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Organic Synthesis in Boric Acid: A Study on the Scope and Developments

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Abstract – Recent years have seen an increase in the use of boric acid [H3BO3]. Here, the most recent developments in boric acid catalysed transformations, such as esterification and transesterification are summarised, as well as the addition of azide and thiazide and the aza- and thia-Michael additions, condensation and the Friedel-Crafts and Tishenko reactions, as well as halogenations, ipso substitutions, decarboxylations, reactions of protection and deprotection, amidation and A number of biologically relevant chemical molecules have been synthesised using Boric acid as a benign, commercially available, and inexpensive catalyst in the recent decade.

Keywords – Acid Catalysis, Boric Acid, Heterocycles, Organic Synthesis

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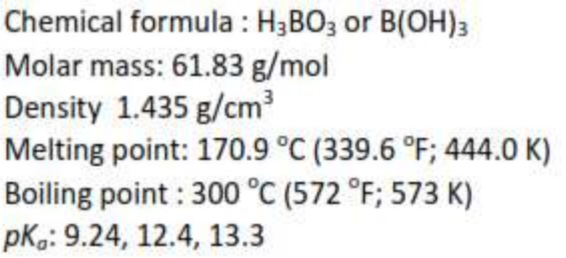
INTRODUCTION

The chemistry of boric acid has advanced rapidly in the last decade. Because of its gentle and highly selective qualities, as well as its environmental friendliness and commercial availability, this increased interest is largely due. A wide variety of simple and complex compounds can be transformed by the use of Boric Acid as an excellent acid catalyst in chemical synthesis. With a focus on current synthetic applications, this paper summarises the value of boric acid. Up to and including the end of 2017, there has been literature coverage.

Weak boric acid, commonly referred to as boracic or orthoboric acid, is a non-toxic inorganic acid that is found in soil. Physically, it is a white crystalline solid with the following:



Chemical formula : H_3BO_3 or $B(OH)_3$

Molar mass: 61.83 g/mol

Density 1.435 g/cm^3

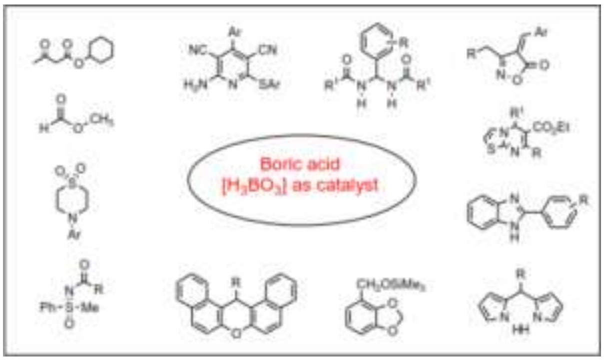
Melting point: 170.9 °C (339.6 °F; 444.0 K)

Boiling point : 300 °C (572 °F; 573 K)

pK_a: 9.24, 12.4, 13.3

Solubility: Water and lower alcohols; pyridine moderately soluble; acetone very slightly soluble.

Hydrogen bonding can be seen in Figure 1A, where the centre boron atom is linked to three hydroxy (-OH) groups. Hydrogen bonds hold its solid crystalline structure together, which is composed of layers of boric acid (Figure 1B). Because of this, it can be used to make a very weak monobasic acid. A variety of acid catalysed reactions have made use of it. As a low concentration of boric acid does not pose any hazard, it is very easy to handle and utilise. Antiseptic, preservative, pesticide and pH buffer are only some of the other uses for this molecule. It is also a precursor to a wide range of valuable chemicals.



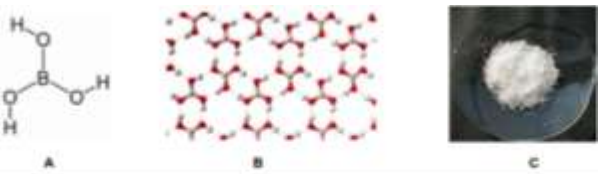


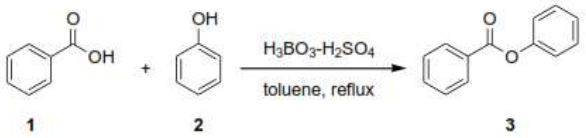
Figure 1. Structure of boric acid (A), parallel layers in solid state (B) and view of crystalline state (C).

