Trends In Carbohydrate Research, Vol.4, No.3 (2012) 18-22 0975-0304/09

Trends in Carbohydrate Research

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Selective anomeric deacetylation of sugar acetates using alkali metal fluorides in PEG-400[1]

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Abstract

Alkali metal fluorides in PEG-400 have been found to serve as an excellent medium for the practical anomeric deacetylation of monosaccharide-per-*O*-acetates. Several acetylated sugars were subjected to the deacetylation protocol successfully. In the case of some of the most common D-hexoses the ease of removal of the anomeric acetate followed the order mannose pentaacetate > galactose pentaacetate > α-glucose pentaacetate, > β-glucose pentaacetate. While the reactivity of the fluoride reagent was proved to be in the order CsF > TBAF > KF, sodium and lithium fluorides were completely ineffective.

Keywords: Carbohydrates; Regioselective anomeric deacetylation; Alkali metal fluorides; PEG-400

Introduction

Protected carbohydrates bearing hemiacetal functionality serve as valuable intermediates in the synthesis of several classes of glycosyl donors used in oligosaccharide synthesis. Examples for these classes of compounds include the glycosyl trichloroacetimidates[2] and the glycosyl halides such as the chlorides[3] and the fluorides.[4] They are also often useful in the synthesis of other naturally occurring complex molecules.[5] There are several methods in the literature for the regioselective anomeric deacetylation of otherwise fully acetylated carbohydrates. These include methods utilizing bis(tributyltin)oxide,[6] tributyltin methoxide,[7] benzylamine,[8] sodium methoxide,[9] ammonium salts,[10] piperidine,[11] Al_2O_3,[12] MgO,[13] mercuric chloride/mercuric oxide,[14] $HClO_4$-SiO_2,[15] and certain lanthanide triflates.[16] An alternative approach is the hydrolysis of glycosyl bromides using aqueous silver salts (example, $AgNO_3$). It can be easily seen that the former category of reactions often require use of either toxic or moisture/air sensitive reagents as well as, frequently, long reaction time/harsh reaction conditions. Thus the need for milder and more effective methods in this context is clearly evident.

The use of metal fluorides is well known in synthetic organic chemistry and they serve the role of a nucleophile as well as a base in chemical reactions. The ZnF_2-assisted conversion of the 1,2-*cis*-linked acetobromogalactose to the corresponding 1,2-*trans*-linked glycosyl fluoride[17] and the CsF-mediated transformation of acetoiodogalactose to the corresponding 2-acetoxyglycal[18] are typical examples. Enhancement of the nucleophilicity of anions such as fluorides by complexation of their counter cations with crown ethers is also well established. Use of polyethylene glycols as an effective substitute for crown ethers has also been documented. Herein we report our observations on the regioselective anomeric deacetylation of various per-*O*-acetylated carbohydrates using alkali metal fluorides in polyethylene glycol as a green solvent for the reaction.[19]

Results and discussion

Initially, using galactose pentaacetate (**1**) as the model per-*O*-acetylated sugar the reaction in the presence of potassium fluoride was performed in some of the common organic solvents such as MeOH/*t*-BuOH (protic) and acetonitrile/tetrahydrofuran/CH_2Cl_2 (polar aprotic). Analysis of the reaction mixture by TLC revealed that in the cases of MeCN, CH_2Cl_2 and *t*-BuOH no reaction had occurred up to a period of 24 h of stirring at rt (entries 1, 4 and 10, Table 1).

