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Boric Acid Catalyzed Chemoselective Esterification of α-Hydroxycarboxylic Acids

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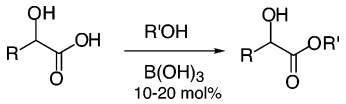
ABSTRACT



Boric acid catalyzes the selective esterification of α-hydroxycarboxylic acids without causing significant esterification to occur with other carboxylic acids. The procedure is simple, high-yielding, and applicable to the esterification of α-hydroxy carboxylates in the presence of other carboxylic acids including *β*-hydroxyacids within the same molecule.

Fischer esterification conditions, a strong protic acid in alcohol solvent, have been used for over a century to convert carboxylic acids to their corresponding carboxylate esters. Boron acids (i.e., boric and boronic) are useful catalysts for a number of synthetic transformations including manipulation of carbonyl-based functional groups and offer milder conditions relative to common mineral acids.[1] On the basis of the affinity of boronic acids for α-hydroxycarboxylic acids in both protic[2] and aprotic solvents[3] and the ability of boronates to catalyze amide formation,[4] we explored the possibility of using boric acid as a catalyst for selective ester formation. An example using boric acid as an esterification catalyst appeared as early as 1971,[5] but this involved high temperature and an additional protic acid. Here, we show that simply using 10−20 mol % boric acid in alcohol solution catalyzes the esterification of α-hydroxycarboxylates selectively at ambient temperature and that other carboxylates are unreactive to these reaction conditions.

As the results in Table 1 show, α-hydroxycarboxylic acids are converted to their methyl esters in excellent yields. Although sodium tetraborate and phenylboronic acid also catalyze this esterification, neither works as efficiently as boric acid at similar concentrations. The procedure is quite simple. In a typical reaction the carboxylic acid was dissolved in methanol, boric acid was added, and the reaction was stirred overnight at room temperature (18 h). When the reaction mixture was then concentrated under vacuum with mild heating (40−50 °C), the majority of the catalyst was removed as its methyl ester (trimethyl borate bp <70 °C).[6] If necessary, the product was further purified through a short silica column, but in most cases it was of sufficient purity for further synthetic manipulation. The reactions for tartrate and mandelate were run on a 2-g scale in 30 mL of methanol. Although fairly concentrated (ca. 0.45 M), this appeared to be sufficient dilution to avoid potential dimer or higher oligomer formation between hydroxyacids. With malic acid, however, significant amounts of diester (>10%) and dimer

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(6) While the reactions were not necessarily complete at room temperature, remaining conversion occurred during evaporation of the solvent under vacuum with heating.

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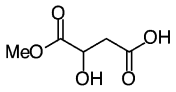
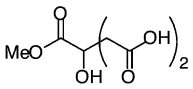
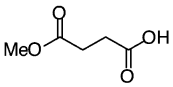
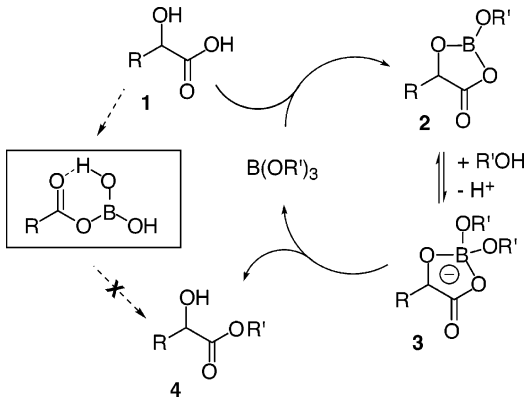
Table 1. Isolated Yields from Boric Acid Catalyzed (10 mol %) Methyl Ester Synthesis (18 h, Room Temperature)

acid	product	% yield
Glycolic	Methyl glycolate	80
Lactic	Methyl lactate	65
DL-Mandelic	Methyl mandelate	99
L-Tartaric	Dimethyl tartrate	98
DL-Malic		71
Citric		83
Succinic		<5
Benzoic	—	nr

(>5%) formed when the reaction was run at 0.5 M concentration. Diluting the reaction mixtures below 0.25 M reduced the amounts of these biproducts and increased the yield of the monoester product. It is important to note that although diacids such as tartrate and malate can form esters upon prolonged reflux in alcoholic solvents, no appreciable amount (<5%) of ester formation occurred after several days at room temperature in the absence of boric acid. Even in the presence of the catalyst, benzoic acid and succinic acid were quite unreactive. While *N*-protected α-amino acids have the potential to serve as chelating ligands for boric and boronic acids, neither *N*-tosylglycine nor *N*-BOC-alanine underwent significant esterification under standard conditions.

Yamamoto has used trifluorophenylboronic acid as a catalyst for amide formation under anhydrous conditions.[3b] In the absence of protic solvents, an OH from the boronate can serve to activate the carbonyl through formation of a mixed anhydride such as the boxed species in Scheme 1.

