Crown Ether Catalyzed *O*-Alkylation of Carbohydrates and Nucleosides

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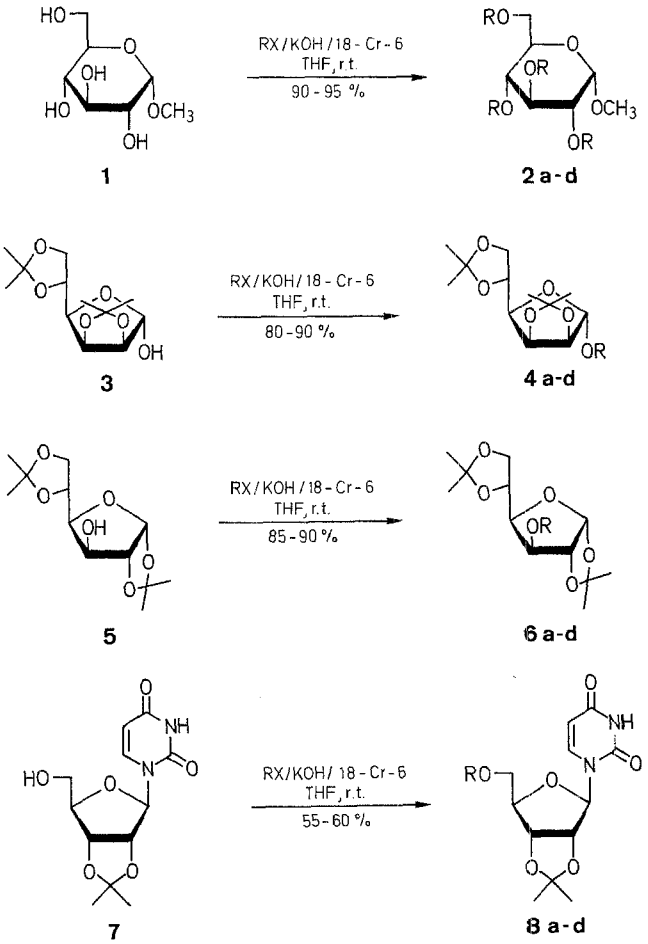
Carbohydrate derivatives as well as nucleosides are readily alkylated with different alkyl halides in tetrahydrofuran using potassium hydroxide in the presence of crown ether.

The synthetic as well as the analytical usefulness of the *O*-alkylation of unprotected or partially protected sugars is well documented. However, most of the methods available require anhydrous conditions and the use of sensitive reagents, and they often result in long reaction time and/or incomplete reactions.[1] More recently the potassium hydroxide- dimethyl sulfoxide system has brought a definite improvement for this type of reactions.[2] However in some instances the use of dimethyl sulfoxide could be detrimental to the purification of the products.

These reasons as well as our interest in the chemistry of natural products and complex carbohydrate derivatives, prompted us to seek a method that would be compatible with the nature of these compounds. We have found that in certain conditions, crown ether (18-crown-6) increases dramatically the rate of alkylation of various carbohydrate and nucleoside derivatives. Thus treatment of a carbohydrate with an alkyl halide and potassium hydroxide in tetrahydrofuran, in the presence of a catalytic amount of 18-crown-6, led smoothly to the corresponding alkylated product. The reaction time is remarkably short and high yields were obtained with four different alkyl halides (Table 1).

The effectiveness of crown ether / tetrahydrofuran is clearly shown by the results summarized in Table 2. Thus the effect of four different solvents were compared for the reaction of compounds **5** and **7** with methyl iodide. Although the reaction occured to some extent without crown ether, it was found to be much longer and often led to complicated mixtures. Complete methylation of the heterocycle of the nucleoside **7** occurred in dimethylformamide, in the absence of crown ether. On the other hand, use of other compounds led to intractable mixtures in this solvent. The alkylation of **7** in the presence of crown ether gave the *O*-alkylation product of the sugar moiety as the major compound, the minor component was identified by ^{1}H-NMR as the dialkylated product (sugar + heterocycle). However, although the alkylation of the sugar was much faster in the presence of crown ether, it was not possible to avoid the



