Removal of Acetal, Silyl, and 4,4′-Dimethoxytrityl Protecting Groups from Hydroxyl Functions of Carbohydrates and Nucleosides with Clay in Aqueous Methanol

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Protection and deprotection of hydroxyl groups are important procedures in carbohydrate and nucleoside/nucleotide chemistry, and cyclic acetals, silyl ethers, and trityl ethers are frequently used. Such derivatives are useful intermediates for the synthesis of biologically active analogues and chemical syntheses of oligonucleotides.[1] Acetic or formic acids and aqueous mineral acids are frequently used for hydrolysis of acetals and trityl ethers. Tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) and other fluoride reagent/solvent combinations are commonly used for deprotection of silyl ethers.[1c,2,3] However, strong acids and/or TBAF often cause difficulties in the workup and purification of products.

Recently, various types of montmorillonite clays have been shown to function as effective heterogeneous acid catalysts for organic syntheses.[4] Positive features of these inexpensive clays include stability, ease of handling, lack of corrosiveness and other environmental hazards, and ease of regeneration. Clays are experimentally convenient with respect to treatment and catalyst removal since they are insoluble. We have recently reported a simple method for the preparation of isopropylidene derivatives of carbohydrates with K 10 clay in acetone[5] and deprotection of acylated nucleosides under neutral or weakly basic conditions.[6,7] We now report a facile method for the deprotection of isopropylidene, silyl, and trityl carbohydrate and nucleoside derivatives with K 10 clay in 50% aqueous methanol.

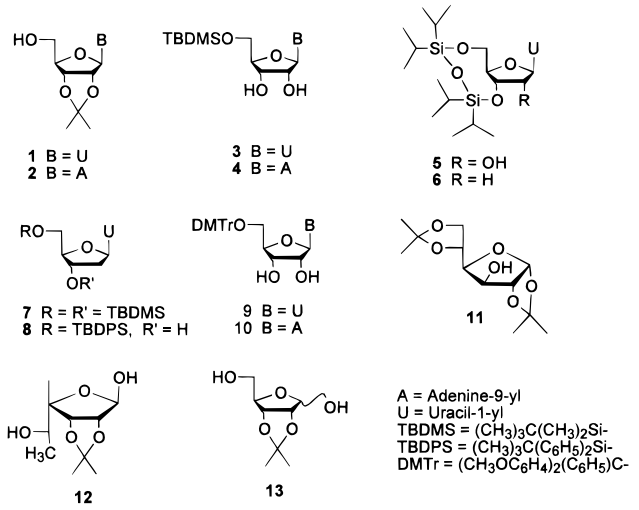

Figure 1.

Treatment of nucleoside derivatives **1**−**10** and isopropylidene sugars **11**−**13** (Figure 1) with K 10 clay in MeOH/H_2O (1:1) at an adequate temperature (ambient, 50 °C, or 75 °C) resulted in deprotection to give adenosine, uridine, 2′-deoxyuridine, D-glucose, L-rhamnose, or D-ribose. The pH of the reaction mixtures was 4.1−5.0 (uridine derivatives), 5.1−5.4 (adenosine derivatives), and 3.6−4.0 (carbohydrate derivatives), and the pH was not remarkably changed during the each deprotection reaction. The pH of the each filtrate from which clay was removed by filtration, was 5.7−6.7. The deprotected compounds were purified by crystallization or silica column chromatography to give TLC homogeneous products with yields listed in Table 1.

Effects of solvent and temperature were examined with 2′,3′-*O*-isopropylideneuridine (**1**) (entry numbers 1−5). Treatment of **1** with K 10 clay (500 mg/mmol of **1**) in MeOH at ambient temperature for 48 h resulted in low conversions (TLC) to uridine (mainly unchanged **1**, entry 1). The use of MeOH/H_2O (1:1) at elevated temperatures accelerated the reaction and increased the isolated yields of uridine (entries 1−5). Similar deprotection of 2′,3′-*O*-isopropylideneadenosine (**2**) with K 10 clay (500 mg/mmol of **2**) in MeOH/H_2O (1:1) at 75 °C for 55 h gave adenosine (80%, entry 6).

