Pergamon

Tetrahedron Letters, Vol. 35, No. 33, pp. 6129-6132, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01212-1

A NOVEL METHOD FOR THE DIRECT ACTIVATION OF ALDEHYDES. SYNTHESIS OF CARBOHYDRATE ACETALS.

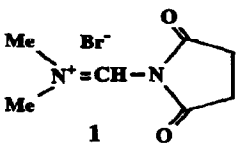
György Hodosi[1]

Institute for Drug Research, 1325 Budapest, P. O. Box 82, Hungary

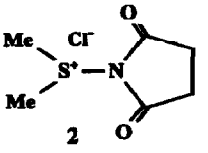
Abstract: A new method for the activation of alkyl and aryl aldehydes to substituted succinimidomethanium salts for the synthesis of cyclic dioxane type acetals of carbohydrates is described.

As protecting groups cyclic acetals play an important role in synthetic transformations of natural compounds, particularly in the synthesis of oligosaccharides[2]. One conventional method utilizes the thermodynamically controlled reaction of benzaldehyde in the presence of a Lewis acid catalyst[2a,3]. Two other procedures have been developed for the production of kinetically controlled acetals, using either benzal bromide[4] in basic conditions or α,α-dimethoxytoluene[5] in the presence of p-toluenesulfonic acid. These reactions are inefficient in that they are slow and require either the use of large amounts of benzaldehyde or a specific reagent. Because of recent interest in selective acetal opening reactions[2ab,6], and to satisfy the growing demand, many groups have sought for more efficient methods of acetal synthesis[7].

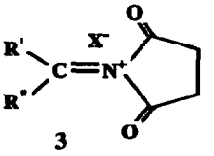
In this communication a new method for the direct activation of various aldehydes is described. Previously, activation of N,N-dimethylformamide[8] (DMF) and dimethylsulfoxide[9] (DMSO) with N-bromo- or N-chlorosuccinimide produced either the N,N-dimethylsuccinimidoformamidinium bromide[8] (**1**) or the dimethylsuccinimidosulfonium[10] chloride (**2**). It could be expected that a similar activation of aldehydes would result in the formation of intermediate **3**; a potentially good reagent for the synthesis of various acetals. In order to advance this hyphothesis, the reaction of benzaldehyde and decanal with triphenylphosphine (TPP) and



