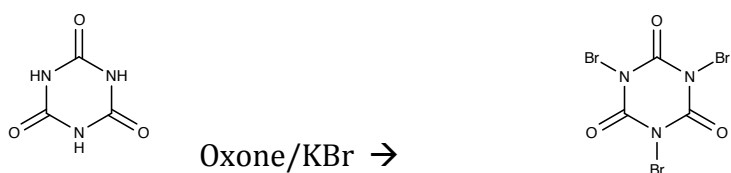


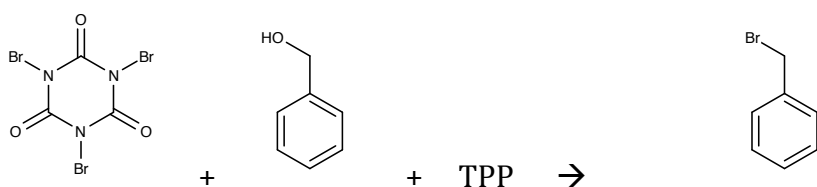
Multistep Synthesis of the Benzyl Ether of Vanillin (fragrance)

Outline: We will synthesize a custom brominating agent, TBCA, tribromoisocyanuric acid, using common swimming pool chemicals, cyanuric acid and oxone, then use it to prepare benzyl bromide from benzyl alcohol. Finally, we will use a traditional Williamson ether synthesis to produce the benzyl ether of vanillin, a commercial fragrance.

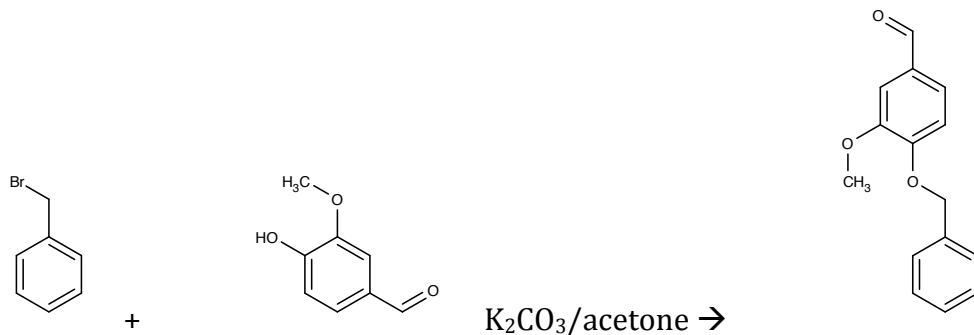
Step 1: Preparation of TBCA, tribromoisocyanuric acid brominating agent.



Step 2. Bromination of benzyl alcohol to benzyl bromide.



Step 3. Williamson etherification of vanillin to form benzyl ether of vanillin fragrance.



Step 1

Tribromoisocyanuric acid, TBCA, a custom brominating agent, is prepared to avoid use of hazardous elemental bromine or expensive pyridinium tribromide in step 2.

Oxone is a commercial name for potassium monopersulfate, KHSO_5 , sold as a triple salt $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ for help clearing the water in swimming pools, thus requiring less chlorine. It is also used as an oxidizing agent in organic synthesis for oxidation of aldehydes and alkenes among other functional groups. (ref. Chemical Reviews (2013), 113, 3329–3371)

Cyanuric acid is a cyclic trimer of urea, commonly used to reduce chlorine loss in outdoor swimming pools caused by sunlight. (Ref. http://jpspi.poolhelp.com/ARTICLES/JSPSI_V4N2_pp09-16.pdf)

Tribromoisocyanuric acid, TBCA, is a brominating agent easily prepared from cyanuric acid, oxone and KBr . (Ref. http://jpspi.poolhelp.com/ARTICLES/JSPSI_V5N2_pp16-19.pdf)

Step 2.

Benzyl bromide is prepared from benzyl alcohol for use in the final Williamson ether step via TBCA prepared in step 1 and TPP, triphenylphosphine.

TPP, triphenylphosphine is a common base, nucleophile and ligand used in organic synthesis.

Benzyl bromide may be also be prepared from toluene, benzyl chloride, benzaldehyde or benzoic acid, but all of these preps have more problems with required reagents, byproducts and reduced yields.

Benzyl chloride does not work as well in the Williamson step, due to its lower reactivity, requiring a longer reaction time and a stronger base, which then creates problems with the aldehyde group of the vanillin.

