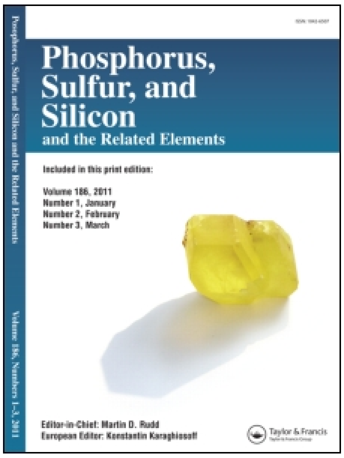

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A NEW METHOD FOR SELECTIVE CONVERSION OF ALCOHOLS TO NITRATES UNDER MILD AND NEUTRAL CONDITIONS

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A NEW METHOD FOR SELECTIVE CONVERSION OF ALCOHOLS TO NITRATES UNDER MILD AND NEUTRAL CONDITIONS

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(Received 18 March 1997)

Treatment of alcohols with triphenylphosphine, N-bromosuccinimide (a positive halogen source), and silver nitrate affords the corresponding alkyl nitrates in excellent yields.

Keywords: Alkyl nitrates; alkoxyphosphonium salts; triphenylphosphine; N-bromosuccinimide; alcohols; Selective replacement of hydroxy groups by nitrate groups

Nitrate esters are useful synthetic intermediates for which there are only two general methods of preparation: Direct esterification of the appropriate alcohol, or substitution of the corresponding halide with silver or mercury nitrate.

A number of reagents and conditions effecting O-nitration of alcohols have been described, including concentrated nitric acid, usually in the presence of urea mixed with sulfuric acid,[1–4] dinitrogen tetroxide,[5] N-nitro-collidinium tetrafluoroborate,[6] nitric acid/acetic anhydride,[7] and thionyl chloride nitrate or thionyl nitrate.[8] Yields of nitrate esters are often quite good, but considerable care must be exercised in carrying out these reactions in order to avoid explosion or side reactions of the substrate.

The second procedure for the synthesis of nitrate esters, treatment of an alkyl halide with silver or mercury nitrates,[9] is experimentally simpler, but implies a two step procedure starting from the corresponding alcohol.

Recently this two step transformation of alcohols into alkyl nitrates was developed into a one pot synthesis via *in situ* formation of the corresponding iodides in good to excellent yields.[10] The method appears to be chemoselective, allowing O-nitration of primary alcohols in the presence of secondary ones.

Selective reactions of a particular functional group in a multifunctional molecule is a challenging task which is often called for in synthesis. Thus reagents which are sufficiently selective to distinquish between functional groups of the same class, *e.g.*, between primary and secondary alcohols are very valuable as they permit operations that are either impossible or dependent on cumbersome and time-consuming protection and deprotecting procedures.

We now report a facile method for selective O-nitration of primary aliphatic, as well as benzylic and allylic alcohols in the presence of other types of hydroxyl and other oxidizable groups, under mild conditions. The method takes advantage of the versatility of alkoxyphosphonium salts as intermediates for the synthesis of a variety of compounds,[11] e.g., amines,[12] alkyl iodides[13] etc., and the necessary solubility of the inorganic nitrate reagent is secured by using finely powdered silver nitrate combined with mixtures of acetonitrile and dichloromethane as the solvent.

Thus, a solution of cholesteryloxyphosphonium bromide was first prepared by adding a slight excess of NBS to a mixture of triphenylphosphine and cholesterol (cf. **1**) in mixed acetonitrile/dichloromethane solvent at low temperature. After stirring for a while, an excess of finely powdered silver nitrate was added. Silver bromide started to separate immediately, and after stirring at room temperature for 0.5 h. cholesteryl nitrate could be isolated in 74% yield. After 4 h the yield increased to 90%.

The scope of the reaction was investigated on a number of alcohols (cf. Table 1). Under the same conditions allylic and benzylic alcohols, likewise afforded high yields, whereas primary aliphatic alcohols needed longer reaction times (as a rule the reactions were run overnight at room temperature). Secondary aliphatic and ordinary cycloaliphatic alcohols were recovered essentially unchanged, demonstrating the high selectivity between different types of alcohols.

As previously outlined[12–18] we believe that the reaction is initiated by a nucleophilic attack of triphenylphosphine at the positive halogen of NBS.

