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Selective esterifications of alcohols and phenols through carbodiimide couplings †

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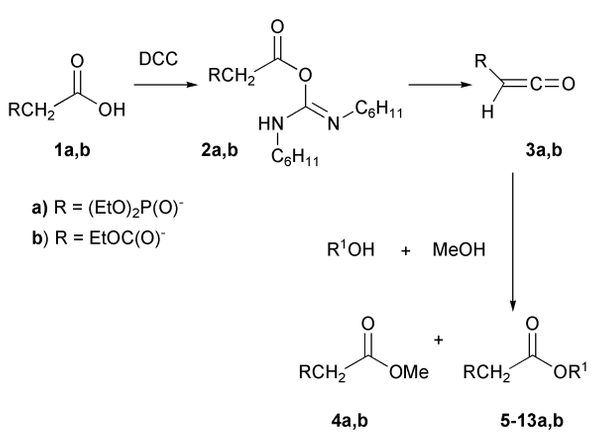
Esterification of carboxylic acids capable of forming ketene intermediates upon treatment with carbodiimides permits the selective acylation of alcohols in the presence of phenols lacking strong electron-withdrawing groups. The selectivity of acylations involving highly acidic phenols could be reversed through the addition of catalytic amount of acid. Esterification of other carboxylic acids was found to proceed through the formation of symmetric anhydrides and provide the opposite chemoselectivity. In both cases the relative acylation rates of substituted phenols are consistent with a reaction mechanism involving an attack of phenolate anions on electrophilic intermediates such as ketenes and symmetric anhydrides, with the carbodiimides serving both as an activating reagent and as a basic catalyst.

Introduction

The condensation of carboxylic acids with a variety of nucleophiles in the presence of dialkylcarbodiimides continues to be one of the most commonly used synthetic methods[1] despite the development of new reagents.[2] While the main application of carbodiimide couplings remains the formation of amide bonds,[3] this method is also highly useful for the preparation of anhydrides,[4] esters,[5] and thioesters.[6]

To adjust carbodiimide couplings to these multiple applications a number of coupling catalysts and additives have been proposed. *N*-Hydroxybenzotriazole (HOBt) and, to a lesser extent, *N*-hydroxysuccinimide (HOSu) as well as substituted phenols are widely used for the preparation of the corresponding active esters capable of the efficient acylation of amino groups in amino acids and peptides with low racemization. Acylation catalysts, mainly pyridine derivatives, are used to increase the reactivity of electrophilic species which is usually necessary for the preparation of esters through carbodiimide couplings.[7]

The nature of electrophilic species in the reaction has been a subject of a prolonged discussion.[8] While it is commonly accepted that *O*-acylureas of type **2** (Scheme 1) are the primary intermediates of the reaction, their formation and conversion into symmetric anhydrides are known to proceed at a comparable rate.[9] With such a variety of applications and modifications of carbodiimide couplings the problem of chemoselectivity of the method, particularly in the preparation of esters, has not been adequately addressed.



Scheme 1

Table 1 Acylation rates of alcohols and phenols with the carboxylic acids **1a**,**b**-DCC relative to methanol in MeCN at 25 °C

Product	R^1	k_{rel} for **1a**	k_{rel} for **1b**	p*K*a of R^1OH
5	$BrCH_2CH_2$–	0.12	0.69	14.4
6	$EtOCH_2CH_2$–	0.21	0.72	14.8
7	Ph–	<0.02	<0.02	9.9
8	4-$MeOC_6H_4$–	<0.02	<0.02	10.2
9	4-CNC_6H_4–	0.07	0.03	7.9
10	4-$NO_2C_6H_4$–	0.35	0.12	7.2
11	2,4,6-$C_6Cl_3H_2$–	14	2.1	6.0
12	C_6F_5–	3.5	0.69	5.5
13	C_6Cl_5–	1.5	0.10	4.7

We have recently described our results on the acylation of alcohols through ketene intermediates,[10] thus indicating that carboxylic acids, possessing a strong electron-withdrawing group in the α-position easily produce ketenes upon treatment with carbodiimides. The resulting ketenes were found to be highly efficient acylating reagents for sterically hindered substrates. In exploring potential applications of this method for polyfunctional substrates we examined the chemoselectivity of carbodiimide-induced esterifications and its dependence and the reaction mechanism.