Step 3

The benzyl ether of vanillin, a commercial fragrance, is prepared by a Williamson ether synthesis from benzyl bromide and vanillin, using K_2CO_3 as the base. Other ethers of vanillin can be prepared in the same way and are also fragrances. (Ref. Bioorganic & Medicinal Chemistry 21 (2013) 856-868).

Vanillin is a common flavoring and fragrance ingredient. Pure vanillin is now made industrially from the lignin byproduct in the manufacturing of paper from wood pulp.

Vanilla extract, used as a flavoring, is an alcohol extract from vanilla beans and contains several related compounds. (Ref. Journal of Chemical Education, 74(9), 1055 1997)

Write up. For each step prepare a list of compounds with their properties and hazards as in our previous experiments. You should also locate IR & HNMR spectra or peak listings for products.

Reactions: Use the general directions found in the reference articles on the next page for each step and rescale amounts. We will modify given procedures as needed.

Scale: We want to produce 20 mmol of final product. Start with 25 mmol of cyanuric acid.

Products will be characterized by FTIR and HNMR at each step.

Step 1. Procedure for Preparation of TBCA

Ref. SYNLETT 2006, No. 10, pp 1515–1518 (not available for free online)

To a stirred solution of cyanuric acid (12.5 mmol), NaOH (37.5 mmol), Na₂CO₃ (18.75 mmol) and KBr (37.5 mmol) in H₂O (180 mL) cooled in an ice bath was added dropwise a solution of Oxone® (37.5 mmol) in H₂O (150 mL). A white solid precipitates during the addition of oxidant solution, forming a dense suspension, which is stirred for 24 h. The product is isolated by vacuum filtration, washed with cold H₂O and dried over P₂O₅ needing no further purification.

Yield 87%; mp not determined because it decomposes on heating.

TBCA Spectral Data:

CP-MAS 13C NMR: δ = 151.8 (C=O) ppm.

FT-IR: 1741, 1724, 1660, 1652, 1481, 1404, 1396, 1331, 1196, 1144, 1051, 736, 717 cm⁻¹

Step 2. General procedure for the preparation of alkyl bromides

Ref. *Journal of the Brazilian Chemical Society*, Vol. 25, No. 5, 975-979, 2014

TBCA (1.4 mmol) was added to a stirred solution of TPP (4 mmol) in CH₂Cl₂ (50 ml). After 5 min, the alcohol (2 mmol) was added and the suspension was stirred at room temperature. After 1.5 h, cyanuric acid was filtered off, the liquid was washed with water (2 x 25 ml) and the organic phase was dried (Na₂SO₄) and evaporated on a rotatory evaporator under reduced pressure. The residue was treated with pentane and filtered through a silica gel (70-230 mesh) pad. The pure alkyl bromide was obtained after evaporation of pentane.

benzyl bromide:

IR (KBr) ν /cm⁻¹ 3086, 3063, 3030, 2967, 2931, 2857, 1601, 1586, 1495, 1453, 1378, 1226, 1201, 1098, 1068, 1028, 917, 812, 757, 694, 604, 547, 454.

¹H NMR (CDCl₃, 200 MHz) δ 4.51 (s, 2H, CH₂Br), 7.27 – 7.44 (m, 5H, CH_{arom});

¹³C NMR (CDCl₃, 50 MHz) δ 33.7 (CH₂Br), 128.5 (C_{arom}), 128.9 (C_{arom}), 129.2 (C_{arom}), 137.9 (C_{arom});

MS (70 eV) m/z 172 (M⁺ + 2), 170 (M⁺), 91 (100%), 74, 65, 51.

Step 3. Williamson Ether synthesis of vanillin benzyl ether.

From *Bioorganic & Medicinal Chemistry*, 21, 856-868 (2013)

5.1.1. 4-(Benzyloxy)-3-methoxybenzaldehyde (2c)

To a solution of 4-hydroxy-3-methoxybenzaldehyde (1c, 7.6 g, 50 mmol) in acetone (150 mL) was added K₂CO₃ (10.4 g, 75 mmol) and BnBr (9.41 g, 55 mmol), and the mixture was heated at reflux for 4 h before it was cooled to room temperature. The solid was filtered off, and the filtrate was concentrated under reduced pressure to get yellow oil, which was purified by flash chromatography (ethyl acetate/petroleum ether = 1:6) to yield 4-(benzyloxy)-3-methoxybenzaldehyde (2c, 11.5 g, 95%) as white solid.

¹H NMR (CDCl₃, 300 MHz): δ 9.85 (s, 1H), 7.44–7.34 (m, 7H), 6.99 (d, J = 8.1 Hz, 1H), 5.26 (s, 2H), 3.96 (s, 3H).