Cerium(IV)-Mediated Synthesis of Tetrahydrofuranyl Ethers

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The reaction of tetrahydrofuran with an alcohol in the presence of ceric triethylammonium nitrate provides a convenient and general procedure for protecting the hydroxyl function. Tetrahydrofuranyl ethers of primary, secondary, and tertiary alcohols were obtained in good yields

Cyclic ethers, such as tetrahydrofuran, have been reported to be oxidized to lactones in the presence of ceric salts.[1] In connection with a program concerning the reactivity of a new cerium(IV) salt, ceric triethylammonium nitrate,[2] soluble in various organic solvents, we decided to investigate the behavior of tetrahydrofuran in the presence of this salt.

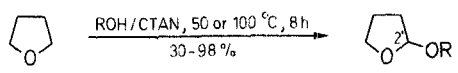
In the light of the possibility that the intermediates of this oxidation could be particularly reactive dihydrofuranyl derivatives, we introduced alcoholic substrates in order to test the possible formation of tetrahydrofuranyl ethers, as the acid-catalysed reaction between hydroxyl groups and commercially available 2,3-dihydrofuran, leading to 2-alkoxytetrahydrofuran, is well known.[3]

In fact, the addition of *n*-octanol to a tetrahydrofuran solution of ceric triethylammonium nitrate (CTAN), using a molar ratio of alcohol to CTAN, 1:1.5, at 50°C for 8 hours, led to the corresponding tetrahydrofuranyl ether in good yield (no carbonyl compounds were detected).

The tetrahydrofuranyl ether was identified on the basis of analytical, spectroscopic data, and regeneration of the starting alcohol by hydrolysis under mild conditions, and on the basis of comparison with an authentic sample.[4]

The protection of hydroxyl groups as tetrahydrofuranyl ethers is important in organic synthesis, since the tetrahydrofuranyl group is preferred sometimes to the more often used tetrahydropyranyl group.[5] The introduction of the acid-labile tetrahydrofuranyl group is usually performed by the methods reported by Kruse[4,6] using the 2-chloro tetrahydrofuran reagent and an acetal exchange with tetrahydrofuranyl diphenylacetate.

In view of the simplicity of our reaction, we undertook to develop a general and convenient procedure for the protection of alcohols (Table). The reactions were performed by using a molar ratio of substrate CTAN 1/1.5 in the presence of excess tetrahydrofuran at 50°C for 8 hours. Primary, secondary, and tertiary alcohols react nearly quantitatively. A higher temperature (100°C), obtained by using a 1:1 mixture of toluene-tetrahydrofuran was required in the case of sterically hindered steroidal alcohols, leading to tetrahydrofuranyl derivatives in 30–40% yields (starting material was recovered in major portion). The THF-ethers of *n*-octanol, cyclohexanol, and *t*-butanol were compared with authentic samples, prepared according to Kruse.[4]



CTAN = ceric triethylammonium nitrate

Table. Conversion of Alcohols into Tetrahydrofuranyl Ethers by CTAN

Substrate	Yield of THF Ethers (%)[a]	m.p. (°C) (solvent) or b.p. (°C)/torr	Molecular Formula[b] or Lit. b.p. (°C)/torr	IR ($CHCl_3$)[c] ν (cm^{-1})[3]
n-Octanol	98	75–77/0.7	74–77/0.7[4]	1450
Cyclohexanol	98	47–49/0.7	48–50/0.7[4]	1450
t-Butanol	95	140–142/760	140–141/760[7]	1450
Menthol	90	43–45 (*n*-hexane)	$C_{14}H_{26}O_2$ (226.3)	1450
3β-Cholestanol	95	100–101 (*n*-hexane)	$C_{31}H_{54}O_2$ (458.7)	1450
Cholesterol	90	101–102	$C_{31}H_{52}O_2$ (456.7)	1640, 1450
3β-Hydroxy-5α--androstan-17-one	90	138–140 (*n*-hexane)	$C_{23}H_{36}O_3$ (360.5)	1720, 1450
3α-Hydroxy-5α--androstan-17-one	30[d]	133–134 (*n*-hexane)	$C_{23}H_{36}O_3$ (360.5)	1720, 1450
3β-Hydroxy-5α--pregnan-20-one	95	120–121 (*n*-hexane)	$C_{25}H_{40}O_3$ (388.6)	1725, 1450
17β-Hydroxy-androst--4-en-3-one	60[d]	112–113 (*n*-hexane)	$C_{23}H_{34}O_3$ (358.5)	1680, 1645,
17α-Methyl-17β-hydroxy-androst-4-en-3-one	40[d]	125–126 (*n*-hexane)	$C_{24}H_{36}O_3$ (372.5)	1680, 1630, 1450
21-Hydroxy-pregn--4-en-3-one	35[d]	98–99 (*n*-hexane)	$C_{25}H_{36}O_4$ (400.5)	1720, 1680, 1640, 1450
3β-Cholestanol	85[e]	94–96 (*n*-hexane)	$C_{32}H_{56}O_2$ (472.8)	1450

[a] Yield of isolated products. All the products gave ^{1}H-NMR data in agreement with their structures.

[b] Satisfactory microanalyses obtained: C ± 0.25, H ± 0.08.

[c] Recorded on a Perkin-Elmer 983 spectrophotometer.

[d] The reaction was conducted at a higher temperature (100°C) using a tetrahydrofuran-toluene (1:1) mixture.

[e] Yield refers to the tetrahydropyranyl derivative.

The presence of a tetrahydrofuran group in the compounds listed in the Table, is clearly seen in their ^{1}H-NMR spectra. Two multiplets appear at δ = 3.9 ppm (5′-protons), and 1.8–2.0 ppm (3′ and 4′-protons). The chemical shifts of 2′-H proton has a characteristic value for protected primary (5.15–5.20 ppm), secondary (5.25 ppm), and tertiary alcohols (5.40 ppm) and appears as a broad singlet.

Thus our method seems suitable for application to other cyclic ethers, such as tetrahydropyran. In fact, we obtained in a good yield the tetrahydropyranyl ethers, using tetrahydropyran. A single example is given in the Table. This work will be the subject of further investigation to obtain evidence on the intermediate responsible for the reaction between a cyclic ether and an alcohol in the presence of CTAN.

Cerium(IV)-Mediated Conversion of Alcohols into Tetrahydrofuranyl Ethers; Typical Procedure:

The alcohol (1 mmol) is added to a solution of dry tetrahydrofuran (30 ml) containing ceric triethylammonium nitrate (1.1 g, 1.5 mmol), prepared according to the published procedure.[2] The resulting mixture is stirred at 50°C for 8 h. Removal of tetrahydrofuran under reduced pressure gives a residue, which is extracted with ethyl acetate (3 × 50 ml). The organic layer is washed with water (100 ml), dried with sodium sulfate, filtered and evaporated *in vacuo* to give a crude residue. Purification is effected by chromatography on silica gel using

benzene/*n*-hexane (9 : 1) as eluent (Table). The reaction could be run in preparative scale to give analytically pure products, in useful yields.

Hydrolysis of Tetrahydrofuranyl Ethers (Table); Typical Procedure:
A solution of tetrahydrofuranyl (1 mmol) in 95% ethanol (2 ml) is stirred at room temperature with *p*-toluenesulfonic acid (17 mg, 0.1 mmol). After 1 h, the solvent is evaporated and the residue is extracted with ethyl acetate (3 × 50 ml), washed with water (30 ml) and dried with sodium sulfate. Removal of the solvent gives quantitatively the starting alcohol.

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