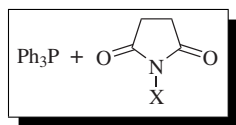


Triphenylphosphine-*N*-Bromosuccinimide¹



(Ph₃P)
[603-35-0] C₁₈H₁₅P (MW 262.30)
InChI = 1S/C18H15P/c1-4-10-16(11-5-1)19(17-12-6-2-7-13-17)
18-14-8-3-9-15-18/h1-15H

InChIKey = RIOQSEWOXXDEQQ-UHFFFAOYSA-N
(NBS)
[128-08-5] C₄H₄BrNO₂ (MW 177.99)

InChI = 1S/C4H4BrNO2/c5-6-3(7)1-2-4(6)8/h1-2H2
InChIKey = PCLIMKBDDGJMGD-UHFFFAOYSA-N
(NCS)

[128-09-6] C₄H₄ClNO₂ (MW 133.54)
InChI = 1S/C4H4ClNO2/c5-6-3(7)1-2-4(6)8/h1-2H2
InChIKey = JRNVBWVKYDBUCA-UHFFFAOYSA-N
(NIS)

[516-12-1] C₄H₄INO₂ (MW 224.99)
InChI = 1S/C4H4INO2/c5-6-3(7)1-2-4(6)8/h1-2H2
InChIKey = LQZMLBORDGWNPD-UHFFFAOYSA-N

(conversion of primary alcohols to alkyl halides)

Physical Data: See *Triphenylphosphine*, *N*-Bromosuccinimide, *N*-Chlorosuccinimide, and *N*-Iodosuccinimide.

Preparative Methods: the mixed reagent is prepared in situ as needed by combining triphenylphosphine, the alcohol, and *N*-halosuccinimide in a suitable solvent (usually DMF) and heating.

Handling, Storage, and Precautions: precautions in handling should be made as described for the individual reagents. This mixed reagent is not appropriate for storage. Recrystallization of the triphenylphosphine and *N*-halosuccinimide is necessary to achieve the most efficient halogenation reaction. In addition, the use of anhydrous solvent is important for the success of the reaction.

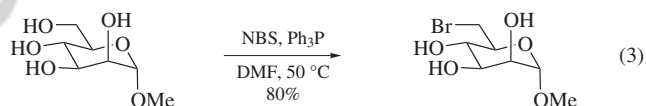
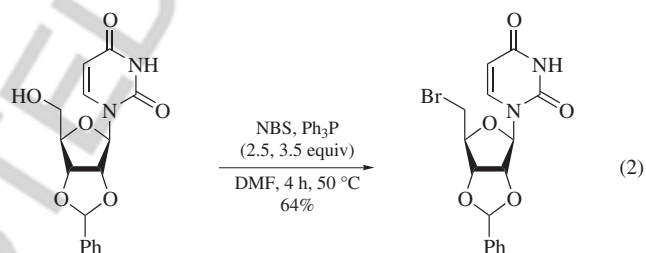
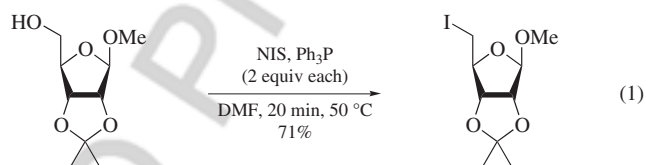
Original Commentary

Scott C. Virgil
Massachusetts Institute of Technology, Cambridge, MA, USA

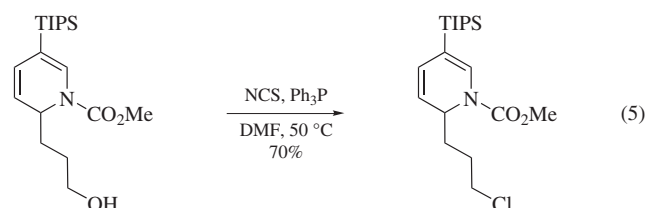
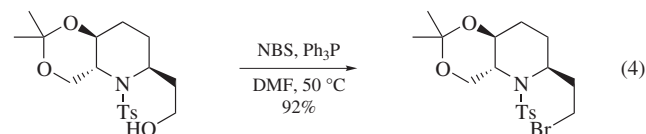
Introduction. The combination of triphenylphosphine and *N*-halosuccinimide was applied by Hanessian² to the preparation of primary halides from carbohydrate precursors. This method is related to a number of other methods for hydroxyl substitution via oxyphosphonium salts as described in a comprehensive review.¹

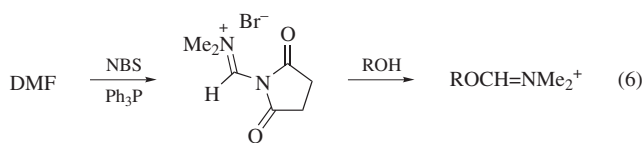
Conversion of Alcohols to Alkyl Halides. The typical procedure² as applied to the preparation of methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene- β -D-ribofuranose (eq 1) involves the addition of 2 equiv of *N*-iodosuccinimide followed by 2 equiv of triphenylphosphine to a cooled solution of the alcohol in anhy-

drous DMF and heating the mixture to 50 °C for 20 min. Methyl alcohol is added to destroy excess reagent, followed by *n*-butanol to aid in the removal of DMF under reduced pressure. After concentration, the product is purified from the byproducts (succinimide and triphenylphosphine oxide) by addition of ether and aqueous extraction followed by column chromatography. Isolated yields of 70–85% are regularly obtained using this procedure for the preparation of chlorides, bromides, and iodides. In addition, the reaction conditions allow the preparation of primary halides in the presence of many functional groups used in carbohydrate chemistry, including the ester, amide, lactone, benzylidene acetal, and acetonide groups (eq 2). In fact, moderate yields (49–82%) of a number of primary halides are obtained using this procedure on sugars containing one or more free secondary hydroxyl groups (eq 3).^{2–4}