Although partial deacetylation was indeed indicated in the case of the reaction in MeOH (entry 7, Table 1) it was found that no compound emerged as a single product. The reaction mixture instead consisted of a complex mixture of several compounds, suggesting random loss of the protecting group, and required long reaction times for even partial conversion to take place. Thus not only the reaction progress was slow but also there was no regioselectivity. The ineffectiveness of even *t*-butanol (entry 10, Table 1) for the purpose was

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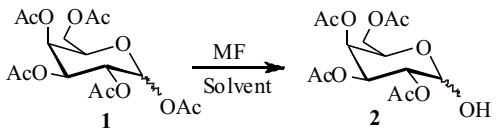
Table 1 Reaction of D-galactose pentaacetate (**1**) with alkali metal fluorides[a]



1 **2**

MF = Alkali metal fluoride

Entry	MF	Solvent	Reaction time (h)	Comments
1	KF	MeCN	24	No product formed
2	CsF		24	No product formed
3	TBAF		24	Traces of product
4	KF	CH_2Cl_2	24	No product formed
5	CsF		24	No product formed
6	TBAF		24	Traces of product
7	KF	MeOH	24	Complex mixture
8	CsF		1	Complex mixture
9	TBAF		2	Complex mixture
10	KF	^{t}BuOH	24	No product formed
11	CsF		24	No product formed
12	TBAF		24	No product formed
13	KF	PEG-400 (**4**)	24	85% yield of **2**
14	CsF		1	87% yield of **2**
15	TBAF		24	40% of **2** + other more polar products

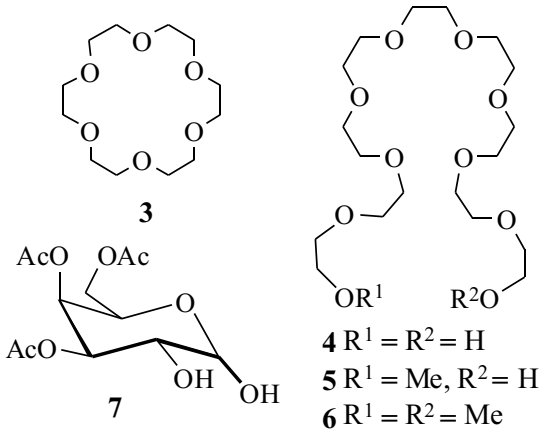
[a] The reaction was carried out using the pentaacetate **1** as the substrate in the respective solvent (1 ml/100 mg **1**) in the presence of the desired alkali metal (6 mol equiv) at rt. The yields shown are those obtained after isolation of **2** by chromatography. Results obtained from reactions using TBAF as the fluoride source are also given for comparison.

somewhat surprising, considering the enhancement of the basicity of the fluoride anion through hydrogen bonding to be expected in the case.[20] Polyethylene glycols in addition to having the hydrogen bonding ability is also known to bind to cationic species much the same way as do crown ethers (for example, 18-crown-6, **3**).[22] Therefore the reaction of galactose pentaacetate was subsequently performed in PEG-400 (**4**) using KF as the fluoride source (entry 13, Table 1). Monitoring the reaction by TLC (EtOAc:Hexanes, 1:1) revealed progressive formation of a product of R_f value equivalent to that of authentic 2,3,4,6-tetra-*O*-acetyl-D-galactopyranose (**2**). However, the reaction was rather slow at rt and took about 24 h to reach completion. Isolation of the pure product was achieved by a standard aqueous work-up followed by chromatography on silica gel (EtOAc:Hexanes, 1:3 to 1:1 as eluent). The product thus obtained in a yield of 85% was spectroscopically consistent with an authentic sample of **2**. It was reasoned that the high lattice energy of KF (822 kJ/mol) was perhaps responsible for the slow reaction rate. Thus, CsF in which the alkali metal ion is of a larger size than that in the former was subsequently employed for the reaction. It was found that selective anomeric de-*O*-acetylation proceeded at a much faster rate in the presence of CsF and was complete in 1 h in PEG-400 under otherwise identical conditions (entry 14, Table 1). As shown in Table 1 (entry 14) in the latter case pure **2** was obtained after chromatographic purification in 87% yield. Although use of PEG-400 as the solvent for the reaction was thus proved very successful, solvents such as MeCN, CH_2Cl_2, MeOH and ^{t}BuOH (entries 2, 5, 8 and 11, Table 1) were again found to be extremely ineffective for the purpose.

