Ceric Ammonium Nitrate-Catalyzed Tetrahydropyranylation of Alcohols and Synthesis of 2-Deoxy-O-Glycosides

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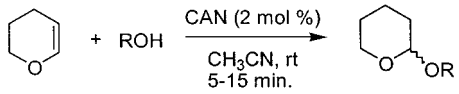
Protection of alcohols as tetrahydropyranyl (THP) ethers is useful in organic synthesis mainly because of their stability under a variety of basic conditions including Grignard reagents, metal hydrides, alkyllithiums, etc. Apart from the commonly used protic and Lewis acids,[1] other reagents such as iodotrimethylsilane,[2] triphenylphosphine hydrobromide,[3] montmorillonite K-10,[4] heteropoly acids,[5] and more recently tantalum chloride,[6] $LiClO_4$,[7] and $LiBF_4$ in acetonitrile[8] have also been reported in the preparation of THP ethers.

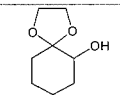
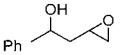
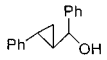
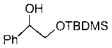
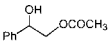
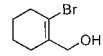
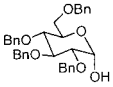
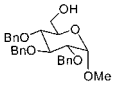
Ceric ammonium nitrate (CAN) has been employed as a useful mild oxidizing agent in organic synthesis.[9] A few years ago we reported[10] a reagent system composed of $NaNO_2$/CAN (2.5:1) in CH_3CN for converting olefins into vicinal nitroamides in one step. To further explore the potential of this reagent system, we studied its behavior on olefins such as 3,4-dihydro-2*H*-pyran **1** (Scheme 1), but the reaction was not clean. To study the effect of solvent, this reaction was carried out in methanol which, to our surprise, was found to add on to **1** to form the corresponding THP ether **2**. Reexamination of the reaction conditions revealed that a variety of alcohols reacted with 2 equiv of dihydropyran in the presence of only a catalytic amount of CAN (2 mol %) in CH_3CN at room temperature, forming the corresponding THP ethers in good to excellent yields in 5−15 min.[11] Our results are summarized in Table 1. At the end of the reaction (TLC monitoring), the reaction mixture was directly concentrated in a vacuum followed by purification by column chromatography. Alternatively, we have also found that

Scheme 1



1 **2**

Table 1. Tetrahydropyranylation of Alcohols Catalyzed by Ceric Ammonium Nitrate (CAN)

Entry	Alcohol	Product	Yield %	Entry	Alcohol	Product	Yield %
1	benzyl alcohol	**2a**[7]	95	10		**2j**	70
2	cyclohexanol	**2b**[7]	92	11		**2k**	77
3	propargyl alcohol	**2c**[7]	94	12		**2l**	91
4	t-butanol	**2d**[7]	65	13		**2m**	71
5	geraniol	**2e**[8]	82	14		**2n**	85
6	cholesterol	**2f**[8]	81	15		**2o**[13]	80
7		**2g**[12]	91	16		**2p**	88
8		**2h**	69	17		**2q**[a]	92
9		**2i**	78	18		**2r**[14]	95

[a] This THP ether was a mixture of two anomers in the ratio of 58/42 and the reaction was carried out in CH_3CN:CH_2Cl_2 (3:1) mixture.

CAN adsorbed on silica gel (column grade) is also equally effective. In this case 2 mol % of CAN adsorbed on 250 mg of SiO_2 (100−200 mesh) is used for the reaction which could be simply filtered off, after the reaction is over, and solvent evaporated to obtain a pure product. Further chromatographic purification was not needed in the cases studied by us.

It is noteworthy that alcohols bearing acid-sensitive groups, such as a ketal (entries 8, 10), an epoxide moiety (entry 11), a cyclopropane unit (entry 12), and an acetal (entry 18), are not affected by the acidic nature[15] of the catalyst. Further, it is also important to note that a TBDMS group remains unaffected (entry 13) under the present reaction conditions (2 mol % CAN in CH_3CN) especially since it has been reported in the literature[12] that TBDMS and THP ethers are cleaved by CAN. However, such a cleavage is observed by using a sto-

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(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991. (b) Paquette, L. A. *Encyclopedia of Reagents for Organic synthesis*; John Wiley & Sons Ltd. England. 1995.