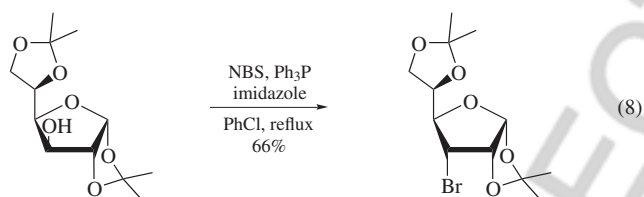
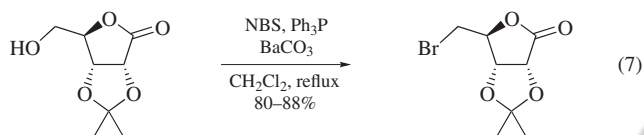


Other examples of the use of this method include the preparation of tetrahydrofurfuryl bromide,⁵ 3 α -cholestanyl bromide (using THF as solvent, 85% yield),⁶ and intermediates toward the syntheses of alkaloids (eqs 4 and 5).⁷ The reaction of the reagent with DMF alone generates the formamidine salt which can ultimately result in the isolation of the formate ester derivative of the alcohol substrate (eq 6).^{1,8} It is therefore important that the *N*-halosuccinimide is added last for the preparation of alkyl halides. Other solvents used for this reaction include CH₂Cl₂ (which can facilitate the workup of the reaction products) and HMPA.⁹





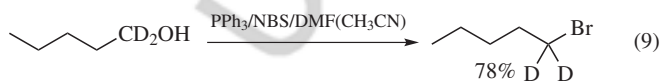
The standard procedure has often been found to be unsatisfactory for substrates which are prone to acid-catalyzed rearrangements (including migration of acetonide protecting groups) and cleavage and is also not suitable for substrates containing labile protecting groups such as THP ethers.^{10,11} In some cases this problem has been circumvented by the addition of various bases such as BaCO₃ (eq 7),¹² *Pyridine*, and *Imidazole*. A recent study has achieved the preparation of 3-bromo-3-deoxy-1,2:5,6-di-*O*-isopropylidene- α -D-allofuranose by addition of 2 equiv of *N*-halosuccinimide to a refluxing solution of the secondary alcohol and 2 equiv each of PPh₃ and imidazole in toluene or chlorobenzene (eq 8). Previous applications of PPh₃ and *N*-halosuccinimide alone afforded only the primary halide products resulting from acetonide migration. The use of pyridine and imidazole have also been found to play an essential role in the conversion of carbohydrates to halides using the reagents *Triphenylphosphine-Iodine* and *Triphenylphosphine-Carbon Tetrachloride*, respectively.¹³



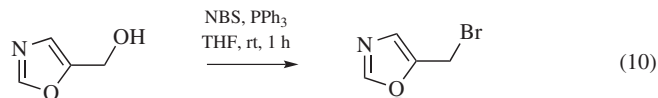
First Update

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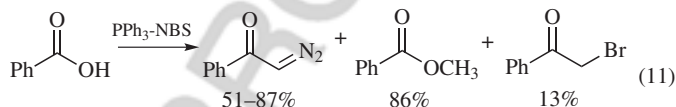
Conversion of Alcohols to Alkyl Halides. A solution of NBS was added dropwise at 0 °C to a stirred DMF solution containing the deuterated alcohol and triphenylphosphine. Stirring was continued for 1 h, and methanol was added to the pale yellow mixture to quench the excess reagent. After 5 min, water was added, the mixture was extracted with pentane, and the organic layers were combined and distilled to obtain the dideuterated bromo derivative (eq 9).¹⁴



It was found that a heterobenzyl bromide was smoothly prepared from the oxazole alcohol using *N*-bromosuccinimide (NBS)-triphenylphosphine (PPh₃) (eq 10).¹⁵

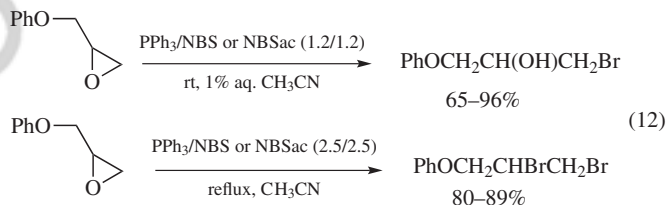


A slight excess of *N*-bromosuccinimide (NBS) was added to an equimolar mixture of benzoic acid and triphenylphosphine in various solvents at 0 °C. After 15 min, excess ethereal diazomethane was added. Diazoacetophenone contaminated by small amounts of bromoacetophenone was obtained in all cases, with THF being the best solvent. In contrast, when the NBS and diazomethane additions were effected at -20 °C (THF), methyl benzoate was the only product (eq 11).¹⁶



Preparation of Vic-halo Alcohols or Dihalides from Epoxides.

The conversion of epoxides to vic-halo alcohols and vic-dihalides has previously employed a combination of PPh₃-DDQ-R₄NBr. The use of PPh₃-*N*-bromo succinimide (NBS), provides a simpler mild, regioselective method for the efficient conversion of epoxides to vic-halo alcohols or symmetrical or unsymmetrical vic-dihalides. In this method, epoxides in the presence of PPh₃-NBS or PPh₃-*N*-bromo saccharine (NBSac) are converted to vic-halo alcohols or symmetrical or unsymmetrical vic-dihalides depending on the molar ratio and the type of halo imide used (eq 12).¹⁷



Q1

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