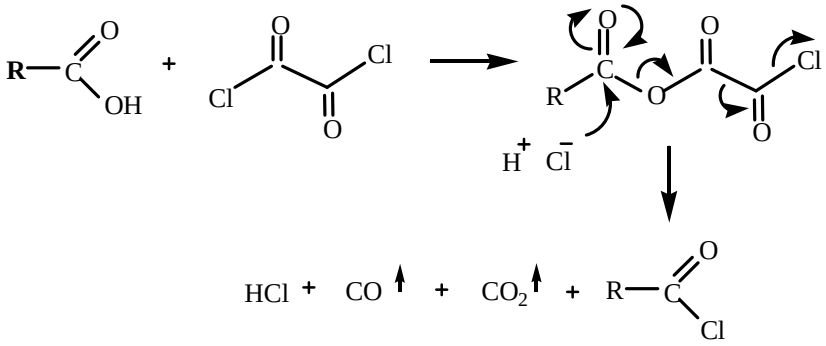
Some of the methods of acid chloride preparations are illustrated (Scheme 2) with advantages, alternatives and disadvantages.

1.1 The methods of preparation from thionyl chloride and Oxalyl chloride

From thionyl chloride



From oxalyl chloride

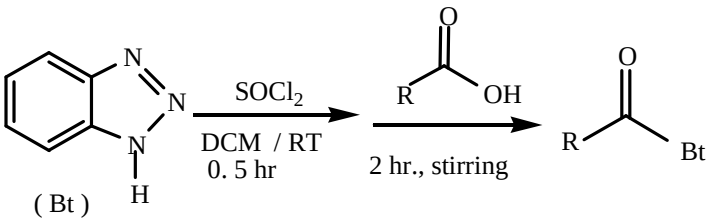


Scheme 2

Thionyl chloride remains the most popular reagent of preparation of acid chlorides with advantages while some disadvantages which can be avoided by using recently developed reagents when required. Thionyl chloride is volatile and excess can be distilled off at the end, leaving acid chloride. Only gaseous by-products are given out, no tedious workup is required for purification of acid chlorides, reacts also with sterically hindered acids and in variety of conditions works well so wide applicability and is non-expensive.

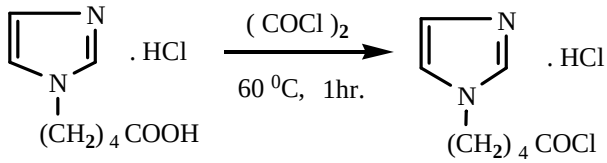
In 1974 Olah and co-workers successfully converted sterically hindered acid to acid chloride by refluxing [25].

A.R.Katritzky and Yuming Zhey in 2003 developed neutral N-acylating reagent for amides and peptide synthesis, N-acylbenzotriazole, which is also the reagent of choice when the acid chlorides are unstable or difficult to isolate otherwise by using $SOCl_2$, for example in RCOCl where R= 4-diethylaminopyridine, 2-pyridyl, 2-indolyl [26] (Scheme 3).