Results and discussion

A Chemoselectivity of the esterification proceeding through ketene intermediates

Our initial studies were focused on the investigation of the influence of electron-withdrawing substituents in alcohols and phenol on their acylation rates using the competitive acylation of a mixture of substrates (Scheme 1) by carboxylic acids **1a**,**b** in the presence of DCC. All reaction products were independently prepared and characterized prior to the competition studies. Reactions were performed with 1 eq. of DCC and 2 eq. of each alcohol and the results are summarized in Table 1.[11,12]

As seen from Table 1, the introduction of electron withdrawing substituents into the beta position of aliphatic alcohols

† Electronic supplementary information (ESI) available: the characterization of new compounds and literature references for known compounds. See http://www.rsc.org/suppdata/ob/b3/b312559a/

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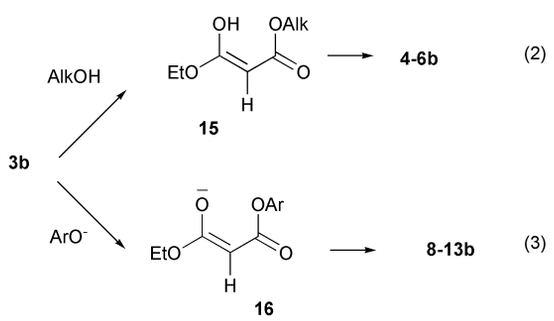
Table 2 The influence of $MeSO_3H$ on the chemoselectivity of the esterification of carboxylic acids **1a**,**b**

	Relative rate for 2,4,6-trichlorophenol : methanol	
Equiv. of $MeSO_3H$	k_{rel} for **1a**	k_{rel} for **1b**
0	14	2.1
0.05	2.3	0.77
0.10	0.38	0.13
0.15	0.08	0.02

substantially decreases the acylation rates for diethylphosphonoacetic acid (**1a**) but only slightly decreases the acylation rate for ethyl malonic acid (**1b**). This different influence can be attributed to the existence of a unique concerted (pseudopericyclic) mechanism of addition of alcohols or water to acylketenes of type **3b** (Scheme 2, eq 2).[13]



Scheme 2

Regular phenols were found to be much less reactive than aliphatic alcohols for both acids **1a**,**b** and therefore the acylation of even sterically hindered aliphatic hydroxy groups could be easily conducted in the presence of aromatic ones.[14] However, the presence of electron withdrawing groups in the phenols resulted in a dramatic increase in their acylation rates for both acids **1a**,**b** (Table 1) reaching a maximum for 2,4,6-trichlorophenol and decreasing for pentafluoro- and pentachlorophenols.

The opposite influence of electron withdrawing groups in alcohols and phenols on the acylation rates can be most reasonably explained by the existence of different mechanisms of acylation for alcohols and phenols. According to this hypothesis, while the reaction of ketene intermediates of type **3a**,**b** with alcohols proceeds through the concerted or zwitterionic transition state with a neutral molecule of an alcohol (Scheme 2, eq. 2), the acylation of phenols proceeds through a nucleophilic attack of phenolate anions on ketenes according to eq. 3, Scheme 2. Consequently, the increase in reaction rates for the formation of **7**–**11a**,**b** could be explained by a higher equilibrium concentration of the corresponding phenolate anions. The decrease in acylation rates for more acidic pentafluoro- and pentachlorophenols *vs*. 2,4,6-trichlorophenol could be explained by decreasing the nucleophilicity of the corresponding phenolates.

