Heteroatom Chemistry
Volume 6, Number 4, 1995

Preparation of Tetra-*n*-butylammonium Peroxydisulfate. Novel Tetrahydrofuranylation [1] and Tetrahydropyranylation of Alcohols

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Received 11 October 1994; revised 30 November 1994

ABSTRACT

Tetra-n-butylammonium peroxydisulfate (Bu_4N^+ $^-OS(O_2)O-O(O_2)SO^-$ $^+NBu_4$: $(TBA)_2S_2O_8$) has been successfully prepared and turned out to be a useful source of the tetra-n-butylammonium sulfate radical in organic solvents. Primary, secondary, and tertiary alcohols containing functional groups, such as benzylic, allylic, and sulfide, reacted with tetrahydrofuran or tetrahydropyran in the presence of $(TBA)_2S_2O_8$ to give the corresponding 2-tetrahydrofuranyl- or 2-tetrahydropyranyl-ether in excellent yields under nearly neutral conditions.

INTRODUCTION

The protection of hydroxyl groups has been extensively investigated and frequently used for the synthesis of polyfunctional organic compounds [2,3]. The acid-labile tetrahydrofuranyl group is usually introduced by methods reported by Kruse [4,5,6] using the 2-chlorotetrahydrofuran reagent and an acetal exchange with tetrahydrofuranyl diphenylacetate. Recently, tetrahydrofuranylation of alcohols using ceric ammonium nitrate was reported by Romeo [7]. In the acetal series, 2-tetrahydropyranyl ether (THPE) has been used in a practical manner [2], and the protecting group can be readily removed with various reagents [8].

In addition, a strong acid is the most common catalyst [9,10]. Owing to its strong acidity, however, this method is still undesirable for alcohols that possess highly acid-sensitive groups. In earlier work on the preparation of THPE, dihydropyran has been used as a starting material with an appropriate acid catalyst: *p*-toluenesulfonic acid [11], pyridinium *p*-toluenesulfonate [12], or amberlyst H-15 [13].

RESULTS AND DISCUSSION

Tetra-*n*-butylammonium peroxydisulfate ($(TBA)_2S_2O_8$) (**2**) has been successfully synthesized by the reaction of potassium peroxydisulfate with 2 equivalents of tetrabutylammonium hydrogen sulfate, and it turned out to be a new, useful source of radical **5**. We have found that various alcohols containing functional groups, such as olefin, sulfide, and acetal, reacted with tetrahydrofuran or tetrahydropyran in the presence of **2** to afford the corresponding tetrahydrofuranyl ether (THFE) or THPE, respectively, in excellent yields under nearly neutral conditions, as shown in Scheme 1. The known inorganic peroxydisulfates, $K_2S_2O_8$, $Na_2S_2O_8$, and $(NH_4)_2S_2O_8$, are soluble only in water and show a strong oxidizing ability in aqueous media. Thermal or photochemical cleavage of $S_2O_8^{2-}$ provides the radical anion $^-OSO_3^-$ [14–17], which is an effective electron transfer agent [14]. The sulfate radical anion reacts with H_2O to form the hydroxyl radical and hydrogen peroxide [14].

It has been demonstrated that the alkoxyl radical is generated from a sulfate anion radical and an alcohol by a one electron transfer from the alcohol to **2** in aqueous media, and the alkoxyl radical fragments further to the alkyl radical [18,19].

Dedicated to Prof. Shigeru Oae on the occassion of his seventy-fifth birthday.