Scheme 3

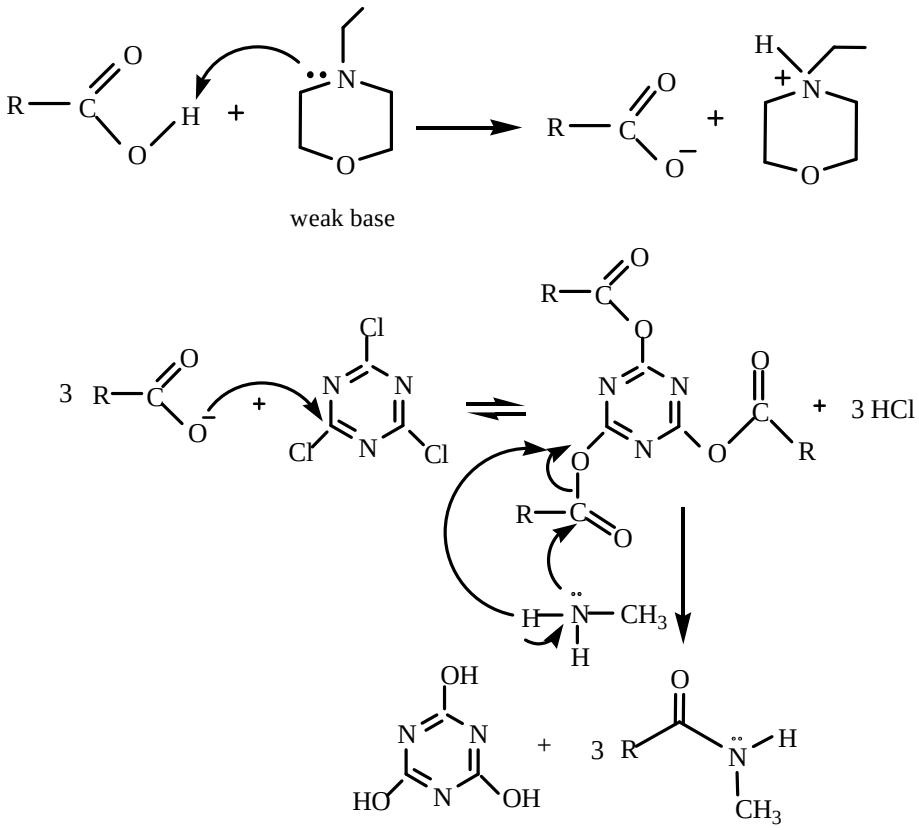
The method of activation of carboxylic acid using thionyl chloride can be avoided in event of unwanted reactions. Use of $SOCl_2$ is avoided in acid chloride preparation of 5-(1-imidazolyl) pentanoic acid, as one would expect it also chlorinate the Imidazole ring under the reaction condition (Scheme 4).



Scheme 4

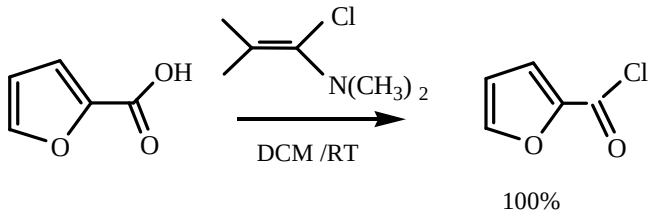
The formation of acid chloride achieved by less aggressive chlorinating agent oxalyl chloride. But care should be taken of complicated handling and three gaseous by-products, one more than in reaction of thionyl chloride.

One of the major disadvantage of thionyl chloride is the by-product, HCl which make the condition acidic which is not tolerate by Boc-protected amines. Alternatively cyanuric chloride process presents many advantages; the preparation of acid chloride [27] illustrated (Scheme 5).



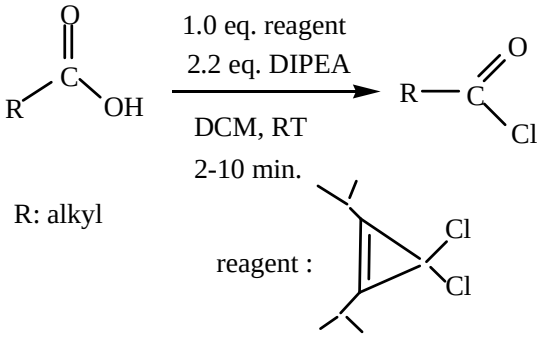
Scheme 5

In presence of weak base particularly N-ethyl morpholine. The procedure is cost effective, since only 0.33 equivalent of reagent is needed, minimize reagent utilization and by-products. Technique of conversion of carboxylic acid to K^+ salts is valuable [28]. Also in neutral condition acid chlorides can be achieved by Ghosez and co-workers method that uses 1-halo N, N-trimethylpropenylamine [29] and DCM (dichloromethane) (Scheme 6).



Scheme 6

Recently in 2010 David J. Hardee and his group developed a method of activation of aliphatic carboxylic acids taking 3, 3-dichlorocyclopropenes in presence of tertiary amine base [30], DIPEA (diisopropylethylamine) (Scheme 7).