Since the equilibrium concentration of phenolate anions is pH dependent, their intermediacy in the reaction with ketenes of type **3a**,**b** could be verified by a variation in pH. It is expected that the addition of a strong acid should result in the suppression of the dissociation of phenols, thus causing a substantial decrease in their acylation rates. At the same time, this pH adjustment should not appreciably affect the acylation of an aliphatic alcohol, so the resultant decrease of pH must result in a substantial change in chemoselectivity of the reaction. Indeed a competitive acylation of acids **1a**,**b** with mixture of methanol and 2,4,6-trichlorophenol (Table 2) clearly illustrates the influence of methanesulfonic acid on relative rates of acylation

Table 3 Acylation rates of alcohols and phenols with the carboxylic acids **1c**,**d**-DCC system relative to phenol in MeCN at 25 °C

	XR[1]	k_{rel} for **1c**	k_{rel} for **1d**	pK_a of R[1]H
17	OMe	<0.02	<0.02	15
18	OCH_2Ac	<0.02	<0.02	14.2
19	OCH_2CF_3	<0.02	<0.02	12.4
20	OC_6H_4-2, 6-Me_2	<0.02	<0.02	10.6
21	OC_6H_4-2-Me	0.5	0.5	10.4
22	OC_6H_4-4-OMe	1	1	10.2
23	OC_6H_4-4-CN	30	20	7.9
24	O-2,4,6-$C_6H_2Cl_3$	20	70	6.0
25	OC_6H_4-4-NO_2	40	90	7.2
26	OC_6Cl_5	100	280	4.7
27	OC_6F_5	400	850	5.5
28	*N*-Oxysuccinimide	3×10^3	1×10^4	6.0
29	SCH_2CH_2OH	10	4	9.5
30	SCH_2CO_2Me	50	110	7.8

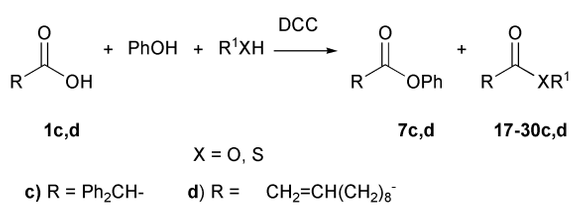
decreasing the ratio of 2,4,6-trichlorophenyl : methyl esters and eventually reversing of the chemoselectivity.

The deprotonation of phenols in these experiments could be reasonably explained by the basic properties of dialkylcarbodiimides used as coupling reagents. Unfortunately, because of the high reactivity of dialkylcarbodiimides, any experimental determination of their basicity is obviously complicated and indeed, to the best of our knowledge no such data is in the literature.[15] Some experiments, however, suggest the existence of basic catalysis from diisopropylcarbodiimide.[16]

B Chemoselectivity in esterification reactions proceeding through an addition–elimination pathway

The investigation of the chemoselectivity of esterification of acids **1a**,**b** prompted us to compare the obtained results with the chemoselectivity and mechanism of other, "conventional" carboxylic acids that are unable to produce ketene intermediates upon the treatment with carbodiimides. Despite a huge amount of preparative work involving the carbodiimide–carboxylic acid esterifications, neither the chemoselectivity nor the mechanism of the reaction are known in detail.[17] It is known that the reaction *per se* does not provide adequate yields of esters and several modifications involving the addition of acylation catalysts such as pyridine or DMAP, have been used,[7] albeit without chemoselectivity studies.

As with carboxylic acid **1a**,**b** we studied the chemoselectivity of esterification of carboxylic acids **1c**,**d** using the competitive acylation of a mixture of two substrates (Scheme 3). Reaction products **21**–**30c**,**d** were prepared and characterized before the competition studies. Relative rates of esterification of carboxylic acids **1c**,**d** were measured using excess of alcohols/phenols in acetonitrile solutions with 1 eq. of DCC. Reaction mixtures were analyzed by ^{1}H NMR and the results are summarized in Table 3 (the rate with PhOH is taken as 1).