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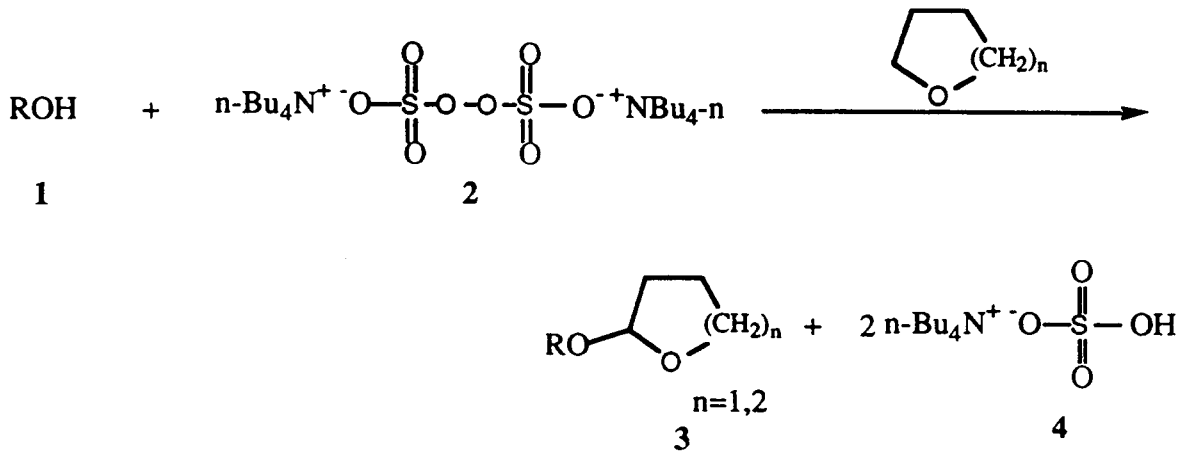


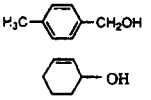
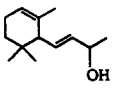
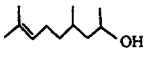
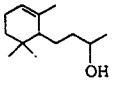
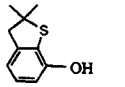
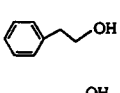
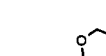
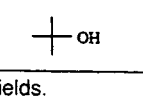
SCHEME 1

Since **2** is very soluble in organic solvents, in contrast to the metal peroxydisulfates, the tetrahydrofuranylation or tetrahydropyranylation could be smoothly carried out under anhydrous conditions. The results obtained are summarized in Tables 1 and 2.

In our procedure, the side products originated from such fragmentations [18,19] could not be observed in the various experiments (Table 1, Runs 5, 7, and 8). The alcohols containing olefine groups were converted into **3** without epoxidation of the double bonds. In the previous articles, sulfides were reported to be oxidized to sulfoxides with $K_2S_2O_8$ [20] and oxidized to sulfones with tetra-*n*-butylammonium oxone [21]. However, the sulfide moieties (Run 6 in Table 1 and Run 9 in Table 2) were not oxidized to either sulfoxides or sulfones. Moreover, the tetrahydrofuranylation or tetrahydropyranylation of alcohols possessing acid-sensitive functional groups, such as allylic hydroxyl, or acetal, could be performed without destroying these functional groups (Runs 1, 3, and 4 in Table 1 and Runs 4 and 8 in Table 2). Oxidation-labile alcohols such as benzylic and allylic alcohols (Runs 1, 4, 5, and 9 in Table 2) were converted into **3** in good yields. When the alcohols were tetrahydrofuranylated with $(TBA)_2S_2O_8$, **4** was also isolated (in 80% yield), and its identify was confirmed by comparing its melting point with that of an authentic sample. The tetrahydrofuranylation of alcohols appears to involve the tetrahydrofuranyl radical **6**, followed by attack by the alcohol on the oxonium ion intermediate **7**, which is formed by some form of a one electron transfer, as shown in Scheme 2.

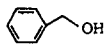
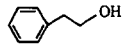
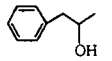
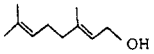
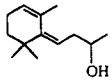
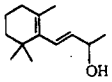
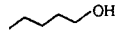
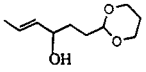
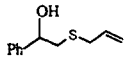
The formation of **6** was verified by the isolation of its dimer **8** (20%), the structure of which was confirmed by its IR, NMR, and mass spectral data. The sulfate anion radical **5** abstracts the hydrogen atom at the 2-position (having the higher

TABLE 1 Protection of Alcohols with $(TBA)_2S_2O_8$ in THF

Run	1 (*0.7 mmol*)	2 (*mmol*)	*Time* (*h*)	*Yield*[a] (%)
1		1.4	4	97
2		1.4	3.5	91
3		1.4	7.5	95
4		1.4	4	88
5		0.77	1.5	81
6		1.4	3.5	85
7		0.77	0.67	94
8		0.77	1	87[b]
9		1.4	6	96
10		1.4	3	94[b]

[a]Isolated yields.
[b]The yield was determined by GC.

