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Mild Method for the Selective Esterification of Carboxylic Acids Based on the Garegg−Samuelsson Reaction

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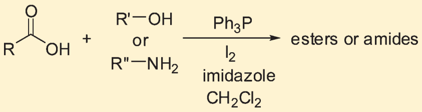
Supporting Information

ABSTRACT: A mild method for the selective esterification of primary alcohols is described. The use of different phosphines, I_2, and imidazole allows the selective esterification of a wide variety of acids with excellent results. The generation of a bulky phosphonium-carboxylate salt as intermediate could justify the selectivity observed in this process. Additionally, amides also can be synthesized with use of this method.

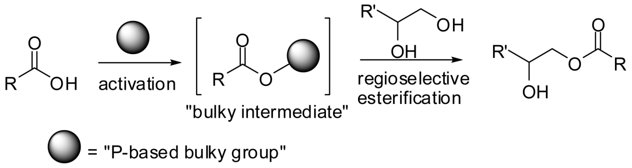


Esters are important products in chemical and pharmaceutical industries, and have been widely used in the production of valuable compounds such as polymers, fragrances, or fatty acids,[1] reaching 25% of all the chemical operations involved in the synthesis of pharmaceuticals.[2,3] For these reasons, esterification of carboxylic acids constitutes a very important and widespread process in organic synthesis and, consequently, numerous chemical methods have been described to accomplish this basic transformation.[4−10] Recent advances have focused on methods able to develop group-tolerant mild reaction conditions, and selective methods able to discriminate between primary and secondary alcohols. Although mild methods have been developed with success, fewer methods have succeeded in the development of a highly regioselective process. It is worth noting that in the synthesis of complex organic compounds where a multitude of functional groups coexist, regioselective reactions are frequently needed, and indeed, group protection reactions as esterifications are highly valuable.

In the present work we have developed a mild and selective esterification reaction (Scheme 1), able to discriminate between primary and secondary alcohols, via formation of a bulky phosphonium-carboxylate salt,[11] based on the Garegg−Samuelsson reaction.[12] The Garegg−Samuelsson reaction is a S_N2-type process used for the efficient conversion of primary and secondary hydroxyl groups into iodo groups, via formation of a $[Ph_3P-OR]^+$ intermediate, which activates the hydroxyl group, favoring the attack of the iodide anion. Inspired by this process, we deemed that the use of similar conditions to the Garegg−Samuelsson reaction could activate "in situ" the hydroxyl group of the carboxylic acid, facilitating the nucleophilic attack of the alcohol or amine, to yield the corresponding ester or amide. Moreover, this method allows the use of different Tolman's cone phosphines that can direct a highly selective process.[13]

To check the feasibility of this process, we applied the Garegg−Samuelsson conditions (1.5 mmol of Ph_3P, 1.5 mmol of I_2, and 3.3 mmol of imidazole in CH_2Cl_2 at room temperature) to the esterification of a model acid **1** with methanol (1.5 mmol). In this way, we obtained the ester **2** with an excellent 92% yield, showing the viability of this procedure for the esterification of carboxylic acids. Encouraged by this excellent result, we decided to optimize the reaction conditions, studying several phosphines with different steric character,[13] heterocyclic bases, and other polar solvents. The results are given in Table 1.[14]

Scheme 1. Selective Esterification of Primary Alcohols



The best results were obtained with imidazole as base and CH_2Cl_2 as solvent, which corresponds with the Garegg−Samuelsson's-type conditions.[12] Other similar heterocyclic bases such as pyridine, 3,5-dimethylpirazole (3,5-DMP), or 2,4,6-collidine (2,4,6-col) (entries 7−9) were also tested, but the results were worse than with imidazole. In the absence of base, the reaction works, but under strong acidic conditions. Additionally, a set of solvents were also studied, yielding in all cases lower yields than with CH_2Cl_2. On the other hand, when other phosphines with different electronic and steric characteristics were used, such as tricyclohexylphosphine (Cy_3P) or $(o\text{Tolyl})_3P$, the results were excellent (entries 2−4).

Using these optimized conditions, we extended our study to the esterification/amidation of model acid **1** with different alcohols (primary and secondary), phenol, and amines (mono- and disubstituted) to determine the scope of this procedure. The results are given in Table 2.