1



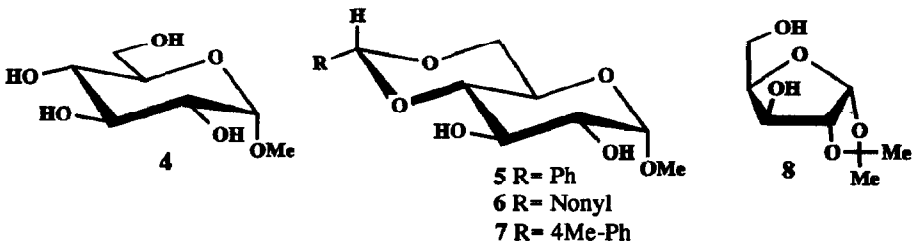
2



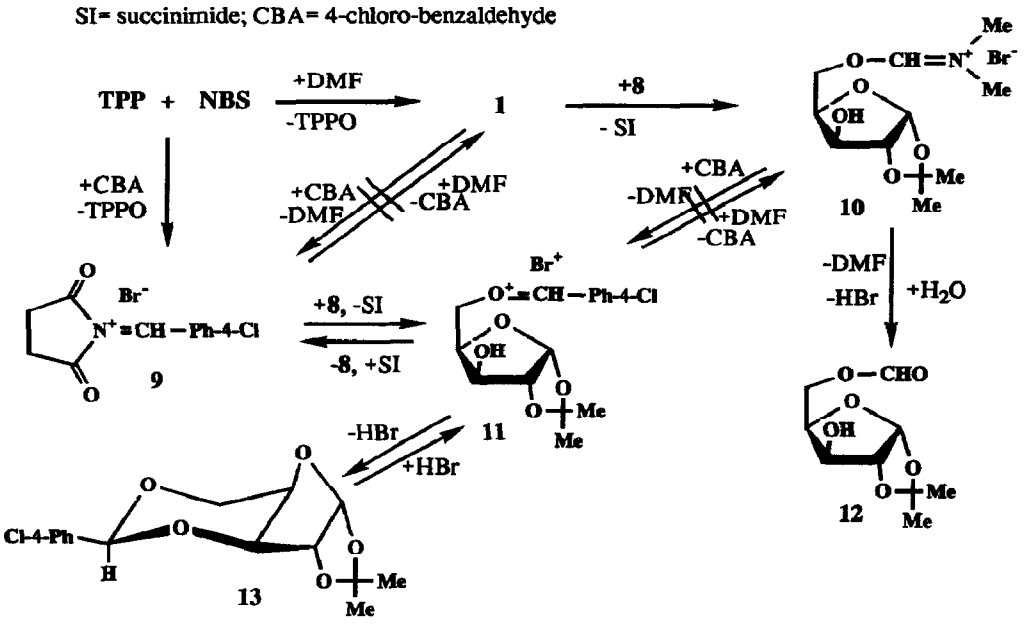
3

X= Cl or Br
R', R"= H, alkyl or aryl

N-chlorosuccinimide (NCS) in dichloromethane solutions was examined. As a substrate for acetal formation methyl α-D-glucopyranoside (**4**) was chosen. Moderate yields of products **5**[11] and **6**[12] (ranging between 60-70%) and the relatively long reaction time (24 h), due to the slight solubility of starting carbohydrate **4**, led us to search for better reaction conditions[13]. Changing the solvent to DMF, seemed to obviate these solubility problems. In addition, being conscious of the published reaction mechanism[8] for the reaction of TPP and N-



bromosuccinimide (NBS) with DMF, we decided to consider every possible mode of addition of reagents to avoid undesirable side reactions. We chose 1,2-O-isopropylidene-α-D-xylofuranose (**8**) as a model compound, and crystalline 4-chlorobenzaldehyde as reagent. **Procedure 1**: TPP and NBS react rapidly at 0-5 °C with DMF in an exothermic reaction[8] to form the formamidinium salt **1**.This could be converted, after addition of substrate **8**, into O-iminium[8] derivative **10**. Theoretically intermediate **10** can react with lastly added 4-chlorobenzaldehyde



via **11** via two equilibrium steps leading to the required double acetal **13**. However, after quenching the reaction mixture by the addition of triethylamine (TEA) either after 5 or 20 hours, the only product observed was the 5-O-formyl derivative **12**[12] (the hydrolysis product of **10**), indicating that it was impossible to prepare double acetal **13** in this way. **Procedure 2**: Another possible pathway leading to **13** is the addition of 4-chlorobenzaldehyde to amidinium salt **1**, leading to the formation of 4-chlorophenylsuccinimidometanium salt **9**, which after the addition of **8** might be able to react forming intermediate **11**. Instead of **13** the only product isolated after several hours was again the O-formyl derivative **12**, indicating preferential reaction between amidinium **1** and carbohydrate **8**. Therefore, the only remaining possibility for reaching **13** was to repeat the

addition sequence of reagents used when running the reaction in dichloromethane. **Procedure 3**: In this case the TPP was added to the viscous solution of 4-chlorobenzaldehyde and NBS in anhydrous DMF forming the methanium salt **9**, followed by the addition of xylofuranose derivative **8**. High concentration and the correct sequence of reagent addition avoided the appearance of an unfavorable side reaction, and after neutralization with TEA, we successfully isolated the desirable double acetal **13**[12]. Following **procedure 3**, the glucose acetal **7**[12] was prepared (for reaction conditions and yields see **Table 1**). For a general method see ref. 14.

Table 1: Reaction conditions and yields of the acetal synthesis at 25°C with 1 mol eq. of substrate

Compound N°	TPP mol eq.	NBS (NCS) mol eq.	aldehyde mol. eq.	solvent	reaction time hours	yield %
5	2.0	(2.0)	3.0 of benzaldehyde	CH_2Cl_2	25	69[a]
6	1.8	(1.8)	2.0 of decanal	CH_3CN	24	63[a]
7	2.0	2.0	2.2 of 4-Me-benzaldehyde	DMF	10	72[a]
12	1.1	1.1	1.1 of 4-Cl-benzaldehyde	DMF	5	77[b]
	1.1	1.1	1.1 of 4-Cl-benzaldehyde	DMF	4	80[c]
13	1.5	1.5	1.5 of 4-Cl-benzaldehyde	CH_2Cl_2	6	64[a]
	1.5	1.5	1.8 of 4-Cl-benzaldehyde	DMF	10	70[a]

[a]Addition sequence of **procedure 3**. [b]Addition sequence of **procedure 2**. [c]Addition sequence of **procedure 1**.

