Carbohydrate Research 416 (2015) 21–23

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Note

One-pot synthesis of per-O-acetylated hemiacetals from free sugars in a deep eutectic solvent

Sunil M. Rokade, Prakash M. Bhate *

Department of Dyestuff Technology, Institute of Chemical Technology (formerly UDCT), N. P. Marg, Matunga, Mumbai 400 019, India

A R T I C L E I N F O

Article history:
Received 15 May 2015
Received in revised form 18 July 2015
Accepted 12 August 2015
Available online 17 August 2015

Keywords:
Per-O-acetylated hemiacetals
Deep eutectic solvent
Anomeric deprotection

A B S T R A C T

Free sugars reacted with acetic anhydride in a deep eutectic solvent made from choline chloride and $ZnCl_2$ at 90 °C to afford the corresponding peracetates that on further heating to 100 °C underwent selective deacetylation at the anomeric position to furnish the corresponding peracetylated hemiacetals in good yield.

Peracetylated hemiacetals of aldoses are important intermediates for the preparation of glycosyl acceptors such as glycosyl trichloroacetimidates[1] and glycosyl halides.[2,3] Such hemiacetals are generally prepared by adopting a two-step protocol. In a majority of cases, the free sugar is first converted into its per-O-acetyl derivative by the action of acetic anhydride and pyridine or dimethylaminopyridine (DMAP) at 0 to 25 °C for 24 h. In the second step, the isolated per-O-acetyl derivative is selectively deacylated at the anomeric position by the action of such reagents as benzylamine,[4] piperidine,[5] hydrazine acetate,[6] bis(tributyltin)oxide,[7] tributyltin methoxide,[8] ammonium carbonate,[9] $FeCl_3$,[10] $HClO_4$– SiO_2,[11] lanthanide triflates[12] and dimethylaminopropylamine (DMAPA).[13] Disadvantages associated with some of these reagents are toxicity[7] and low regioselectivity.[5,6,10]

Deep eutectic solvents (DES), an intensively investigated class of alternative reaction media,[14] are defined as salts that melt point below the boiling point of water. Deep eutectic solvents possess an exceptional combination of physical properties such as low flammability, stability towards air and moisture, excellent solvation potential, low water content, and high thermal stability. On account of their high heat capacity, density and conductivity together with negligibly low vapour pressure these eutectics have been explored as green solvents for carrying out several organic reactions. An illustrative but by no means exhaustive list includes the Fischer indole synthesis,[15] the Friedlander heteroannulation reaction,[16]the

Scheme 1. Preparation of per-O-acetyl-D-glucose hemiacetal .

Table 1
Screening of DES

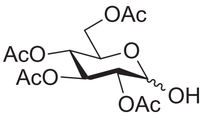
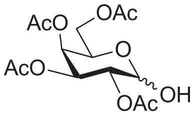
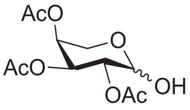
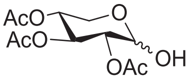
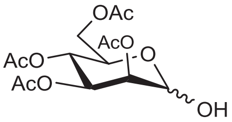
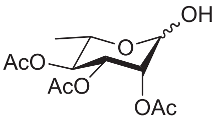
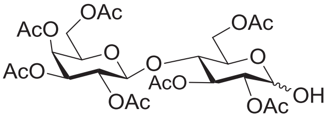
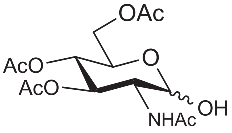
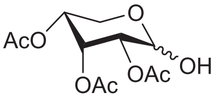
Sr. no.	DES	Time (h)	Temperature (°C)	Yield %
1	ChCl:$ZnCl_2$	8.0	RT	Traces
2		7.5	40	30
3		6.0	70	80
4		5.5	100	88
5	ChCl:Malonic acid	8.0	RT	Traces
6		7.5	40	27
7		6.0	70	67
8		5.5	80	76
9	ChCl:Oxalic acid	8.0	RT	Traces
10		7.5	40	20
11		6.0	70	70
12		5.5	80	72
13	ChCl:TsOH	8.0	RT	Traces
14		7.5	40	24
15		6.0	70	72
16		5.5	80	76

---

* Corresponding author. Department of Dyestuff Technology, Institute of Chemical Technology (formerly UDCT), N. P. Marg, Matunga, Mumbai 400 019, India. Tel.: +91 22 3361 1111/+91 2222/2706; fax: +91 022 3361 1020.
E-mail address: pm.bhate@ictmumbai.edu.in (P.M. Bhate).

http://dx.doi.org/10.1016/j.carres.2015.08.007
0008-6215/© 2015 Elsevier Ltd. All rights reserved.