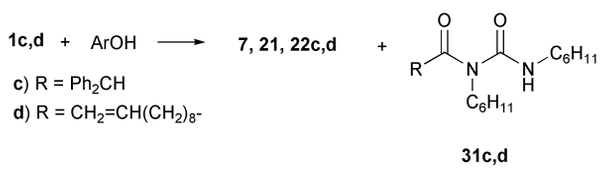
Scheme 3

As seen from Table 3, aliphatic alcohols did not produce any detectable (by ^{1}H NMR) amounts of acylation products. Instead, the ^{1}H NMR spectrum of the reaction mixture showed only peaks of the corresponding symmetric anhydrides and *N*-acylureas that do not undergo any reaction with alcohols under these reaction conditions.[18] Even if alcohols (methanol) are used as reaction solvents only minor amounts of the

corresponding esters could be observed. Numerous data involving successful esterifications in the presence of acylation catalysts such as pyridine and dimethylaminopyridine[5,7a] should be attributed to the activation of the intermediate symmetric anhydride or, less likely, a direct trapping of *O*-acyl isourea intermediate. More acidic alcohols like trifluoroethanol and acetol[19] under the reaction conditions also did not produce any appreciable amounts of the corresponding esters.

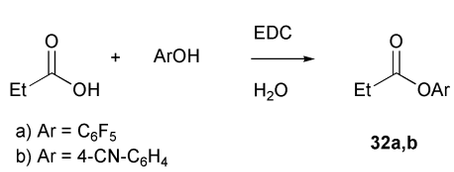
In contrast to aliphatic alcohols, the reactions with phenols proceeded smoothly giving the corresponding aryl esters as major reaction products. Carbodiimide couplings of carboxylic acid **1c**,**d** with substituted phenols provided isolated yields of the esters **7c**,**d**, **22c**,**d** in the range of 70–75% and that of the esters **23**–**27c**,**d** in the range of 88–98%. Aromatic acids reacted similarly and benzoic acid produced 4-methoxyphenyl ester in a 75% yield. We were surprised to find only a few isolated reports describing acylation of regular phenols with carbodiimides.[20] In contrast, reactions of carboxylic acid–carbodiimide systems with pentachloro-, pentafluoro-, and 4-nitrophenol as well as *N*-hydroxysuccinimide and *N*-hydroxybenzotriazole, have been extensively used for decades for the preparation of active esters.[21] In line with their acidity thiols were also acylated smoothly to give thioesters **29**, **30c**,**d**.

Acylation of phenol and 4-methoxyphenol with carboxylic acids **1c**,**d** is accompanied by the formation of *ca*. 20% of *N*-acyldicyclohexyl ureas **31c**,**d** (Scheme 4).[22] No traces of *N*-acyldicyclohexyl ureas **31c**,**d** have been detected in reactions with more reactive phenols.



Scheme 4

The difference in acylation rates between aromatic and aliphatic hydroxy groups is substantial and therefore can be useful for chemoselective acylation of polyfunctional substrates containing both types of hydroxyls. It should be mentioned that the commonly used DMAP catalysis for carbodiimide couplings substantially decreases this chemoselectivity.[14a] Moreover, this difference in reactivity could be used for conducting esterification in aqueous solutions (Scheme 5). In order to compensate for the hydrolysis of intermediate *O*-acylisoureas more than 1 eq. of carbodiimide should be used. The necessary excess of carbodiimide depends on the reactivity of the phenol and its concentration. For propionic acid and 1 M concentrations of reagents acceptable yields of pentafluorophenyl **32b** (79%) or 4-cyanophenyl **32a** (62%) esters could be obtained with 2 eq. of water-soluble carbodiimide EDC.[23] Similarly, the treatment of an aqueous solution of propionic acid with EDC (2 eq.) in the absence of phenols produced propionic anhydride (70%).

