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Chemoselectivity in reactions of esterification

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This review is devoted to the problem of chemoselective formation of ester functions in polyfunctional molecules. The review covers most typical approaches to chemoselective acylation of hydroxy groups in molecules containing an amino, mercapto, or another hydroxy functionality as well as chemoselective esterification of di- and polycarboxylic acids.

Introduction

Esterification is one of the most general and widely used reactions in organic chemistry. With numerous applications of esterification ranging from natural products syntheses to industrial scale production of bulk chemicals, a substantial number of different synthetic approaches have been suggested[1] to comply with modern standards of efficiency and atom economy.

Nevertheless, if organic molecules contain other functional groups capable of competing with hydroxy or carboxy functions, such as amino, mercapto, or additional hydroxy/carboxy groups, the reaction of esterification tends to yield mixtures of isomeric products of mono- and polyacylation. The problem of chemoselectivity of esterification is particularly acute in multistep syntheses where the possibility for accurate predictions of chemoselectivities on advanced stages of a synthetic project is one of the most important requirements for the overall success.

With some important exceptions,[1,2] the chemoselectivity data are scattered between dozens of original papers. Available reviews dealing with the preparation of esters tended to concentrate on mechanistic aspects of the problem and the introduction of new reagents. The objective of this review is to provide a more utilitarian, outcome-oriented outlook on this problem that is especially important in the development of multistep synthetic strategies. The current review covers preparative approaches for chemoselective acylation of hydroxy groups in polyfunctional compounds. The following reactions are considered:

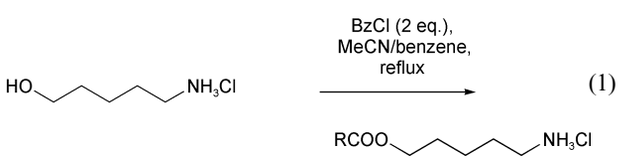
1. Acylation of hydroxy groups in the presence of primary or secondary amino groups.
2. Acylation of hydroxy groups in the presence of thiol groups and *vice versa*.
3. Selective acylation of alcohols in the presence of phenols and *vice versa*.
4. Selective acylation of hydroxy groups in polyols.
5. Selective monoesterification of carboxy groups in dicarboxylic acids.

Due to the shortage of space, the stereoselectivity aspects of the esterification have not been included in this review. This area is constantly updated in the literature, and a number of very recent reviews are available.[3] Also left aside is the important, but highly specialized, problem of acylation of carbohydrates, providing only references to relevant reviews.

Chemoselectivity between amines and alcohols

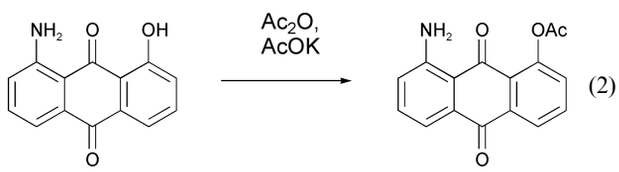
Because of the much higher reactivity of the amino group and higher thermodynamic stability of amides *vs*. esters, the selective *O*-acylation of hydroxy groups is not a trivial task. As a result, the common strategy for the selective acylation of hydroxy groups in the presence of an amino group involves the protection of the amino group by its conversion into the corresponding ester or carbamate,[4] followed by the acylation of the hydroxy functionality and final selective *N*-deprotection.

Nevertheless, several methods for direct acylation of aliphatic hydroxy groups in the presence of an unprotected alkyl amino function were suggested. A few attempts for selective *O*-acylation that were undertaken use a highly acidic media to ensure the protonation of aliphatic amino groups. This approach is similar to the acid catalyzed esterification of amino acids that proceed with a complete chemoselectivity[5] but in the presence of a large excess of the alcohol. However, as in the case of amino alcohols even the presence of a substantial excess of acid does not fully prevent acylation of amino groups. The most convenient *O*-acylation of amino alcohols (eqn. (1)) involves the reaction of a two-fold excess of acyl chlorides with hydrochlorides of amino alcohols in an acetonitrile–benzene mixture. Isolated yields were from low to moderate (up to 58%) and highly solvent dependent.[6]



(1)

For compounds possessing aromatic amino groups obtaining a selective *O*-acylation is simpler, especially in the case of very unreactive hydroxy substituted aromatic amines. In the example seen in eqn. (2), hydroxy substituted aminoquinones can be selectively *O*-acylated with basic catalysis[7] owing both to very low nucleophilicity of aminoquinones and easy deprotonation of aromatic hydroxy groups.



(2)

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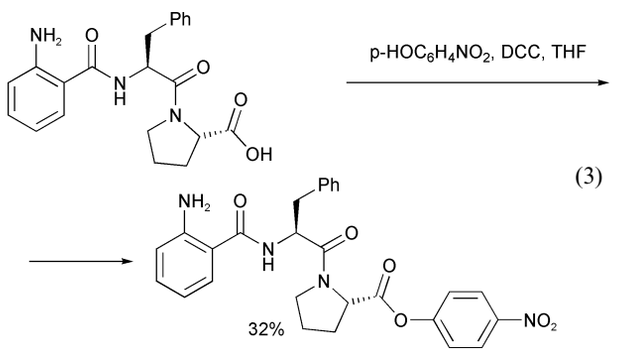
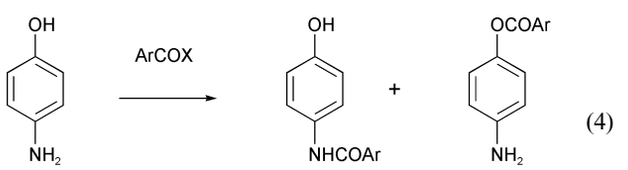
Similarly, due to the ease of deprotonation, the selective acylation of acidic phenols and formation of corresponding active esters can be carried out in the presence of aromatic amino groups. The reaction (eqn. (3)) proceeds through carbodiimide couplings and provides only low to moderate yields.[8] These low yields however may also be attributed to difficulties in isolation of active esters possessing a primary or secondary amino group rather than the lack of intrinsic chemoselectivity.



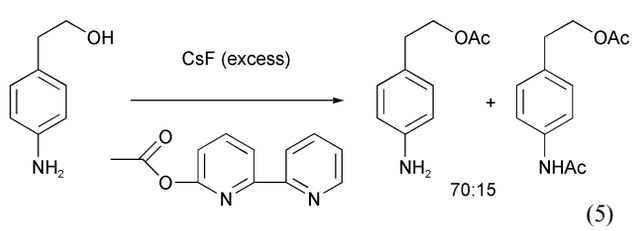
(3)

A high selectivity towards the acylation of phenolic hydroxy groups in amino phenols was achieved using *N*-methyl-*N*-nitroso-*p*-nitrobenzamide (eqn. (4)).[9] Acylation of amino phenols with *p*-nitrobenzoyl chloride produced exclusively products of *N*-acylation.



