Indian Journal of Chemistry
Vol. 40B, September 2001, pp. 842-845

Note

New versatile halogenating reagents for hydroxy groups

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Received 16 February 2000; accepted (revised) 3 July 2000

Two new halogenating reagents, viz. allyltriphenoxyphosphonium bromide (ATPB) and allyltriphenoxyphosphonium chloride (ATPC) have been prepared and characterised. These have been evaluated for their potential application in bromination/ chlorination of a variety of compounds including aliphatic straight chain alcohols, branched chain alcohols and also 3′- and 5′-hydroxy groups of deoxyribonucleosides.

Halogenation is one of the most important chemical process, as many halogenated derivatives are potential synthetic intermediates. Many commercially important compounds such as pesticides, disinfectants, antiseptics and synthetic drugs are halogen derivatives. Much effort has been made to develop halogenating reagents that can be used to halogenate deoxyribonucleosides. These are extensively exploited for the synthesis of cyclonucleosides[1], nucleotides[2], sulphur analogues, phosphonic acid derivatives[3], deoxynucleosides[4], unsaturated sugars and amino sugars[5]. In some cases they have proved to be of primary biological importance[6-8] as antiviral agents[9]. Though there are some useful reagents such as quasiphosphonium halides developed by Rydon *et al.*[10] and tris(2,4,6-tribromophenoxy)dichloro phosphorane (BDCP) reported by Hata *et al.*[11,12], they have some limitations. Quasiphosphonium halides are useful only for iodination, whereas BDCP is fairly unstable. Therefore there is quest for developing better halogenating reagents which have longer shelf-life, can give stable solutions and are non-toxic. In the present note we report the synthesis and characterisation of two new brominating / chlorinating reagents viz., allyltriphenoxyphosphonium bromide (ATPB) and allyltriphenoxyphosphonium chloride (ATPC), and their application in bromination / chlorination of a variety of compounds ranging from normal alcohols to branched chain alcohols and 3′- and 5′-hydroxyls of deoxyribonucleosides.

Results and Discussion

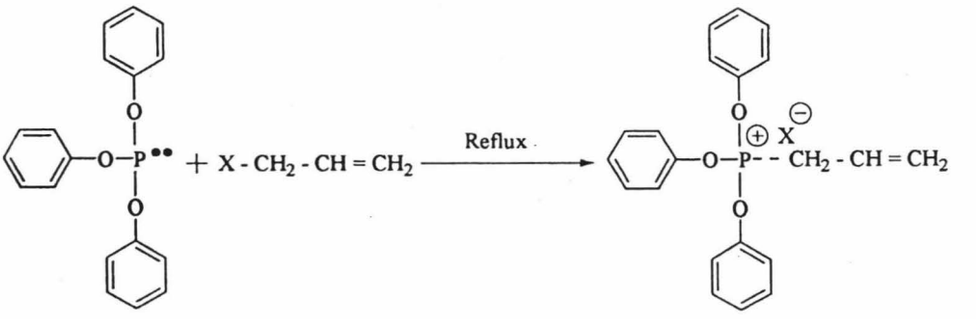
ATPB was prepared by refluxing triphenylphosphite with allyl bromide under anhydrous conditions. The reaction was monitored by gradual increase in temperature from 73°C to 122°C during a period of 40 hr. After cooling to r. t. it was washed exhaustively with dry ether and product was obtained in pure form as gum after removing ether in 90% yield. ATPC was synthesised by a procedure parallel to reported above for ATPB by refluxing triphenylphosphite with allyl chloride. The temperature in this case increased from 48°C and attained a constant value of 110°C in 24 hr. Usual work-up as mentioned for ATPB afforded ATPC in appreciable yield (85%). Both the reagents were characterised by TLC, UV and elemental data. Both reagents could be stored under anhydrous conditions. No appreciable decomposition was noticed (**Scheme I**).

Simple alcohols like propanol, pentanol and butanol could be halogenated by stirring these in 1 : 1.2 molar ratio of ATPB and ATPC at r.t. for different duration of time. The corresponding alkyl bromides / chlorides were obtained in quantitative yields by distillation at atmospheric pressure (**Scheme II**).

Selective bromination / chlorination of 3′- and 5′-hydroxyls of thymidine and adenosine was accomplished by using ATPB and ATPC, respectively. However, the functional sites in the respective pyrimidine / purine bases had to be protected by benzoylation. The bromination gives comparatively better yields, while in chlorination the yields were far from satisfactory.