(2) Olah, G. A.; Hussain, A.; Singh, B. P. *Synthesis* **1985**, 703.

(3) Bolitt, V.; Mioskowski, C.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1988**, *29*, 4583.

(4) Hoyer, S.; Laszlo, P.; Orlovic, M.; Polla, E. *Synthesis* **1986**, 655.

(5) Molnar, A.; Beregszaszi, T. *Tetrahedron Lett.* **1996**, *37*, 8597.

(6) Chandrasekhar, S.; Takhi, M.; Ravindra Reddy, Y.; Mohapatra, S.; Rama Rao, C.; Reddy, V. *Tetrahedron* **1997**, *53*, 14997.

(7) Sobhana Babu, B.; Balasubramanian, K. K. *Tetrahedron Lett.* **1998**, *39*, 9287.

(8) Sobhana Babu, B.; Balasubramanian, K. K. *Synlett* **1999**, *8*, 1261.

(9) Hwu, J. R.; Chen, K.-L.; Ananthan, S. *Chem. Commun.* **1994**, 1425 and references therein.

(10) Reddy, M. V. R.; Mehrotra, B.; Vankar, Y. D. *Tetrahedron Lett.* **1995**, *36*, 4861.

(11) Under special experimental conditions [mildly basic with borate/HCl buffer (pH 8)] using CAN, acetals and ketals are hydrolyzed to the corresponding carbonyl compounds, see Markó, I. E.; Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C. *Angew. Chem., Int. Ed.* **1999**, *38*, 3207.

(12) Gupta, A. D.; Singh, R.; Singh, V. K. *Synlett* **1996**, 69.

(13) Barco, A.; Pollini, G. P.; Traverso, G. *Farmaco, Ed. Sci.* **1970**, *25*, 669; *Chem Abstr.* **1970**, *73*, 98346.

(14) Manfredini, S.; Baraldi, P. G.; Bazzanimi, R.; Guarneri, M.; Simoni, D. *Tetrahedron Lett.* **1994**, *35*, 5709.

(15) The pH of the solution was found to be 1.1 throughout the reaction.

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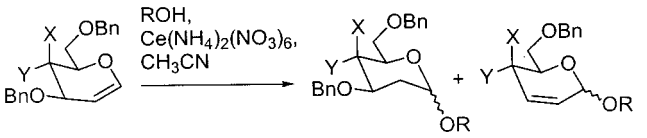
Scheme 2



3: X: OBn; Y: H
4: X: H; Y: OBn

5: X: OBn; Y: H
6: X: H; Y: OBn

7: X:H; Y: OBn

ichiometric amount of CAN in MeOH as solvent, other solvents such as CH_3CN-H_2O (19:1) or benzene−MeOH (2:1) give poor results of the THP or TBDMS ethers cleavage.

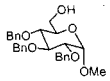
In an effort to further explore the scope of this reaction, we have found that glycals **3** and **4** (Scheme 2) undergo addition of alcohols to form the corresponding 2-deoxy-O-glycosides **5** and **6**, respectively. Because of the importance of 2-deoxy sugars[16] as structural units in many biologically active natural products such as anthracyclins, aureolic acids, compactin, enediynes, etc., several approaches have been reported in the literature to construct 2-deoxy-α-(or *β*)-O-glycosides stereoselectively. Stereoselective routes to α or *β*-2-deoxy-O-glycosides are known from preformed[17] 2-deoxy sugars bearing a leaving group at the anomeric center. Besides these, there have been some direct approaches also where alcohols are added to glycals under protic or Lewis acid catalysis.