Interestingly, in the case of the reaction of **1** with CsF in PEG-400, on chromatographic purification of the crude product obtained after the aqueous work-up of the reaction mixture, a small amount (approximately 10%) of a slower-moving compound also got eluted out following the completion of the elution of the desired 2,3,4,6-tetra-*O*-acetyl-D-galactopyranose. This product was found to be a triacetate [δ_H 2.14 (3H, s, OCOCH_3) 2.06 (6H, s, 2 x OCOCH_3)] using NMR spectroscopic analysis. Consistent with this observation, and also with the polarity it showed on TLC, was the absorption band it showed in its IR spectrum (ν 3409 cm^{-1}) which was typical of compounds containing hydroxyl groups. The compound was finally identified as 3,4,6-tri-*O*-acetyl-D-galactopyranose (**7**).

The anomeric deacetylation reaction of compound **1** was also attempted by using tetrabutylammonium fluoride[21] as the fluoride reagent (instead of CsF, entries 3, 6, 9, 12 and 15, Table 1). And as can be seen from the Table, the results (Table 1) showed it to be also unsuitable for carrying out the desired regioselective deacetylation. In the presence of CsF in **4**, not surprisingly though, the rate of regioselective

deacetylation was also found to be dependent on the amount of PEG (that is, the concentration/dilution of the reaction mixture) employed for the reaction. Thus, at higher dilutions a slower reaction was observed as expected.



An interesting observation made while performing the above reactions was that on dissolution of the reactants (**1** and CsF) in **4** the solution (reaction mixture) turned deep amber in color (see Fig 1). This clearly pointed towards the possible complex formation of **4** as envisaged in the literature reports.[22] In order to investigate this further, the selective anomeric deacetylation reaction described above was therefore subsequently carried out with **5** and **6**, the two commercially available derivatives of **4**. This allowed verifying whether or not the hydroxy groups in **4**/**5** played any definite role in facilitating the reaction. The results are shown in Fig 1. Thus, while the reaction mixture in which the PEG monomethyl ether **5** was employed for the reaction developed color similar to that of uncapped PEG (**4**) described above, the reaction mixture that employed the dimethyl ether derivative **6** as solvent for the reaction remained largely unaffected (turned light amber brown, see Fig 1; see also the UV-visible absorption spectra for comparison). In agreement with this was also the observation on the progress of the reaction. Thus, while in **4** the reaction went to completion in 1 h, the turnover was to the extent of only about 80% in the monomethyl ether **5** and virtually none in the case of reaction in the dimethyl ether **6**, clearly demonstrating the role for the hydroxy group(s) in **5**/**6**.