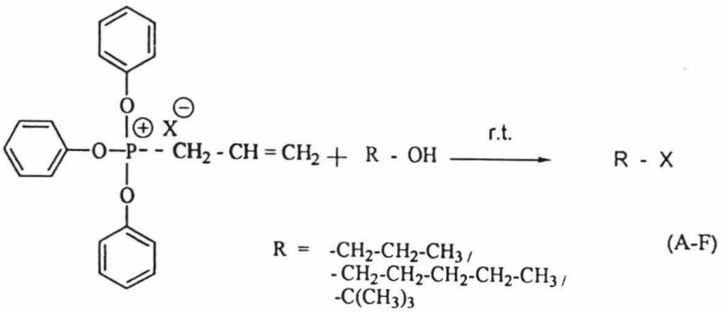
These halogenating reagents are versatile in their application and have certain advantages vis-à-vis the other reagents reported so far. In case of simple alcohol no heating is required and in case of nucleoside the corresponding halogenated derivatives are obtained in good yield, specially the bromo derivative and halogenation of both primary and secondary hydroxyls of sugar moiety is equally facile (**Scheme III**).

Thus ATPB / ATPC can be employed for bromination / chlorination of variety of compounds with certain advantages. ATPB is more versatile for its applicability in oligonucleotide chemistry for brominating 3′- and 5′- hydroxyl of deoxyribonucleosides.

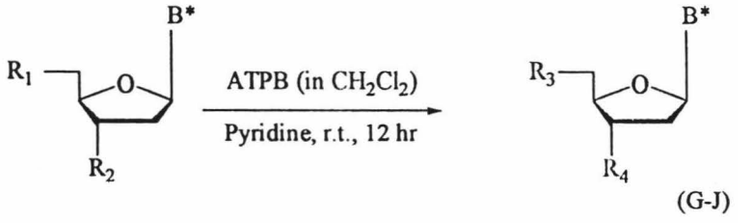


X = Br ; Allyltriphenoxyphosphonium bromide (ATPB)
X = Cl ; Allyltriphenoxyphosphonium chloride (ATPC)

Scheme I



Scheme II



R_1 = -OH, R_2 = $-OCOC_6H_5$, B* = N^3-benzoylthymine, R_3 = Br , R_4 = $-OCOC_6H_5$, (G)
R_1 = DMTrO-, R_2 = -OH, B* = N^3-benzoylthymine, R_3= DMTrO-, R_4 = Br, (H)
R_1 = -OH, R_2 = $-OCOC_6H_5$, B* = N^6-benzoyladinine, R_3 = Br , R_4 = $-OCOC_6H_5$, (I)
R_1 = DMTrO-, R_2 = -OH, B* = N^6-benzoyladinine, R_3= DMTrO-, R_4 = Br, (J)

Scheme III

Experimental Section

Triphenylphosphite was purchased from Merk-Schuchdart, Germany. Allyl chloride and allyl bromide were obtained from Spectrochem. Pvt. Ltd, Mumbai, India. Thymidine and adenine were purchased from Sigma Chemical Co. USA. All solvents used were Qualigens Analytical grade which were purified, prior to use. TLC was carried out on silica gel G plates. UV spectra were measured using Hitachi 220 S spectrophotometer. All the reactions were carried out under anhydrous conditions.

ATPB (Allyltriphenoxyphosphonium bromide)

Triphenyl phosphite (7.8 ml, 30 mmoles) and allyl bromide (3.4 ml, 40 mmoles) were mixed and refluxed under anhydrous conditions. The reaction was monitored by gradual increase in the temperature from 73°C to constant value of 122°C during a period of 40 hr. Reaction mixture was allowed to cool to r.t. and after cooling, washed thoroughly with dry ether. ATPB was obtained in pure form as gum, yield 15.5 g (90 %), R_f 0.58 (benzene), UV (MeOH) : 270 nm.

ATPC (Allyltriphenoxyphosphonium chloride)

Triphenylphosphite (2.6 ml, 10 mmoles) and allyl chloride (1.0 ml; 13 mmoles) were mixed and refluxed. The temperature was gradually increased from 48°C to a constant value of 110°C during a period of 24 hr, which marks the completion of the reaction. After cooling to room temperature and thorough washing with dry ether, ATPC was obtained in pure form as gum, yield 4.3 g (85 %), R_f 0.57 (benzene), UV (MeOH) : 273 nm.

Bromination/chlorination of alcohols and nucleosides : General procedure. Method A — Bromination / chlorination of alcohols was carried out by mixing the respective alcohols with ATPB / ATPC and stirring the reaction mixture at r.t. for 5 - 10 hr and collecting the corresponding bromo / chloro derivative by fractional distillation (**Table I**).