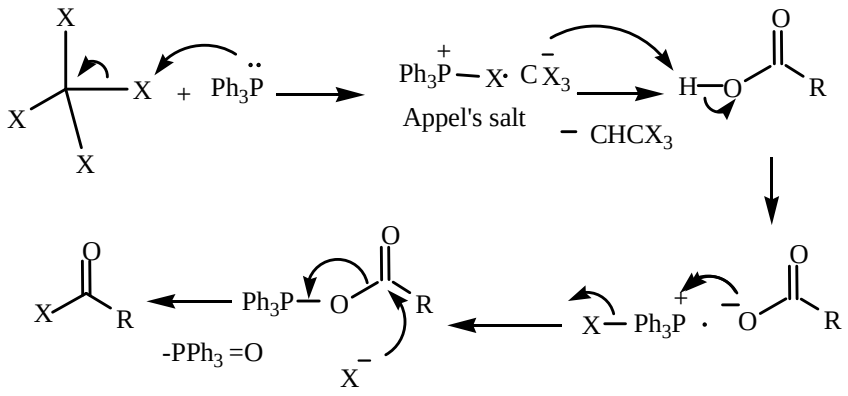


Scheme 7

Racemization is frequent in the course of coupling reaction at the C-terminal amino acid residue due to the ionization of the α-hydrogen atom and formation of an oxazolone intermediate in peptide synthesis [31], so of course this will not reagent of choice in peptide synthesis, where suitable peptide coupling reagent can be selected, which is out of scope of this review.

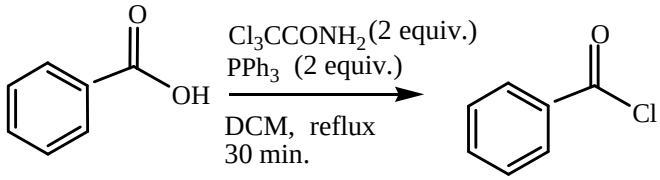
1.2 The methods of preparation from phosphine-halogen reagents

Phosphine-Halogens reagents are emerging as neutral and mild reagents in acid chlorides and amide synthesis. Appel's reaction discovered by Jie Jack Li, in 1971 is a mild and neutral condition reaction among the pioneer works [32], (Scheme 8).



Scheme 8

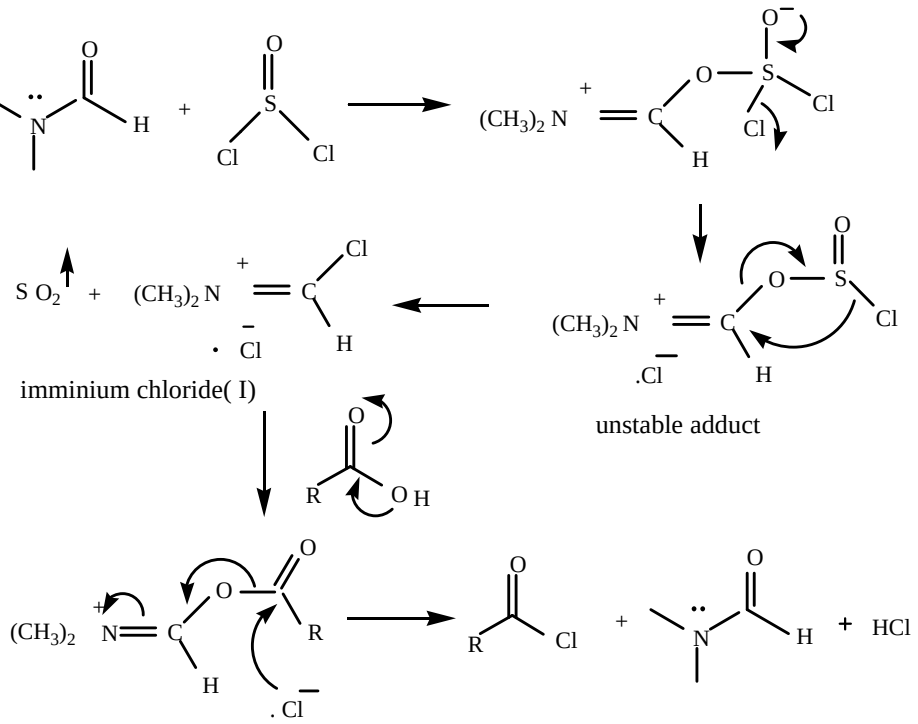
The reaction is slow and required high temperature. Villeneuve and his group in 1997 have reported that carboxylic acids can be converted to acid chloride by Hexachloroacetone-TPP at low temperature [33]. Similarly Trichloroacetonitrile-TPP found on same line. Recently, Skydow in 2009, introduced a reagent, Trichloroacetamide-TPP which promoted by authors as superior among [34], (Scheme 9).