However, because of the competing Ferrier reaction,[18] not all the acids or Lewis acids permit addition of alcohols to glycals. In this regard, acids such as MeOH·HCl,[19] cation-exchange resin AG $50WX_2$,[20] Ph_3P/HBr,[21] BCl_3 (or BBr_3)[22] have been systematically studied to obtain 2-deoxy-O-glycosides. In all these cases, varying α/*β* ratio of the glycosides are observed with α products being the major ones.

In the present study, CAN (2 mol %) led to the formation of 2-deoxy-O-glycosides in good yields along with formation of the corresponding Ferrier products **7**, albeit, in only trace amounts. Further, in most cases, α-O-glycosides were formed as the major products. Our results are summarized in Table 2. One disaccharide was also synthesized using the present methodology (entry 8, Table 2). Although galactal **3** and glucal **4** both reacted readily with a variety of alcohols, reactions with **3** were cleaner. Initial experiments with glucal **4** using only 2 mol % of CAN, as used for galactal based reactions, indicated the formation of more amount of the Ferrier product[23] (entries 9−12, Table 2). On the other hand, when 4 equiv of CAN in CH_3CN were used in these reactions, 2-deoxy products were formed as the major products along with only trace amount of the Ferrier products. These 2-deoxy-O-glycosides were formed as a mixture of two anomers in which α-anomer was the major one in the cases studied (entries 13, 14). Except for the studies using BBr_3 (or BCl_3),[22] the results from other catalysts are comparable with the present work in terms of the α/*β* ratio. Mechanistically, it is therefore proposed that CAN reacts with alcohols generating HNO_3 (a Brønsted acid) which presumably activates glycals (or dihydropyran) and then the alkoxide moiety is transferred leading to the formation of 2-deoxy-O-glycosides (or THP ethers) as shown in Figure 1.

The present procedure is simple requiring only 2 mol % of CAN which is easy to handle and is relatively cheap. Also, it is noteworthy that *tert*-butyl alcohol undergoes addition in these reactions. We therefore expect that our findings to procure THP ethers as well as 2-deoxy-O-glycosides using CAN will be useful in organic synthesis.

Table 2. Synthesis of 2-Deoxy-O-Glycosides via Ceric Ammonium Nitrate Catalyzed Addition of Alcohols to Glycals

Entry	Glycal	Nucleophile	Glycoside	Yield %	Anomer Ratio α/β
1	3	methanol	5a	78	32/1
2	3	isopropyl alcohol	5b	63	5/1
3	3	allyl alcohol	5c	74	4/1
4	3	benzyl alcohol	5d	60	3.5/1
5	3	cholesterol	5e	26	1.5/1
6	3	cyclohexanol	5f	63	8/1
7	3	t-butanol	5g	51	1.7/1
8	3		5h	52	2/1
9	4	methanol	6a (7a)	56 (38)[a]	1.7/1 (5/1)[b]
10	4	allyl alcohol	6b (7b)	60 (23)[a]	1.1/1 (4.7/1[b]
11	4	cyclohexanol	6c (7c)	65 (18)[a]	11.5/1 (only α)[b]
12	4	t-butanol	6d (7d)[d]	34 (44)	1.8/1 (4.8/1[b]
13	4	methanol	6a	82	2/1[c]
14	4	t-butanol	6d	62	4/1[c]

[a] Isolated yield of the corresponding Ferrier products in parentheses. [b] α/*β* ratio of the corresponding Ferrier products in parentheses. [c] Experiments conducted with 4 equiv of CAN. [d] Compounds **6d** and **7d** were inseparable.

(16) Jütten, R.; Greven, R. *Polysaccharides in Medicinal Applications*; Dumitriu, S., Ed.; Marcell Dekker: New York, 1996; pp 339−410. (b) Wright, D. E. *Tetrahedron* **1979**, *35*, 1207. (c) Kirschning, A.; Bechthold, A. F. W.; Rohr, J. *Topics Curr. Chem.* **1997**, *188*, 1.