Cleavage of the silyl ether groups from 5′-*O*-TBDMS-Urd (**3**), 5′-*O*-TBDMS-Ado (**4**), 3′,5′-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)Urd (**5**), 3′,5′-*O*-TIPDS-dUrd (**6**), and 3′,5′-di-*O*-TBDMS-dUrd (**7**) occurred readily upon treatment of **3**−**7** with 500 mg of K 10 clay/mmol of substrate in MeOH/H_2O (1:1) at 75 °C (entries 7−11). However, attempted deprotection of 5′-*O*-TBDPS-dUrd (**8**) under these conditions for 48 h resulted in low conversions to dUrd (entry 12). The enhanced stability of **8** against hydrolysis by K 10 clay is in agreement with the generally more vigorous acidic requirements for hydrolyses of *tert*-butyldiphenylsilyl ethers.[1c,8]

Cleavage of dimethoxytrityl ethers was investigated with 5′-*O*-(4,4′-dimethoxytrityl)Urd (**9**) and 5′-*O*-(4,4′-dimethoxytrityl)Ado (**10**). Deprotection of **9** and **10** occurred readily with 500 mg of K 10 clay/mmol of

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(1) (a) De Belder, A. N. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 179. (b) Clode, D. M. *Chem. Rev.* **1979**, *79*, 491. (c) Lalonde, M.; Chan, T. H. *Synthesis* **1985**, 817. (d) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991; pp 53−86, 119−142 and references therein.

(2) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(3) (a) Shekhani, M. S.; Khan, K. M.; Mahmood, K. *Tetrahedron Lett.* **1988**, *29*, 6161. (b) Monger, S. J.; Parry, D. M.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1989**, 381. (c) Cormier, J. F. *Tetrahedron Lett.* **1991**, *32*, 187. (d) Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177 and references therein.

(4) (a) Hoyer, S.; Laszlo, P. *Synthesis* **1986**, 655. (b) Kawai, M.; Onaka, M.; Izumi, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2157. (c) Labiad, B.; Villemin, D. *Synthesis* **1989**, 143. (d) Labiad, B.; Villemin, D. *Synth. Commun.* **1989**, *19*, 31. (e) Higuchi, K.; Onaka, M.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1035. (f) Tsujimoto, M.; Matsubara, Y.; Yoshihara, M.; Maeshima, T.; Asakura, J. *Chem. Express* **1991**, *6*, 825. (g) Onaka, M.; Shinoda, T.; Izumi, Y.; Nolen, E. *Chem. Lett.* **1993**, 117. (h) Fukase, K.; Winarno, H.; Kusumoto, S. *Chem. Express* **1993**, *8*, 409. (i) Onaka, M.; Ohno, R.; Yanagiya, N.; Izumi, Y. *Synlett* **1993**, 141. (j) Tateiwa, J.; Horiuchi, H.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 4039 and references therein.

(5) Asakura, J.; Matsubara, Y.; Yoshihara, M. *J. Carbohydr. Chem.* **1996**, *15*, 231.

(6) Asakura, J.; Tomura, T. *Nucleosides Nucleotides* **1988**, *7*, 245.

(7) Asakura, J. *Nucleosides Nucleotides* **1993**, *12*, 701.

(8) Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797.

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Table 1. K 10 Clay-Catalyzed Deprotection of 1−13[a]

entry	compd	solvent	temp, °C	time, h	product[b]	(yield %)[c]
1	**1**	MeOH	rt	48	**Urd**	(trace)[d,e]
2	**1**	MeOH	50	48	**Urd**	(<60)[e]
3	**1**	MeOH	75	48	**Urd**	(<80)[e]
4	**1**	MeOH/H_2O (1:1)	50	50	**Urd**	(90)
5	**1**	MeOH/H_2O (1:1)	75	26	**Urd**	(94)
6	**2**	MeOH/H_2O (1:1)	75	55	**Ado**	(80)
7	**3**	MeOH/H_2O (1:1)	75	5	**Urd**	(95)
8	**4**	MeOH/H_2O (1:1)	75	10	**Ado**	(93)
9	**5**	MeOH/H_2O (1:1)	75	36	**Urd**	(97)
10	**6**	MeOH/H_2O (1:1)	75	60	**dUrd**	(90)
11	**7**	MeOH/H_2O (1:1)	75	12	**dUrd**	(94)
12	**8**	MeOH/H_2O (1:1)	75	48	**dUrd**	(trace)[d,e]
13	**9**	MeOH/H_2O (1:1)	75	0.5	**Urd**	(96)
14	**9**	MeOH/H_2O (1:1)	rt	12	**Urd**	(95)
15	**10**	MeOH/H_2O (1:1)	75	0.5	**Ado**	(94)
16	**10**	MeOH/H_2O (1:1)	rt	20	**Ado**	(95)
17	**11**	MeOH/H_2O (1:1)	75	72	**Glu**	(77)
18	**11**	MeOH/H_2O (1:1)	75	72	**Glu**	(83)[f]
19	**12**	MeOH/H_2O (1:1)	75	12	**Rham**	(90)
20	**13**	MeOH/H_2O (1:1)	75	5	**Rib**	(73)
21	**13**	MeOH/H_2O (1:1)	50	72	**Rib**	(75)
22	**13**	MeOH/H_2O (1:1)	rt	50	**Rib**	(trace)[d,e]