Method B—Bromination of nucleoside was carried out in similar way but in this case suitably protected nucleoside was used. Protected nucleosides were dis-

Table I—Physical data of compounds **A-F**

Compd	R	X	Yield (%)	b.p. °C
A	$-CH_2-CH_2-CH_3$	Br	52	71-73
B	$-CH_2-CH_2-CH_3$	Cl	60	47-49
C	$-CH_2-CH_2-CH_2-CH_2-CH_3$	Br	47	129-31
D	$-CH_2-CH_2-CH_2-CH_2-CH_3$	Cl	62	106-10
E	$-C(CH_3)_3$	Br	62	48-50
F	$-C(CH_3)_3$	Cl	55	50-54

Table II—Characterisation data of compounds **G-J**

Compd	R_3	R_4	B*	Yield (%)	UV (MeOH) (in nm)	^{1}HNMR ($CDCl_3$) (δ, ppm)
G	Br	$-OCOC_6H_5$	N^3-benzoyl thymine	64	272	1.99 (s, 3H, C_5-CH_3), 2.35 - 2.46, 2.58 - 2.65 (m, 2H, 2′-H), 4.0 (2H, 5′-H), 4.43 - 4.44 (m, 1H, 4′-H), 5.29 - 5.31 (m, 1H, 3′-H), 6.41 - 6.47 (m, 1H, 1′-H), 7.26 - 8.01 (m, 5H, Ar-H).
H	DMTr-O-	Br	N^3-benzoyl thymine	62	272	1.91(d, 3H, C_5-CH_3), 2.39 - 2.46, 2.85 - 2.97 (m, 2H, 2′-H), 3.42-3.48, 3.67-3.73 (m, 2H, 5′-H), 4.29-4.35 (m, 1H, 4′-H), 4.46-4.50 (m, 1H, 3′-H), 5.97- 6.41 (m, 1H, 1′-H), 7.30-8.00 (m, 21H, Ar-H and 6-H of thymidine).
I	Br	$-OCOC_6H_5$	N^6-benzoyl adenine	63	262	1.83(1H, 5′-OH), 2.64-2.70, 3.30-3.40 (m,2H, 2′-H), 4.00-4.1(m, 2H, 5′-H) 4.50 (s, 1H, 4′-H), 5.85-6.00 (m, 1H, 3′-H), 6.45-6.50 (m, 1H, 1′-H), 7.45-8.20 (m, 10H, Ar-H), 8.80 (s, 1H, 2-H of adenine), 9.15 (s, 1H, 8-H of adenine).
J	DMTr-O-	Br	N^6-benzoyl adenine	60	262	2.74-2.80, 2.92-3.20 (m, 2H, 2′-H),3.38-3.48, 3.55-3.70 (m, 2H, 5′-H), 4.35-4.41 (m, 1H, 4′-H) 4.60-4.65 (m, 1H, 3′-H), 6.45-6.80 (m, 1H, 1′-H), 7.00-7.85 (m, 20H, Ar-H), 8.41 (s, 1H, 2-H of adenine), 8.68 (s, 1H, 8-H of adenine).

solved in pyridine and mixed with ATPB and stirred at r.t. for 10 - 12 hr. After complete bromination, the reaction mixture was transferred to cold water and product was extracted with DCM. The organic layer after drying over sodium sulphate, evaporated to a gum. The product was purified by column chromatography using DCM : Hexane gradient (**Table II**). Chlorination of nucleoside with ATPC gives very poor yield.

Acknowledgement

Financial support from Department of Science & Technology, New Delhi (to SK) and NVS Chemicals Pvt. Ltd. Moradabad (to Y S), is gratefully acknowledged.

References

1 Brown D M, Todd A R & Varadarajan S, *J Chem Soc,* **1957,** 868.

2 Anand A, Clark V M, Hall A R & Todd A R, *J Chem Soc,* **1952,** 3665.

3 Bannister B & Kagan F, *J Am Chem Soc,* 82, **1960**, 3363.

4 Wempen I Doerr I L & Fox J J, *J Am Chem Soc,* 82, **1960**, 1624.

5 Barnett J E G, *Advanced Carbohyd Chem,* 22, **1967,** 177.

6 (a) Jahn W, *Arch Exp Pathol Pharmacol,* 251, **1965**, 95
(b) Langen P & Kowollik G, *Eur J Biochem,* 6, **1968**, 344

7 Suhadolnik R J, *Nucleoside Antibiotics,* (Wiley Interscience, NY, New York), **1970**.

8 Ohuchi S, Singh R K, Wada T & Hata T, *Chem Lett,* **1992**, 1505.

9 Mitsuya H & Border S, *Proc Natl Acad Sci USA,* 83, **1986,** 1911.

10 (a) Landauer S R & Rydon H N, *J Chem Soc,* **1953**, 2224.
(b) Coe D G, Landauer S R & Rydon H N, *J Chem Soc,* **1954**, 2281.
(c) Rydon H N & Tonge B L, *J Chem Soc,* **1956,** 3043.

11 (a) Hotoda H, Wada T, Sekine M & Hata T, *Tetrahedron Lett,* 28, **1987,** 1681.
(b) Hotoda H, Wada T, Sekine M & Hata T, *Nucleic Acids Res,* 17, **1989**, 5291.

12 (a) Wada T, Hotoda H, Sekine M & Hata T, *Tetrahedron Lett,* 29, **1988,** 4143.
(b) Wada T, Hotoda H, Sekine M & Hata T, *J Org Chem,* **1991,** 56