Scheme 1. Possible Mechanisms of Catalysis



Because simple carboxylates do not react under the esterification conditions described here, it is unlikely that the same mechanism of activation is occurring in these reactions. Both the neutral ester **2** and anionic species **3** may be present in alcohol solution, but once esterification occurs to produce **4**, neither of these complexes can form. It is unclear at present whether a free alcohol molecule attacks the carbonyl carbon of either **2** or **3** to yield product or whether the alcohol is transferred in an intramolecular manner through **3** to produce **4**. In either case, an electrophilic boron species will then be regenerated to catalyze another esterification (Scheme 1).[7] It is interesting to note that this reaction did not occur to any appreciable extent when equimolar amounts of α-hydroxyacid, alcohol, and boric acid were mixed in aqueous solution at room temperature. The amount of borate ester will be greatly reduced under these conditions, and it is apparently necessary that the alcohol be present in excess to react with this species. Even in 2:1 water/methanol solvent systems, no appreciable reaction occurred after 24 h. This result was important to us because it ensured that undesired esterification did not interfere with fluorescent sensing measurements of α-hydroxyacid binding by boronates.[2] Although rigorously dried alcohol solvents were not necessary for the esterification reactions, reagent grade material was used in all cases. The lower yield observed for lactic acid is likely due to the fact that this acid contained ca. 12% water in the commercial form used.

Two entries in Table 1 demonstrate that the reaction conditions allow for selective methyl esterification of α-hydroxycarboxylic acids in the presence of *β*-hydroxycarboxylates. Malic acid contains a hydroxy group that is in the α-position relative to one carboxylic acid and in the *β*-position relative to another. Citric acid contains two such *β*-carboxylates in addition to the α-hydroxyacid. The carboxylate adjacent to the hydroxy group in both malic and citric acid reacts more rapidly, providing their respective monomethyl esters as the major products with very little diester (<10%) formed in either case. The malate monoester can also be synthesized by hydrolysis of malic acid anhydrides,[8] but such selective ring-opening reactions are only amenable to diacids that are capable of forming cyclic anhydrides. The protocol described here is not limited in this regard. The citrate *sym*-monomethyl ester has previously been synthesized in two steps using formaldehyde to create an acetal that reacts with methanol to create the methyl ester.[9] This monoester can alternatively be synthesized through selective saponification of trimethyl citrate.[10] The procedure described here requires only one step.

Other alcohols can be used as solvents to create esters using this method (Table 2). In these cases, reactions proceeded more slowly at room temperature (the conversion to diethyl L-tartrate was only 50% complete after 24 h at

(7) A number of exchanging boron species are likely to be present at any one time in alcohol solution and these are simply represented here as $B(OR')_3$ where R′ = H and/or Me(Et/*i*Pr).

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Table 2. Yields of Ester (Diester for Tartrate) Using 20 mol % Boric Acid, 18 h, Room Temperature or 10 mol % Boric Acid, 18 h, Reflux [*]

	ROH		
acid	ethanol	2-propanol	*tert*-butyl alcohol
mandelic	68%	93%	nr
tartaric	97%*	92%*	nr
malic	65%	59%[a]	nr

[a]The isopropyl malate ester is a mixture of regioisomers (see text).

room temperature and the diisopropyl L-tartrate was <20%) so 20 mol % boric acid catalyst was used or the reactions were refluxed. For the tartrate diesters and mandelate esters, aqueous bicarbonate wash was used to remove the catalyst and any unreacted carboxylic acid to provide the pure esters. As before, selectivity was observed for the α-hydroxy acid over the β-hydroxy acid in ethyl DL-malate; however, significant amounts of esterification occurred at this position when the reaction was run in 2-propanol (α-/β-ester 3:1).[11] The major product was again accompanied by small amounts (10%) of diester removed by flash column chromatography. Interestingly, no significant conversion occurred in *tert*-butyl alcohol at room temperature or with heating (65 °C).

Because of the simple and mild nature of this procedure, it should be applicable to selective esterification of a wide range of α-hydroxyacids. More efficient, cost-effective, and environmentally friendly esterification reagents are continually being sought;[12] thus, the chemoselective ability of boric acid, an inexpensive, easily handled solid esterification catalyst, should prove valuable.

Acknowledgment. The authors are grateful for start-up funds from Griffith University (to T.A.H.) and the University of Queensland (to J.T.B.) that supported this work.

Supporting Information Available: Experimental details for the synthesis of each of the methyl, ethyl, and isopropyl esters of DL-mandelic acid and DL-malic acid and ^{1}H NMR spectra for products from all reactions including one biproduct (dimethyl malate). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) It is known that less polar solvents can increase the association constant of boric acid with 1,3-diols while decreasing the association constant of borate and 1,2-diols relative to that in more polar solvents. The increased hydrophobicity of 2-propanol must alter the coordination of boron to malic acid. Wirth, T. M.; Miller, V. R. *Abstracts of Papers*, 215th ACS National Meeting, Dallas, March 29−April 2, 1998; American Chemical Society: Washington, DC, 1998; CHED-524.

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