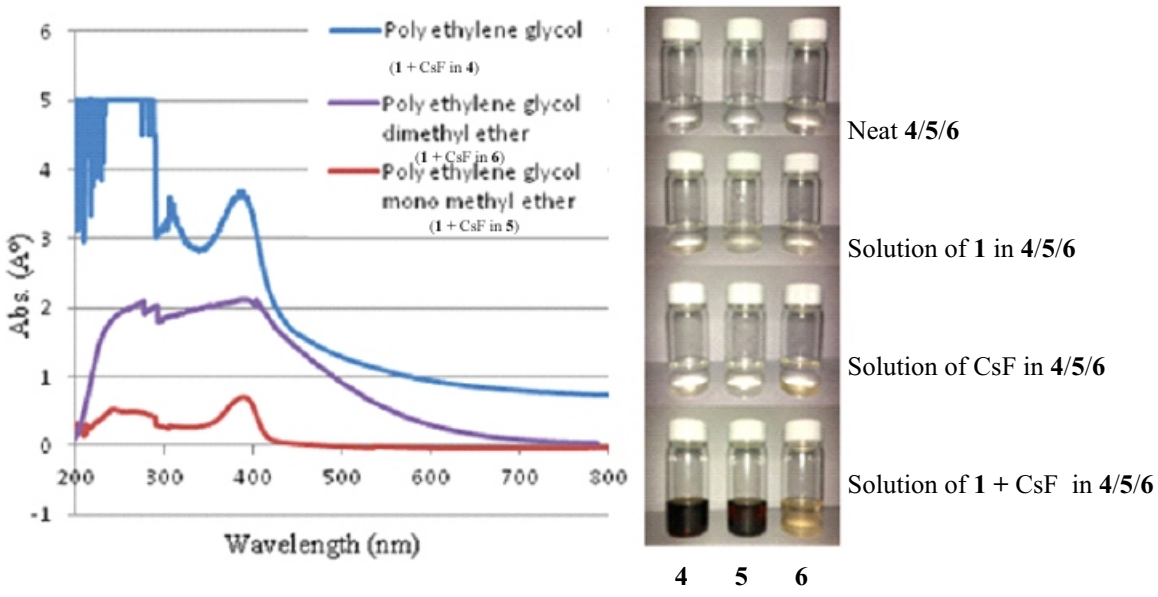
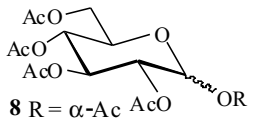
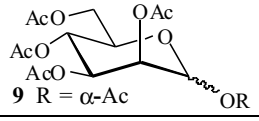
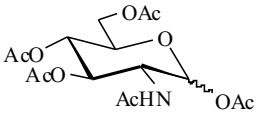
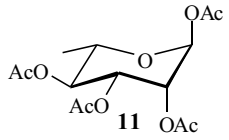
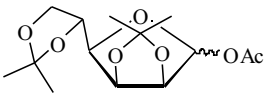
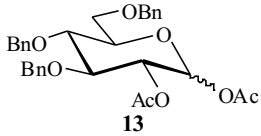
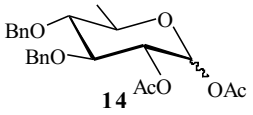


Fig. 1: UV-Visible spectra (LHS) of the reaction mixtures and their photomicrographs (RHS) for comparison. The reaction was performed on galactose pentaacetate (**1,** 1 mmol) using CsF (6 mmol) in the respective PEG/its derivative (5 ml) at 30 °C

Table 2 Selective anomeric deacetylation of sugar derivatives by CsF in polyethylene glycol (**4**)

Entry	Sugar derivative R = Ac ⟶ R = H	Time (h)	Yield (%) (α:β)
1	 **8** R = α-Ac	1	73 (1:0.11)
2	 **9** R = α-Ac	1	95 (1:0.11)
3	 **10**	4	89 (1:0.05)
4	 **11**	24	92 (1:0.19)
5	 **12**	4	96 (1:0)
6	 **13**	2	85 (1:0.33)
7	 **14**	1.5	86 (1:0.28)

The next point to be investigated was on the possibility of PEG acting as a possible acceptor for the acyl residue lost from the sugar acetate upon reaction. This was attempted by subjecting the reaction mixture to mass spectroscopic analysis. Analysis of the reaction mixture by MALDI-TOF-MS revealed, however, that the spectrum was heavily dominated by the presence of ions derived from the solvent molecules (namely, those of **4**/**5** used for the reaction). It may be recalled that PEG-400 molecules possess mass in the same range as that of the sugar derivatives in the reaction mixture. The initial MS experiments therefore were proved inadequate and hence failed to produce any result helpful in resolving the above question; and calls for detailed future experiments in this regard.

After having found the optimum conditions for the desired selective anomeric deacetylation of the galactose acetate **1**, the reaction was extended to other sugar acetates of interest for checking the general applicability of the developed method. Thus, per-*O*-acetylated glucose, mannose, glucosamine, and rhamnose (**8**,[23] **9**, **10** and **11**, respectively; entries 1-4, respectively, Table 2), acetal-protected mannofuranosyl acetate **12** (entry 5, Table 2), ether-protected *gluco*-configured pyranosyl acetates **13** and **14** (entries 6 and 7, respectively, Table 2) were also subjected to the reaction. In all the cases the desired hemiacetal was obtained in excellent yields (Table 2).