Scheme 9

1.3 Effect of solvent and catalyst in activation reaction

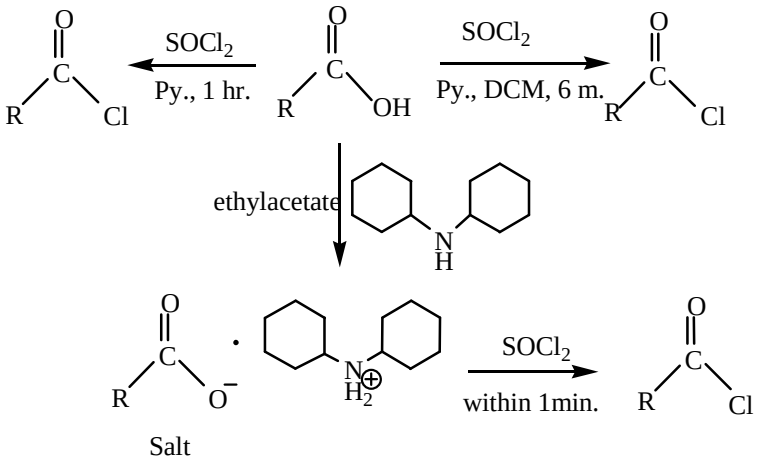
In 1959, Bosshard achieved acid chloride of p-nitrobenzoic acid, unreactive as such to thionyl chloride using DMF as a catalyst [35], (Scheme 10).



Scheme 10

DMF allows milder condition and accelerates the reaction, effect conversion in less time. Wilsmayer in 1971 has proposed that, the active reagent is an imminium chloride (I). Also assumed to the possibility of participation of the initially formed unstable adduct [36].

Mastuda in 1985, successfully tuned condition to get acid chloride within 1 min. by combination of solvent and catalyst [37], (Scheme 11).



Scheme 11

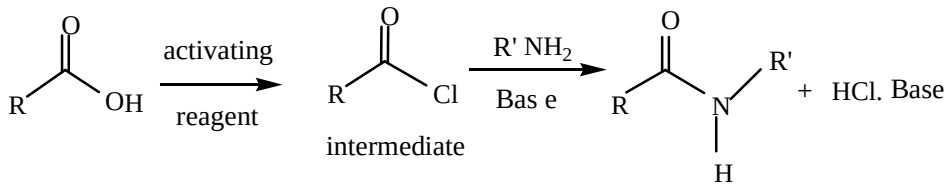
Recently in 2009, Joong-Gon, Khim, used cupric oxide as catalyst and coupling reagent in N-acylation of aliphatic amines [38].

2. N-Acylation in non-aqueous medium

The treatment of acid halides with NH_3 or amines is a very general reaction of synthesis of amides. The acylation of amines has been known since 1853, when Gerhardt reported the acylation of anilines [39], before that in 1845, Fownes, crystallizes amide from the reaction of oil

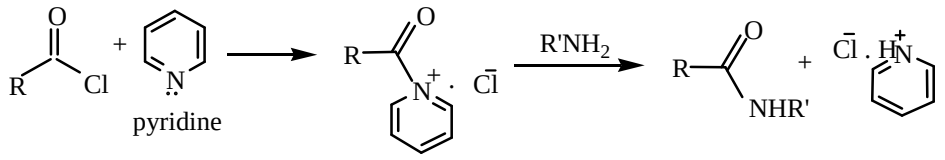
called furfurole with ammonia. The reaction is highly exothermic and must be carefully controlled by cooling the reaction mixture or performing the reaction in very dilute solution.

The typical acyaltion reaction is carried out by slow drop wise addition of an amine in suitable dry solvent to solution of acid chloride in situ in presence of non-nucleophilic tertiary organic bases [40] like pyridine, DMAP(dimethylaminopyridine), TEA, 4-picoline, N-methyl morpholine and sodium 2-ethylhexanoate (Scheme 12).