The results obtained in the esterification/amidation of model acid **1** under the optimized reaction conditions were, in general,

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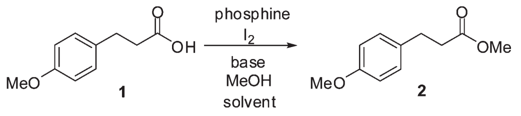
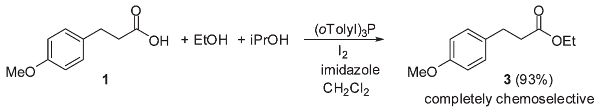
Table 1. Esterification of Acid 1 with MeOH, Using Different Reaction Conditions



entry	phosphine[a]	base[b]	solvent	yield (%)
1	Ph_3P	imidazole	CH_2Cl_2	92
2	$(Cy)_3P$	imidazole	CH_2Cl_2	97
3	Ph_2(*p*Tolyl)P	imidazole	CH_2Cl_2	92
4	(*o*Tolyl)$_3$P	imidazole	CH_2Cl_2	100
5	$P(OEt)_3$	imidazole	CH_2Cl_2	N.R.
6	Ph_3P	-	CH_2Cl_2	85
7	Ph_3P	pyridine	CH_2Cl_2	62
8	Ph_3P	3,5-DMP	CH_2Cl_2	N.R.
9	Ph_3P	2,4,6-col.	CH_2Cl_2	48
10	Ph_3P	imidazole	MeCN	10
11	Ph_3P	imidazole	THF	N.R.
12	Ph_3P	imidazole	DMF	9
13	Ph_3P	imidazole	AcOEt	8
14	Ph_3P	imidazole	toluene	20

[a] 1.5 mmol was used. [b] 3.3 mmol was used. N.R.: No reaction.

Scheme 2. Chemoselective Esterification of Acid 1 in the Presence of a Mixture of EtOH and *i*PrOH



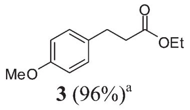
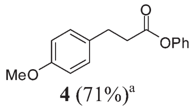
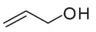
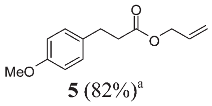
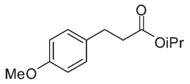
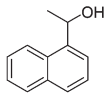
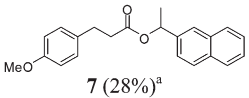
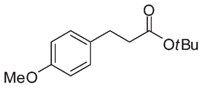
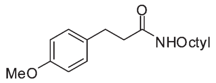
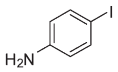
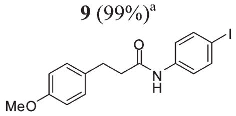
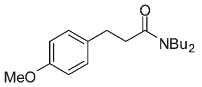
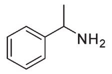
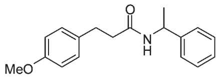
good to excellent. Thus, when alcohols and phenol were used (entries 1−6) we obtained the corresponding esters in excellent yield, but only when primary alcohols were used. However, when more hindered hydroxyl groups (secondary or tertiary, entries 4−6) were studied, poor results or no reaction products were observed.[15] When (*o*Tolyl)$_3$P was used instead of Ph_3P, the yields of the esterifications were decreased to 20% and 9%, respectively (entries 4 and 5), showing that a selective use of more hindered phosphines[13] would allow the selective esterification of primary alcohols in the presence of secondary alcohols. The same trend was observed when Cy_3P was used. Thus, when we treated acid **1** with a mixture of EtOH (1.5 mmol) and *i*PrOH (1.5 mmol) in the presence of Ph_3P or (*o*Tolyl)$_3$P, 92%[16] and 93% yields of ester **3** were obtained, respectively (Scheme 2). Additionally, treatment of diol **13** under the same reaction conditions led exclusively to the regioselective esterification of the primary alcohol (compound **14**, 99% yield, Scheme 3),[17] showing again the high selectivity of our process.

The excellent chemical profile of our method may contribute to a precise control over the individual reactivity of functional groups within a complex molecular architecture, allowing the use of less protective groups, which constitutes an important objective in modern organic chemistry.[18]

In the case of amidation reactions (entries 7−10), good to excellent yields of the corresponding amides (**9**−**12**) were obtained, both for primary and secondary amines, showing that our method is also a good alternative to the known amidation processes.[5a]

Once we studied the usefulness of our method for the different kinds of alcohols, we decided to establish the versatility of our process. For it, we extended the method to other acids with different functional groups, such as multiple C−C bonds, labile

Table 2. Esterification/Amidation of Acid 1, with Different Alcohols/Amines under the Optimized Reaction Conditions

Entry	Acid	Alcohol	Product
1	**1**	EtOH	 **3** (96%)[a]
2	**1**	PhOH	 **4** (71%)[a]
3	**1**		 **5** (82%)[a]
4	**1**	*i*PrOH	 **6** (37%)[a] (34%)[b] (20%)[c]
5	**1**		 **7** (28%)[a] (7%)[b] (9%)[c]
6	**1**	*t*BuOH	 **8** (0%)[a]
7	**1**	*N*-octylamine	 **9** (99%)[a]
8	**1**		 **10** (60%)[a]
9	**1**	nBu_2NH	 **11** (32%)[a]
10	**1**		 **12** (94%)[a]

[a] Ph_3P was used. [b] $(Cy)_3P$ was used. [c] (*o*Tolyl)$_3$P was used.