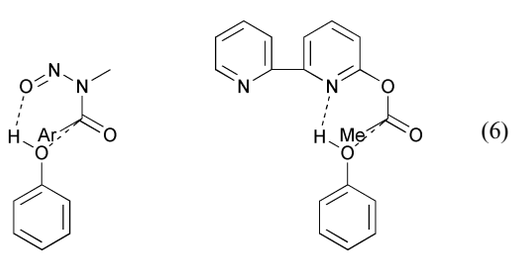
(4)

Similarly to eqn. (4), selective *O*-acylation of *p*-aminophenol can also be achieved using bipyridyl esters as acyl transfer reagents in the presence of a large excess of CsF (eqn. (5)).[10] This method also provides a substantial selectivity towards the acylation of aliphatic primary hydroxy group *vs.* aromatic amino groups, although with a substantial amount of diacylation product.



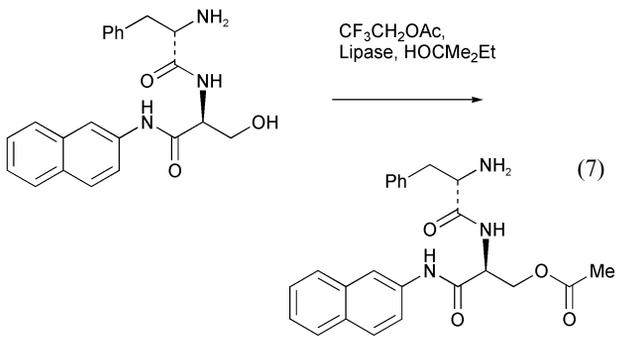
(5)

While no explanations of this dependence of the chemoselectivity (eqns. (4) and (5)) have been provided, it should be mentioned that both *N*-methyl-*N*-nitroso and bipyridynyl leaving groups are potentially capable of concerted proton transfer through a 6-centered non-planar transition state shown on eqn. (6). Such a concerted proton transfer[11] could substantially accelerate *O*-acylation producing the observed chemoselectivity.



(6)

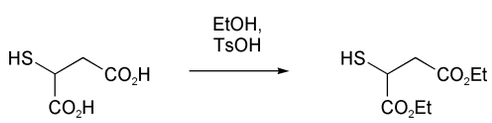
Lipase catalyzed transesterification has been applied for the selective esterification of a hydroxy group in the presence of a primary amino group (eqn. (7)).[12] While a certain degree of selectivity was indeed found, it is probably too low for practical applications.



(7)

Chemoselectivity between thiols and alcohols

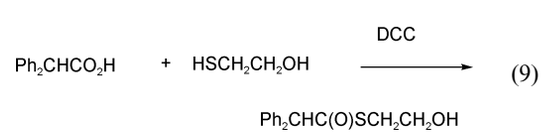
Selective *O*- or *S*-acylation of mercapto alcohols is synthetically important but there are not many examples in the literature. The most common example of selective *O*-acylation involves acid catalyzed esterifications of thiol-substituted carboxylic acids. In the presence of a large excess of an alcohol, all these reactions, like the one shown on eqn. (8), proceed with complete chemoselectivity, thus producing corresponding mercapto esters without any *S*-acylation products.[13]



(8)

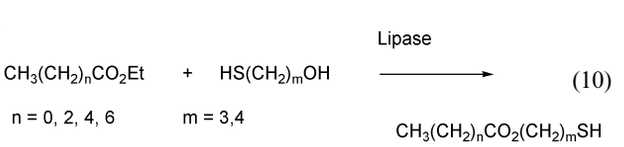
Acid catalyzed esterification could also be used with equimolar amounts of alcohols or mercapto alcohols. Chemoselective *O*-acetylation of mercaptoethanol with moderate (65%) yield was achieved in the esterification with heterogeneous yttria–zirconia-based Lewis acid catalyst.[14] In general, proton and Lewis acid catalyzed thioesterifications are disfavored by lower equilibrium constants between carboxylic acids and thioesters as well as a higher energy transition state.[15]

Alternatively, selective *S*-acylation of mercaptoethanol was obtained in carbodiimide coupling without acylation catalysts (eqn. (9)).[16] As indicated by the relative rates of thioesterification, the origin of chemoselectivity in this reaction is the acidity of the mercapto group resulting in the attack of the thiolate anion on the intermediate symmetric anhydride.



(9)

Lipase catalyzed selective acylation of linear ω-mercapto alcohols produced the corresponding ω-mercapto esters with high chemoselectivity through a transesterification of the ethyl ester used as a solvent (eqn. (10)).[17] At the same time, mercapto alcohols with secondary thiol and hydroxy groups were found to possess extremely low transesterification rates. The chemoselectivity of these reactions is probably enzyme-specific as lipase catalyzed thioesterifications have also been reported.[18]



(10)

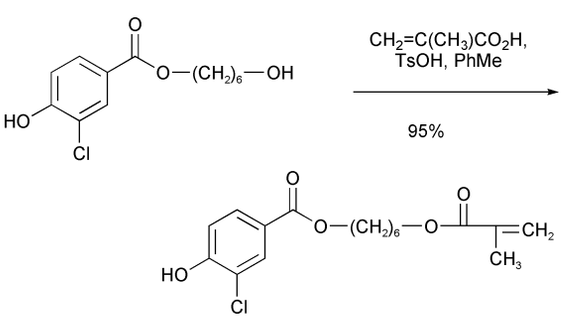
Overall, a certain analogy can be drawn between the difference in reactivity of hydroxy *vs.* thiol groups and phenols *vs.* alcohols. Acidic conditions favor *O*-acylation while basic conditions produce products of *S*-acylation. It can be reasonably assumed that many methods developed for the discrimination between aliphatic and aromatic hydroxy groups could be used for the selective acylation of mercaptoalcohols.

Chemoselectivity between phenols and alcohols

The most commonly used acylation reagents, like acyl halides and anhydrides, often provide comparable rates for the acylation of phenols and alcohols. Several acylation methods for the acylation of vanilinol were checked.[19]. Reactions of symmetric and mixed anhydrides and acyl chlorides in the presence of pyridine or triethylamine/DMAP were found to be non-selective. In reactions of a carboxylic acid/carbodiimide/DMAP system with polyfunctional substrates, there are also rather similar rates for the formation of alkyl and aryl esters.[19] Low selectivity of the acylation was also observed in reactions with acetic anhydride with $Cu(OTf)_2$ as a catalyst.[20]