The further investigation of the scope and limitation of the reported method are in progress including the extension of this reaction to the synthesis of oxolane type acetals. The carbohydrates were chosen as substrates because the synthesis of their acetals is more difficult and complex, however the method could serve as a general method for the synthesis of any acetals.

References and Notes

1. Present address: University of Toronto, Department of Medical Genetics and Immunology, Toronto, Ontario, Canada M5S 1A8.
2. (a) Belder, A. N. de. *Adv. Carbohydr. Chem. Biochem.* **1977**, 34, 179-241. (b) Gelas, J. *Adv. Carbohydr. Chem. Biochem.* **1981**, 39, 71-156. (c) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, 34, 1045-1053.
3. Fletcher, H. G. In *Methods in Carbohydrate Chemistry*; R. L. Whistler; New York, 1963, Vol. II, 307-308.
4. (a) Bock, K; Meyer, B.; Thiem, J. *Angew. Chem.* **1978**, 17, 447-449. (b) Kahn, R. *Carbohydr. Res.* **1974**, 32, 375-379.
5. (a) Evans, M. E. *Carbohydr. Res.* **1972**, 21, 473-475. (b) Takeo, K.; Fukatsu, T.; Yasako, T. *Carbohydr. Res.* **1982**, 107, 71- 90. (b) Takeo, K.; Shinmitzu, K. *Carbohydr. Res.* **1984**, 133, 135-145.
6. (a) Bhattacharjee, S. S.; Gorin, P. A. J. *Can. J. Chem.*, **1969**, 47, 1195-1215. (b) Lipták, A.; Jodál, I. Nánási, P. *Carbohydr. Res.* **1975**, 44, 1-11. (c) Garegg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1981**, 93, c10-c11. (d) Garegg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, 108, 97-101.
7. (a) Katlehner, W.; Gutbrod, H. D.; Groß, P. *Liebigs Ann. Chem.* **1979**, 522-527. (b) Katlehner, W.; Gutbrod, H. D. *Liebigs Ann. Chem.* **1979**, 1362-1369. (c) Mani, N. S. *Ind. J. Chem.* **1989**, 28B, 602-603. (d) Li, C.; Vasella, A. *Helv. Chim. Acta* **1993**, 76, 211-221. (e) Kerékgyártó, J.; Lipták, A. *Carbohydr. Res.* **1993**, 248, 361-364.