Scheme 3. Regioselective Esterification of Acid 1 with Diol 13

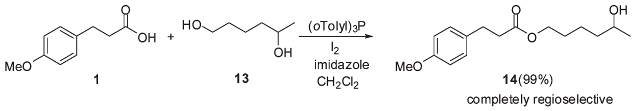
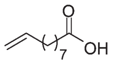
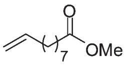
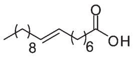
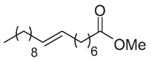
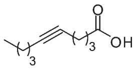
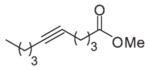
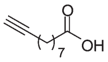
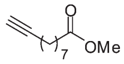
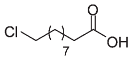
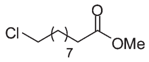
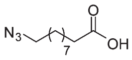
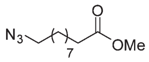
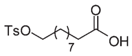
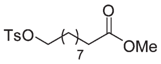
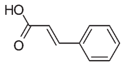
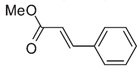
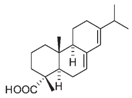
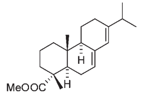
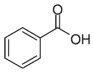
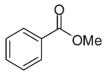
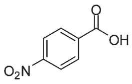
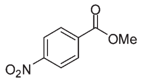
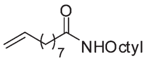
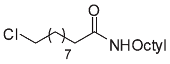
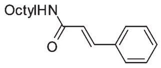
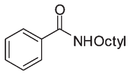


Table 3. Esterification/Amidation of Carboxylic Acids 15−25 under the Optimized Reaction Conditions

Entry	Acid	Alcohol	Product
1	 **15**	MeOH	 **26** (98%)
2	 **16**	MeOH	 **27** (100%)
3	 **17**	MeOH	 **28** (89%)
4	 **18**	MeOH	 **29** (91%)
5	 **19**	MeOH	 **30** (86%)
6	 **20**	MeOH	 **31** (90%)
7	 **21**	MeOH	 **32** (74%)
8	 **22**	MeOH	 **33** (79%)
9	 **23**	MeOH	 **34** (84%)
10	 **24**	MeOH	 **35** (70%)
11	 **25**	MeOH	 **36** (100%)
12	**15**	*N*-octylamine	 **37** (89%)
13	**19**	*N*-octylamine	 **38** (85%)
14	**22**	*N*-octylamine	 **39** (88%)
15	**24**	*N*-octylamine	 **40** (91%)

Scheme 4. Mechanistic Proposal for the Esterification/Amidation of Carboxylic Acids under the Garegg−Samuelsson's Type Conditions

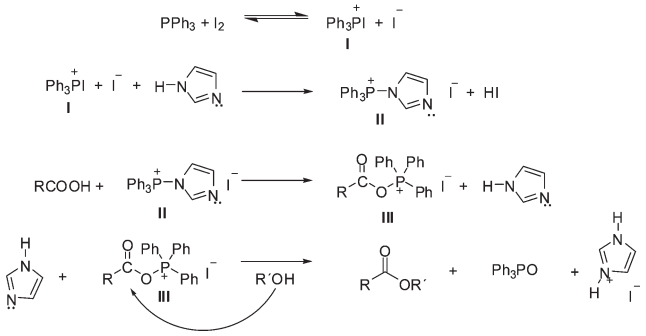


Table 4. ^{31}P Chemical Shifts for the Proposed Species

entry	species	chemical shift (ppm)	bibliographic shift (ppm)
1	Ph_3P	−5.51[a]	−5.5[23]
2	**I**	49.7[b]	49.7[c,24]
3	**II**	40.9[a]	
4	Ph_3PO	27.5[a]	23.7[b,23]

[a] CH_2Cl_2 was used as solvent. [b] In $CDCl_3$. [c] In $CHCl_3$.

groups which can suffer nucleophilic attack, aromatic rings, α,*β*-unsaturated carboxylic acids, etc., and we treated them under the optimized reaction conditions established above, using MeOH as alcohol for the esterification. Additionally, amidation reaction was also studied over some of these substrates, and *n*-octylamine was chosen for it. The results are given in Table 3.