TABLE 2 Protection of Alcohols with $(TBA)_2S_2O_8$ in THP

Run	Substrate	Time	Yield[a] (%)
1		3	94
2		3	92
3		4	95
4		6	87
5		9	86
6		11	85
7		4	94[b]
8		8	88
9		6	90

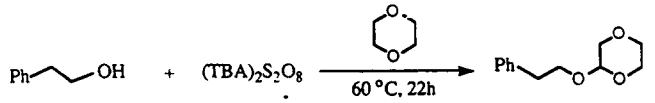
[a]Isolated yield.
[b]The yield was determined by GC.

electron density) in THF to form **6**, which then couples to give **8**.

6 **8**

As an alternative possible mechanism, a direct coupling of **5** with a tetrahydrofuranyl radical could occur to form an intermediate, the 2-tetrahydrofuranyl sulfonate anion, which could then be attacked by an alcohol to form the product **3**. However, when alcohols were treated directly with **2**, formation of such an intermediate could not be observed.

The 1,4-dioxane-2-yl ether is a good protecting group for steroid alcohols, because it has no methylene proton that overlaps the ^1H NMR resonances between δ 0.5 and 2 [22]. When 2-phenylethanol was treated with $(TBA)_2S_2O_8$ in 1,4-dioxane, 1,4-dioxane-2-yl ether was obtained in 35% yield together with other unidentified products.



In summary, direct tetrahydrofuranylation or tetrahydropyranylation of alcohols can be carried out using **2** under nearly neutral conditions in THF or THP as substrate and also solvent. These clean-cut procedures may be widely utilized for the protection of hydroxyl groups.