Table 2
Preparation of per-O-acetyl hemiacetals

Entry	Sugar	Product	Observed		Reported		Ref.
			Time (h)	Yield (%)	Time (h)	Yield (%)	
1	D-Glucose **1a**	 **2a**	5.5	88	25.2	90	11
2	D-Galactose **1b**	 **2b**	5.5	86	25.8	90	11
3	L-Arabinose **1c**	 **2c**	5.0	88	18	88	11
4	D-Xylose **1d**	 **2d**	5.0	88	18	89	11
5	D-Mannose **1e**	 **2e**	5.5	87	18	84	10
6	L-Rhamnose **1f**	 **2f**	5.0	88	18	88	11
7	D-Lactose **1g**	 **2g**	6.2	80	28	80	10
8	D-Glucosamine **1h**	 **2h**	6.0	85	16	82	13
9	D-Ribose **1i**	 **2i**	5.5	88	18	88	11

Mannich reaction,[17] the Perkin reaction,[18] and synthesis of substituted pyrrole derivatives.[19]

Here we report a one pot protocol for the preparation of per-O-acetylated hemiacetals of aldoses by reaction of free sugars with acetic anhydride in a DES made from choline chloride and $ZnCl_2$. Operational simplicity, no further purification steps and recyclability of DES are key features of this protocol.

We initially treated D-glucose **1a** (3.0 g) with acetic anhydride (8.5 mL) at 90 °C for 1.5 h in a DES (15 g) made from choline chloride and $ZnCl_2$ (Scheme 1). Thin layer chromatography (TLC) analysis indicated the formation of per-O-acetyl-D-glucose. We then heated the reaction mixture to 100 °C and continued the reaction. TLC analysis now indicated the formation of a polar product. Its concentration progressively increased while that of the less polar per-O-acetyl-D-glucose progressively decreased. The less polar starting material completely disappeared after stirring at 100 °C for 5.5 h. The ^{1}H NMR spectrum of the isolated (88% yield) polar material was identical to that reported for per-O-acetyl-D-glucose hemiacetal **2a** indicating selective anomeric deprotection. When other eutectics were used (see Table 1), we obtained lower yield.

Per-O-acetyl-D-glucose was not formed even at 120 °C when D-glucose was treated with acetic anhydride in the presence of a

Table 3
Recyclability of deep eutectic solvent

Sr. No	Number of runs	Yield %	Amount of DES obtained, g
1	Fresh	88	–
2	First	88	15
3	Second	86	15.08
4	Third	85	15.20
5	Fourth	82	15.43

catalytic quantity of DES.[a] This result demonstrates the dual role of DES as a source of acidity as well as an enabling solvent.

We next applied this technique to D-galactose, D-mannose, D-xylose, L-arabinose, D-fructose, D-ribose, L-rhamnose, D-glucosamine and D-lactose. In all cases we obtained the corresponding per-O-acetylated hemiacetals (**2a–2i**) in 80–88% yield and in significantly lesser time than that previously reported (see Table 2). TLC of hemiacetals **2a–i** showed a single spot. ^{1}H NMR spectra (see Supplementary material) also indicated absence of impurities. Thus further purification is not required.

The recovery and reuse of DES was studied in the reaction of D-glucose with acetic anhydride. Residual DES after extraction of the reaction mass with ethyl acetate (*see* section 1.2) was treated with water (5 mL) and the resulting mass was dehydrated under vacuum on a rotary evaporator at 70 °C for 1 h. The dehydrated DES was directly used for repeating the reaction. Table 3 presents data obtained after four such recycles. The results indicate that DES can be recycled three times without significant loss in activity.

In conclusion, we have developed a clean, efficient, and high yielding one pot protocol for the preparation of per-O-acetylated hemiacetals from free sugars by using DES made from choline chloride and $ZnCl_2$ as the solvent. The hemiacetals so prepared do not require further purification. DES used can be readily recycled.

