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Cerium(III) chloride-promoted chemoselective esterification of phenolic alcohols

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Dedicated to Professor Dr. Iwao Ojima on occasion of his 60th birthday

Abstract—A mild and operationally simple method for the chemoselective esterification of phenolic alcohols is described. The reaction overcomes the tyranny of protection, and capitalizes on the activation of acyl halides with cerium(III) chloride to selectively esterify alcohol hydroxyls in the presence of phenolic ones. The generality of the reaction was demonstrated with a series of phenolic alcohols of dietary relevance (vanillol, hydroxytyrosol, epicatechin), providing an expeditious entry into a series of compounds of relevance for biomedical research, some of which previously available only by enzymatic methods.

Despite the current excitement for the potential beneficial effects of polyphenols on human health,[1] there is still a great shortage of methods for the chemical modification and synthesis of these compounds, that generally occur as complex mixtures of analogues/homologues and are therefore difficult to obtain in pure form by isolation.[2] Of special relevance is the development of protocols to streamline the manipulation of hydroxy groups, releasing polyphenols chemistry from what has been cogently described as the 'protection racket'.[3] One of the most elementary synthetic problems in polyphenol chemistry is the chemoselective esterification of (poly)phenolic alcohols, since the ester moiety is widespread within dietary phenolics.[1] Under conditions of nucleophilic catalysis, phenols can be deprotonated, and therefore their reactivity in acylation reactions competes, and generally prevails, with that of alcohols.[3] The shift from acyl- to alkyl activation is an alternative and rational strategy to overcome this problem, and in previous work we have demonstrated the potential of the Mitsunobu reaction for the chemoselective esterification of phenolic alcohols.[3] Removal of the spent triphenylphosphine-azodicarboxylate redox pair, a major problem of the Mitsunobu reaction, could be solved in a simple way by gel-permeation on Sephadex LH-20.[3] However, relatively apolar compounds like the fatty esters of phenolic alcohols were not sufficiently retained by this stationary phase, and required a careful conventional chromatographic purification. Furthermore, when applied to secondary stereogenic centers, the Mitsunobu reaction leads to inversion of configuration, with breaching of the configurational integrity of a template, and unpredictable consequences on bioactivity. While undoubtedly an asset for diversity-oriented synthesis,[4] this stereochemical bias is a drawback for target-directed synthesis relying on a specific template.

To address these issues, we have investigated another mechanistic alternative to nucleophilic catalysis[5] for the acylation of phenolic alcohols, namely the Lewis acid catalysis by lanthanide salts.[6] Despite some nonencouraging literature precedents[7] and the sensitivity of polyphenolic alcohols to acids,[2] we found that, with

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the proper choice of promoter and acylating reagent, both issues could be solved.

The vanillyl ester **1c** is a simpler analogue of capsiate (**1b**), the nonpungent, NF-κB inhibitory[1] and fat-burning principle of bell peppers,[8] and shows the same biological profile of the natural product.[9] Its synthesis from vanillol (**1a**) was used to benchmark the effect of various Lewis acids and acylating reagents on the outcome of the esterification reaction, integrating proof of principle and target relevance. In a first set of experiments, cerium(III) chloride, indium(III) chloride and ytterbium(III) triflate were investigated (at 20% loading) as promoters, using THF as solvent and an equimolecular ratio of alcohol and acylating agent (chloride, anhydride). Indium(III) chloride was unable to promote the acylation of **1a** with nonanoyl chloride, while, as expected,[7] ytterbium(III) triflate gave a mixture of phenyl and alkyl esters. Conversely, cerium(III) chloride afforded nordihydrocapsiate (**1c**) as the only reaction product in a rewarding 53% yield. Though we had originally planned to screen a wider range of lanthanide salts, this promising result focused our attention on the use of cerium(III) chloride. Under the same conditions, nonanoic anhydride gave a disappointingly low conversion (15%), while a decrease of the lanthanide salt load to 0.5% had a remarkable upgrading effect on yield, that climbed to 70%. This somewhat unexpected result is presumably due to a decreased degradation of the reaction product, an unstable pro-quinoid compound,[10] in the reaction mixture. The optimized protocol[11] was next extended to the synthesis of other fatty esters of vanillol (compounds **1d**,**e**), obtaining yields comparable or even better to those achieved with the Mitsunobu esterification (see Table 1) (Fig. 1).