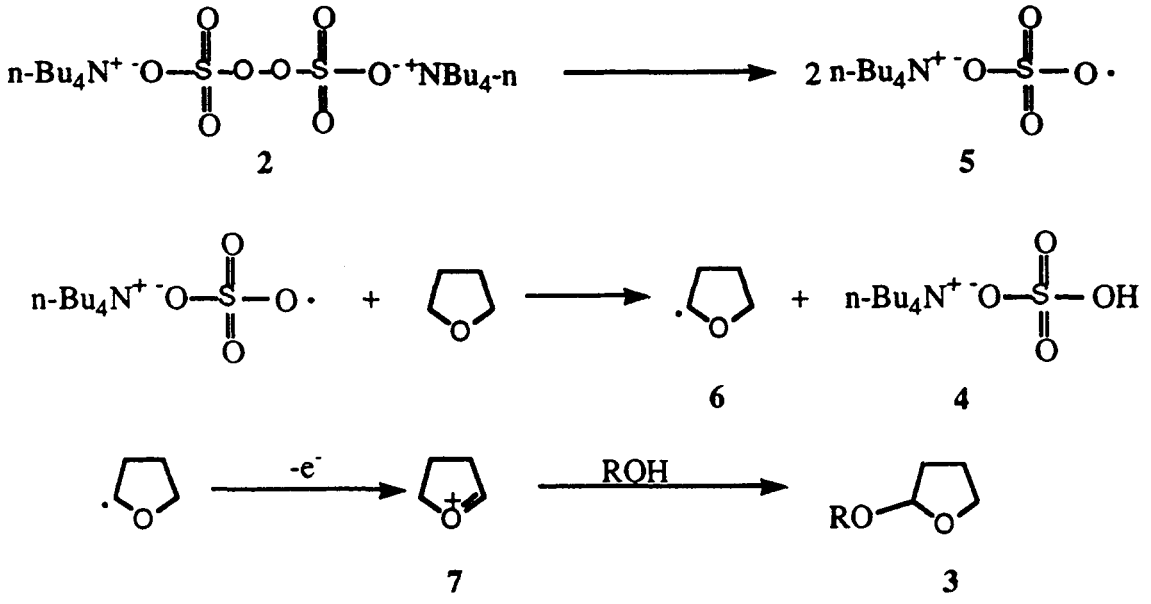
EXPERIMENTAL

Preparation of Tetra-n-butylammonium Peroxydisulfate

Tetra-*n*-butylammonium hydrogen sulfate (4 mmol, 1.32 g) and potassium peroxydisulfate(2 mmol, 0.54 g) in distilled water (10 mL) were stirred at room temperature. After having been stirred for 30 minutes at room temperature, the reaction mixture was filtered, and the filtrate was extracted with methylene chloride (30 mL). The methylene chloride layer was twice washed with distilled water (100 mL × 2), and the methylene chloride extract was dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent gave a white solid (83%, 1.22 g); ^1H NMR ($CDCl_3$) δ 3.2 (br, $4CH_2$), 1.4 (br, $8CH_2$), 0.7 (br, $8CH_2$), 0.7 (br, $4CH_3$); IR (CCl_4) 2951, 2874, 1476 1382, 1263, 1041, 676 cm^{-1}; mp 119°C (dec). Anal. calcd for $C_{22}H_{72}N_2S_2O_8$: C, 56.7; H, 10.7; N, 4.14. Found: C, 56.9; H, 10.8; N. 4.15.

Synthesis of 6-(1,3-Dioxan-2-yl)-2-hexen-4-ol

About 1 mg of iodine and magnesium turnings (15 mmol, 365 mg) was introduced into a 100 mL three-necked round-bottomed flask fitted with a dropping funnel, reflux condenser, and stopper, while more purple vapor arose from the iodine. Anhydrous THF (5 mL) was added to the flask, and a small amount of a solution of 2-(2-bromoethyl)-1,3-dioxane (15 mmol, 2.926 g) in anhydrous THF (10 mL) was added to the magnesium turnings and iodine. Occasional hand warming was used to initiate spontaneous boiling. Then, the remaining 2-(2-bromoethyl)-1,3-dioxane solution was added slowly to keep the reaction mixture refluxing gently until formation of the Grignard reagent was completed. Crotonaldehyde (15 mmol, 1.051 g) in anhydrous THF (15 mL) was slowly added to the solution of the Grignard reagent at −60°C with vigorous stirring. After having been stirred at −60°C for 3.5 hours, the reaction mixture was concentrated in vacuo. Aqueous saturated ammonium chloride (40 mL) was added to the residue, which was poured into a separatory funnel, and extracted with ether (100 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The product was isolated by column chromatography (silica gel, ether/*n*-hexane = 1/1, v/v) to give 6-(1,3-dioxan-2-yl)-2-hexen-4-ol (80%, 2.232 g); ^1H NMR ($CDCl_3$) δ 5.65–5.25 (m, 2H, HC=CH), 4.45 (m, 1H, CH), 4.2–3.4 (m, 5H, CH, $2CH_2$), 2.2 (m, 2H, CH_2),



SCHEME 2

1.75–1.45 (m, 7H, CH_3, $2CH_2$); IR (NaCl, neat) 3427, 1143, 1080, 986, 930 cm^{-1}.

Tetrahydrofuranylation of 4-Methylbenzyl Alcohol

A solution of 4-methylbenzyl alcohol (0.7 mmol, 85 mg) and tetra-*n*-butylammonium peroxydisulfate (1.4 mmol, 948 mg) in anhydrous THF (7 mL) was refluxed with vigorous stirring. After a reflux period of 4 hours solvent was carefully removed under reduced pressure and distilled water was added. The aqueous layer was extracted with ether (15 mL × 2). The combined organic layers were dried over anhydrous magnesium sulfate and filtered through filter paper. Evaporation of solvent gave a residual oil. The residual oil was applied to column chromatography (silica gel, ether/*n*-hexane = 1/6, v/v) to give the tetrahydrofuranyl ether of 4-methylbenzyl alcohol (97%, 130 mg); Rf, UV, 0.5; ^1H NMR ($CDCl_3$) δ 7.1 (s, 4H, C_6H_4), 5.18 (m, 1H, O–CH–O), 4.5 (dd, 2H, CH_2), 3.95 (m, 2H, CH_2–O), 2.16 (s, 3H, CH_3), 1.96 (m, 4H, $2CH_2$); IR (NaCl, neat) 1086, 1036, 920 cm^{-1}.