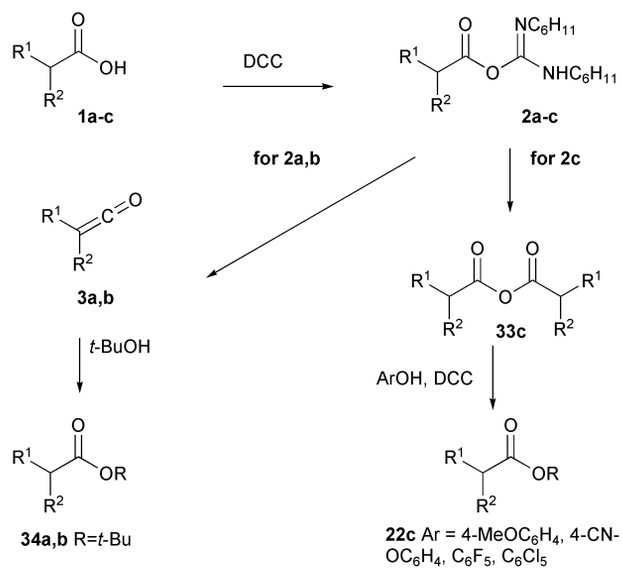


Scheme 5

As in the case of carboxylic acids **1a**,**b**, the comparison of the reactivities of phenols possessing similar steric properties like tri-/pentachlorophenol or phenol/4-cyanophenol/4-nitrophenol shows a clear correspondence between acylation rates and their pK_a values pointing to the participation of phenolate anions in the nucleophilic attack on a reactive intermediates.

C The intermediacy of symmetric anhydrides in esterifications

According to literature data, depending on reaction conditions, both protonated *O*-acyl isourea and symmetric anhydrides can be active intermediates.[24,25] In order to determine the reactive species in the esterification of phenols the acylation of 4-methoxyphenol with a deficiency of DCC (Scheme 6 and Table 4) was carried out. As seen from Table 4, when less than 0.5 eq. of DCC were added, only minor amounts of the ester **22c** could be observed while the anhydride **33c** was the main reaction product. The anhydride **33c** was also separately prepared by the treatment of the acid **1c** with 0.5 eq. of DCC. The addition of 4-methoxyphenol and 0.5 eq. of DCC to the preformed anhydride **33c** produced ester **22c** with the yield that was identical to the original procedure.



a) R^1=$(EtO)_2P(O)$, R^2=H; **b**) R^1=EtO_2C, R^2=H; **c**) R^1= R^2= Ph

Scheme 6

Similar results for the esterification of carboxylic acid **1c** with 0.5 eq. of carbodiimide were also obtained for other phenols (Table 4). In all these cases variable amounts of anhydride **33c** were detected in the reaction mixture (except the acylation of *N*-hydroxysuccinimide) that decreased for more reactive phenols.

These results are consistent with the formation of the symmetric anhydrides of type **33c** on the first step of the reaction with DCC followed by a slower reaction of the resultant anhydride **33c** with phenol, and not with a direct trapping of *O*-acylisourea intermediates of type **2** (Scheme 6). While it is known that anhydrides do not acylate alcohols or phenols in the absence of acylation catalysts the presence of DCC could provide the necessary basic catalysis for the deprotonation of phenols.[16] Indeed, we found that acetic anhydride readily acetylates 4-methoxyphenol, pentafluorophenol, and pentachlorophenol in the presence of 0.5 eq. of DCC producing the corresponding acetate esters with good yields. No reaction with 4-methoxyphenol without DCC or with DCC in the absence of phenols took place. It could be concluded that in these reactions the molecule of carbodiimide provides the basic catalysis for the acylation of phenols with symmetric anhydrides and converts the released carboxylic acid back into a symmetric anhydride.

