Tetrahedron Letters,Vol.30,No.23,pp 3081-3084,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

PREPARATION OF GLYCOSYL HALIDES UNDER NEUTRAL CONDITIONS

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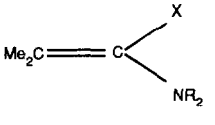
Summary: *The anomeric hydroxyl group of various furanose and pyranose hemiacetals can be replaced by a fluorine, chlorine, bromine or iodine atom under neutral conditions using haloenamines.*

Glycosyl chlorides and bromides have been used for over eighty years as electrophiles in glycosidic bond formation [1]. Since 1981 the more stable glycosyl fluorides have been applied for effective glycosylation reactions [2]. A few isolated examples of glycosylation reactions starting from glycosyl iodides have also been reported [3].

Preparation of glycosyl halides directly from the corresponding hemiacetals has been achieved e.g. using hydrogen fluoride/pyridine [2c], diethylaminosulfur trifluoride (DAST) [4], modified Mitsunobu conditions [5], PPh_3/N-halosuccinimide [6] or PBr_3 [7].

We have found that α-haloenamines 1a-1e are highly effective for the direct, one-step, high-yield and gram-scale conversion of various furanose and pyranose hemiacetals into the corresponding glycosyl halogenides under neutral conditions.

The use of the tetramethyl-α-haloenamines 1b - 1e has been reported for the preparation of several acyl halides [8]. Also, a few examples of the chlorination of primary, secondary and tertiary alcohols using 1-chloro-N,N,2-trimethyl-propenylamine 1c have been published [9]. The preparation of the haloenamines 1b - 1e is accomplished in large scale starting from the corresponding amide 2b according to a procedure published by Ghosez et al. [10]. The haloenamines can be stored under argon at room temperature. 1-Fluoro-2-methyl-N,N-diisopropyl-propenylamine was obtained from 2a by a similar approach.



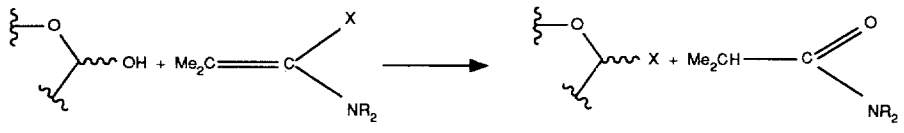
	1a	1b	1c	1d	1e
X	F	F	Cl	Br	I
R	iPr	Me	Me	Me	Me

Our new procedure for the preparation of glycosyl halides is compatible with commonly used hydroxyl-protecting groups such as benzyl, benzoyl, acetyl, acetonide or silyl functionalities, as they do not interfere with these neutral halogenation conditions.
A broad variety of solvents can be used. In CH_2Cl_2, $CHCl_3$, CCl_4 or 1,2-dichloroethylene, the halogenation takes place in a few hours, but in benzene, toluene, xylene or diethyl ether, the rate of the reaction is considerably reduced.

For the synthesis of the glycosyl fluorides both fluoroenamines 1a and 1b can be used. Rate and yield of the fluorination are generally better with 1a.

Since the only byproduct is the relatively inert N,N-dimethyl isobutyramide (2a, R = Me) and N,N-diisopropyl isobutyramide (2b, R = iPr), respectively, the isolation of the glycosyl halides for further reactions will often be unnecessary.

Our results are summarized in Table 1. Anomeric ratios were determined by ^{1}H-NMR (cf. ref [11]) in comparison with literature data [3, 4b, 5, 6, 12]. The configurations at C(1) of the mannoses 15 - 18 were assigned with the aid of the magnitude of the one-bond coupling between C(1) and H-C(1) [13].