Tetrahydrofuranylation of 2-Cyclohexen-1-ol

Yield: 91%; ^1H NMR ($CDCl_3$) δ 5.75 (m, 2H, CH=CH), 5.2 (m, 1H, CH), 4.2–3.7 (m, 3H, CH, CH_2), 2.2 (m, 4H, $2CH_2$), 2.0–1.5 (m, 6H, $3CH_2$); IR (NaCl, neat) 2924, 1120, 1083, 1035, 1012, 932, 806 cm^{-1}.

Tetrahydrofuranylation of α-Ionol

Yield: 95%; ^1H NMR ($CDCl_3$) δ 5.45–5.0 (m, 4H, CH, CH=CH, =CH), 4.2–3.6 (m, 3H, CH, CH_2), 2.2–0.7 (m, 21H, $3CH_3$, $4CH_2$, CH); IR (NaCl, neat) 2924, 1079, 1005, 922, 823 cm^{-1}.

Tetrahydrofuranylation of Geraniol

Yield: 88%; ^1H NMR ($CDCl_3$) δ 5.5–5.0 (m, 3H, 2CH=, CH), 4.2–3.7 (m, 4H, $2CH_2$), 2.2–1.4 (m, 17H, $3CH_3$, $4CH_2$); IR (NaCl, neat) 2921, 1077, 1030, 921, 842 cm^{-1}.

Tetrahydrofuranylation of Reduced α-Ionol

Yield: 81%; ^1H NMR ($CDCl_3$) δ 5.4–5.1 (m, 2H, 2CH), 4.0–3.6 (m, 3H, CH, CH_2), 2.3–1.8 (m, 25H, $4CH_3$, $6CH_2$, CH); IR (NaCl, neat) 2932, 1090, 1027, 921, 807 cm^{-1}.

Tetrahydrofuranylation of 2,2-Dimethyl-7-hydroxymethyl-2,3-dihydrobenzothiofuran

Yield: 85%; ^1H NMR ($CDCl_3$) δ 7.0 (m, 3H, C_6H_3), 5.2 (m, 1H, CH), 4.5 (dd, 2H, CH_2), 2.0 (m, 4H, $2CH_2$), 1.55 (s, 6H, $2CH_3$); IR (NaCl, neat) 1106, 1038, 920 cm^{-1}.

Tetrahydrofuranylation of Phenethyl Alcohol

Yield: 94%; ^1H NMR ($CDCl_3$) δ 7.3 (s, 5H, C_6H_5), 5.2 (m, 1H, CH), 4.1–3.6 (m, 4H, $2CH_2$), 3.0 (t, 2H, CH_2), 2.0 (m, 4H, $2CH_2$); IR (NaCl, neat) 3027, 2923, 1122, 1093, 1041, 921 cm^{-1}.

Tetrahydrofuranylation of 6-(1,3-Dioxan-2-yl)-2-hexen-4-ol

Yield: 96%; ^1H NMR ($CDCl_3$) δ 5.8–5.4 (m, 2H, CH=CH), 5.4–5.0 (m, 2H, 2CH), 4.6 (m, 1H, CH),

4.2–3.7 (m, 6H, $3CH_2$), 2.1–1.6 (m, 13H, CH_3, $5CH_2$); IR (NaCl, neat) 2955, 2866, 1146, 1076, 1018, 925 cm^{-1}.

Dehydrodimer of Tetrahydrofuran

The dimer **8** of **6** was isolated in 40% yield, based on phenethyl alcohol in the reaction of phenethyl alcohol with **2** in THF under the same reaction conditions, and its identity was confirmed by comparing IR and ^1H NMR spectra with those from the known data of **8** and by the mass spectrum. (IR (NaCl, neat) 2959, 2871, 1063 cm^{-1}; ^1H NMR (CDCl3, 60 MHz) δ 3.8 (m, 6H, $2CH_2$, 2CH), 1.8 (m, 8H, $4CH_2$); mass (70 eV) m/z = 142 (M=, 2.0), 71 (100), 70 (24.2), 43 (40.8), 42 (10.9), 41 (29.8), 39 (19.2)).