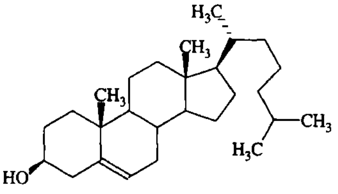
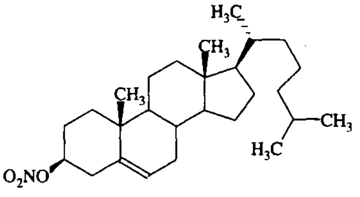
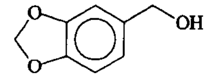
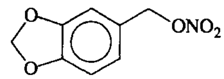
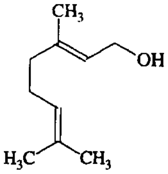
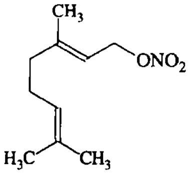
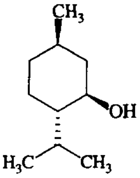
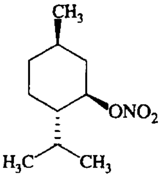
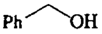
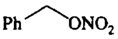
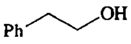
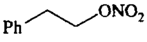
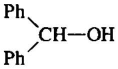
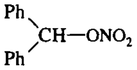
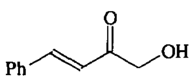
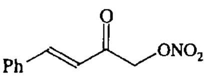
The primary phosphonium salt so formed reacts immediately, even at −40°, with alcohols, leading to the corresponding alkoxyphosphonium bromide.

The final step of the reaction (esterification), would be expected to proceed either through direct nucleophilic attack of the nitrate ion at the alkoxy carbon of the alkoxyphosphonium ion **III**, or, perhaps more likely, via the pentacoordinated species **IV** (Scheme **1**).

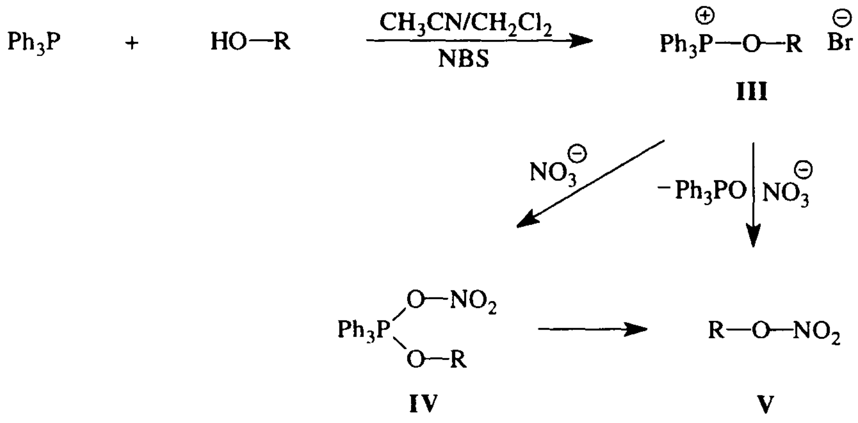
This offers some interesting mechanistic possibilities: A reaction initiated through nucleophilic attack of the nitrate ion at the alkoxy carbon of the phosphonium salt as represented by **VI** (Scheme **2**), would lead to inversion of configuration at this carbon atom. Thus, from studies of the related conversion of optically active alcohols[19–23] to the corresponding chlorides through the Ph_3P/CCl_4 reagent, there is ample evidence that the transformations are largely stereoselective, with inversion of configuration at the secondary carbon atom.

TABLE I

Conversion of alcohols to alkyl nitrates

Entry	Alcohol	Alkyl nitrate	Yield (%)
1			90
2			94
3			91
4			0
5			96
6			95
7	 $Ph_2CH{-}OH$	 $Ph_2CH{-}ONO_2$	90
8	$CH_3(CH_2)_9OH$	$CH_3(CH_2)_9ONO_2$	97
9	$CH_3CH(OH)(CH_2)_2OH$	$CH_3CH(OH)(CH_2)_2ONO_2$	89
10			91

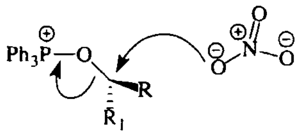
In principle, the pentacoordinated intermediate **IV** could decompose in two ways (cf. Scheme **2**): One way would lead to retention at the alkyl carbon atom (cf. **VII**); the other to inversion (cf. **VIII**). In an effort at discerning between these two possibilities, the cholesteryl nitrate (cf. **1**) obtained as described above



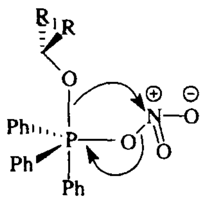
was transformed back to the alcohol stage by reduction with zink in acetic acid, a process which leaves the carbon centre untouched.