In conclusion, we have developed an effective fluoride-assisted method for the selective anomeric deacetylation of monosaccharide acetates that utilize PEG-400 as an environment-friendly medium for the reaction.

Experimental

All the reagents were used as purchased without purification. PEG (Mn~400) was purchased from Alfa Aser while Poly(ethylene glycol) methyl ether (Mn~550) and Poly(ethylene glycol) dimethyl ether (Mn~500) were purchased from Sigma-Aldrich. Reactions were monitored by TLC, which was performed using 0.2 mm Merck pre-coated silica gel 60 F254 aluminium sheets. Compounds were detected by dipping the TLC plates in an ethanolic solution of sulphuric acid (5% v/v) and thereafter heating them. NMR spectra were recorded on Bruker Avance DPX (300 or 400 MHz) spectrometer. ^{1}H NMR and ^{13}C NMR spectra were referenced using either residual solvent signals, or tetramethylsilane in the respective deuterated solvents. Coupling constants (*J*) are reported in Hertz. Mass spectra were recorded on MALDI (Bruker Daltonics, Ultraflex TOF/TOF) Spectrometer. All the compounds described in this study have been reported previously.

General Procedure for Anomeric deacetylation

PEG-400 (6 ml/g of the sugar) was added to the acetylated sugar (1 g) taken in a round bottom flask and was stirred at room temparature till dissolution was complete. CsF (6 mol equiv) was added to it and the stirring was continued. Following completion of the reaction (Table 2) the mixture was washed with water (3-4 times), concentration *in vacuo* subsequently gave the crude product which was purified by chromatography on a column of silica gel using Hexane/EtOAc (97:3) as eluent.

2,3,4,6-Tetra-*o*-acetyl-D-galactopyranose (α:β=1:0.41): $[\alpha]_D$=+110.5 (c 1, $CHCl_3$); ^{1}H NMR (400

MHz, $CDCl_3$): δ = 5.52 (1H, m, H-1α), 5.48 (1H, m, H-4β), 5.42 (1H, m, H-4α), 5.39 (1H, m, H-3), 5.16 (1H, dd, *J* = 10.4 Hz, H-2α), 5.08 (2H, m, H-2β, H-3β), 4.70 (1H, t, *J* = 7.7 Hz, H-1β), 4.47 (1H, t, *J* = 6.6 Hz, H-5α), 4.16-4.06 (4H, m, H-6a(α/β), H-6b(α/β), 3.96 (1H, t, *J* = 7.2 Hz, H-5β), 3.83 (1H, m, OH(β)), 3.41 (1H, m, OH(α)), 2.16 (1H, s, OCOCH_3(β)), 2.15 (3H, s, OCOCH_3(α)), 2.11 (3H, s, OCOCH_3(β)), 2.10 (3H, s, OCOCH_3(α)), 2.06 (3H, s, OCOCH_3(α/ β)), 2.00 (3H, s, OCOCH_3(α/ β)); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.61, 170.57, 170.44, 170.29, 170.22, 170.12, 170.07, 95.99, 90.67, 71.02, 70.36, 68.32, 68.20, 67.24, 67.14, 66.23, 61.83, 61.47, 20.83, 20.73, 20.67, 20.65, 20.63, 20.57 ppm.