To our satisfaction, the results obtained in the esterification of the acids **15**−**25** and amidation of acids **15**, **19**, **22**, and **24** were, in general, good to excellent. Thus, the reactions are completely compatible with the presence of alkenes and alkynes, both terminal and internal, and no products of addition of iodine over these multiple bonds were observed. Additionally, in the presence of labile functional groups prone to suffer nucleophilic attack, as halogen or tosyl groups (entries 5−7 and 13) the reaction was excellent, showing a good selectivity for this kind of compounds. Aromatic and α,*β*-unsaturated carboxylic acids gave also excellent yields (entries 8, 10−11, and 14−15). It is worth noting that relatively hindered abietic acid was efficiently methylated with our method (entry 9, 84%). Although several methods have been described for the methylation of these terpenic structures, normally using basic media and high temperatures,[19] our procedure proceeds under milder conditions, avoiding possible decomposition or collateral reactions with other functional groups present in the molecules, which is very important in the synthesis of complex natural products.[18]

As we mentioned above, our method for the esterification/amidation of carboxylic acids is based on the Garegg−Samuelsson reaction,[12] which proposes the formation of an alkoxyphosphonium intermediate that suffers the nucleophilic attack to generate the iodo compound.[12] The results obtained in our study suggested that a similar intermediate is formed in our reaction, between the hydroxyl group present in the carboxylic acid and the phosphine (intermediate **III**, Scheme 4), which has been previously proposed in other processes,[11] following a similar mechanism to that proposed by Garegg−Samuelsson for their reaction.[12] In our case, this carboxylic intermediate **III** would suffer the nucleophilic attack by the alcohol, to give the final ester compound. The formation of the different species proposed in the mechanism (see Scheme 4) has been studied by ^{31}P NMR experiences.[20] Thus, important changes in phosphorus chemical shifts were observed for the different Ph_3P derivatives (see Table 4), which suggested the formation of the proposed intermediates **I** and **II**.[21] In fact, the ^{31}P NMR signals observed matched those described for the proposed species. Although no spectroscopic data for the Ph_3P-imidazole species **II** are available, compounds with P−N bonds have been previously studied by ^{31}P NMR,[22] showing chemical shifts at 40 ppm, similar to that observed for our proposed intermediate.

The selectivity observed in our reaction could be explained by the formation of this much hindered intermediate **III**. Thus, when **III** suffers attack by primary alcohols, the corresponding ester is obtained easily. However, when more hindered alcohols are used, a bigger steric repulsion appears between the ligands of the phosphine and the substituents of the alcohols, avoiding the nucleophilic addition. However, we could not detect the intermediate **III** using ^{31}P NMR experiments, the signal corresponding to Ph_3PO appearing exclusively. This fact can be due to the high reactivity of the intermediate **III**, which in the absence of alcohol can suffer the attack of a second molecule of the acid to generate an anhydride and Ph_3PO.[25]

In conclusion, a mild, safe, and economic method for the esterification/amidation of carboxylic acids based on the Garegg—Samuelsson's type conditions is described. This method allows the selective esterification of primary alcohols in the presence of more hindered hydroxyl groups with complete selectivity, which may be of interest in the synthesis of polyfunctionalized substrates. The "in situ" activation of the carboxylic acid makes our method an excellent alternative to the known esterification procedures, useful for the synthesis of complex natural products.

EXPERIMENTAL SECTION

General Procedure for the Esterification/Amidation of Carboxylic Acids with Phosphine/I_2/Base. To a solution of I_2 (1.5 mmol) in dry CH_2Cl_2 (20 mL) was added the phosphine (1.5 mmol), giving the solution a brown-yellow color. Then, imidazole (3.3 mmol) was added, changing the color to light yellow. Subsequently, the carboxylic acid (1 mmol) was added and the solution was stirred for 5 min at room temperature, and then the alcohol or amine (1.5 mmol) was added. The mixture was stirred until completely consumption of the starting material (checked by TLC, around 12—24 h). Then, CH_2Cl_2 was added, and the solution was washed with 2 N HCl and water before being dried with anhyd Na_2SO_4 and the solvent removed. The residue was submitted to flash chromatography (EtOAc/hexane) to give the corresponding esters/amides. Products **2**—**12**, **14**, and **26**—**40** were purified by flash chromatography on silica gel (hexane:EtOAc) and characterized by spectroscopic techniques.[26] The yields obtained are reported in Tables 1—3.

ASSOCIATED CONTENT

Ⓢ Supporting Information. General experimental details, synthesis of acids **18**, **20**—**21**, ^{1}H NMR and ^{13}C NMR spectra of all new compounds, and ^{31}P NMR for proposed intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The esterification of **1** in MeOH, in the presence of highly acidic conditions (*p*TsOH, 10% mol) under reflux, yields 90% of ester **2**.

(15) In the case of secondary alcohols, amounts of iodination products from the classical Garegg—Samuelsson reaction were observed.

(16) Some amounts of compound **6** were obtained.

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(20) See the Supporting Information for more details.

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(25) To a preformed mixture of Ph_3P, I_2, and imidazole was added benzoic acid and the ^{13}C NMR was recorded immediately, showing the appearance of a new carbonyl signal corresponding to benzoic anhydride.

(26) All new compounds are fully described in the Supporting Information.