The resulting cholesterol, which was isolated in high yield, showed $[\alpha]^{20}{}_{D}$ (c = 2, $CHCl_3$) = −39.8°. The starting material, obtained from from Fluka Chemie, was measured to $[\alpha]^{20}{}_{D}$ (c = 2, $CHCl_3$) = −39.2°, which is, within the experimental error, the same specific rotation.

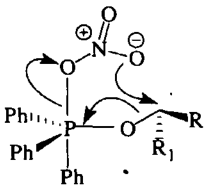
Thus it appears that the esters formed during the present transformation of alcohols have the same stereochemistry as the starting alcohols, and that a mechanism passing through **VII** (retention) is to be favoured over **VIII** (inversion) or **VI** (inversion). This path of reaction of the nitrate ion is in striking contrast to that of ordinary organic nucleophiles, for which an attack corresponding to **VI** (inversion) is commonly assumed.[11] The present results bring further evidence for the theory that pentacoordinated species are occurring as transition states, and perhaps as discrete intermediates, in many chemical reactions involving phosphorus.



VI



VII



VIII

In theory, the two oxygen groups on phosphorus may be placed in four possible ways: (i) both equatorial, (ii) nitrate apical and alkoxy equatorial, (iii) alkoxy apical and nitrate equatorial, and (iv) both in apical positions.

The most electronegative ligands preferentially occupy apical sites,[24] hence (i) has to be ruled out. In (ii) and (iii) the 4-ring transition state **VII** (and its analogue) is possible; whereas in (iv) any interaction between the two oxygen containing groups is precluded.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were taken at operating frequencies of 200 and 50.3 MHz on a Varian Gemini-200 spectrometer. The mass spectra were obtained on a JMS-DX 303 mass spectrometer. IR spectra were measured as films, partly with a Perkin Elmer 1310, partly with a Nicolet Magna 550 FT infrared spectrophotometer. Column chromatography was carried out using Merck No. 9385 silica gel 60. Melting points, determined with a Reichert Thermopan melting point microscope, are uncorrected.

General Procedure for the Preparation of Alkyl Nitrates (1–10)

The reactants, triphenylphosphine and alcohol (5 mmol of each) were dissolved under nitrogen in a mixture of acetonitrile (5 ml) and dichloromethane (2 ml). The reaction mixture was cooled to about −35° (ethanol/granular CO_2), and vigorously stirred while NBS (0.91 g, 5.1 mmol) was added in small portions. After a couple of min. the yellowish reaction mixture became colourless. Silver nitrate (6 mmol) was added as a fine powder in one portion after about 5 min. A few moments after the addition of $AgNO_3$, the reaction mixture turned yellow from suspended particles of silver bromide. The cooling bath was thereafter removed. Stirring was continued at room temperature, in most cases overnight. Piperonyl alcohol (reaction time 3h.), and cholesterol (0.5 h. and 4 h.) were the only exceptions.

The progress of the reaction could be conveniently followed by observing the characteristic absorptions of the alkyl nitrate at approximately 1630 and 1280 cm^{-1}, or the likewise very strong and characteristic IR absorption of the forming triphenylphosphine oxide at about 1180 cm^{-1}. At the end of the reaction, most of the solvents were removed at reduced pressure and the alkyl nitrate extracted with pentane, or, in the case of **9**, with ether/pentane (1:1). The product was further purified by column chromatography (flash chromatography) with Merck

No. 9385 silica gel 60 as stationary phase, using ether/hexane (1:4), or in the case of **9**, ether/hexane (2:1) as eluent. All products except cholesteryl nitrate **1** and diphenylmethyl nitrate **7** were oils.

1 and **7** were both recrystallized from pentane.