1 **2a-d** **3** **4a-d** **5** **6a-d** **7** **8a-d**

2, 4, 6, 8	R	X in RX used
a	CH_3	I
b	$CH_2CH{=}CH_2$	Br
c	$CH_2CH_2CH_3$	Br
d	$CH_2C_6H_5$	Br

Table 1. Compounds **2**, **4**, **6**, **8** Prepared

Product	Reaction Time	Yield[a] (%)	mp (°C)	Molecular Formula[b] or Lit. $[\alpha]_D$	$[\alpha]_D$[c]	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)
2a	1.75 h	80	oil	+147°[6] ($c = 1$, H_2O)	+107°	3.41 (s, 3H, CH_3); 3.42 (s, 3H, CH_3); 3.51 (s, 3H, CH_3); 3.54 (s, 3H, CH_3); 3.63 (s, 3H, CH_3); 4.83 (d, 1H, $J = 3.8$, H-1)
2b	2.25 h	80	oil	$C_{19}H_{30}O_6$ (354.4)	+245°	3.39 (s, 3H, OCH_3); 4.77 (d, 1H, $J = 3.2$, H-1); 5.2–5.4 (m, 8H, 4 × $CH_2CH=CH_2$); 5.8–6.0 (m, 12H, 4 × $CH=CH_2$)
2c	12 h	80	oil	$C_{19}H_{38}O_6$ (362.5)	+103.7°	0.85 (t, 12H, $J = 7.3$, 4 × CH_3); 1.6 (m, 8H, 4 × CH_2CH_3); 3.39 (s, 3H, OCH_3); 4.78 (d, 1H, $J = 3.4$, H-1)
2d	30 min	90	oil	+32.2°[7] ($c = 5$, $CHCl_3$)	+33°	3.36 (s, 3H, OCH_3); 3.63 (m, 6H, H-4, H-5, H-6, CH_2Ph); 3.99 (t, 1H, $J = 9$, H-3); 4.45–5.0 (m, 8H, H-1, H-2, 3 × CH_2Ph); 7.25 (s, 20H_{arom})
4a	30 min	95	oil	+46.0°[3,4] ($c = 1$, MeOH)	+42.5°	3.32 (s, 3H, CH_3); 3.91 (dd, 1H, $J = 3.6$, 7.7, H-4); 4.07 (dd, 1H, $J = 4.3$, 8.7, H-6); 4.13 (dd, 1H, $J = 6.2$, 8.7, H-6); 4.41 (ddd, 1H, $J = 6.1$, 4.4, 7.7, H-5); 4.56 (d, 1H, $J = 6$, H-3); 4.77 (dd, 1H, $J = 6$, 3.6, H-2); 4.88 (s, 1H, H-1)
4b	15 min	95	oil	$C_{15}H_{24}O_6$ (300.4)	+75°	3.92–4.16 (m, 5H, $CH_2CH=CH_2$, H-6, H-4); 4.4 (ddd, 1H, $J = 6.2$, 4.4, 7.7, H-5); 4.62 (d, 1H, $J = 6$, H-2); 4.79 (dd, 1H, $J = 5.9$, 3.6, H-3); 5.03 (s, 1H, H-1); 5.26, 5.88 (m, 3H, $CH=CH_2$)
4c	25 min	90	oil	$C_{15}H_{26}O_6$ (302.4)	+66.2°	0.92 (t, 3H, $J = 7.3$, CH_3); 3.35, 3.59 (m, 4H, $CH_2CH_2CH_3$); 3.93 (dd, 1H, $J = 7.6$, 3.4, H-4); 4.04, 4.13 (m, 2H, H-6); 4.41 (m, 1H, H-5); 4.6 (d, 1H, $J = 5.7$, H-2); 4.79 (dd, 1H, $J = 5.4$, 3.6, H-3); 4.98 (s, 1H, H-1)
4d	15 min	90	oil	+76.5°[5] ($c = 1.1$, acetone)	+69.6°	3.97 (dd, 1H, $J = 3.3$, 7.5, H-4); 3.98 (dd, 1H, $J = 4.2$, 8.7, H-6); 4.11 (dd, 1H, $J = 6.2$, 8.7, H-6); 4.41 (ddd, 1H, $J = 6.2$, 4.4, 7.6, H-5); 4.49 (m, 2H, CH_2Ph); 4.66 (d, 1H, $J = 5.8$, H-2); 4.8 (dd, 1H, $J = 3.6$, 5.9, H-3); 5.08 (s, 1H, H-1); 7.32 (m, 5H, Ph)
6a	8 min	90	oil	−34°[8] ($c = 1.2$, EtOH)	−31.7°	3.46 (s, 3H, CH_3); 3.78 (d, 1H, $J = 3$, H-3); 4.0 (dd, 1H, $J = 5.5$, 8.5, H-6); 4.08 (dd, 1H, $J = 6.1$, 8.5, H-6); 4.1 (dd, 1H, $J = 7.8$, 3.1, H-4); 4.3 (dt, 1H, $J = 7.5$, 5.9, H-5); 4.57 (d, 1H, $J = 3.8$, H-2); 5.87 (d, 1H, $J = 3.7$, H-1)