3,4,6-Tri-*o*-acetyl-D-galactopyranose (α:β=1:0.35): $[\alpha]_D$ = +82.5 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.40-5.38 (3H, m, *H*-4β, H-4α, H-1α), 5.19 (1H, dd, *J* = 10.4 Hz and 3.2 Hz, H-3α), 4.94 (1H, dd, *J* = 10.2 Hz and 3.3 Hz, *H*-3β), 4.70 (1H, d, *J* = 7.5 Hz, *H*-1β), 4.43 (1H, t, *J* = 6.5 Hz, *H*-5α), 4.14-4.08 (5H, m, *H*-5β, H-6a(α), H-6b(α), H-6a(β), H-6b(β)), 3.96 (1H, m, *H*-2α), 3.79 (1H, m, *H*-2 β), 2.14 (3H, s, OCOCH_3), 2.06 (6H, s, 2xOCOCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.39, 171.09, 170.78, 170.73, 170.68, 170.30 (O*C*OCH$_3$ (α/β)), 97.19 (*C*-1β), 95.66 (*C*-1α), 72.62 (*C*-3β), 70.93 (*C*-4α/β), 71.50 (C-3α), 70.42 (*C*-2β), 67.41 (C-2α), 66.55 (C-5α), 61.98, 61.71, 60.49 (C-6a/b(α/β), C-5β), 21.05, 20.86, 20.73, 20.65, 20.61 (OCO*C*H$_3$(α/β)) ppm.

Acknowledgement

MT acknowledges the Council of Scientific & Industrial Research (CSIR), New Delhi for a Senior Research Fellowship.