Analogous symmetric anhydrides could also be considered as intermediates in reactions of carboxylic acids **1a**,**b** serving as precursors for ketenes of type **3a**,**b**. However, in contrast to diphenylacetic acid (**1c**), analogous reactions with *tert*-butanol in the deficiency of DCC (Table 4) failed to produce even traces of the corresponding anhydrides **33a**,**b** (according to ^{1}H NMR

Table 4 Effect of DCC deficiency on the esterification of carboxylic acids **1a**–**c**

Acid	Equiv. of DCC	Ester[a]/mol%	Acid/mol%	Anhydride/mol%
1c	0.2	3 (**22c**)	61 (**1c**)	18 (**33c**)
1c	0.4	9 (**22c**)	43 (**1c**)	48 (**33c**)
1c	0.5	12 (**22c**)	12 (**1c**)	75 (**33c**)
1c	0.6	42 (**22c**)	7 (**1c**)	52 (**33c**)
1c	0.8	78 (**22c**)	5 (**1c**)	17 (**33c**)
1c	1.0	100 (**22c**)	0 (**1c**)	0 (**33c**)
1c	0.5	38 (**23c**)	34 (**1c**)	28 (**33c**)
1c	0.5	21 (**24c**)	27 (**1c**)	52 (**33c**)
1c	0.5	41 (**27c**)	45 (**1c**)	14 (**33c**)
1c	0.5	43 (**28c**)	57 (**1c**)	0 (**33c**)
1a	0.2	20 (**34a**)	80 (**1a**)	0 (**33a**)
1b	0.2	18 (**34b**)	82 (**1b**)	0 (**33b**)
1a	0.4	41 (**34a**)	59 (**1a**)	0 (**33a**)
1b	0.4	40 (**34b**)	60 (**1b**)	0 (**33b**)

[a] Ester **22c** is contaminated with 20% *N*-acylisourea **31c**.

analysis of the reaction mixture) giving instead equivalent amounts of the *tert*-butyl esters **34a**,**b** as sole reaction products. It should be therefore be concluded that for carboxylic acids **1a**,**b** the elimination of dicyclohexyl urea and the formation of ketenes of type **3a**,**b** proceed at a much higher rate than the formation of symmetric anhydrides of type **33a**,**b**.

Conclusions

Carboxylic acids that are capable of forming ketenes upon the treatment with DCC preferably acylate aliphatic hydroxy groups in the presence of aromatic ones while carboxylic acids possessing only alkyl or aryl groups in the α-position provide the opposite chemoselectivity. The relative acylation rates of the substituted phenols in all cases are consistent with a reaction mechanism involving an attack of phenolate anions on electrophilic intermediates such as ketenes and symmetric anhydrides, with the carbodiimides serving both as an activating reagent and as a basic catalyst.

Experimental

General

Unless otherwise stated, all reagents used are from commercially available sources. The characterization of new compounds and literature references for known compounds are provided as ESI. †

General procedure A for the preparations of esters 5–13a,b

To a solution of carboxylic acid **1a**,**b** (1 mmol) and a corresponding alcohol/phenol (1 mmol) in acetonitrile (5 ml) was added a solution of DCC (1 mmol) in acetonitrile (1 ml). After 15 min the reaction mixture was filtered, the filtrate was evaporated and purified by flash chromatography. During chromatography compounds **9**–**13a**,**b** undergo rapid hydrolysis on silica gel so isolated yields were very low (10–25%). Compounds **9a**,**10a** cannot be isolated by chromatography or vacuum distillation and ^{1}H NMR spectra of reaction mixtures before chromatography are provided as ESI. †

General procedure B for the determination of relative rates of esterification of acids 1a,b

To a mixture of two substrates (1 mmol of each) and carboxylic acid **1a**,**b** (0.5 mmol) in acetonitrile (5 ml) was added DCC (0.5 ml of 1 M solution in acetonitrile). The reaction mixture was stirred for 1 h at room temperature, filtered, and evaporated. After integration of peaks of α-hydrogens in the ^{1}H NMR of the residue relative rates were calculated using the ratio of logarithms.

General procedure C for the determination of relative rates of acylation in the presence of methanesulfonic acid

To a mixture of methanol (1 mmol), trichlorophenol (1 mmol), methanesulfonic acid (0, 0.025, 0.05, 0.075 mmol) and carboxylic acid **1a**,**b** (0.5 mmol) in acetonitrile (5 ml) wass added DCC (0.5 ml of 1 M solution in acetonitrile). The reaction mixture was stirred for 30 min at room temperature, isopropanol (2 mmol) was added to be used for detecting possible transesterification, and the reaction mixture was filtered, and evaporated. After integration of characteristic peaks in the ^{1}H NMR of the residue relative rates were calculated. ^{1}H NMR of the reaction mixture did not show any visible signals of protons associated with isopropyl ester group indicating that no appreciable acid-catalyzed transesterification took place in the work-up.