Esterification Reactions

Among organic synthesis' most essential chemical reactions, esterification is one of the oldest and most commonly utilised chemical transformations. Esterification is employed in a wide range of chemical sectors, including the pharmaceutical and food industries. To synthesise natural compounds, these reactions are used in carboxylic acid protection or kinetics resolution, and intramolecular reactions to produce lactones. Boric acid has been used to study the esterification of carboxylic acids, hydroxy acids, and sugar acids.

Esterification of carboxylic acids

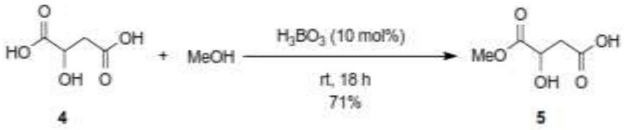
Boric acid and sulfuric acid combine to catalyse the esterification of phenols with aromatic and aliphatic carboxylic acids. The reaction is not catalysed by either boric acid or sulfuric acid alone. Toluene with phenol, benzoic acid, and a little amount of boric and sulfuric acid was used to generate phenyl benzoate (3) in a near-quantitative yield when water was removed by azeotropic distillation.



Scheme 1. Boric acid catalyzed esterification of carboxylic acid.

Esterification of α-hydroxy acids

According to Houston and coworkers, boric acid can be used to chemo-selectively esterify hydroxy acids. 2 a high yield of monoester 5 was produced by reacting boric acid with malic acid (4) (a dicarboxylic acid containing a hydroxyl group that is in the -position relative to one carboxylic acid and in the -position respect to another) and methanol overnight at room temperature (Scheme 2). To the -hydroxy group, the -CO2H group was unaltered. In relation to carboxylate, the effect of the -OH group was addressed. Esterification reactions are accelerated by the formation of a five-membered cyclic neutral ester 6 and an anionic species 7 (Figure 2).



Scheme 2. Boric acid catalyzed methyl ester synthesis of α-hydroxy acid.

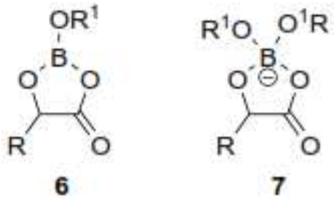
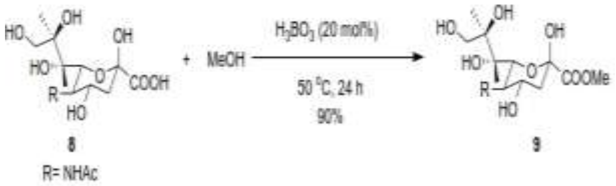


Figure 2. Compounds 6 and 7, possible intermediates in the esterification of an α-hydroxy acid.

Esterification of sugar acids

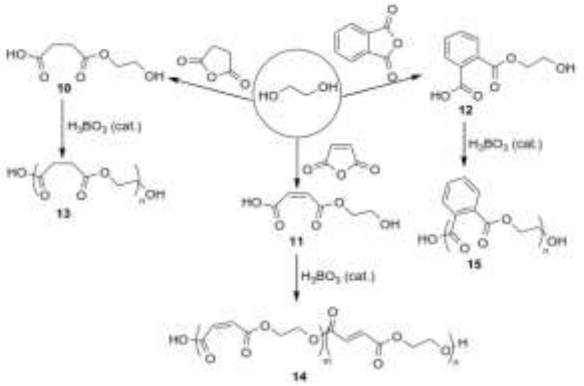
Sugar acids can be esterified by using methanol and boric acid in combination. The sugar acid sialic acid (8) was reacted with anhydrous methanol in a nitrogen environment at 50 0C, with a catalytic quantity of boric acid, to produce methyl ester 9 in a 90% yield (Scheme 3). 3 This reaction was highly efficient when carried out on specific sugar acid compounds, but it is extremely substrate-dependent when carried out on other molecules. Three-deoxy-D-manno-octa-2-ulonic acid (KDO), which has a -hydroxycarboxylate motif, and glutcuronic acid with a -hydroxycarboxylate motif failed to esterify in methanol under the influence of boric acid catalysis.