6b	10 min	90	oil	$C_{15}H_{24}O_6$ (300.4)	−17.5°	3.91 (d, 1H, $J = 2.6$, H-3); 3.96 (dd, 1H, $J = 5.8$, 2.5, H-4); 4.1 (m, 4H, H-6, $CH_2CH=CH_2$); 4.29 (dt, 1H, $J = 7.6$, 5.8, H-5); 4.52 (d, 1H, $J = 3.5$, H-2); 5.23 (m, 2H, $CH=CH_2$); 5.85 (d, 1H, $J = 3.6$, H-1); 5.87 (m, 1H, $CH=CH_2$)
6c	3 h	85	oil	$C_{15}H_{26}O_6$ (302.4)	−22.5°	0.87 (t, 3H, $J = 7.4$, CH_3); 1.68 (dd, 2H, $CH_2CH_2CH_3$); 3.47–3.57 (m, 2H, $CH_2CH_2CH_3$); 3.85 (d, 1H, $J = 3.1$, H-3); 3.98 (dd, 1H, $J = 8.5$, 6.1, H-6); 4.07 (dd, 1H, $J = 8.6$; 6.1, H-6); 4.13 (dd, 1H, $J = 7.5$, 3.1, H-4); 4.32 (dt, 1H, $J = 7.5$, 6.2, H-5); 4.53 (d, 1H, $J = 3.7$, H-2); 5.87 (d, 1H, $J = 3.7$, H-1)
6d	15 min	85	oil	−25.2°[9] ($c = 0.6$, EtOH)	−20.8°	4.01 (d, 1H, $J = 3$, H-3); 4.1 (m, 2H, H-6); 4.15 (dd, 1H, $J = 7.8$, 3, H-4); 4.36 (m, 1H, H-5); 4.57 (d, 1H, $J = 3.5$, H-2); 4.64 (m, 2H, CH_2Ph); 5.89 (d, 1H, $J = 3.6$, H-1); 7.3 (s, 5H, Ph)
8a	12 min	55	115	–[10,e]	+20°	3.3 (s, 3H, OCH_3); 3.84 (dd, 1H, $J = 12$, 2.9, H-5); 3.96 (dd, 1H, $J = 12$, 2.3, H-5); 4.33 (dd, 1H, $J = 5.7$, 2.9, H-4); 5.0 (dd, 1H, $J = 6.4$, 3.2, H-3); 5.04 (dd, 1H, $J = 6.5$, 2.8, H-2); 5.58 (d, 1H, $J = 2.8$, H-1); 5.79 (d, 1H, $J = 8$, $CH=CH-N$); 7.4 (d, 1H, $J = 8$, $CH=CH-N$)
8b	45 min	60	84	–[11,e]	−6.2°	4.34 (dd, 1H, $J = 5.5$, 2.7, H-4); 4.5 (m, 2H, $CH_2CH=CH_2$); 4.97 (dd, 1H, $J = 6.4$, 2.8, H-3); 5.0 (dd, 1H, $J = 6.4$, 2.6, H-2); 5.2 (m, 2H $-CH=CH_2$); 5.66 (d, 1H, $J = 2.4$, H-1); 5.78 (d, 1H, $J = 8$, $CH=CH-N$); 5.8 (m, 1H, $CH=CH_2$); 7.49 (d, 1H, $J = 8$, $CH=CH-N$)
8c	4.5 h	60	oil	$C_{15}H_{22}N_2O_6$ (326.4)	−7.5°	0.92 (t, 3H, $J = 7.4$, CH_3); 1.6 (m, 2H, $CH_2CH_2CH_3$); 3.8 (m, 2H, $CH_2CH_2CH_8$); 3.81 (dd, 1H, $J = 12.4$, 3.6, H-5); 3.92 (dd, 1H, $J = 12$, 2.5, H-5); 4.33 (dd, 1H, $J = 5.7$, 2.9, H-4); 4.96 (dd, 1H, $J = 6.5$, 2.9, H-3); 5.0 (dd, 1H, $J = 6.4$, 2.6, H-2); 5.63 (d, 1H, $J = 2.6$, H-1); 5.74 (d, 1H, $J = 8$, $CH=CH-N$); 7.44 (d, 1H, $J = 8$, $CH=CH-N$)
8d	40 min	60	oil	$C_{19}H_{22}N_2O_6$ (374.4)	+2.5°	3.76 (dd, 1H, $J = 11.8$, 2.7, H-5); 3.88 (dd, 1H, $J = 12$, 2.4, H-5); 4.29 (m, 1H, H-4); 4.95 (m, 2H, H-3, H-2); 5.1 (d, 2H, CH_2Ph); 5.64 (s, 1H, H-1); 5.74 (d, 1H, $J = 8$, $CH=CH-N$); 7.45 (s, 5H, Ph); 7.5 (d, 1H, $J = 8$, $CH=CH-N$)

