Pergamon

Tetrahedron Letters, Vol. 36, No. 30, pp. 5343-5346, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01027-0

N-Tetrachlorophthaloyl-Protected Trichloroacetimidate of Glucosamine as Glycosyl Donor in Oligosaccharide Synthesis[1]

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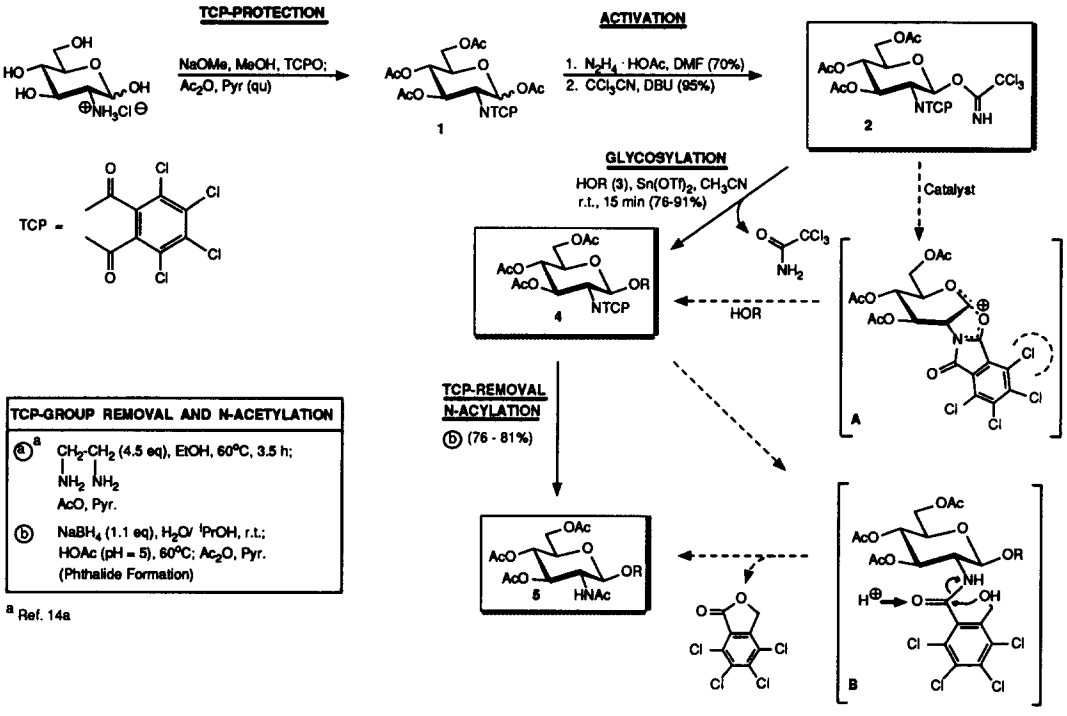
Abstract: N-Tetrachlorophthaloyl (TCP) protection of glucosamine could be readily carried out with tetrachlorophthalic anhydride and then treatment with acetic anhydride in pyridine. Ensuing reaction with $N_2H_4 \cdot$ HOAc and then base-catalyzed activation with trichloroacetonitrile afforded N-TCP protected glucosamine donor **2**. Glycosylation of acceptors **3a-d** in acetonitrile with $Sn(OTf)_2$ as the catalyst gave β-glycosides **4a-d** in high yields, thus exhibiting the high reactivity and diastereoselectivity of **2**. For TCP cleavage $NaBH_4$ reduction followed by acid catalyzed phthalide formation and then treatment with acetic anhydride was employed, thus giving N-acetyl-glucosamine containing oligosaccharides **5a,c,d** in a convenient, highyielding procedure.