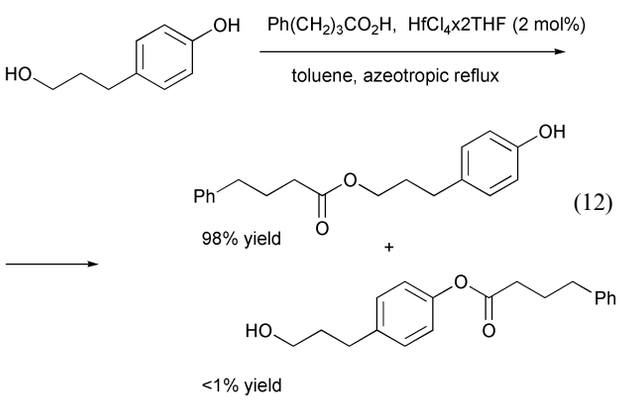
Methods for the selective preparation of aliphatic esters

Acid catalyzed esterification of carboxylic acids shows a high selectivity toward the formation of aliphatic esters. Acid catalyzed esterification of phenolic carboxylic acids usually proceeds with a complete selectivity when an excess of alcohol is used. After certain modifications, the acid catalyzed esterification is also useful for the chemoselective preparation of esters with a 1 : 1 acid–alcohol ratio. Using azeotropic removal of water, high conversions with a 1 : 1 ratio may be achieved under protic acid catalysis (typical example in eqn. (11)).[21]



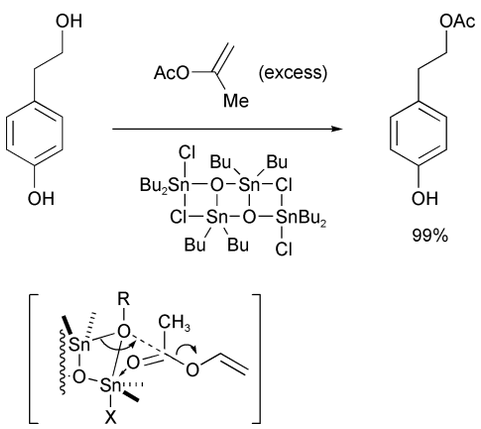
(11)

Lewis acid catalyzed esterification provided excellent selectivity between alcohols and phenols. Hafnium chloride was found to be a highly efficient reaction for the selective esterification of the aliphatic hydroxy group of *p*-(3-hydroxypropyl)phenol with more than 99 : 1 selectivity.[22] The high chemoselectivity observed in eqns. (11) and (12) may be attributed to the generally lower basicity and nucleophilicity of the oxygen atom in phenols (K_b of phenol is about 10^6 times lower than that of methanol). This is true for reactions involving neutral molecules like protic and Lewis acid-catalyzed esterifications while the presence of basic catalysis can radically alter the chemoselectivity.



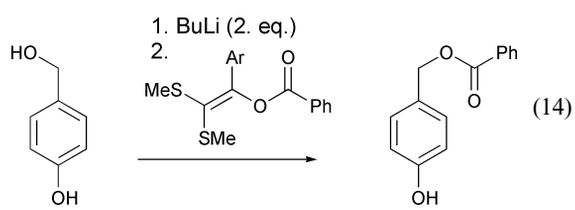
(12)

A complete selectivity between alcohol and phenol functionalities was obtained in the catalyzed transesterification of alkenyl esters shown in eqn. (13). This method necessitates the use of a large excess of alkenyl esters but provides essentially neutral reaction conditions. This method tolerates a variety of sensitive functional groups, making it highly useful for acylation of highly functionalized molecules.[23] The suggested mechanism[24] involves the formation of the four-membered chelate complex of distannoxane catalyst with an alcohol followed by the acyl transfer on the three-coordinated oxygen atom through the transition state seen of eqn. (13). Although no reasons for the observed complete chemoselectivity were suggested, it is probably related to the geometry of the transition state. Both the stability of the four-membered chelate complex and the reactivity of the remaining lone pair on the three-coordinated oxygen atom should be higher for alcohols than for phenols.



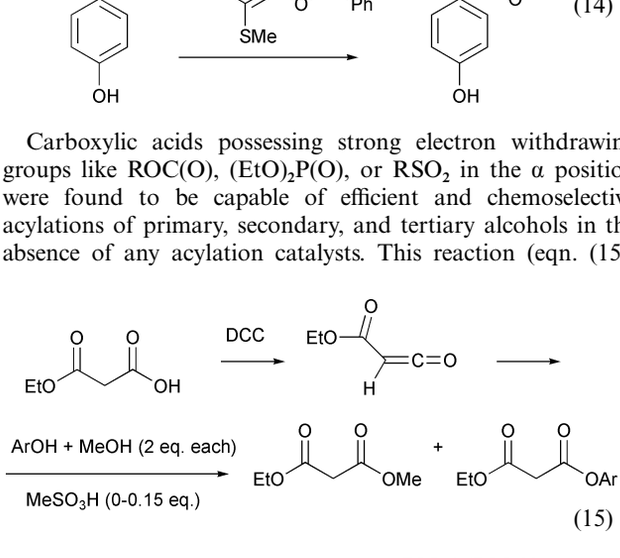
(13)

Complete ionization of both hydroxy functions with BuLi followed by the acylation of the resulting salt with 1 eq. of enol ester shown in eqn. (14) was used for discrimination between aliphatic and aromatic hydroxyls.[25]



(14)

Carboxylic acids possessing strong electron withdrawing groups like ROC(O), $(EtO)_2P(O)$, or RSO_2 in the α position were found to be capable of efficient and chemoselective acylations of primary, secondary, and tertiary alcohols in the absence of any acylation catalysts. This reaction (eqn. (15))

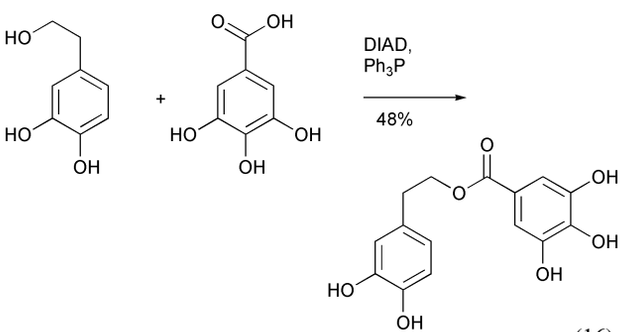


(15)

ECO_2Ar/RCO_2Me	
Ar=Ph, no $MeSO_3H$	<0.02
Ar=2,4,6-$C_6H_2Cl_3OH$, no $MeSO_3H$	2.1
Ar=2,4,6-$C_6H_2Cl_3OH$, 0.05 eq. $MeSO_3H$	0.77
Ar=2,4,6-$C_6H_2Cl_3OH$, 0.15 eq. $MeSO_3H$	0.02

proceeds through ketene intermediates and shows a high selectivity towards the acylation of aliphatic hydroxy groups. Highly acidic phenols showed comparable reaction rates to alcohols but their acylation can be suppressed using catalytic amounts of acids.[16]