(17) Schene, H.; Waldmann, H. *Synthesis* **1999**, 1411. (b) Capozzi, G.; Mannocci, F.; Meichetti, S.; Nativi, C. *Chem. Commun.* **1997**, 2291. (c) Toshima, K.; Kasumi, K.; Matsumura, S. *Synlett* **1999**, 1332. (d) Roush, W. R.; Narayan, S. *Org. Lett.* **2000**, *1*, 899 and references therein.

(18) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1996**, *24*, 199. (b) Ferrier, R. J.; Prasad N. *J. Chem. Soc. C* **1999**, 570.

(19) Hadfield, A. F.; Sartorelli, A. C. *Carbohydr. Res.* **1982**, *101*, 197.

(20) Sabesan, S.; Neira, S. *J. Org. Chem.* **1991**, *56*, 5468.

(21) Bolitt, V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812.

(22) Toshima, K.; Nagai, H.; Ushiski, Y.; Matsumura, S. *Synlett* **1998**, 1007.

(23) For a recent report on the use of CAN for effecting the Ferrier reaction see: (a) Linker, T.; Sommermann, T.; Gimisis, T.; Chatgilaloglu, C. *Tetrahedron Lett.* **1998**, *39*, 9637, and (b) Yadav, J. S.; Reddy, B. V. S.; Pandey, S. K. *New J. Chem.* **2001**, *25*, 538.

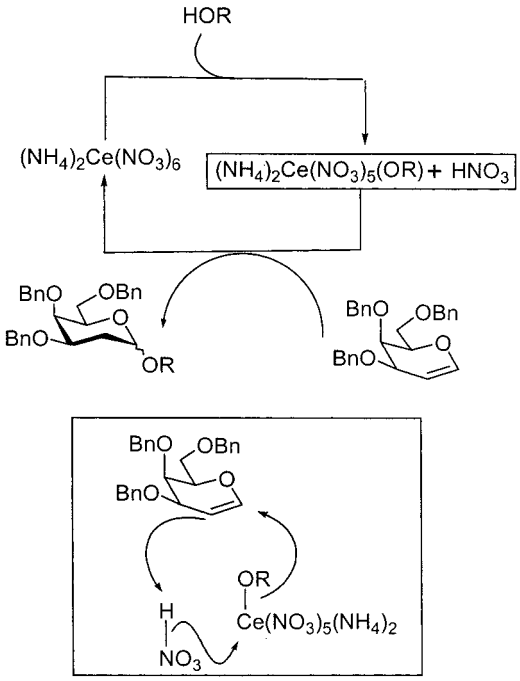


Figure 1.

Experimental Section

General. Infrared spectra were recorded on Bruker FT/IR Vector 22 spectrometers. ^{1}H and ^{13}C NMR spectra were recorded on JEOL LA-400 NMR spectrometer in solutions of $CDCl_3$ using tetramethylsilane as the internal standard. FAB mass spectra were obtained using JEOL SX 102/DA-6000 spectrometer. Elemental analyses were carried out in Coleman automatic C, H, N, O analyzer.

Acetonitrile was distilled from P_2O_5 followed by distillation from CaH_2 prior to use. Ceric ammonium nitrate was purchased from Merck (India) Ltd., Bombay, and was dried at 80 °C.

General Procedure for the Preparation of Tetrahydropyranyl Ethers. To a stirred solution of an alcohol (5 mmol) and CAN (0.1 mmol, 2 mol %) in dry CH_3CN (5 mL) is added a solution of 3,4-dihydro-2*H*-pyran (10 mmol) in dry CH_3CN (2 mL) dropwise over a period of 5 min. After the addition, stirring is continued for another 5−15 min and the solvent removed on a rotary evaporator under reduced pressure. The residue is passed through a pad of silica gel to obtain the pure product.

Using SiO_2. To a stirred solution of CAN (55 mg, 0.1 mmol) in dry CH_3CN (5 mL) were added 250 mg of SiO_2 (100−200 mesh), an alcohol (5 mmol), and 3,4-dihydro-2*H*-pyran (10 mmol) in dry CH_3CN sequentially. After the reaction was over, it was filtered and the filtrate evaporated to yield the pure product.