Glucosamine is an important constituent of various glycoconjugates[2]. Most frequently it is N-acetylated and found in β-glycosidic linkage. Glycoside bond formation with donors derived from N-acetylglucosamine results generally via neighboring group participation first in oxazoline formation[3]. However, even under strong acid catalysis this intermediate does not exert strong glycosyl donor properties because the methyl substituted N-protonated oxazolinium system is rather stable. Therefore, various glucosamine donors, possessing modified or latent amino functionalities, have been investigated for this endeavour, amongst which the pthalimido group[4] and the azido group[2,5] gained wide use. The azido group serves as an excellent latent functionality for the amino group and, for instance in combination with trichloroacetimidate activation, reactive donors not only for β- but also for the less frequently occurring α-glycosidic linkages are available[5,6]. However, the preparation of the required azidoglucose is still not very economical[5]. The phthalimido group can be readily attached to the amino group of glucosamine and again in combination with trichloroacetimidate formation good glycosyl donors for β-glycoside bond formation via highly reactive N-acylated oxazolinium intermediates are available[5]. However, the phthalimido cleavage requires basic conditions which often lead to partial product decomposition[7]. Basic cleavage conditions have been also employed for the recently introduced N-sulfonyl[8] and N-haloacetyl groups[9]. For the N-trichloroacetyl group also a chlorine/hydrogen exchange based on radical chemistry has been proposed[10]; however, hydrogenations in the presence of this group may lead to undesired side reactions[11]. We initiated a program to overcome these problems and present our first results in this paper[12].

Obviously, electronwithdrawing substituents at the phthalimido group should alleviate its cleavage, hopefully without inhibiting its neighboring group participation for highly β-selective glycosylations. Because of the ready availability and the low cost we concentrated on the tetrachlorophthaloyl (TCP) group in combination with trichloroacetimidate activation[5] to ensure high glycosyl donor properties (Scheme 1). For the cleavage first a reductive opening of the TCP moiety and then a weakly acid catalyzed intramolecular phthalide

formation was envisaged[13], thus avoiding basic conditions and formation of free amine. While this work was in progress, the TCP group has been also employed by Fraser-Reid et al.[14]. The difference in the leaving group employed and in the cleavage procedure is reason to report on our results in oligosaccharide synthesis.