Scheme 12

Rate determining step in the formation of amide by acylation is usually attack of nucleophile on the carbonyl group rather than the subsequent reformation of the π- bond and displacement of leaving group, therefore the electron withdrawing X-atom is able to stabilize the T.S. and tetrahedral intermediate. During acylation the presence of base is crucial to neutralize the one equivalent acid formed, otherwise it will consume the amine and diminish the yield. These organic bases act as catalysts in the reaction (Scheme 13).



Scheme 13

Similarly Vedejs in 1993 proved that DMAP and TEA combination is superior in acylation of alcohol with acetic anhydride [41]. He believed that the reason could be the TEA prevents acetic acid from destroying the DMAP catalyst. The same combination can be applied to acylation of amines.

N-acylation reaction is well studied, using acetyl chloride and acetic anhydrides reagents, which take place in variety of manners [42]. Jacobson observed that the introduction of first aryl group markedly reduces the nucleophilicity of the amine for the further acylation. So acylation can be tuned to desire aim, to stop at monoacyl step or to proceed for diacylation, in variety of manners. High conc. and fast addition of acid halide and less mixing and high temperature combination could give diacyl derivative in case of acetyl halide and acetic anhydride reagents [43]. In our attempt to synthesized diazolylderivative of various substituted anilines treating with azole-1-acetylchlorides, yield was found below 12%, the reason may be steric effect of bulkier azole-1-acetyl chlorides [44].

The majority of acylation reactions are conducted in aprotic organic solvents such as benzene, toluene, diethyl ether, acetonitrile, acetone, dioxane, DMF, THF, HMPA, 4-picoline, TEA DCM [45,46], DMAC (dimethylacetamide) [47], pyridine [48,49], and catalysts utilized are pyridine, DMAP, CuO.

2.1 Effect of substituents and steric effect

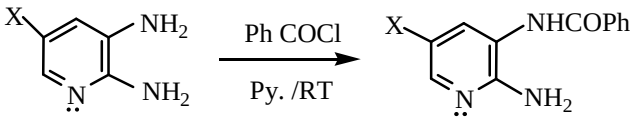
Sudborough in 1901 have shown that a methyl (positive) group or a second hydrogen residue in the o-position to the amino group favour the formation of diacetylderivative when refluxed [50]. L.C. Raiford and co-workers in 1924 observations supports the study of Sudborough when they studied the acylation of aromatic amines with acetic anhydrides, found that o-substituent did not retard the reaction, but frequently accelerate it [51].

2.2 N-acylation reactions in synthesis

Some N- acylation reactions are given which will definitely throw light on the chemistry of acylation and progress in the field (Schemes 14-18).

H.R.Snyder and his group in 1954 carried out the acylation of crotonyl chloride in dry benzene with several hours' addition of diethyl amine at 0^{o}C, yielded N, N-diethyl crotonamide [52]. Successively as the methodology of the synthesis of amides has been continuously studied in search of convenient reaction conditions in variety of substrates, newer challenges and solutions are coming up.

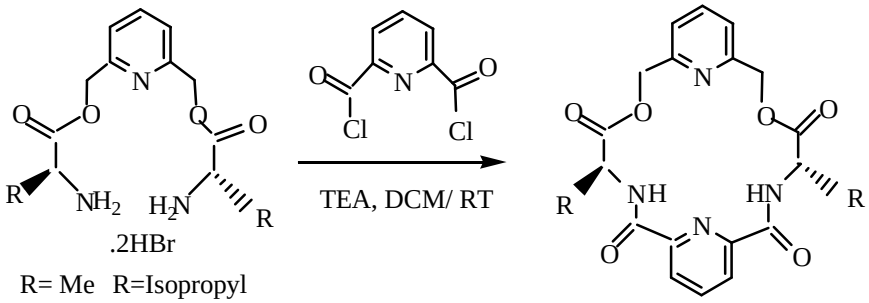
P. K. Dubey and co-workers in 2000 reported acylation of 2, 3-diaminopyridine by benzoyl chloride in presence of pyridine at RT, obtained monoacetyl derivative only [53], (Scheme 14).