THP ether 2m: ^{1}H NMR δ 0.03, 0.01 (2s, 6H), 0.90 (s, 9H), 1.5−2.0 (m, 6H), 3.4−3.89 (m, 4H), 4.57 (m, 2H), 7.26−7.40 (m, 5H). ^{13}C NMR δ −5.54, −4.81, 18.29, 18.94, 19.35, 25.4, 25.79, 25.85, 30.5, 61.82, 67.8, 79.17, 99.0, 126.27−142.5 (6C). MS (FAB) *m*/*z* (relative intensity): 337 (2) [$M^+ + 1$]. Anal. Calcd for $C_{19}H_{32}O_3Si$: C, 67.81; H, 9.58. Found: C, 67.80; H, 9.32.

General Procedure for the Synthesis of 2-Deoxy Sugars. A glycal (1 mmol) and an alcohol (1 mmol) were combined with a catalytic amount (2 mol %) of CAN in anhydrous CH_3CN (4 mL) and stirred at ambient temperature. After 3−5 h, the reaction mixture was extracted with ether and washed with $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in a vacuum. The residue was purified by column chromatography to obtain products as a mixture of α and β anomers which were characterized by spectroscopic and analytical means and compared the data wherever available in the literature (**5a**,[24] **5b**,[25] **5e**,[26] **5h**,[27] **6a**,[24] **6c**,[28] **6d**,[29] **7a**,[30] **7b**[31]). Attempts to separate the anomers were not successful.

Allyl 2-deoxy-3,4,6-tri-*O*-benzyl-α/β-D-galactopyranoside 5c: ^{1}H NMR δ 2.0−2.04 and 2.2−2.28 (m, 2H), 3.46−3.64 (m, 2H), 3.90−4.0 (m, 4H), 4.14 (dd, 1H, J = 4.87, 9.75 Hz), 4.4−4.90 (m, 6H), 5.02 (d, J = 1.95 Hz, H-1) 5.17−5.27 (m, 2H), 5.85−5.95 (m, 1H), 7.25−7.35 (m, 15H). ^{13}C NMR δ 31.10, 67.87, 69.50, 69.88, 70.44, 72.94, 73.43, 74.26, 74.75, 97.06 (C-1), 117.03, 127.29−128.38 (18 C), 134.26. Characteristic signals for the β-anomer: ^{1}H NMR:δ 4.64 (dd, J = 3.7, 9.3 Hz, H-1). ^{13}C NMR: δ 103 (C-1). MS (FAB) *m*/*z* (relative intensity) 475 (3) [$M^+ + 1$], 474 (100) [M^+]. Anal. Calcd for C_{30} H_{34} O_5: C, 75.92; H, 7.22. Found: C, 75.80; H, 7.31.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectral data of **2h**−**l**, **2n**, **2p**, **2q**, **5b**, **5d**, **5f**, **5g**, and **7c**. This information is available free of charge via the Internet at http://pubs.acs.org.

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(24) Truelove, J. E.; Hussain, A. A.; Kostenbauder, H. B. *J. Pharm. Sci.* **1980**, *69*, 231.
(25) Toshima, K.; Kasumi, K.; Matsumura, S. *Synlett* **1999**, 813.
(26) Schene, H.; Waldmann, H. *Synthesis* **1999**, 1411.
(27) Hao, L.; Meijin, C.; Kang, Z. *Tetrahedron Lett.* **1997**, *38*, 6143.
(28) Takeuchi, K.; Higuchi, S.; Mukaiyama, T. *Chem. Lett.* **1997**, 969.
(29) Hashimoto, S.-I.; Ai, S.; Sakamoto, H.; Hakajima, M.; Yanagiya, Y.; Ikegami, S. *Synlett* **1995**, 1271.
(30) Descotes, G.; Martin, J. C. *Carbohydr. Res.* **1977**, *56*, 168.
(31) Lesueur, C.; Nouguier, R.; Bertrand, M. P.; Hoffmann, P.; De Mesmaeker, A. *Tetrahedron* **1994**, *50*, 5369.