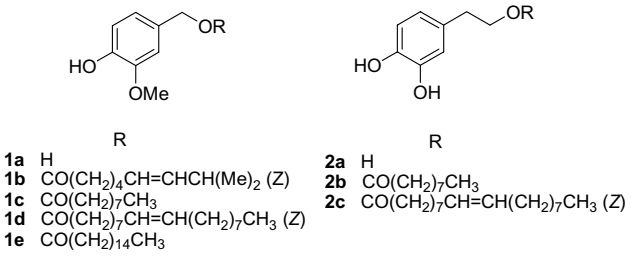

Figure 1.

Hydroxytyrosol (**2a**), the major antioxidant of olive oil,[12] was next investigated, since, in animal experiments, its fatty esters show potent protective activity against cardiovascular and neurodegenerative diseases.[13] The reaction of hydroxytyrosol, a catecholic alcohol, with nonanoyl and oleoyl chlorides afforded alkyl esters as the only reaction products (**2b**,**c**, 53% and 60% yield, respectively), validating the reaction also for nonbenzylic polyphenolic alcohols.[14] Due to the inorganic nature of the promoter and its use in catalytic amounts, the crude reaction mixtures were devoid of major impurities and could be purified in a quick way under normal aerobic laboratory conditions (Fig. 1).[15]

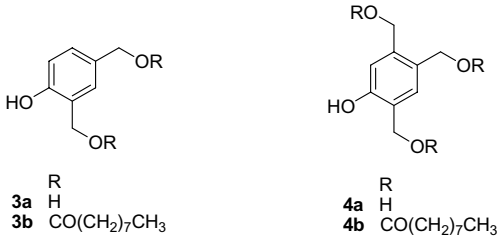

Figure 2.

Excellent chemoselectivity was also observed in the esterification of 2,4-bis(hydroxymethyl)phenol (**3a**) and 2,4,6-tris(hydroxymethyl)phenol (**4a**), two popular starting materials for the construction of dendrimers,[16] pointing to a broad utility of the reaction (Fig. 2).

Table 1. Acylation of (poly)phenolic alcohols with the couple $CeCl_3$–RCOCl[a]

Entry	Phenolic alcohol	Ester	Yield (%)
1	Vanillol (**1a**)	**1c**	70 (67)[b]
2	Vanillol (**1a**)	**1d**	60 (55)[b]
3	Vanillol (**1a**)	**1e**	58 (42)[b]
4	Hydroxytyrosol (**2a**)	**2b**	53 (41)[b]
5	Hydroxytyrosol (**2a**)	**2c**	52 (34)[b]
6	**3a**	**3b**	66
7	**4a**	**4b**	60
8	Epicatechin (**5a**)	**5b**	28[c]
9	Epicatechin (**5a**)	**5c**	26[c]
10	Epicatechin (**5a**)	**5d**	22[c]
11	Isoacetovanillol (**6b**)	**6c**	28
12	Isoacetovanillol (**6b**)	**6d**	27

[a] General conditions: THF (ca. 5 mL/mmol of substrate), RCOCl (1 mol equiv), $CeCl_3$ (0.05 mol equiv), rt.

[b] Yields from the Mitsunobu esterification (see Ref. 3 for the experimental conditions).

[c] No reaction occurred under the conditions of Mitsunobu esterification.[3]

To further extend the scope of the reaction, we investigated the esterification of epicatechin (**5a**), a labile flavan-3-ol. The esterification of the secondary hydroxyl of epicatechin gives compounds of remarkable antioxidant properties and a wealth of potential application in the realm of nutrition and of cosmetics.[17] Compounds of this type have never been prepared before by direct esterification of epicatechin, but only by enzymatic hydrolysis of its peracylated derivatives,[18] and their chemical synthesis is therefore a daunting task. Epicatechin (**5a**) was totally unreactive under the conditions of the Mitsunobu esterification, presumably because of steric congestion,[19] but its reaction with nonanoyl, oleoyl and palmitoyl chlorides afforded the corresponding 3-esters (**5b**–**d**) with excellent chemoselectivity, and overall yield (28%, 26% and 22%, respectively) more than acceptable for compounds of this type (Fig. 3).[20]

Esters of acetovanillol (**6a**) proved too elusive to be isolated because of their pro-quinoid nature, but the corresponding and more stable isoacetovanillol esters (compounds **6c**,**d**) could be synthesized and characterized (Fig. 3).[21]