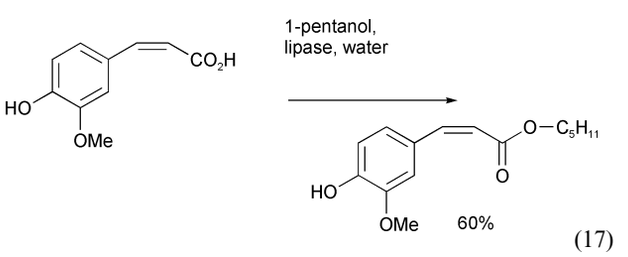
Ester function can be prepared indirectly through the alkylation of carboxylates. This alkylation usually does not interfere with unprotected phenolic hydroxyls and can be used for the selective preparation of alkyl esters. Alkylation of carboxylic acids through the Mitsunobu reaction (eqn. (16)) was found to be a selective method for the preparation of polyphenolic esters.[19]



(16)

Similarly, the alkylation of phenolic carboxylic acid with ethyl, isopropyl, and benzyl iodides using a CsF–Celite catalyst was reported to proceed with high chemoselectivity giving the corresponding esters. This method requires two-fold excesses of alkyl iodides and was not proven on more complicated alkyl halides.[26]

Enzymes were employed for the chemoselective discrimination between phenolic and alcoholic hydroxyl groups present in the same molecule. Selective acylation of 2- and 4-hydroxymethylphenols was achieved with *Aspergillus niger* lipase.[27] A number of experiments with highly selective acylation of hydroxymethylated phenolic compounds with vinyl acetate were conducted with lipases.[28] In general, both lipases[29] and esterases[30] (eqn. (17)) selectively catalyze acylation of aliphatic hydroxy groups.

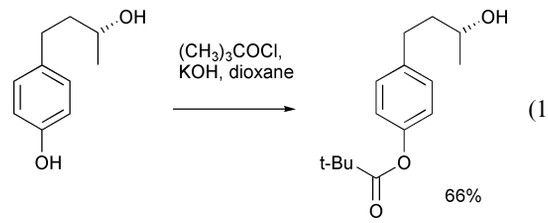


(17)

Because of the substantially higher reactivity of aryl esters towards nucleophilic reagents, a selective hydrolysis of polyesters could be applied for the selective preparation of aliphatic esters[31]. Despite extensive use in the past, the use of this method is not necessary as the difference in electronic properties between alcohols and phenols is large enough to enable selective acylation.

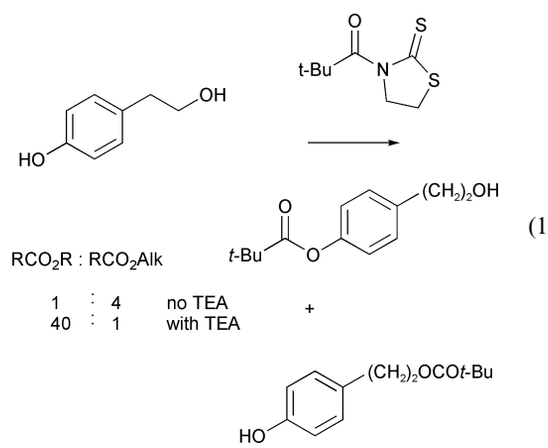
Selective acylation of phenols

The large difference in the acidity between alcohols and phenols can be used for the selective acylation of phenols in the presence of alcohols. In the presence of even weak bases the deprotonation of the phenolic moiety tends to be the main factor controlling the chemoselectivity of acylation. Reactions in the presence of bases produce phenolate anions that can be efficiently and selectively acylated without touching the less acidic hydroxy groups (eqn. (18)).[32] This selectivity, however, completely disappears in the presence of commonly used acylation catalysts like DMAP and pyridine.[19]



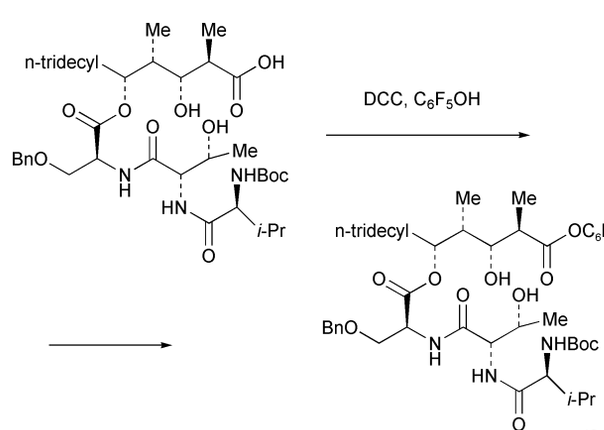
(18)

The addition of triethylamine was found to reverse the chemoselectivity in the acylation of phenolic alcohols by 3-acyl-1,3-thiazolidine-2-thiones (eqn. (19)).[33]



(19)

Acylation of phenols with carboxylic acid–carbodiimide systems (except carboxylic acids that are capable of reacting through ketene intermediates) in the absence of acylation catalysts were found to proceed much faster than the acylation of alcohols.[16] Reaction rates rapidly increased with the acidity of the phenol. Even less acidic phenols like *p*-methoxyphenol were acylated easily. The selective acylation of highly acidic phenols through carbodiimide couplings was achieved in the presence of multiple aliphatic hydroxy groups (eqn. (20)) resulting in the formation of the corresponding active esters[34]



(20)

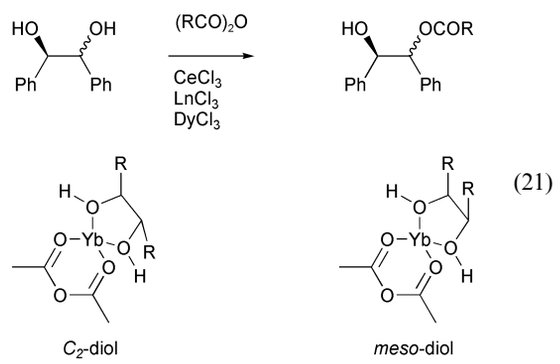
Selective acylation of a phenolic hydroxyl in the presence of a secondary hydroxy group was obtained by solid state acetylation using acetylimidazole.[35]

Monoacylation of polyols

Monoacylation of symmetric diols

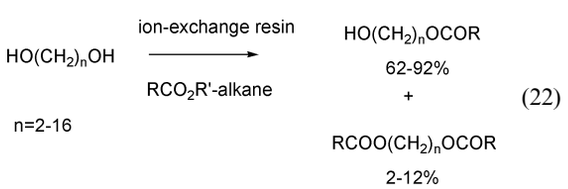
Selective monoacylation of symmetric diols is substantially more complicated and the formation of a statistical mixture of

mono- and diacylated products is frequent. For primary and secondary 1,2- and 1,3-diols selective monoacylation with symmetric anhydrides is possible (eqn. (21)).[36] The reaction proceeds through the formation of chelate metal complexes with Lewis acid catalysts. Cerium, dysprosium, and ytterbium chlorides were checked with the latter generally providing better results. The use of an excess of the symmetric anhydride is essential for the reaction. The proposed mechanism of the acylation involves the coordination of both diol and symmetric anhydride with a lanthanide cation followed by the intramolecular transfer of the acyl group. The high chemoselectivity of monoacylation is due to the higher stability of bidentate complexes of lanthanide catalysts with diols *vs.* monodentate complexes of monoesters. This mechanism[37] is also supported by substantially higher acylation rates of C_2 symmetric diols *vs.* analogous *meso* diols.