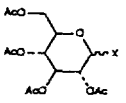
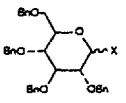
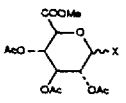
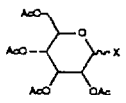
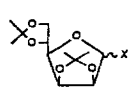
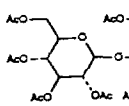


1 2

A typical experimental procedure is represented by the chlorination of 2, 3, 4, 6-tetra-O-benzyl-D-glucopyranose. This hemiacetal (540 mg, 1mmol) was treated rapidly at room temperature in a stirred solution of $CHCl_3$ (5 ml) under argon with 156 µl (1.1 mmol) of 1-chloro-N, N, 2-trimethylpropenylamine (1c). After 6 hours, tlc. indicated completion of the reaction. Evaporation of the reaction mixture and flash chromatography of the residue (silica gel 0.040 - 0.063 mm, pet. ether : ethyl acetate = 2 : 1) yielded 517 mg (92%) of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl chloride.

In conclusion, based on the mild and neutral reaction conditions this new method is very attractive for the preparation of even highly sensitive glycosyl halides (e. g. 9 and 10).

Table 1: Yields and configurations of the glycosyl halides obtained by halogenation with haloenamines 1a - e

Product	X = F	Cl	Br	I
	3, 85%, α:β=25:75[1]	4, 91%, α	5, 77%, α	6, 84%, α
	7, 99%, α:β=28:72[1]	8, 92%, α	9, quant[2], α	10, quant[2], α
	11, 76%, α:β=10:90[1]	12, 88%, α:β=18:82[1]	13, quant[2], α	14, quant[2], α
	15, 98%, α:β=86:14[1]	16, 75%, α	17, 84%, α	18, 79%, α
	19, 77%, α:β=26:74[1]	20, 78%, α	21, 90%, α	22, 72%, α
	23, 90%, β	-	24, 89%, α	-

[1] Anomeric ratios were determinded by ^{1}H-NMR [11].

[2] Due to the instability of these glycosyl halides a modified work-up was used : after completion of the reaction the solvent was evaporated and the residue was dried at room temperature / 0.01 torr. By using this work-up glycosyl halides of high purity were obtained.

References:

[1] K. Igarashi, Adv. Carbohydrate Chem. Biochem. 34, 243 (1977).

[2] a) T. Mukaiyama, Y. Murai, S. Soda, Chem. Lett. 1981, 431; b) T. Mukaiyama, Y. Hashimoto, S. Shoda, Chem. Lett. 1983, 935; c) S. Hashimoto, M. Hayashi, R. Noyori, Tetrahedron Lett. 25, 1379 (1984); d) K. C. Nicolaou, R. E. Dolle, D. P. Papahatjis, J. L. Randall, J. Am. Chem. Soc. 106, 4189 (1984).

[3] F. J. Kronzer, C. Schuerch, Carbohydr. Res 34, 71 (1974).

[4] a) W. Rosenbrook, Jr., D. A. Riley, P. A. Lartey, Tetrahedron Lett. 26, 3 (1985); b) G. H. Posner, S. R. Haines, Tetrahedron Lett. 26, 5 (1985).

[5] H. Kunz, W. Sager, Helv. Chim. Acta 68, 283 (1985).

[6] S. Hanessian, M. M. Ponpipom, P. Lavalle, Carbohydr. Res. 24, 45 (1972).

[7] R. R. Schmidt, E. Rücker, Tetrahedron Lett. 21, 1421 (1980).

[8] a) A. Devos, J. Remion, A.-M. Frisque-Hesbain, A. Colens, L. Ghosez, J. Chem. Soc. Chem. Commun. 1979; 1180 b) U. Schmidt, M. Kroner, U. Beutler, Synthesis 1988, 475.

[9] a) L. Ghosez in E. C. Taylor (Ed.). Advances in Organic Chemistry, Vol. 9, part 1, p 421 (1976); b) U. Schmidt, A. Lieberknecht, H. Griesser, R. Utz, T. Beutler, F. Bartkowiak, Synthesis 1986, 361; c) B. Ernst, B. Wagner, Helv. Chim. Acta. 72, 165 (1989); d) for additional examples see the preceeding paper by F. Munyemana, A.-M. Fisque-Hesbain, A. Devos, L. Ghosez, Tetrahedron Lett. 1989.