[a] Isolated pure products.
[b] Satisfactory microanalyses obtained: C ±0.4, H ±0.32, exception: **8a** (C +0.75).
[c] Measured at room temperature with a Roussel Jouan Quick polarimeter, $c = 0.1$ (MeOH), unless otherwise stated.
[d] Recorded on a Bruker MSL-300 spectrometer. Data given only for relevant protons.
[e] $[\alpha]_D$ not reported.

Table 2. Effect of Solvent on Alkylation

Product	CH_2Cl_2	THF	CH_3CN	DMF
6a	1 h	8 min	15 min	1.25 h
8a	3.5 h	12 min	30 min	12 min

alkylation of the heterocycle in 7. The ratio of *O*- versus *O,N*-alkylated products was found to be 7:3 after flash chromatography on silica gel column eluted with hexane/ethyl acetate (2:8). It is noteworthy that in the case of compound **1** the only detectable product was the tetraalkylated compound. Even the less reactive propyl bromide led to the tetrapropyl product in reasonable time.

***O*-Alkylation of Carbohydrates and Nucleosides; General Procedure:**
To a solution of the substrate (1 mmol) in THF (2 mL) are added successively, freshly powdered potassium hydroxide (0.1 g, 1.8 mmol), 18-crown-6 (11 mg, 0.04 mmol) and the alkyl halide (1.1 mmol). The mixture is stirred at room temperature and the reaction is monitored by TLC; at the end of the reaction the mixture is diluted with CH_2Cl_2 and washed several times with water. Evaporation of the organic phase gives

the pure alkylated product. When necessary, the product is purified by flash chromatography on silica gel eluting with mixtures of hexane and EtOAc. (The ratio of hexane to EtOAc = 9:1 for **2a–d, 4b–d, 6a–d**; 7:3 for **4a** and 2:8 for **8a–d**, respectively).

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