General procedure D of esterification of carboxylic acids 1c,d

To a solution of carboxylic acid **1c**,**d** (1 mmol) in acetonitrile (5 ml) were consequently added a solution of a phenol or a thiol (1.2 mmol) in acetonitrile (1 ml) and a solution of DCC (1 mmol) in acetonitrile (1 ml). The reaction mixture was stirred for 1 h at room temperature, the residue was evaporated, dissolved in 7 : 3 ethyl acetate : 40–60 petroleum ether mixture (20 ml), and filtered through a cintered glass. The filtrate was washed with 1 M NaOH (3 × 5 ml), brine, dried, and evaporated. Resulting aryl esters **23**–**30c**,**d** were pure and could be used in this form. Aryl esters **7c**,**d**, **21**–**22c**,**d** contain approx. 20% of *N*-acyl ureas and were purified by column chromatography.

General procedure E for the determination of relative rates of esterification of acids 1c,d

To a mixture of two substrates (1 mmol of each) and carboxylic acid **1c**,**d** (0.5 mmol) in acetonitrile (5 ml) was added DCC (0.5 ml of 1 M solution in acetonitrile). The reaction mixture was stirred for 1 h at room temperature, filtered, and evaporated. After integration of characteristic peaks in the ^{1}H NMR of the residue, relative rates were calculated. Relative rates for compounds **21**–**23c**,**d**, **29c**,**d** were calculated with competition against phenol. Relative rates for compounds **24**–**27**, **30c**,**d** were calculated with competition against 4-cyanophenol and recalculated to phenol. Relative rates for *N*-hydroxysuccinimide (compounds **28c**,**d**) were calculated against pentafluorophenol using 1.2 eq. *vs*. 4 eq. ratio.

General procedure F for the esterification of propionic acid in water solutions using EDC

To a solution of propionic acid (1 mmol) and a phenol (1.1 mmol) in water (1 ml) was added neat EDC. The reaction mixture was stirred 10 min at room temperature, and was

extracted by 3 : 7 ethyl acetate : 40–60 petroleum ether mixture (20 ml), washed with 1 M NaOH, brine, dried, and evaporated.

General procedure G for the preparation of symmetric anhydrides 33c–d

To a solution of carboxylic acid **1c**,**d** (1 mmol) in dichloromethane (5 ml) was added a solution of DCC (0.5 mmol) in dichloromethane (1 ml). The reaction mixture was stirred for 1 h at room temperature, the residue was evaporated, dissolved in 3 : 7 ethyl acetate : 40–60 petroleum ether mixture (20 ml), and filtered through a cintered glass. The filtrate was washed with 1 M NaOH (3 × 5 ml), brine, dried, and evaporated, the residue was purified by flash chromatography.

General procedure H for reactions with deficiency of DCC

To a solution of carboxylic acid **1a**–**c** (1 mmol) in acetonitrile (5 ml) were consequently added a solution of 1.2 mmol of 4-methoxyphenol (for **1c**) or *t*-BuOH (for **1a**,**b**) in acetonitrile (1 ml) and a solution of 1 M solution of DCC in acetonitrile (0.2–1.0 ml). The reaction mixture is stirred for 1 h at room temperature, the residue is evaporated, filtered, evaporated, and the residue was analyzed by ^{1}H NMR.

General procedure I for the acylation of phenols with acetic anhydride

To a solution of a phenol (1 mmol) and acetic anhydride (0.5 mmol) in acetonitrile (2 ml) is added a solution of DCC in acetonitrile (0.5 mmol). The reaction mixture is stirred for 1 h at room temperature, filtered, and evaporated to give the acetylated phenols.

Acknowledgements

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