Synthesis of the Tetrahydropyranyl Ether of Benzyl Alcohol

A solution of benzyl alcohol (1 mmol, 108 mg) and tetra-*n*-butylammonium peroxydisulfate (1.4 mmol, 984 mg) in anhydrous THP was refluxed with vigorous stirring. After the mixture had been refluxed for 3 hours, solvent was carefully removed under reduced pressure, and then distilled water was added. The aqueous layer was extracted with ether (15 mL × 2). The combined organic layer was dried over anhydrous magnesium sulfate and filtered. Evaporation of solvent gave a residual oil. The residual oil was purified by column chromatography (silica gel, eluent; ether: *n*-hexane = 1:6) to give the THP ether of benzyl alcohol (^1H NMR ($CDCl_3$) δ 1.4–1.8 (m, 6H), 3.3–4.1 (m, 2H), 4.6 (m, 2H), 4.7 (brs, 1H), 7.3 (s, 5H)).

Tetrahydropyranylation of Geraniol

Yield: 87%; ^1H NMR ($CDCl_3$) δ 1.4–1.9 (m, 15H), 2.0–2.3 (m, 4H), 4.7 (brs, 1H), 5.2 (brt, 1H), 5.45 (t, 1H).

Tetrahydropyranylation of Phenethyl Alcohol

Yield: 92%; ^1H NMR ($CDCl_3$) δ 1.45–1.95 (m, 8H), 3.38–4.05 (m, 2H), 4.43 (brs, 1H), 4.09 (M, 2H), 7.26–7.46 (m, 5H).

Tetrahydropyranylation of α-Ionol

Yield: 86%; ^1H NMR ($CDCl_3$) δ 5.45–5.0 (m, 4H, CH, CH=CH, =CH), 4.2–3.6 (m, 3H, CH, CH_2), 2.2–0.7 (m, 23H, $3CH_3$, $4CH_2$, CH).

Tetrahydropyranylation of β-Ionol

Yield: 81%; ^1H NMR ($CDCl_3$) δ 5.4–5.1 (m, 2H, 2CH), 4.0–3.6 (m, 3H, CH, CH_2), 2.3–1.8 (m, 27H, $4CH_3$, $6CH_2$, CH).

Tetrahydropyranylation of 6-(1,3-Dioxan-2-yl)-2-hexen-4-ol

Yield: 85%; ^1H NMR ($CDCl_3$) δ 5.8–5.4 (m, 2H, CH=CH), 5.4–5.0 (m, 2H, 2CH), 4.6 (m, 1H, CH), 4.2–3.7 (m, 6H, $3CH_2$), 2.1–1.6 (m, 15H, CH_3, $5CH_2$).

Synthesis of the 1,4-Dioxan-2-yl Ether of 1-Phenyl-2-Propanol

A solution of 1-phenyl-2-propanol (0.1 mmol, 61 mg) and tetra-*n*-butylammonium peroxydisulfate (1.4 mmol, 984 mg) in anhydrous 1,4-dioxane was refluxed with vigorous stirring. After the mixture had been refluxed for 22 hours, solvent was carefully removed under reduced pressure. The solid was filtered off and washed with ether. Then the filtrate was extracted with distilled water. The aqueous layer was extracted with ether (15 mL × 2). The combined organic layer was dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent gave a residual oil. The residual oil was purified by column chromatography (silica gel, eluent; ether: *n*-hexane = 1:2) to give the 1,4-dioxan-2-yl ether of 1-phenyl-2-propanol (35%, 43 mg). ^1H NMR ($CDCl_3$) δ 7.25–7.30 (m, 5H), 4.21–4.61 (tt, 1H), 3.81–3.89 (m, 1H), 3.5–3.8 (m, 6H), 2.61–2.80 (m, 2H), 1.11–1.21 (dd, 3H).

ACKNOWLEDGMENT

This work was supported by the Center for Biofunctional Molecules through the Korea Science and Engineering Foundation.

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