X : H or B r

Scheme 14

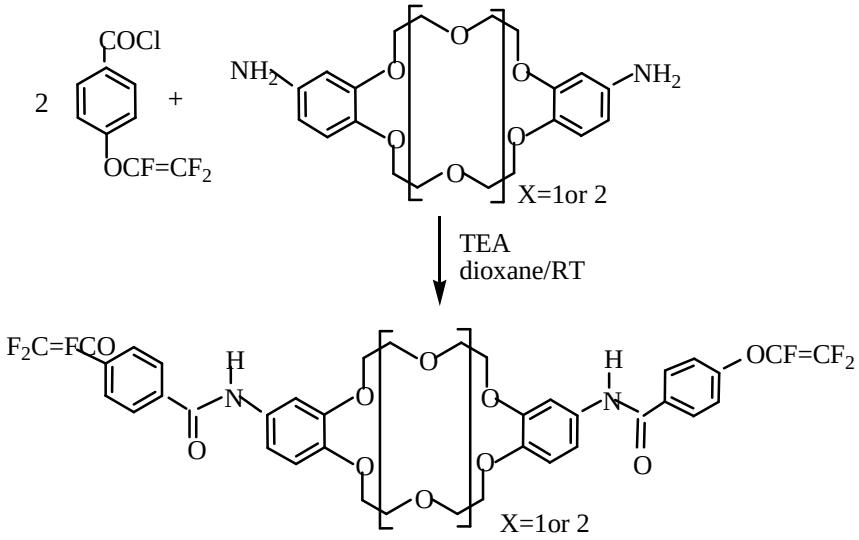
In 2000 Hongwu Zhao and his group synthesized a macro cycle by acylation of chiral diamine dihydrobomide intermediate in highly diluted solution when treated with 2, 6-pyridinedicarbonyl dichloride at RT, using TEA in DCM [54], (Scheme 15).



R= Me R=Isopropyl

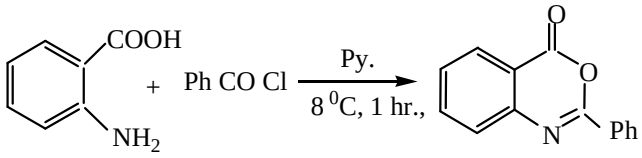
Scheme 15

Similarly S.C.Ligon and his group in 2004 synthesized macromolecule dyads by acylation in dioxane using TEA at RT [55], (Scheme 16).



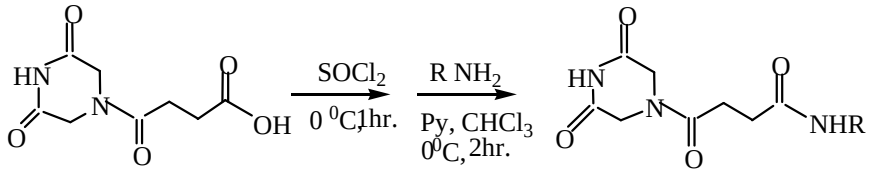
Scheme 16

V. P. Trivedi and his group in 2004 carried out acylation of anthranilic acid with benzoylchloride in presence of pyridine at 8 ^{0}C , which resulted in ring closure within 1hr [56], (Scheme 17).



Scheme 17

Irena Svedaite in 2007 studied acylation of 4-(3, 5-dioxopiperazine-1-yl)-4-oxabutanoic acid in chloroform at 0 ^{0}C [57], (Scheme 18).



Scheme 18

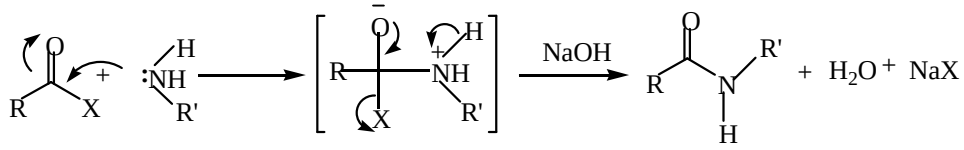
3. Aqueous N-acylation Schotten-Baumann method

In 1884 C. Schotten reported a method for the synthesis of N-benzoylpiperidine from piperidine and benzoyl chloride in aqueous medium in presence of sodium hydroxide. After a couple of year in 1886 E. Baumann showed the formation of ethyl benzoate from ethanol and benzoyl chloride under the same reaction conditions.