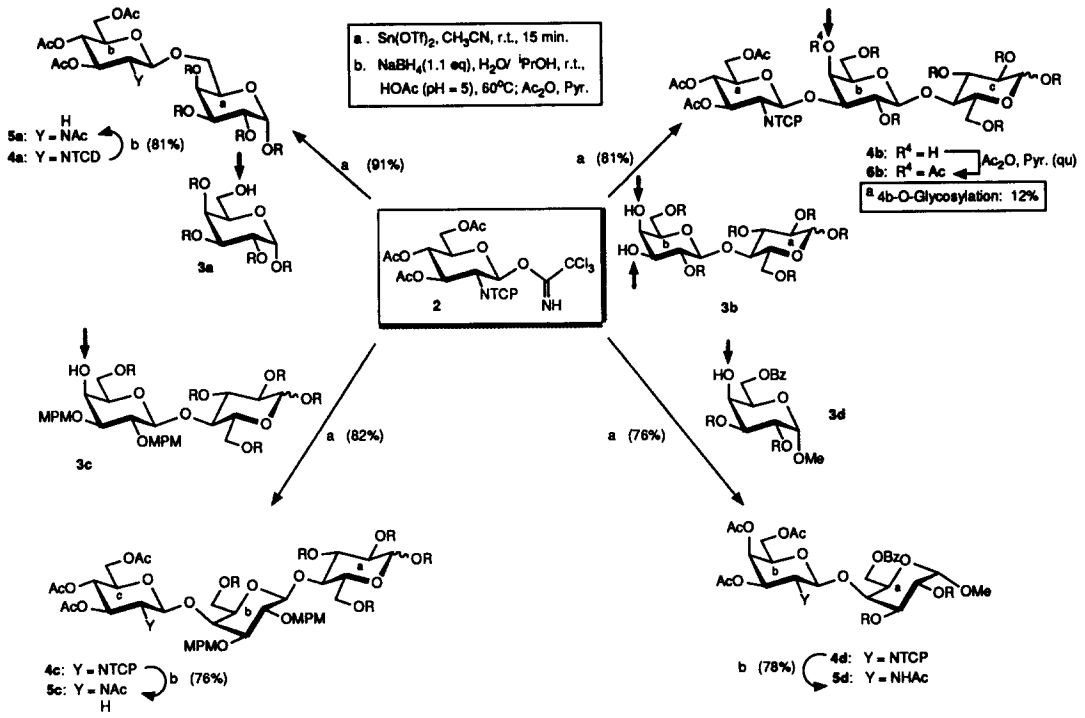
Scheme 1



The introduction of the TCP group into glucosamine could be readily carried out by adding one equivalent of NaOMe in MeOH to the hydrochloride and then tetrachlorophthalic anhydride (TCPO) (Scheme 1). Treatment of the generated N-acyl intermediate with acetic ahydride in pyridine furnished N-TCP-protected per-O-acetyl derivative **1** in practically quantitative yield. Regioselective removal of the 1-O-acetyl group with hydrazinium acetate[15] in DMF and then adding CCl_3-CN in the presence of DBU afforded the desired donor **2**[16] in very high overall yield. As already found for N-phthaloyl-protected glucosamine and lactosamine[2a], only the β-isomer of **2** was obtained. Due to neighboring group participation in the glycosylation of acceptors **3** via intermediate **A**, only β-product formation was expected. Investigation of the glycosylation of **2** in various solvents and in the presence of various catalysts exhibited that acetonitrile as solvent and tin(II) trifluoromethanesulfonate [$Sn(OTf)_2$] as catalyst furnished high yields of β-product **4**. Thus, neighboring group participation of the carboxyl group and presumably also the steric demand of the chlorine atom next to the anomeric center support the high diastereocontrol (see **A** in Scheme 1). The electronwithdrawing character of the four chlorine atoms in the TCP moiety leads to increased glycosyl donor properties compared with the pthaloyl moiety as clearly shown by the examples compiled in Scheme 2. Reaction of **2** with the highly reactive 6-hydroxy group of galactose derivative **3a**[17] afforded **4a**[16] in almost quantitative yield. Also the 3b,4b-O-unprotected lactose derivative **3b**[17] gave high trisaccharide yields; however, due to the high reactivity of **2** not only regioselective 3b-O- (69% of **4b**[16]) but also 4b-O-reaction (12% of β-product) was found[12]. The

regioselectivity in product **4b** can be readily derived from the NMR-data of O-acetylated derivative **6b**[16]. Not surprisingly, the 4b-O-unprotected lactose derivative **3c**[17] gave **4c**[16] in 82% yield and the even less reactive 6-O-benzoyl protected 4-O-unprotected galactose derivative **3d**[17] furnished **4d**[16] in 76% yield.

Scheme 2



Oligosaccharides **4a-d** are important building blocks in glycoconjugate synthesis, therefore, liberation of the amino group is also a decisive step. The phthaloyl group has been generally removed with hydrazine and derivatives[4,7,14b] or with ethylenediamine[7d]. The latter procedure has been also employed in ref. 14a. Because under basic conditions acyl migration, decomposition, etc. have to be considered, we employed $NaBH_4$-reduction of one carbonyl group of the TCP moiety (not a big excess of $NaBH_4$[13], only 1.1 equivalents were required) and then intramolecular phthalide formation via **B** under slightly acidic conditions (pH = 5), thus to complete the deprotection; treatment with acetic anhydride/pyridine furnishes then the desired target molecules, as shown in Scheme 2 for **5a,c**, and **d**, in very high yields.