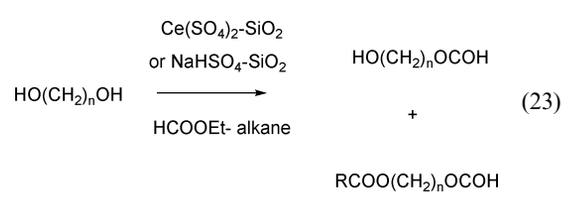
(21)

Similarly high chemoselectivity was obtained in the acylation of symmetric 1,3 and 1,4-diols with cerium(III) chloride.[38] Monoesterification of diols possessing a larger distance between hydroxy groups requires a different approach. Because of the substantial difference in hydrophilicity between diols and their monoesters, monoacylation of 1,*n*-diols, ranging from 1,2-ethanediol to 1,16-hexadecanediol was achieved by transesterification in ester/alkane mixtures catalyzed by strongly acidic ion-exchange resins (eqn. (22)). At 70–80% conversions a good selectivity 20 : 1–15 : 1 was achieved after the optimization of ester–alkane ratio. The selectivity decreases at higher conversions and different from the optimal ester–alkane ratio. The suggested mechanism of the selectivity toward monoacylation is based on the formation of a strongly acidic aqueous layer on the surface of ion-exchange resin beads. The preferential acylation of 1,*n*-diols is explained by their higher solubility in the water layer where the transesterification proceeds.[39]



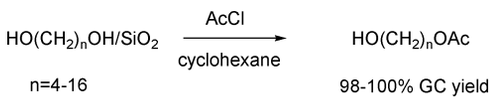
(22)

A similar mechanism of selectivity was also proposed for the selective monoesterification of different 1,*n*-diols with an ester–alkane mixture catalyzed by silica supported $Ce(SO_4)_2$ and $NaHSO_4$ shown in eqn. (23). The selectivity is in the 20 : 1 to 10 : 1 range for C_2 to C_{16} diols at 75–90% conversions, and was particularly high when isopropyl acetate was used as an acyl donor. Secondary diols can also be monoformylated by the reaction with ethyl formate. Similar but lower selectivity was observed for the catalysis with unsupported $NaHSO_4$.[40]



(23)

Another, but probably related, approach to monoesters of α,ω-diols involves the acylation of preadsorbed diols on silica gel with acetyl chloride in refluxing cyclohexane (eqn. (24)).[41] This method is remarkable because of the practically quantitative chemoselectivity for primary diols up to 1,16-hexadecanediol. Secondary and benzylic diols produced much lower selectivity.



(24)

Selective acylation of hydroxy groups in non-symmetric diols/polyphenols

Selective monoacylation of non symmetric polyols is one of the most common synthetic problems. Different steric requirements in primary, secondary, and tertiary alcohols in most cases produce a substantial difference in acylation rates that can be further enhanced using special acylation methodologies.

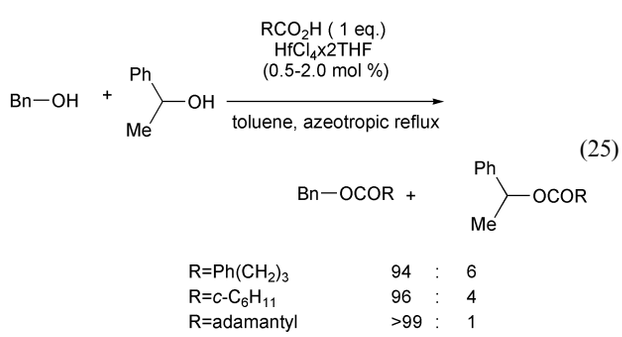
In general, tertiary alcohols are about two orders of magnitude less reactive than secondary ones and more than 10^3 less reactive than primary alcohols. Consequently, the acylation of primary and secondary hydroxy groups in the presence of tertiary hydroxyls is trivial in most cases.[2,42] Moreover, the acylation of tertiary hydroxy groups in complex substrates is often a profound synthetic problem that can be tackled using new reagents.[2]

In contrast, achieving highly selective monoacylation of primary hydroxy groups in the presence of secondary ones is complicated. The difference in acylation rates between primary and secondary alcohols is about one order of magnitude and the acylation of diols containing both types of hydroxyls provides substantial amounts of a corresponding secondary ester and/or diester. Low selectivity of the acylation was also observed in reactions of acetic anhydride with both $Cu(OTf)_2$ and DMAP catalysis.[43] Low selectivity in the acylation of unsymmetric diols was obtained by solid state acetylation using acetylimidazole.[17]

A general approach for selective acylation of a primary hydroxy group is the amplification of the different steric hindrance of primary and secondary hydroxy groups through the use of sterically hindered acylation reagents.

A high degree of selectivity between menthol/borneol and primary alcohols was obtained in the biphasic esterification of a 1 : 1 carboxylic acid–alcohol mixture using fluoroalkyldibutoxystannane catalysts.[44]

The hafnium–zirconium catalyzed direct esterification[45] shown in eqn. (25) provides relatively high (>95%) selectivity in the acylation of primary alcohols.

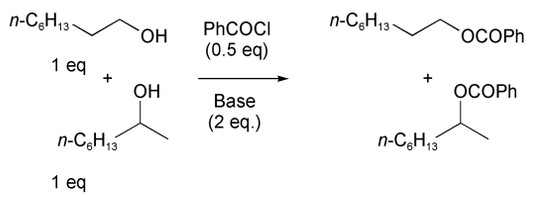


(25)

However, the steric bulk of acylating reagents does not always provide a substantially higher discrimination of primary *vs.* secondary hydroxy groups. Pivaloyl chlorides and other derivatives of bulky pivalic acid[33] were found to give a distribution of acylation products on 1,5-hexanediol that is very

similar to a simple acetylation. It is probable that direct acid-catalyzed esterifications show more sensitivity towards the steric hindrance than the acylation of alcohols by other carboxylic acid derivatives.

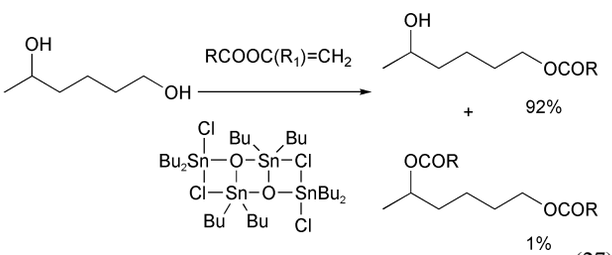
Probably the most efficient and practical method for the selective acylation of primary hydroxy groups involves the use of acyl chlorides in combination with bulky amines such as diisopropylethylamine or 2,4,6-collidine (eqn. (26)).[46] The use of 2,4,6-collidine was found to provide more consistent results—the chemoselectivity was beyond 94% for all tested acyl chlorides (with the exception of Cl_3COCl).