1. Experimental

1.1. General methods

Starting materials and reagents were purchased from commercial suppliers. Thin-layer chromatography (TLC) was performed on aluminium plates pre-coated with Merck silica gel, spots were observed by spraying the plates with a solution of 10% (v/v) aqueous H_2SO_4 with subsequent heating. ^{1}H NMR spectra were recorded on a Varian (500, 400 MHz) spectrometer. Chemical shifts are expressed in parts per million (ppm) with TMS as internal standard. Coupling constants (J) are given in Hz.

1.2. General procedure for the preparation of per-O-acetylated hemiacetals

Acetic anhydride (8.5 g) was added to a solution of the free sugar (**1a–i**) (3 g) in DES (15 g) made[20] from choline chloride (6.0 g) and $ZnCl_2$ (9 g), and the resulting mixture was stirred at 90 °C for 1.5 h. The temperature was raised to 100 °C and stirring continued for 4–6 h. The reaction mixture was cooled to ambient temperature and extracted with ethyl acetate (3 × 20 mL). The combined ethyl acetate layer was washed with saturated aqueous $NaHCO_3$, dried over anhydrous sodium sulphate and evaporated under vacuum to afford the corresponding per-O-acetylated hemiacetal.

Acknowledgements

S.M.R. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, India for providing a research fellowship. The authors acknowledge work done in the area of DES by Dr. G. S. Shankarling and co-workers of Department of Dyestuff Technology at Institute of Chemical Technology, Mumbai, India.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.carres.2015.08.007.

References

1. Schmidt RR, Kinzy W. *Adv Carbohydr Chem Biochem* 1994;**50**:21–3.
2. Caputo R, Kunz H, Mastroianni D, Palumbo G, Pedatella S, Solla F. *Eur J Org Chem* 1999;3147–50.
3. Yokoyama M. *Carbohydr Res* 2000;**327**:5–14.
4. Conchie J, Levvy GA. *Methods Carbohydr Chem* 1963;**2**:345–7.
5. Rowell RM, Feather MS. *Carbohydr Res* 1967;**4**:486–91.
6. Excoffier G, Gagnaire D, Utille JP. *Carbohydr Res* 1975;**39**:368–73.
7. Watanbe K, Itoh K, Araki Y, Ishido Y. *Carbohydr Res* 1986;**154**:165–76.
8. Nudelman A, Herzig J, Gottlieb HE, Keinan E, Sterling J. *Carbohydr Res* 1987;**162**:145–52.
9. Mikano M. *Carbohydr Res* 1989;**191**:150–3.
10. Sambaiah T, Fanwick PE, Cushman M. *Synthesis* 2001;**10**:1450–2.
11. Tiwari P, Misra AP. *Tetrahedron Lett* 2006;**47**:3573–6.
12. Tran AT, Deydier S, Bonnaffé D, Narvor CL. *Tetrahedron Lett* 2008;**49**:2163–5.
13. Andersen SM, Heuckendorff M, Jensen HH. *Org Lett* 2015;**17**:944–7.
14. a) Florindo C, Oliveira FS, Rebelo LPN, Fernandes AM, Marrucho IM. *ACS Sustainable Chem Eng* 2014;**2**:2416–9;b) Smith EL, Abbott AP, Ryder KS. *Chem Rev* 2014;**114**:11060–82;c) Rub C, Konig B. *Green Chem* 2012;**14**:2969–82.
15. Morales RC, Tambyrajah V, Jenkins PR, Davies DL, Abbott AP. *Chem Commun* 2004;158–9.
16. Ma FP, Cheng GT, He ZG, Zhang ZH. *Aust J Chem* 2012;**65**:409–16.
17. Keshavarzipour F, Tavakol H. *Catal Lett* 2015;**145**:1062–6.
18. Pawar PM, Jarag KJ, Shankarling GS. *Green Chem* 2011;**13**:2130–4.
19. a) Hu HC, Liu YH, Li BL, Cui ZS, Zhang ZH. *RSC Adv* 2015;**5**:7720–8;b) Rokade SM, Garande AM, Ahmad NAA, Bhate PM. *RSC Adv* 2015;**5**:2281–4;c) Kalmode HP, Vadagaonkar KS, Murugan K, Prakash S, Chaskar AC. *RSC Adv* 2015;**5**:35166–74.
20. Hekmatshoar R, Mousavizadeh F, Rahnamafar R. *J Chem Sci* 2013;**125**:1009–13.

---

[a] The authors thank a referee for suggesting this experiment.