8. Hodosi, G.; Podányi, B.; Kuszmann, J. *Carbohydr. Res.* **1992**, 230, 327-342.
9. Hodosi, G. *Carbohydr. Res.* **1994**, 252, 291-296.
10. (a) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, 94, 7586-7587. (b) *J. Org. Chem.* **1973**, 38, 1233-1234. (c) *Tetrahedron Lett.* **1974**, 287-290.
11. (a) W. A. van Ekenstein, J. J. Blanksma. *Rec. Trav. Chim.* **1906**, 153-160. (b) B. Coxon. *Tetrahedron*, **1965**, 21, 3481-3503.
12. All compounds gave satisfactory analitycal and spectroscopic data. The analytical and spectroscopic data of **6**: R_f 0.6 (ethyl acetate); mp 50-52°C; $[\alpha]_D^{25}$ +91.7° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.76 (d, 1H, $J_{1,2}$ 3.7 Hz, H1), 4.54 (t, 1H, $J_{decylidene, CH2(CH2)7CH3}$ 5.1 Hz, decylidene), 4.32 (dd, 1H, $J_{4,5}$ 4.7 Hz, H4), 3.84 (t, 1H, $J_{6a,6b}$ 9.3 Hz, H6a), 3.64 (td, 1H, $J_{5,6a}$ 9.0 and $J_{5,6b}$ 9.6 Hz, H5), 3.56 (dd, 1H, $J_{2,3}$ 10.3 Hz, H2), 3.50 (t, 1H, $J_{3,4}$ 9.9 Hz, H3), 3.43 (s, 3H, CH_3O), 3.25 (t, 1H, H6b), 1.65 (m, 2H, $CH_2(CH_2)_7CH_3$), 1.30 (m, 14H, $CH_2(CH_2)_7CH_3$), 0.85 (t, 3H, $CH_3(CH_2)_8$). **7**: R_f 0.45 (ethyl acetate); mp 166-67°C; $[\alpha]_D^{25}$ +114.3° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, 2H, $J_{2',3'=5',6'}$ 8.0 Hz, H3',5'), 7.17 (d, 2H, H2',6'), 5.49 (s, 1H, benzylidene), 4.78 (d, 1H, $J_{1,2}$ 3.9 Hz, H1), 4.28 (dd, 1H, $J_{4,5}$ 3.6 Hz, H4), 3.92 (t, 1H, $J_{6a,6b}$ 9.3 Hz, H6a), 3.79 (td, 1H, $J_{5,6a}$ 9.6 Hz, H5), 3.72 (t, 1H, H6b), 3.62 (m, 1H, $J_{2,3}$ 9.3 Hz, H2), 3.42 (t, 1H, $J_{3,4}$ 9.0 Hz, H3), 3.4 (s, 3H, CH_3O), 2.93 (d, 1H, OH), 2.45 (m, 1H, OH), 2.35 (s, 3H, CH_3Ph). **12**: R_f 0.45 (ethyl acetate, hexane 1:1); mp 75.5-77°C; $[\alpha]_D^{25}$ +20.8 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 8.1 (s, 1H, CHO), 5.95 (d, 1H, $J_{1,2}$ 3.8 Hz, H1), 4.57 (d, 1H, $J_{2,3}$ ~0 Hz, H2), 4.55 (t, 1H, $J_{5a,5b}$ 13.0 Hz, H5a), 4.35 (t, 1H, H5b), 4.32 (td, 1H, $J_{4,5a}$ 8.3 and $J_{4,5b}$ 6.0 Hz, H4), 4.22 (d, 1H, $J_{3,4}$ 2.0 Hz, H3), 1.5 and 1.32 (each s, 6H, $(CH_3)2C$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 161.3 (CHO), 112.0 (Me_2C), 104.8 (C1), 85.2 (C2), 78.1 (C4), 74.6 (C3), 61.3 (C5), 26.7 and 26.1 (each CH_3). **13**: R_f 0.7 (ethyl acetate, hexane 1:1); mp 149-151°C; $[\alpha]_D^{25}$ +7.2° (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.41 and 7.33 (each d, 4H, $J_{2',3'=5',6'}$ 8.1 Hz, H2',3',5',6'), 6.06 (d, 1H, $J_{1,2}$ 3.7 Hz, H1), 5.43 (s, 1H, benzylidene), 4.63 (d, 1H, $J_{2,3}$ ~ 0, H2, 4.46 (d, 1H, $J_{5a,5b}$ 15.0 Hz, H5a), 4.42 (d, 1H, $J_{3,4}$ 1.9 Hz, H3), 4.15 (t, 1H, H5b), 4.10 (dd, 1H, $J_{4,5a}$ ~ 0 and $J_{4,5b}$ 8.2 Hz, H4), 1.51 and 1.33 (each s, 6H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 136.4 (C4'), 128.4 and 127.6 (C1',2',3',5',6'), 111.9 (Me_2C), 105.6 (C1), 98.5 (PhCH), 83.8 (C-2), 79.0 (C3), 72.1 (C4), 66.7 (C5), 26.7 and 26.1 (each CH_3).
13. It should be noted that attempts to similarly activate aldehydes with either p-toluenesulfonyl chloride or acetic anhydride failed.
14. General procedure for substrates soluble in CH_2Cl_2: Triphenylphosphine (2.07 g, 7.89 mmol) was added in small portions to the stirred ice-cooled solution of aldehyde (7.89 mmol) and N-bromosuccinimide (1.4 g, 7.89 mmol) in anhydrous dichloromethane (20 mL). Then the cooling bath was removed and the solution stirred at 25 °C for 1 h, and the substrate (5.25 mmol) was added. After the disappearance of substrate, the reaction mixture was cooled and neutralized by the addition of triethylamine. Dichloromethane (200 ml) was added, and washed with saturated sodium hydrogen carbonate solution and water, dried, and evaporated. The semicrystalline residue was dissolved in diethyl ether, the crystallized triphenylphosphine oxide was filtered, the filtrate evaporated to dryness and purified by column chromatography.
General procedure for substrates soluble in DMF: For the same amount of substrate 10 ml of anhydrous DMF and 2 mol. equivalent of reagents were used. After neutralization the reaction mixture was evaporated and purified by column chromatography.

(*Received in UK* 25 *March* 1994; *revised* 17 *June* 1994; *accepted* 24 *June* 1994)