(26)

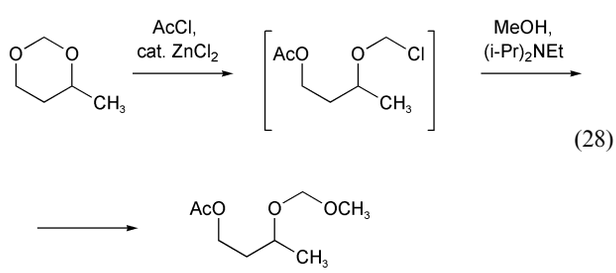
Base	Total yield	% of primary ester
Pyridine	89%	88%
2,4,6-collidine	64%	98%
i-PrNEt$_2$	30%	95%

Distannoxane catalyzed transesterification of alkenyl esters was also found to possess a very high sensitivity towards steric differences in alcohols (eqn. (27)). Reported examples showed almost complete absence of acylation of secondary hydroxy groups in diols.[47] The observed high sensitivity of the reaction towards the steric bulk of alcohols is probably related to the reaction mechanism that involves the formation of the highly sterically crowded transition state shown in eqn. (13). This method requires the use of a large excess of alkenyl ester.



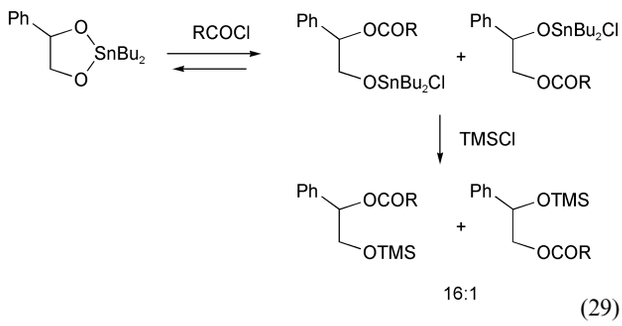
(27)

Reaction of methylene acetals of unsymmetric 1,3-diols with acetyl chloride proceeds with complete chemoselectivity from the less hindered side as shown in eqn. (28).[48] Acetals of unsymmetric 1,2-diols react with substantially lower (3 : 1) selectivity that can be only marginally improved through the use of bulky pivaloyl chloride instead of AcCl.



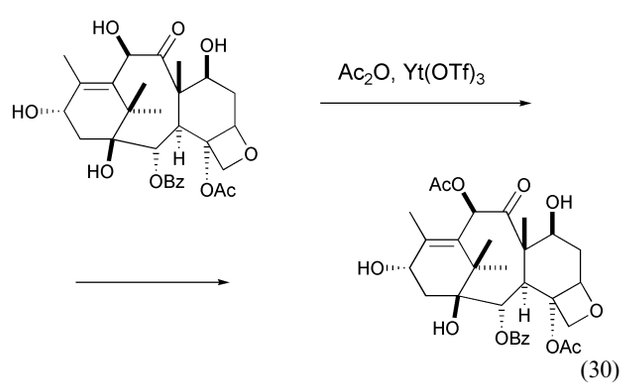
(28)

An opposite chemoselectivity in the monoacylation of unsymmetric diols was achieved by the preliminary conversion of diols into dibutylstannylene acetals followed by the acylation (eqn. (29)). The reason for the unusual chemoselectivity is the reversibility of the opening of dibutylstannylene acetals on the first stage of the reaction. As a result, the major product after the first stage is the secondary ester which is more thermodynamically stable as the most bulky chlorodibutyltin group is attached to the less hindered primary position. The initial selectivity is in the range of 2–4 : 1 but the subsequent silylation or acylation of the resultant stannyl monoesters provided much higher chemoselectivities.[49]



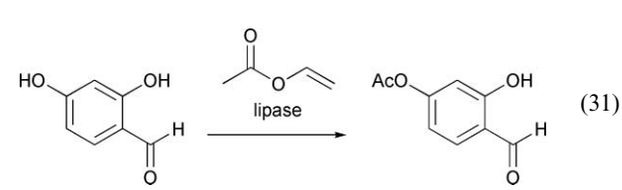
(29)

Chemoselectivity can also be achieved through the Lewis acid assisted formation of chelate complexes with a neighboring group. Only small (1–3 mol%) quantities of ytterbium triflate catalysts produce selective acylation of Taxol derivatives with acetic anhydride giving >95% selectivity as shown in eqn. (30).[50] Other lanthanide Lewis acids provided similarly high chemoselectivity but substantially slower reaction rates. The reaction mechanism and chemoselectivity are probably common to other lanthanide Lewis acid catalyzed acylations[36,37] and involve the formation of a cyclic transition state.



(30)

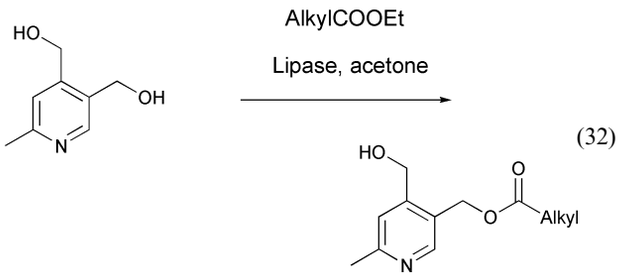
Formation of chelate complexes with copper salts was also used for the selective esterification of polyhydroxyanthraquinones.[51] A substantial chemoselectivity between *metalpara vs. ortho* hydroxy groups in carbonyl-substituted polyphenols was achieved in an enzymatic transesterification (eqn. (31)).[52]



(31)

The difference in steric environment for secondary hydroxy groups can be substantial enough to ensure selective acylation in the case where one of them is attached to a cyclic scaffold. Numerous examples of high chemoselectivity in acylations of this type of substrates are known in the chemistry of natural products, especially carbohydrates[56] and steroids.[53]

Selective acylation of sterically and electronically similar hydroxy groups in non-symmetric diols and polyols can be efficiently achieved using enzymatic methods. Despite the remarkable selectivity achieved in selected cases like monoacylation of rather similar primary hydroxy groups, as shown in eqn. (32),[54] the prediction of chemoselectivity is somewhat complicated. A number of enzymatic reactions have been reviewed.[55]



(32)

Selective acylation of carbohydrates is a highly important application of chemoselective esterification. A number of methods targeting both the selective acylation of primary *vs*. secondary as well as different secondary hydroxyls in partially protected and non-protected carbohydrates have been developed. A substantial part of older accumulated experimental data before 1975 has been thoroughly reviewed.[56] Most results in chemoselective esterification of carbohydrates, however, are not general and are restricted for certain types of carbohydrates. Since the publication of the reviews,[56] there has been a substantial advance in the field of selective protection of carbohydrates involving enzymatically catalyzed transesterification of enol, trifluoromethyl, and oxime esters.[57] Enzymatic methods may provide selective acylations of primary *vs*. secondary hydroxy groups and *vice versa*, as well as highly selective discrimination between different secondary hydroxyls.