The method of synthesis of amide from amines and ester from alcohol with reaction of acid halide or acid anhydride in the presence of aqueous base is known as Schotten-Baumann method. The reaction has wide applicability in synthesis of simple amides under aqueous medium [58, 59], and can be recognized as green synthesis of amides utilizing nonhazardous one of the solvent, water of the biphasic system.

The reaction is based on the fact that the reaction of an acid halide with an amine is much faster than the hydrolysis of the acid halides by aqueous alkali. The mechanism of the reaction is illustrated (Scheme 19).

The addition of an additional equivalent amount of base to neutralize the acid formed is required, similar to non-aqueous acylation.



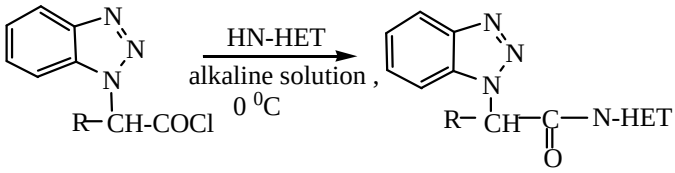
R & R' =1°,2°,3° alkyl or aryl

Scheme 19

In a typical Schotten-Baumann acylation the amine or its salt is dissolved in a slight excess of an alkali, sodium hydroxide (8-15%) solution. A small excess of acid chloride in organic solvent is then added and the mixture is vigorously stirred at R.T. The other solvent used may be DCM, Diethyl ether etc. Alternatively amine hydrochloride salt in aqueous solution can be treated with acid chloride or acid anhydride in presence of Na_2CO_3 which liberates free amine and reacts with activated derivative of acid and converts the liberated carboxylic acid to sodium-carboxylate in aqueous medium. Reactions of aliphatic carboxylic acid chlorides containing two or more carbon atoms are well studied by Sonntag, N.O.V. in 1953 [60].

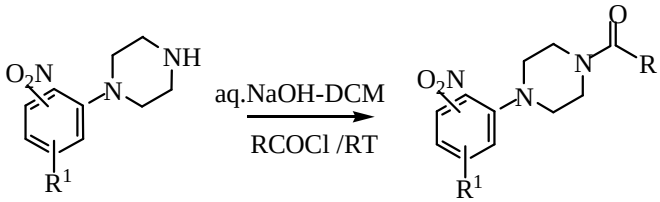
3.1 Schotten-Baumann reaction in amide synthesis

S. K. Shrivastava and his group in 1995 reported N-acylation of NH-Het. System, Imidazole with various substituted 1H-benzotriazole-1-yl- acid chloride in ice cooled alkaline solution [61], (Scheme 20).



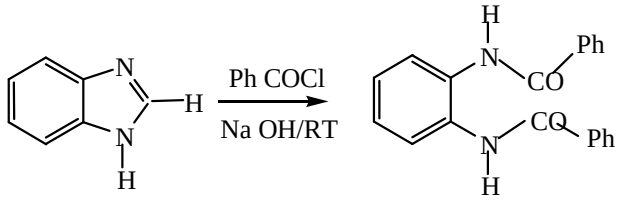
Scheme 20

Luc Neuville's group in 1997 studied Schotten-Baumann reaction of N-substituted aryl piperazines with various acid chlorides at RT in aq. NaOH-DCM, biphasic system [62], (Scheme 21).



Scheme 21

K. Ramaiah and co-workers in 1999 observed ring opening when benzimidazole condensed with benzoyl chloride in alkaline solution at RT [63], (Scheme 22).



Scheme 22

CONCLUSION

Methods of amide synthesis in non-peptide compounds are being studied with new reagents for activation of carboxylic acids and coupling reagents too. Phosphine-halogen reagents in activation of carboxylic acids, catalysts in N-acylation like DMAC, CuO and trichloroisocyanuric acids are notable. N-acylbenzotriazole, coupling reagent in synthesis of simple amides and acylation in aqueous medium in variety of substrates in various conditions are useful to synthesize simple monosubstituted amides.

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