[a] Deprotection reactions were effected with 500 mg of starting material, and 500 mg of K 10 clay/mmol of substrate in 20 mL of solvent. [b] Urd = uridine, Ado = adenosine, dUrd = 2′-deoxyuridine, Glu = D-glucose, Rham = L-rhamnose, Rib = *d*-ribose. [c] Isolated yields of homogeneous products. [d] Starting material was mainly unchanged (TLC). [e] Estimated by TLC. [f] 1 g of K 10 clay/mmol of substrate.

substrate in MeOH/H_2O (1:1) at 75 °C. Urd and Ado were obtained in excellent yields (95%) even at ambient temperature (entries 13−16). As expected, clay-catalyzed hydrolysis of dimethoxytrityl ethers proceeded more readily than cleavage of silyl ethers and isopropylidene groups.

Treatment of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**11**) or the monoprotected 2,3-*O*-isopropylidene-β-L-rhamnofuranose (**12**) and 2,3-*O*-isopropylidene-D-ribofuranose (**13**) derivatives with 500 mg of K 10 clay/mmol of substrate in MeOH/H_2O (1:1) at 75 °C afforded the deprotected sugars in good yields (73−90%, entries 17, 19, 20). A larger ratio of K 10 clay (1 g/mmol) increased the yield slightly with **11** (83%, entry 18), and treatment of **13** for 5 h at 75 °C gave cleaner deprotection to D-ribose.[9]

In summary, treatment of isopropylidene-, silyl-, and 4,4′-dimethoxytrityl-protected nucleosides with K 10 clay in 50% aqueous methanol effected efficient hydrolysis to give the parent nucleosides. Analogous treatment of isopropylidene-monosaccharides gave the deprotected sugars in good to excellent yields under mild reaction conditions with straightforward workup. Investigation of other acid-catalyzed organic reactions with K 10 clay as a mild and convenient alternative catalyst are in progress.

Experimental Section

General Methods. Uncorrected melting points (and mixed melting points with authentic samples) were determined on a hot-stage apparatus. ^{1}H NMR spectra were recorded with a JEOL JNM GX-400 spectrometer at 400 MHz (solutions in TMS/DMSO-d_6 or TSP/D_2O). FAB-HRMS were determined with a JEOL HX-100 spectrometer in the negative ion mode. UV spectra were obtained with a Hitachi U-3000 spectrophotometer (solutions in MeOH). Specific rotations were determined with a Jasco DIP-140 polarimeter. Elemental analyses were determined by the Analytical Center of Dainippon Pharmaceutical Co., Ltd. The pH was measured with Horiba M-8 AD pH meter. TLC was performed on Merck kieselgel 60 F-254 sheets, and compounds were detected by visualization under 254 nm light or by spraying the plates with H_2SO_4/MeOH. Merck kieselgel 60 (230−400 mesh) was used for column chromatography. Protected starting materials were prepared by literature methods,[5,10−15] and "diffusion crystallization" was performed as described.[16]

Deprotection Procedure. Mixtures of 500 mg of the substrate (**1**−**13**), K 10 clay, and solvent (20 mL) were stirred for indicated periods under the noted reaction conditions (Table 1). Mixtures were filtered (Celite pad) and washed with MeOH. Combined filtrates were concentrated, and the residues were coevaporated (× 3) with EtOH/toluene (1:2) under reduced pressure. Purification of deprotected products gave compounds with data noted in the following summaries and Table 1. Byproducts were not isolated or characterized.