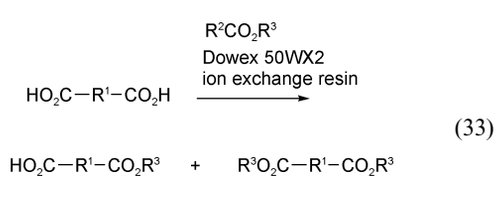
Monoesterification of symmetric dicarboxylic acids

Selective esterification of organic molecules possessing multiple acidic functionalities is an important process both in research and industry. Selective esterification of carboxylic groups in the presence of other acidic groups like -P(O)OH and SO_3H is facile using acid catalyzed esterifications, which provide exclusively esters of carboxylic acids. At the same time, selective monoesterification of di- and polycarboxylic acids demands special methods.

Selective monoesterification of symmetric dicarboxylic acids

For symmetric dicarboxylic acids capable of forming 5- or 6 membered cyclic anhydrides monoesterification through the corresponding cyclic anhydrides is straightforward. Malonic acid cannot form cyclic anhydrides but it can be monoesterified with a variety of alcohols using carbodiimide couplings[58]. The reaction proceeds through ketene intermediates and provides good chemoselectivity and yield.

Monoesterification of longer chain dicarboxylic provides a substantial synthetic challenge and in many cases statistical mixtures of the diacid, mono-, and diesters are obtained. However, careful control of experimental conditions and reaction kinetics can provide substantially better than statistical selectivity although very few examples of such selectivity have been reported. The difference in the hydrophilicity between carboxylic and esters functionalities is the most promising way for obtaining selective monoesterification. Strongly acidic ion-exchange resins catalyze the transesterification of symmetric acids in aliphatic ester–octane/hexane mixture (eqn. (33)) providing the corresponding monoesters with at least 10 : 1 chemoselectivity[59] at 70–95% conversions. Other



(33)

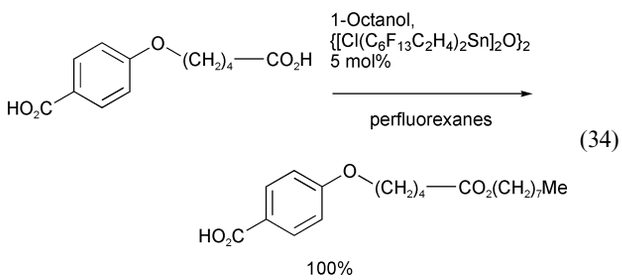
$R^1 = (CH_2)_{4\text{-}12}$; 1,2- or 1,4-cyclohexyl; CH=CH

strongly acidic ion-exchange resins were found to work similarly.

This methodology is similar to the one used in the monoacylation of symmetric diols.[39] The mechanism of the selectivity is the preferential solubility of the diacid in the aqueous layer formed on the surface of the strongly acidic ion-exchange resins beads. Other methods developed for the selective monoacylation of 1,ω-diols[40,41] may well be applicable for 1,ω-dicarboxylic acids.

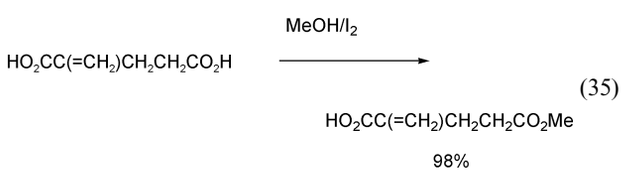
Selective esterification of non-symmetric carboxylic acids

Numerous examples provide evidence that the conjugation of carboxylic groups with an aromatic ring or a double bond results in a substantial decrease of esterification rates. A careful monitoring of the reaction progress enables the selective preparation of monoesters in conditions of acidic catalysis.[60] A complete discrimination between aromatic and aliphatic carboxylic acids can be obtained in a biphasic esterification of a 1 : 1 carboxylic acid : alcohol mixture using fluoroalkyldistannoxane catalysts (eqn. (34)).[44]



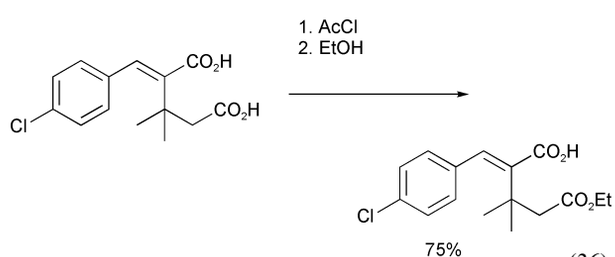
(34)

Similar considerations are behind a very high chemoselectivity in the esterification of methyleneglutaric acid with MeOH and iodine (eqn. (35)).[61] A high selectivity between saturated and aromatic/α,β-unsaturated carboxylic acids and excellent yields was achieved during the formation of methyl esters with CBr_4/MeOH systems.[62]



(35)

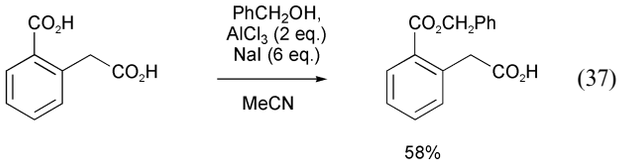
Opening of cyclic anhydrides possessing both types of carboxylic groups proceed in a similar way, producing selectively monoesters (eqn. (36)).[63]



(36)

Similarly high chemoselectivity is also obtained in lipase catalyzed esterifications.[64] The opposite selectivity has been very recently described, although without details about reaction mechanism. Treatment of aromatic and α,β-unsaturated carboxylic acids with primary, secondary, and tertiary alcohols in the presence of $AlCl_3$/NaI produced esters in good yields while no products of esterification of aliphatic carboxylic acids were found (eqn. (37)).

Selective esterification of non-symmetric carboxylic acids with two aliphatic carboxylic groups is more complicated and

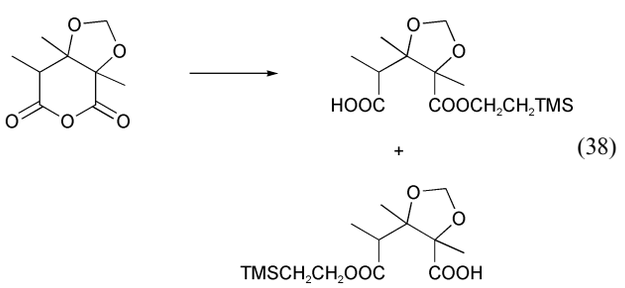


(37)

formation of mixtures of two possible monoesters and diester can be expected in many cases. The influence of steric effects on esterification rates of different carboxylic groups can be estimated on the grounds of data from esterification rates of substituted monocarboxylic acids.[65] In contrast to alcohols, the prediction of relative esterification rates of different carboxylic groups is not simple because the steric volume both in the α and β positions to the carboxylic group were found to influence the esterification rates. A large difference in esterification rates should be expected only in selected cases, for example for acids possessing three substituents in the α-position. Even in this case the outcome is not completely predictable.