In conclusion, the TCP moiety in combination with trichloroacetimidate activation, affords highly reactive glucosamine donors which give, even with low-reactive acceptors, high yields of β-glycosides. Their deprotection can be readily accomplished via reduction and intramolecular phthalide formation at pH = 5, thus minimizing other side reactions. The extension of this method to other N-phthaloyl derivatives and to muramic acid and to galatosamine, other important 2-amino-2-deoxy sugars, is under investigation.

References and Notes

1. This work was supported by the Deutscher Akademischer Austauschdienst (DAAD), the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie. – J.C. C.-P. is grateful for a DAAD stipend. – Glycosylimidates, Part 72. For Part 71, see J.M. Lassaletta, R.R. Schmidt, *Tetrahedron Lett.*, in print.

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16. Values of $[\alpha]_D$ were measured at 20°C and ^{1}H-NMR spectra were recorded in $CDCl_3$ at 250 MHz. **2**: $[\alpha]^{20}$ = -40.1° (c = 1, $CHCl_3$), ^{1}H-NMR: δ = 4.55 (dd, $J_{1,2}$ = 10.7 Hz, $J_{2,3}$ = 10.3 Hz, 1 H, 2-H), 8.68 (s, 1 H, NH). **4a**: $[\alpha]^{20}$ = -37.6° (c = 1, $CHCl_3$), ^{1}H-NMR: δ = 3.72 (dd, $J_{2,3}$ = 8.5 Hz, $J_{3,4}$ = 2.1 Hz, 1 H, 3a-H), 3.80 (dd, $J_{3,4}$ = 2.1 Hz, $J_{4,5}$ = 1.8 Hz, 1 H, 4a-H), 3.95 (dd, $J_{1,2}$ = 0.8 Hz, $J_{2,3}$ = 8.5 Hz, 1 H, 2a-H), 4.32 (dd, $J_{1,2}$ = 10.1 Hz, $J_{2,3}$ = 10.3 Hz, 1 H, 2b-H), 4.45 (d, $J_{1,2}$ = 0.8 Hz, 1 H, 1a-H), 5.12 (dd, $J_{3,4}$ = $J_{4,5}$ = 9.8 Hz, 1 H, 4b-H), 5.22 (d, $J_{1,2}$ = 10.1 Hz, 1 H, 1b-H), 5.65 (dd, $J_{2,3}$ = 10.3 Hz, $J_{3,4}$ = 9.8 Hz, 1 H, 3b-H). **5a**: $[\alpha]^{20}$ = -20.5° (c = 1, $CHCl_3$), ^{1}H-NMR: δ 3.94 (m, 1 H, 2b-H), 4.43 (d, $J_{1,2}$ = 0.8 Hz, 1 H, 1a-H), 4.96 (d, $J_{1,2}$ = 9.5 Hz, 1 H, 1b-H), 4.88 (dd, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.8 Hz, 1 H, 4b-H), 5.10 (dd, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.2 Hz, 1 H, 3b-H), 5.52 (d, 1 H, NH). **4b**: $[\alpha]^{20}$ = -38.3° (c = 1, $CHCl_3$), ^{1}H NMR: 4.71 (d, $J_{1,2}$ = 9.2 Hz, 1 H, 1b-H), 4.30 (dd, $J_{1,2}$ = 9.8 Hz, $J_{2,3}$ = 10.3 Hz, 1 H, 2c-H), 5.00 (dd, $J_{3,4}$ = $J_{4,5}$ = 10.1 Hz, 1 H, 4c-H), 5.20 (d, $J_{1,2}$ = 9.8 Hz, 1 H, 1c-H), 5.51 (dd, $J_{2,3}$ = 10.3 Hz, $J_{3,4}$ = 10.1 Hz, 1 H, 3c-H). **6b**: $[\alpha]^{20}$ = -40.1° (c = 1, $CHCl_3$), ^{1}H-NMR: 4.75 (d, $J_{1,2}$ = 9.3 Hz, 1 H, 1b-H), 4.32 (dd, $J_{1,2}$ = 9.8 Hz, $J_{2,3}$ = 10.3 Hz, 1 H, 2c-H), 5.00 (dd, $J_{3,4}$ = $J_{4,5}$ = 10.1 Hz, 1 H, 4c-H), 5.15 (dd, $J_{3,4}$ = 0.8 Hz, $J_{4,5}$ = 1.2 Hz, 1 H, 4b-H), 5.25 (d, $J_{1,2}$ = 9.8 Hz, 1 H, 1c-H), 5.50 (dd, $J_{2,3}$ = 10.3 Hz, $J_{3,4}$ = 10.1 Hz, 1 H, 3c-H). **4c**: $[\alpha]^{20}$ = +48.2° (c = 1, $CHCl_3$), ^{1}H-NMR: 4.29 (dd, $J_{1,2}$ = 10.1 Hz, $J_{2,3}$ = 10.5 Hz, 1 H, 2c-H), 4.65 (d, $J_{1,2}$ = 8.9 Hz, 1 H, 1b-H), 5.01 (dd, $J_{3,4}$ = $J_{4,5}$ = 10.5 Hz, 1 H, 4c-H), 5.48 (d, $J_{1,2}$ = 10.1 Hz, 1 H, 1c-H), 5.63 (dd, $J_{2,3}$ = $J_{3,4}$ = 10.5 Hz, 3c-H). **5c**: $[\alpha]^{20}$ = +50.1° (c = 1, $CHCl_3$), ^{1}H-NMR: 3.89 (m, 1H, 2c-H), 4.59 (dd, $J_{3,4}$ = 9.8 Hz, $J_{4,5}$ = 10.5 Hz, 1 H, 4c-H), 4.64 (d, $J_{1,2}$ = 8.9 Hz, 1 H, 1b-H), 5.01 (d, $J_{1,2}$ = 10.0 Hz, 1 H, 1c-H), 5.10 (dd, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 9.8 Hz, 1 H, 3c-H), 5.70 (d, 1 H, NH). **4d**: $[\alpha]^{20}$ = -28.2° (c = 1, $CHCl_3$), ^{1}H-NMR: 4.10 (dd, $J_{1,2}$ = 0.8 Hz, $J_{2,3}$ = 9.2 Hz, 1 H, 2a-H), 4.20 (dd, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 1.2 Hz, 1 H, 3a-H), 4.25 (dd, $J_{1,2}$ = 10.2 Hz, $J_{2,3}$ = 10.5 Hz, 1 H, 2b-H), 4.30 (dd, $J_{3,4}$ = 1.2 Hz, $J_{4,5}$ = 0.9 Hz, 1 H, 4a-H), 4.60 (d, $J_{1,2}$ = 0.8 Hz, 1 H, 1a-H), 5.09 (dd, $J_{3,4}$ = $J_{4,5}$ = 10.1 Hz, 1 H, 4b-H), 5.50 (d, $J_{1,2}$ = 10.2 Hz, 1 H, 1b-H), 5.65 (dd, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 10.1 Hz, 1 H, 3b-H). **5d**: $[\alpha]^{20}$ = -32.1° (c = 1, $CHCl_3$), ^{1}H-NMR: 3.99 (m, 1 H, 2b-H), 4.10 (dd, $J_{3,4}$ = 1.2 Hz, $J_{4,5}$ = 0.9 Hz, 1 H, 4a-H), 4.55 (d, $J_{1,2}$ = 0.8 Hz, 1 H, 1a-H), 4.68 (dd, $J_{3,4}$ = $J_{4,5}$ = 10.0 Hz, 1 H, 4b-H), 5.00 (d, $J_{1,2}$ = 9.5 Hz, 1 H, 1b-H), 5.15 (dd, $J_{2,3}$ = 9.4 Hz, $J_{3,4}$ = 10.0 Hz, 1 H, 3b-H).
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(*Received in Germany* 23 *May* 1995; *accepted* 7 *June* 1995)