Cholesteryl nitrate 1

Chromatography of the raw product followed by evaporation of the eluent gave virtually pure **1** as a white solid, which after recrystallization from pentane melted at 114°, lit.[10] 114–116°; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.66 (s, 3H, CH_3), 0.86 (d, 6H, CH_3), 0.92 (d, 3H, CH_3), δ 0.95–2.1 (m, 29H, CH_3, CH_2 and CH), δ 2.4 (m, 2H, CH_2), δ 4.8 (m, 1H, CH), δ 5.4 (m, 1H, CH); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 11.89, 18.75, 19.23, 21.09, 22.59, 22.84, 23.88, 24.30, 26.01, 28.04, 28.24, 31.83, 31.94, 35.81, 36.27, 36.63, 36.84, 38.55, 39.72, 42.34, 49.99, 56.18, 56.68, 83.34, 123.86, 138.33; MS (70 eV): m/z (%) 431.7 (1.3, M^+), 369.7 (32), 368.7 (100), 255.5 (12.4), 247.5 (29.4), 244.4 (10.8), 220.4 (47.8), 219.4 (15.5), 206.4 (12.3), 205.4 (71.4), 178.25 (10.5), 167.2 (16.4), 161.3 (12.8), 149.2 (14), 145.25 (15), 135.2 (12.7), 123.2 (28.8), 121.2 (11), 113.2 (12), 112.2 (20.2), 111.2 (14), 99.2 (10.3), 97.2 (14.3); IR (film) 1655 and 1280 cm^{-1}.

Reduction of cholesteryl nitrate

To a mixture of 0.35 g of finely divided **1** in concentrated acetic acid (15 ml) was added zink (0.7 g) as a fine dust. The mixture was stirred at room temperature for 45 min. An equal volume of ether was added, the solids collected by filtration and the organic solvents removed at reduced pressure. The residue was dissolved in ether and dried over magnesium sulfate. After filtration, the solvent was removed *in vacuo* to yield 0.27 g (87%) of virtually pure cholesterol. The white solid was recrystallized from pentane.

M.p. 147–150°, lit.[25] 149.5–150°. $[\alpha]^{20}_D$ (c = 2, $CHCl_3$) −39.8°. The commercial starting material obtained from Fluka chemie had m.p. 146–149° and $[\alpha]^{20}_D$ (c = 2, $CHCl_3$) −39.2°.

Piperonyl nitrate 2

Chromatography of the raw product from extraction with pentane, followed by evaporation of the eluent gave virtually pure **2** as a colourless oil, which rapidly turned brown even when kept under nitrogen in a refrigerator. ^{1}H NMR (200

MHz, $CDCl_3$): δ 5.33 (s, 2H, CH_2), 5.95 (s, 2H, CH_2), 6.68–6.92 (m, 3H, $H_{aromatic}$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 74.88, 101.34, 108.29, 109.46, 123.48, 125.42, 147.91, 148.45; MS (70 eV): m/z (%) 198.2 (10.2), 197.2 (100, M^+), 151.2 (33.1), 150.2 (27.1), 149.2 (69.3), 136.2 (10.4), 135.2 (88), 123.2 (10.3), 122.1 (13), 121.1 (92.5), 93.1 (80.6), 91.1 (19); IR (film) 1632 and 1286 cm^{-1}.

Geranyl nitrate 3

Chromatography of the material from extraction with pentane gave the pure product (**3**) as a colourless oil; ^1H NMR (200 MHz, $CDCl_3$): δ 1.60 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.09 (s, 4H, CH_2), 4.94 (d, 2H, J = 7.3 Hz, CH_2), 5.0–5.15 (m, 1H, $H_{vinylic}$), 5.35 (m, 1H, $H_{vinylic}$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 16.58, 17.61, 25.58, 26.05, 39.51, 69.97, 114.32, 123.25, 132.11, 147.14; MS (70 eV): m/z (%) 154.1 (1.2), 153.1 (7.2, M^+), 137.1 (20), 123.1 (100), 121.1 (11.6), 108 (15.4), 95 (51.3), 93 (43.3), 91 (19.6), 83 (11), 81 (59.8), 79 (21.2), 77 (18.7); IR (film) 1620 and 1280 cm^{-1}.

Benzyl nitrate 5

Column chromatography of the residue from the extraction with pentane gave virtually pure **5** as a colourless oil; ^1H NMR (200 MHz, $CDCl_3$): δ 5.41 (s, 2H, CH_2), 7.39–7.42 (m, 5H, $H_{aromatic}$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 74.79, 128.27, 128.49, 128.88, 131.63; MS (70 eV): m/z (%) 168.1 (10.1), 167.1 (100, M^+), 105.1 (43.5), 104.1 (41.2), 103.1 (25.7), 92.1 (77.9), 91 (88.7), 90 (21.8), 89 (34); IR (film) 1630 and 1280 cm^{-1}.