References

1. Novel selectivity in carbohydrate-reactions VIII. For Part VII see Malik, S, Tyagi, M, Kartha, K P R, Regioselective oligosaccharide synthesis using benzo bromo sugar as glycosyl donors under silvertrifluoromethanesulfonate catalysis, *Trends Carbohydr Res,* **2011**, *4*, 20-29.
2. Schmidt, R R, Kinzy, W, Anomeric-Oxygen activation for glycoside synthesis: the trichloroacetimidate method, *Adv Carbohydr Chem Biochem,* **1994**, *50*, 21-123.
3. Caputo, R, Kunz, H, Mastroianni, D, Palumbo, G, Pedatella, S, Solla, F, Mild synthesis of protected α -D-Glycosyl Iodides, *Eur J Org Chem,* **1999**, *4*, 3147-3150.
4. (a) Shimizu, M, Togo, H, Yokoyama, M, Chemistry of Glycosyl Fluorides, *Synthesis,* **1998**, 799-822; (b) Yokoyama, M, Methods of synthesis of glycosyl fluorides, *Carbohydr Res,* **2000**, *327*, 5-14.
5. Kanie, O, Ohtsuka, I, Ako, T, Daikoku, S, Kanie, Y, Kato, R, Orthogonal Glycosylation reactions on solid phase and synthesis of a library consisting of a complete set of fucosyl galactose isomers, *Angew Chem Int Ed,* **2006**, *45*, 3851-3855.
6. Watanbe, K, Itoh, K, Araki, Y, Ishido, Y, A comparision of bis(tributyltin) oxide, potassium cyanide and potassium hydroxide as reagents for the regioselective 1-*O*-deacetylation of fully acetylated sugar, *Carbohydr Res,* **1986**, *154*, 165-176.
7. (a) Nudelman, A, Herzig, J, Gottlieb, H E, Keinan, E, Sterling, J, Selective deacetylation of anomeric sugar acetates with tin alkoxides, *Carbohydr Res,* **1987**, *162*, 145-152; (b) Herzig, J, Nudelman, A, Gottlieb, H E, Methanolysis of acetylated sugars and glycosides in the presence of tin oxides and alkoxides, *Carbohydr Res,* **1988**, *177*, 21-28.
8. Helferich, B, Portz, W, Uber N-glycoside. II. mitteilung, *Chem Ber,* **1953**, *86*, 604-612.
9. Itoh, K, Takamura, H, Watanbe, K, Araki, Y, Ishido, Y, A facile procedure for regioselective 1-*O* -deacetylation of fully acylated sugars with sodium methoxide, *Carbohydr Res,* **1986**, *156*, 241-246.
10. Mikamo, M, Facile 1-*O*-deacylation of 1-*O*-acyl aldoses, *Carbohydr Res,* **1989**, *191*, 150-153.
11. Rowell, R M, Feather, M S, Synthesis and properties of anomerically unsubstituted hepta-*O*-acetyl disaccharides, *Carbohydr Res,* **1967**, *4*, 486-491.
12. Herzig, J, Nudelman, A, Regioselective heterogeneous-*O*-deacylation of polyacylated sugars, *Carbohydr Res,* **1986**, *153*, 162-167.
13. Schneider, G, Weisz-Vincze, I, Vass, A, Kovács, K, Selective deacetylation and stereospecific acyl migration of steroid acetate on aluminium oxide, *Tetrahedron Lett,* **1972**, *32*, 3349-3352.
14. Sambaiah, T, Fanwick, P E, Cushman, M, Regioselective 1-*O*-acyl hydrolysis of peracylated glycopyranoses by mercuric chloride and mercuric oxide, *Synthesis,* **2001**, 1450-1452.
15. Tiwari, P, Misra, A K, Selective removal of anomeric-*O*-acetate groups in carbohydrates using HCl04-Si02-tr, *Tetrahedron Lett,* **2006**, *47*, 3573-3576.
16. Tran, A T, Deydier, S, Bonnaffé, D, Narvor, C L, Regioselective green anomeric deacetylation catalyzed by lanthanide triflates, *Tetrahedron Lett,* **2008**, *49*, 2163-2165.
17. Goggin, K D, Lambert, J F, Walinsky, S W, Synthesis of peraceto-β-D-glycosyl fluorides using zinc fluoride, *Synlett,* **1994**, *3*, 162-164.
18. (a) Mugunthan, G, Kartha, K P R, Carbohydrates and nucleoside chemistry by ball milling, *Trends Carbohydr Res*, **2009**, *1*,1-9. Also see Jain, (b) S, Suryawanshi, S N, Bhakuni, D S, Simple synthesis of 2-acetoxyglycals, *Ind J Chem,* **1987,** *27b*, 866-867.
19. Chen, J, Spear, S K, Huddleston, J G, Rogers, R D, Polyethylene glycol and solutions of polyethylene glycol as green reaction media, *Green Chem*, **2005**, *7*, 64-68.
20. Lee, J W, Yan, H, Jang, H B, Kim, H K, Park, S, Lee, S, Chi, D Y, Song, C E, Bis-terminal hydroxy polyethers as all-purpose, multifunctional organic promoters: A mechanistic investigation and applications, *Angew Chem Int Ed,* **2009**, *48*, 7683-7686.
21. While this work was towards completion, another report describing observations on a tetrabutylammonium fluoride-mediated deacetylation with an unexpected regioselectivity in cellulose was published. Xu, D, Edgar, K J, TBAF and cellulose esters: unexpected deacylation with unexpected regioselectivity, *Biomacromol,* **2012**, *13*, 299-303.
22. Pedersen, C J, Cyclic polyethers and their complexes with metal salts, *J Am Chem Soc,* **1967**, *89*, 2495-2496.
23. 3,4,6-Tri-*O*-acetyl-D-glucopyranose to an extent of 15-20% was isolated from the mixture obtained after the reaction of α-D-glucose pentaacetate with CsF/PEG-400. It has also been reported as a by-product in the regioselective deacetylation reaction previously. For details see: Hanessian S; Kagotani M. Carbohydr Res, **1990**, 202, 67-69. β-D-glucose pentaacetate (**8β**) on the other hand reacted at a rate much lower than that of **8α**. Thus it was observed that only 20-30% of **8β** had been consumed at the time when complete consumption of **8α** had occurred, that is 1 h. Moreover, in the case of **8β** allowing the reaction to continue was found to lead to by-products resulting from the loss of acetyl group at other positions on the pyranosyl ring as well.