Uridine. The residue was treated with charcoal (EtOH/Δ) and crystallized [EtOH/hexanes (diffusion)] to give Urd (needles): mp 166.5−167 °C; UV_{max} 262 nm (ε 10 000), min 230 nm (ε 2100); FAB-HRMS *m*/*z* 243.0600 ([M$^-$ − H] $C_9H_{11}N_2O_6$ = 243.0617).

2′-Deoxyuridine. The residue was treated with charcoal (EtOH/Δ) and crystallized [EtOH/hexanes (diffusion)] to give dUrd (needles): mp 164−164.5 °C; UV_{max} 262 nm (ε 10 000), min 230 nm (ε 1900); FAB-HRMS *m*/*z* 227.0695 ([M$^-$ − H] $C_9H_{11}N_2O_5$ = 227.0668).

Adenosine. The residue was treated with charcoal (MeOH/Δ) and crystallized (MeOH) to give Ado (needles): mp 225−227 °C dec; UV_{max} 260 nm (ε 14 800), min 228 nm (ε 2100); FAB-HRMS *m*/*z* 266.0889 ([M$^-$ − H] $C_{10}H_{12}N_5O_4$ = 266.0889).

D-Glucose. The residue was treated with charcoal (EtOH/Δ) and crystallized [MeOH/Et_2O (diffusion)] to give D-glucose (fine plates): mp 147−151 °C; $[\alpha]^{21}_D$ +52.7° (*c*, 1.05; H_2O); FAB-HRMS *m*/*z* 179.0577 ([M$^-$ − H] $C_6H_{11}O_6$ = 179.0556).

L-Rhamnose. The residue was treated with charcoal (EtOH/Δ) and crystallized [EtOH/Et_2O (diffusion)] to give L-rhamnose (fine plates): mp ~ 92 °C; $[\alpha]^{21}_D$ +8.0° (*c*, 1.01; H_2O); FAB-HRMS *m*/*z* 163.0619 ([M$^-$ − H] $C_6H_{11}O_5$ = 163.0606).

D-Ribose. The residue was purified by dry-packed column chromatography [60 g, 2.2 × 30 cm; EtOAc/*i*-PrOH/H_2O (4:1:2, upper phase)] to give homogeneous product. An analytical sample was prepared by treatment of this product with charcoal (EtOH/Δ) and crystallization [EtOH/Et_2O (diffusion)] to give D-ribose (fine plates): mp 77−80 °C; $[\alpha]^{21}_D$ −19.7° (*c*, 0.96; H_2O); FAB-HRMS *m*/*z* 149.0452 ([M$^-$ − H] $C_5H_9O_5$ = 149.0450).

^{1}H NMR spectra and physical data on these known compounds were identical with those measured with commercial samples. Elemental analyses agreed with calculated values.

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(9) In the case of **13**, elevated reaction temperatures and/or longer reaction times resulted in increased formation of byproducts (TLC).

(10) Fromageot, H. P. M.; Griffin, B. E.; Reese, C. B.; Sulston, J. E. *Tetrahedron* **1967**, *23*, 2315.
(11) Nair, V.; Buenger, G. S. *Org. Prep. Proc. Int.* **1990**, *22*, 57.
(12) (a) Markiewicz, W. T. J. *J. Chem. Res. (S)* **1979**, 24. (b) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.
(13) Ogilvie, K. K.; Thompson, E. A.; Quilliam, M. A.; Westmore, J. B. *Tetrahedron Lett.* **1974**, *33*, 2865.
(14) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
(15) (a) Smith, M.; Rammler, D. H.; Goldberg, I. H.; Khorana, H. G. *J. Am. Chem. Soc.* **1962**, *84*, 430. (b) Hakimelahi, G. H.; Proba, Z. A.; Ogilvie, K. K. *Can. J. Chem.* **1982**, *60*, 1106.
(16) Robins, M. J.; Mengel, R.; Jones, R. A.; Fouron, Y. *J. Am. Chem. Soc.* **1976**, *98*, 8204.