2-Phenethyl nitrate 6

Column chromatography of the residue after extracting the raw product with pentane followed by evaporation of the eluent *in vacuo*, gave pure **6** as a colourless oil; ^1H NMR (200 MHz, $CDCl_3$): δ 3.03 (t, 2H, J = 7.0 Hz, CH_2), 4.65 (t, 2H, J = 7.1 Hz, CH_2), 7.24–7.35 (m, 5H, $H_{aromatic}$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 33.19, 73.30, 126.96, 128.63, 128.74, 135.94; MS (70 eV): m/z (%) 153.1 (18.4, M^+), 107.1 (11.3), 106.1 (12.8), 105.1 (21.7), 91.1 (27.9), 79.1 (35.7), 78.1 (16.1), 77 (100); IR (film) 1625 and 1280 cm^{-1}.

Diphenylmethyl nitrate 7

Extraction of the raw product with pentane followed by evaporation of the solvent *in vacuo* yielded a colourless residue.

The residue was dissolved in a little ether and chromatographed with ether/hexane as eluent. The residue, after removal of solvents *in vacuo*, crystallized after some time in the refrigerator and was recrystallized from pentane. M.p. 37°, lit[26] 36.7–37.7°; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.42 (s, 1H, CH), 7.50 (m, 6H, $H_{aromatic}$), 7.82 (m, 4H, $H_{aromatic}$); MS (70 eV): m/z (%) 229.0740 (3.5, M^+), calculated: 229.0738; IR (film) 1660 and 1280 cm^{-1}.

1-Decanyl nitrate 8

Extraction of the raw product with pentane yielded a colourless residue after evaporation of the solvent *in vacuo*.

The residue was dissolved in ether, chromatographed with ether/hexane (1:4). Solvents were removed at reduced pressure, yielding **8** as a colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 6.5 Hz, CH_3), 1.27 (m, 14H, CH_2), 1.72 (m, 2H, CH_2), 4.44 (m, 2H, J = 6.7 Hz, CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.07, 22.67, 25.63, 26.74, 29.11, 29.27, 29.39, 29.46, 31.87, 73.43; MS (70 eV): m/z (%) 203.17 (8.4), M^+), 173.14 (14.3), 159.13 (13), 141.15 (30.5), 112.11 (20), 111.11 (24.2), 110.1 (10.4), 99.1 (14.3), 98.1 (18.7), 97.1 (31.9), 96.1 (16), 95.1 (13.1), 85.1 (36.8), 84.1 (25.6), 82.0 (24.3), 81 (16.5), 78 (11.3), 71.1 (43.9), 70.1 (25.7), 69.1 (47); IR (film) 1628 and 1278 cm^{-1}.

3-Hydroxy-1-butanyl nitrate 9

Extraction with pentane - ether (1:1) yielded a colourless residue. The residue was dissolved in a little ether and chromatographed with ether/hexane (2:1). Evaporation of the solvent *in vacuo* yielded pure **9** as a colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (d, 3H, J = 6.2 Hz, CH_3), 1.63 (s, 1H, OH), 1.85 (m, 2H, CH_2), 3.98 (m, 1H, CH), 4.60 (m, 2H, CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 23.87, 35.69, 64.53, 70.48; MS (70 eV): m/z (%) 135.0678 (100, M^+), calculated: 135.0533; IR (film) 1625 and 1280 cm^{-1} 3350 cm^{-1} (broad, OH).

Cinnamyl nitrate 10

Chromatography of the raw product followed by evaporation of the eluent gave virtually pure **10** as a colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.06 (d, 2H, J = 6.9 Hz, CH_2), 6.18–6.33 (m, 1H, CH), 6.76 and 6.84 (1H, CH, J =

15.9 Hz, CH), 7.26–7.46 (m, 5H, $H_{aromatic}$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 73.62, 118.39, 126.28, 128.11, 128.18, 134.71, 137.36; MS (70 eV): m/z (%) 179.2 (30.1, M^+), 133.2 (20.9), 131.2 (17.7), 117.2 (46), 115.2 (20.6), 105.2 (73.1), 104.2 (21.3), 103.2 (100), 102.2 (20), 91.1 (19.9), 79.1 (26.3), 78.1 (20.9), 77.1 (71), 63.1 (11); IR (film) 1630 and 1277 cm^{-1}.

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