A high degree of selectivity for the esterification of carboxylic acids with primary *vs.* tertiary substituents in the α-position were observed by using biphasic esterification of a 1 : 1 carboxylic acid : alcohol mixture with fluoroalkyl dibutoxystannane catalysts.[44] While direct competition results were not present, in all experiments carboxylic acids possessing a quaternary carbon atom in the α-position consistently showed a very low (<20%) yield of esters in the conditions providing >99.9% esterification yields for carboxylic acids like $PhCH_2CH_2COOH$.

At the same time, formation of mixtures (5 : 1) was observed in the cleavage of the non-symmetric anhydride shown in eqn. (38).[66]

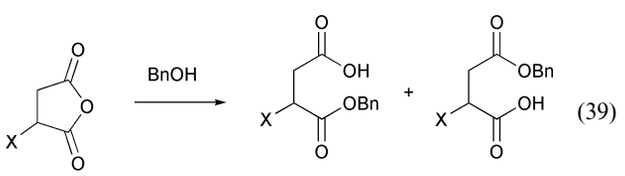


(38)

This difference in selectivity is similar to the one observed in the esterification of primary *vs.* secondary alcohols. Acid (protic or Lewis) catalyzed esterification consistently showed substantially higher sensitivity towards steric factors than reactions of various carboxylic acids derivatives in the conditions of basic catalysis.

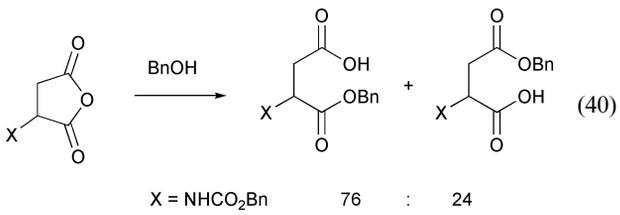
Electronic factors and chelation substantially influence the esterification rates of carboxylic acids but their influence on the chemoselectivity of esterification has not been systematically investigated. The importance of these factors on relative esterification rates is evident from the chemoselectivity of esterification of aspartic and glutamic acid derivatives.

Alcoholysis of hydrobromides of L-aspartic acid anhydrides[67] proceeds with a complete selectivity providing exclusively α-esters (eqn. (39)) owing to the presence of a strong electron-withdrawing group in the α-position. Triethylamine- or pyridine-catalyzed alcoholysis of a neutral *N*-benzyloxycarbonyl anhydride or diacid possessing a much weaker



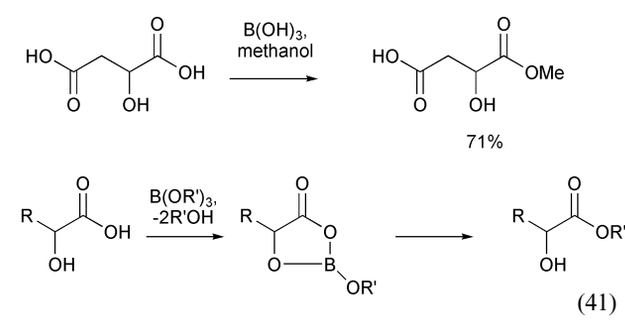
(39)

electron-withdrawing (acylamino) group in the α position (eqn. (40)) resulted in a much lower or even opposite chemoselectivity of the alcoholysis.[68]



(40)

The opposite chemoselectivity of esterification can be easily achieved through the esterification of the corresponding copper chelates of aspartic or glutamic acids.[69] Boric acid was found to efficiently catalyze the esterification of α-hydroxy carboxylic acids. The reaction involves the formation of the alkylboronate ester followed by the intramolecular transfer of the alcohol to the chelated carboxylic group as shows the eqn. (41). Carboxylic acids that do not contain a hydroxy group in α or β positions, including *N*-protected α-amino acids, do not undergo esterification under the reaction conditions. Malic acid can be monoesterified with a reasonable regioselectivity but minor amounts of diester are also formed indicating that β-hydroxy carboxylic acids can also be esterified by this method.



(41)

Relatively low selectivity based on different acidities could be obtained using the methylation of lithium salts of carboxylic acids.[70]

Existing kinetic data[71] on the hydrolysis and alcoholysis rates of substituted esters can be exploited to estimate the chemoselectivity of selective hydrolysis of diesters or alcohololysis of cyclic anhydrides. According to these data, the presence of a heteroatom (O, Hal) or another electron withdrawing (CN, CO) group in the α-position to the ester function provide at least a 50 times increase in its hydrolysis rates.

Enzymatic methods were successfully applied for the selective monoesterification of dicarboxylic acids and are especially useful in the cases where there are no substantial electronic or steric differences between the carboxylic groups.

Conclusions

Chemoselective esterification is an important field which continues to attract considerable attention. Existing methods reliably enable the selective acylation of alcoholic OH groups in the presence of thiol and phenolic functionalities by direct esterifications catalyzed by protic and Lewis acids. The opposite chemoselectivity can be easily obtained with basic catalysis. The use DMAP or pyridine catalysis, however, drastically reduces the chemoselectivity of the reaction.

Selective acylation of a hydroxy group in the presence of unprotected primary or secondary amino groups is possible but in most cases this route is less practical than indirect methods involving the protection of amino groups. Important exceptions are the esterification of amino acids and the *O*-acylation of aminophenols.

Selective monoacylation of polyols is easy in cases of a considerable difference in the steric environment of the hydroxy groups. A high degree of discrimination between primary, secondary, and tertiary hydroxy groups in polyols is possible with a number of reagents. Selective acylation of similarly sterically shielded hydroxy groups is possible if one of them selectively form chelate complexes. Enzymatic methods are capable of discrimination of similarly sterically shielded hydroxy groups but the chemoselectivity and reactivity in these reactions cannot be reliably predicted. Monoacylation of symmetric diols can be done with moderate to excellent selectivity if there is a substantial difference in hydrophilicity between the diols and their monoesters.

Selective esterification of aliphatic carboxylic groups in di- and polycarboxylic acids is possible in the presence of aromatic/α,β-unsaturated ones and *vice versa*. Different aliphatic carboxylic groups can be selectively esterified if selective chelation of one carboxylic group is possible. In contrast to polyols, the difference in steric shielding of carboxy groups alone usually provides only moderate chemoselectivity in esterification of dicarboxylic acids.

The development of molecular modeling methods for predicting the influence of the steric environment on the reactivity may provide a substantial advance in the field of chemoselective esterification.

Acknowledgements

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