Scheme 3. Boric acid catalysis of sialic acid (8) esterification.

Polyesterification of monohydroxyethyl ester of dicarboxylic acids

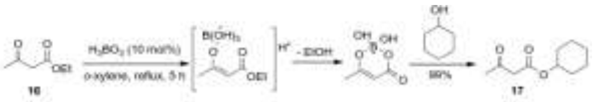
The polyesterization of monohydroxyethyl esters of succinic acid, maleic acid, and phthalic acid can be facilitated by a boric acid-pyridine mixture, according to Alemdar et al. 4. Colorless polyesters 13, 14, and 15 of low molecular weights (M: 1650-1950) were produced within four hours at 130 o C using the catalyst system (Scheme 4).



Scheme 4. Polyesterification of the monohydroxyethyl esters of 10, 11 and 12 with boric acid.

Transesterification Reactions

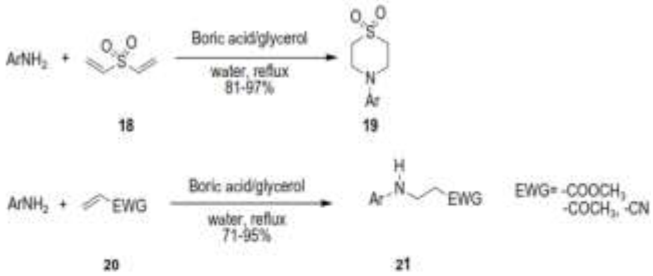
Boric acid has been used to transesterify esters with alcohols. It was shown that boric acid, when used in conjunction with various alcohols such as propargyl alcohol, allylic alcohol, and primary and secondary alcohols that are sterically inhibited, provided good to exceptional transesterification rates for ethoxyacetoacetate (16). A specific example is the use of boric acid in refluxing xylene to prepare the transesterified 17-ketoester from 16-acetoacetate ethyl and cyclohexanol. This is the fifth scheme.



Scheme 5. Postulated mechanism of boric acid catalyzed transesterification reactions.

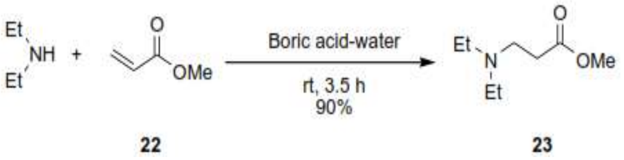
Aza-Michael Addition Reactions

For good to exceptional addition yields without polymerization, boric acid/glycerol in water was used to catalyse the Aza-Michael addition of aromatic amines to divinyl sulfones (18) and electron deficient alkenes (20). From compounds 18 and 20, Nsubstituted thiomorpholine-1,1-dioxides 19 and -amino ester/ketone/nitrile 21 can be produced (Scheme 6).



Scheme 6. Boric acid catalyzed aza-Michael addition reactions.

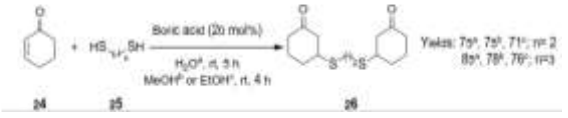
Administering boric acid (10 mole percent) in water at room temperature to the acrylate ester (22), Chaudhuri et al. obtained the aza-Michael addition product 23 from the Michael donors in moderate to high yield (Scheme 7). 7



Scheme 7. Boric acid catalyzed aza-Michael addition of amine to α,β-unsaturated ester.

Thia-Michael Addition Reactions

Boric acid can be used as a catalyst for the addition of aromatic and thiols to,-unsaturated nitriles, esters, ketones, and aldehydes at room temperature. In MeOH or EtOH, the reactions take place more quickly than in water. Thia-Michael addition of 24 to 25 yielded 26 in good yields under identical experimental conditions (Scheme 8).



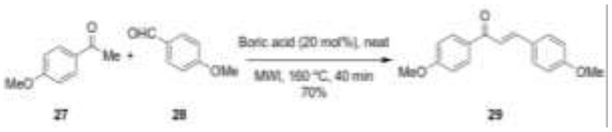
Scheme 8. Boric acid catalyzed thio-Michael addition of dithiols to α,β-unsaturated ketone.