[10] a) B. Haveaux, A. Dekoker, M. Rens, A. R. Sidani, J. Toye, L. Ghosez, Org. Synth. 59, 26 (1979); b) A. Colens, M. Demuylder, B. Téchy, L. Ghosez, Nouv. J. Chim. 1, 369 (1977).

[11] NMR (300 MHZ, $CDCl_3$) data for the anomeric hydrogen are given below:
3 : 5.77 (dd, $J_{1,F}$ = 53, $J_{1,2}$ = 3, ß-H-C (1) and 5.37 (dd, $J_{1,F}$ = 52, $J_{1,2}$ = 6, α-H-C (1)); 4 : 6.30 (d, J = 3.9, ß-H-C (1)); 5 : 6.61 (d, J = 4, ß-H-C (1)); 6 : 6.99 (d, J = 4, ß-H-C (1)); 7 : 5.55 (dd, $J_{1,F}$ = 53, $J_{1,2}$ = 2.8, ß-H-C (1)) and 5.25 (dd, $J_{1,F}$ = 52.7, $J_{1,2}$ = 6.5, α-H-C (1)); 8 : 6.06 (d, J = 3.7, ß-H-C (1)); 9 : 6.43 (d, J = 3.7, ß-H-C (1)); 10 : 6.85 (d, J = 4, ß-H-C (1)); 11 : 5.82 (dd, $J_{1,F}$ = 53, $J_{1,2}$ = 3, ß-H-C (1)) and 5.45 (dd, $J_{1,F}$ = 51, $J_{1,2}$ = 5, α-H-C (1)); 12 : 6.34 (d, J = 4, ß-H-C (1)) and 5.36 (d, J = 8, α-H-C (1)); 13 : 6.64 (d, J = 4, ß-H-C (1)); 14 : 7.02 (d, J = 4.4, ß-H-C (1)); 15 : 5.58 (dd,$J_{1,F}$ = 48.5, $J_{1,2}$ = 1.9, ß-H-C (1)) and 5.55 (dd, $J_{1,F}$ = 49.5, $J_{1,2}$ = 1.7, α-H-C (1)); 16 : 5.99 (d, J = 1.7, ß-H-C (1)); 17 : 6.30 (d, J = 1.6, ß-H-C (1)); 18 : 6.71 (d, J = 1.6, ß-H-C (1)); 19 : 5.69 (d, $J_{1,F}$ = 59.3, ß-H-C (1)) and 5.51 (dd, $J_{1,F}$ = 66.6, $J_{1,2}$ = 3.7, α-H-C (1)); 20 : 6.08 (s, ß-H-C (1)); 21 : 6.39 (s, ß-H-C (1)); 22 : 6.63 (d, J = 1, ß-H-C (1)); 23 : 5.36 (dd, $J_{1,F}$ = 52.7, $J_{1,2}$ = 5.6, α-H-C (1)); 24 : 6.54 (d, J = 3.6, ß-H-C (1)).

[12] a) L. D. Hall, J. F. Manville, N. S. Bhacca, Can. J. Chem. 47, 1 (1969); b) K. Heyns, W.-P. Trautwein, F. G. Espinosa, H. Paulsen, Chem. Ber. 99, 1183 (1966); c) D. Horton, W. N. Turner, J. Org. Chem. 30, 3387 (1965); d) J. Thiem, B. Meyer, Chem. Ber. 113, 3075 (1980); e) P. Kováč, H. J. C. Yeh, G. L. Jung, J. Carbohydr. Chem. 6, 423 (1987); f) V. D. Grob, T. G. Squires, J. R. Vercellotti, Carbohydr. Res. 10, 595 (1969); g) J. Leroux, A. S. Perlin, Carbohydr. Res. 67, 163 (1978); h) N. Pravdić, D. Keglević, Carbohydr. Res. 7, 167 (1968).

[13] cf. e.g. V. S. Rao, A. S. Perlin, Carbohydr. Res. 92, 141 (1981) and ref. cited therein.

(Received in France 4 April 1989)