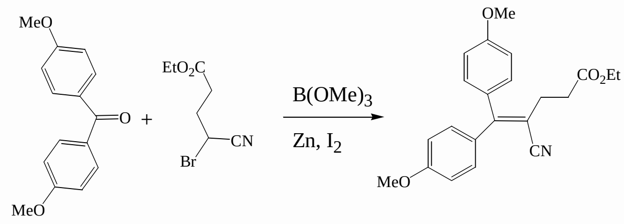
Trimethyl Borate Pure

Precursor for Boronic Acids/Esters

Product Description

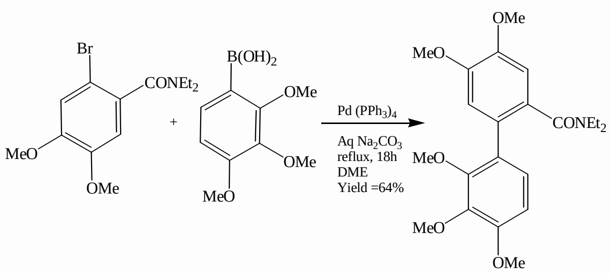
Trimethyl borate (TMB) is a weak Lewis acid, with various possible applications in organic synthesis.

One application is the use of $B(OMe)_3$ for coupling ketones with halides to form alkenes[1].



Another well established application is to use $B(OMe)_3$ as a precursor in the production of boronic acids/esters. The last find synthetic use in C-C coupling reactions.

Suzuki Coupling Reactions

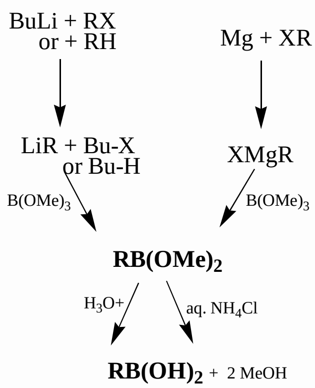


Promising carbon-carbon couplings are the ones combining an organic boronic acid/ester with an organic electrophile in the presence of a palladium catalyst and base, also known as Suzuki couplings[2-5]. Synthesis chemists all over the world are becoming convinced that Suzuki couplings will take an important place in the C-C bond forming tool kit. Suzuki chemistry provides an efficient, cost effective, mild and environmentally safe methodology for the selective formation of C-C bonds on an industrial scale. As opposed to the Stille coupling[8], Suzuki reagents do not involve highly toxic (tin) reagents. As compared to the traditional organo-lithium and magnesium compounds, they are compatible with various functional groups.

Methods for making Organic Boronic Acids from Trimethyl Borate[2-6]

Aryl halides (or Ar-H) are reacted with either butyl lithium or magnesium metal to form the corresponding lithiated or Grignard reagent. These reagents are reacted with trimethylborate ($B(OMe)_3$) to form the boronic acid ester which are hydrolyzed with either aqueous HCl or aqueous NH_4Cl to form the corresponding boronic acid.

In case the reaction of Trimethylborate would yield the *di*alkylated product R_2BOH, then there are 2 options :
often, dialkylated boronic acid does a coupling in much the same way its mono-substituted analog
if not : a lower reaction temperature will yield mono-alkylated boronic acid.



In the manufacturing of boronic acids, Prof. Dr. Suzuki typically used *triisopropyl*borate as the precursor borate ester. Recently it has been acknowledged that *trimethyl*borate offers a cost-effective alternative thereto. Especially in case di-alkylated boronic acids can be used for the subsequent Suzuki coupling, then TMB may be required in only half the concentration of other borate precursor esters. Therefore, TMB is becoming the raw material of choice for large-scale boronic acids synthesis.

In addition to the standard (min. 99% pure) TMB quality, Rohm and Haas has developed higher quality grades, which are available upon request.

Indeed, in the synthesis of boronic acids/esters for Suzuki couplings, it is imperative that the TMB precursor is free of protic traces (from water, methanol, …). The lack of any moisture or alcohol residue in Rohm and Haas' higher-quality grade of TMB, may result in a significant yield improvement of a given boronic intermediate synthesis.

Applications

Pharmaceutical

A study of the patent literature has uncovered many reaction schemes of pharmaceuticals which are currently in clinical trials which incorporate the use of boronic acids precursors and the Suzuki coupling methodology.

Synthesis of Polymers

Combining aryl *bis*-boronic acids with *bis*-halo-aryl compounds using the Suzuki coupling methodology form high molecular weight poly (p-phenylene) polymers[9].

Solid Phase Synthesis

The Suzuki coupling methodology can be used in conjunction with solid phase synthesis techniques to synthesis complex organic molecules[10].

Handling and Storage

TMB is stable in the absence of moisture. It hydrolyses in the presence of water, depositing finely divided crystals of boric acid. When protected from air and moisture, TMB is stable indefinitely.

TMB is an inherent source of methanol – upon hydrolysis with water, TMB yields both boric acid and methanol. Methanol is toxic when absorbed through the skin, and it can cause blindness upon ingestion. Personnel handling TMB should wear safety goggles, impervious gloves and coveralls or appropriate chemical resistant suits.

TMB is classified as Harmful, and (only) *moderately* irritating to eyes. However, as for methanol, it causes eye injury which may result in permanent damage.

In case of contact with the skin, flush immediately with water; for eyes, immediately flush with water and get medical attention.

TMB is a flammable liquid and vapor – it should be kept away unnecessarily from heat, sparks and flames. Foam, carbon dioxide and dry chemicals are acceptable for extinguishing agents.

Product Stewardship

Rohm and Haas sells Trimethyl Borate as part of a comprehensive Product & Services package, which includes :

- high standard TMB ***product quality***
- higher-than-99% ***purity grades*** available upon request
- the availability of a choice of ***package sizes***
- safety audits and ***training***
- ***technical advice*** with regards to both the safe handling and the cost-efficient synthetic use

References:

1) Yamagishi, Y.; Akasaka, K.; Suzuki, T.; Miyamoto, M.; Nakamoto, K.; Okano, K.; Abe, S.; Ikuta, H.; Hayashi, K.; Yoshimura, H.; Fujimori, T.; Harada, K.; Yamatsu, I. AU 8770085; EP 0238973; JP 87223164; JP 88010743
2) Miyaura, N.; Suzuki, A. *Chem. Rev.* 1995, *95*, 2457
3) Suzuki, A., In Metal-catalyzed Cross-coupling Reactions (eds. Diederich, F and Stang, P.J.) Willey-VCH, Weinhelm, 1988, 49-97
4) Alo, B.I.; Kandil, A.; Patil, P.A.; Sharp, M.J.; Siddiqui, M.A.; Snieckus, V.; Josephy, P.D. *J. Org. Chem.* **1991**, *56*, 3763
5) Suzuki, A *J. Organomet. Chem.* 1999, *576*, 147
6) Derick D Winckle and Kevin M Schaab, *OPRD* 2001, **5**, 450-451
7) Martin A.R.; Yang, Y. *Acta Chem. Scand.* 1993, *47*, 221
8) Stille, J.K. *Angew. Chem. Int. Ed.* 1986, *25*, 508
9) Goodson. F.E.; Wallow, T.I.; Novak, B.M. *Macromolecules* 1998, 31, 2047
10) Ruhland, B.; Bombrun, A.; Gallop, M.A. *J. Org. Chem* 1997, *62*, 7820

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