CONDENSATION REACTIONS

When aldehydes and ketones are combined, a chemical reaction known as cross-aldol condensation is used to synthesize,unsaturated carbonyl compounds. They are employed as intermediates in the manufacture of medicines, agrochemicals and fragrances, among other products. When carbonyl compounds are combined with indoles and pyrrole, they produce dipyrromethanes that have a wide range of biological properties. 13 The reactions were found to be efficiently catalysed by boric acid.

Condensation of carbonyl compounds and active methylene compounds

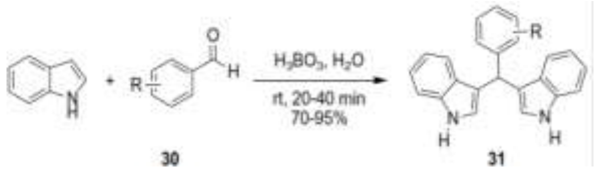
Using microwave irradiation and solvent-free conditions, Brun and his coworkers14 shown that boric acid can be an effective Lewis acid catalyst for the cross-aldol condensation reactions of acetophenone derivatives/activated methylene compounds with aldehydes. Condensed products 29 were easily formed when boric acid was extensively combined with a solution of compounds 27 and 28 and microwave radiation was applied (Scheme 9). On the other hand, Offenhauer and Nelsen15 have cited boric acid to facilitate the aldol condensation of acetophenone and other aldehydes to produce,-unsaturated ketones in high yield in the presence of boric acid.



Scheme 9. Cross-aldol condensation reaction catalyzed by boric acid.

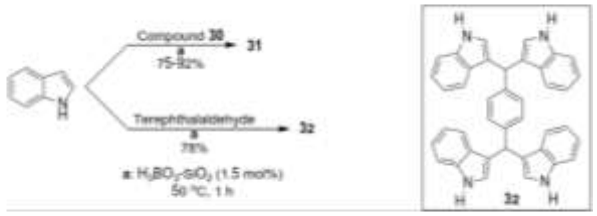
Condensation of carbonyl compounds and indoles

In order to synthesise diindolylmethanes, Meshram and his team discovered that boric acid can be employed in the condensation of indoles with aromatic aldehydes (30). (31). As a result, in just 20-40 minutes after adding boric acid to a water solution agitated with indole and an aromatic aldehyde, the product 31 was synthesised in high yield (Scheme 10). 16 Under solvent-free circumstances, Yadav et al.17 reported the same condensation reaction.



Scheme 10. Boric acid promoted condensation reactions between indole and aldehydes.

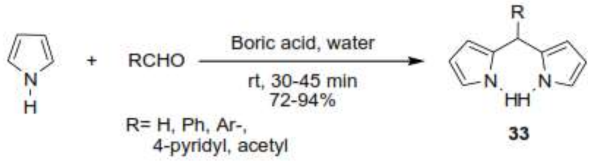
Kumar and his group generated bisindolylmethanes and tetra-indolyl derivatives by combining indoles with mono-aldehydes 30 and di-aldehydes like terephthalaldehyde in a stirring mixture at room temperature using silica-supported boric acid (Scheme 11).



Scheme 11. H3BO3-SiO2 catalyzed condensation of aldehydes and indole.

Condensation of carbonyl compounds and pyrrole

Pratibha 19 demonstrated the use of boric acid as a catalyst for the production of dipyrromethanes (33). When boric acid was added to water, two equivalents of pyrrole and one equivalent of aldehyde yielded 33 at room temperature (Scheme 12). Singhal et al. 20 used boric acid to perform the same condensation reaction in an aqueous medium.



Scheme 12. Boric acid catalyzed synthesis of dipyrromethanes by condensation of pyrrole with aldehydes.

CONCLUSION

This paper provides an overview of current research in the use of boric acid as a catalyst in synthetic chemistry. With its helpful acidic qualities, cost-effectiveness, and commercial availability boric acid has attracted a lot of attention in recent years. Catalytic boric acid chemistry has seen a considerable uptick in activity. Organic transformations including C-C, C-N, C-O and C-S bond formation in numerous synthetically significant molecules are covered by these applications of boric acid. Currently, boric acid-catalyzed organic transformations are a hot topic among organic methodologists worldwide, and this review is expected to have a significant impact.

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