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Removal of some common glycosylation by-products during reaction work-up

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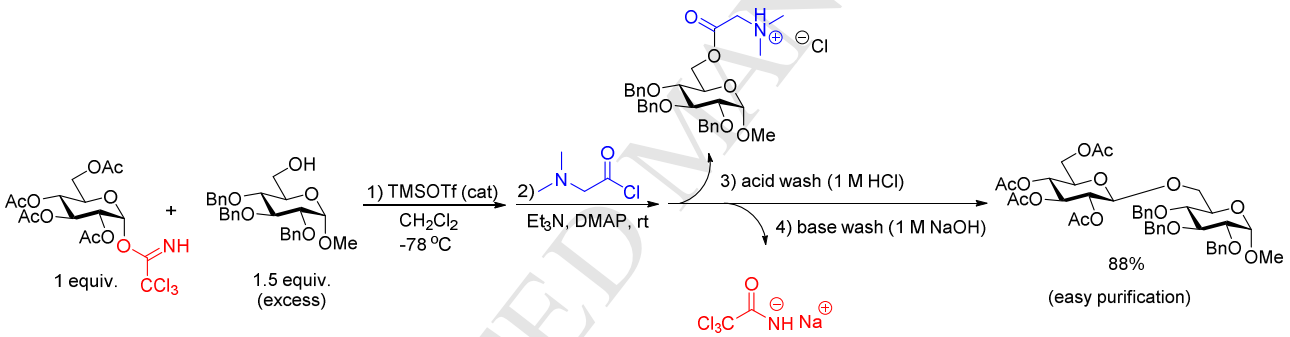


Abstract

With the aim of improving the general glycosylation protocol to facilitate easy product isolation it was shown that amide by-products from glycosylation with trichloroacetimidate and *N*-phenyl trifluoroacetimidate donors could be removed during reaction work-up by washing with a basic aqueous solution. Excess glycosyl acceptor or lactol originating from glycosyl donor hydrolysis could equally be removed from the reaction mixture by derivatization with a basic tag and washing with an acidic solution during reaction work-up.

Keywords

Tagging; trichloroacetamide; non-chromatographic purification

Introduction

Chromatographic purification of reaction mixtures is not always sufficient for obtaining a clean reaction product.[1] This is especially true for glycosylation reactions where many by-products are customarily observed[2] and a time consuming screening of chromatography eluents are not always the solution. In the case of having chemically benign impurities, the experimentalist, however unsatisfactory, could choose to carry out the next step and hope the subsequent purification would be easier and report the yield over two synthetic steps.

There are many protocols in the literature to facilitate easier purification of synthetic oligosaccharides.[3] Solid phase oligosaccharide synthesis inspired by similar techniques in oligopeptide and oligonucleotide synthesis, was championed by the Seeberger group[4] with contribution from other groups[5],[6] is undoubtedly an elegant solution to an otherwise challenging task of easily separating the product from by-products. One pronounced benefit of solid phase techniques in comparison to solution phase techniques is the possibility of using a large excess of reagents and repeated treatment with fresh reagents to push reactions to completion at little other expense than having to perform a simple filtration after the reaction to remove all compounds not attached to the solid support. Other approaches used in carbohydrate chemistry to assist product purification are fluorous liquid[7]/solid phase[8] separations, ionic tags,[9] PEG tag,[10] lipophilic tags.[11] In common for all these methods is the need for special equipment, reagents and knowledge, which is expensive and/or not accessible to many average carbohydrate chemists.

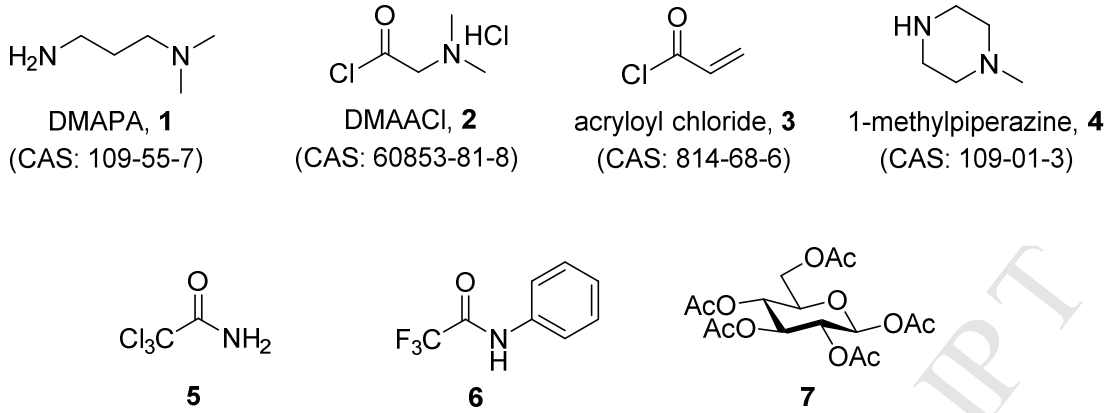


Figure 1.

Recently, we have developed a simple protocol for anomeric deacylations using the cheap bulk chemical 3-(dimethylamino)-1-propylamine (DMAPA, **1**), in which the by-product ($AcNH(CH_2)_3N(CH_3)_2$) could be removed by a simple acid wash procedure of the organic phase in a separatory funnel during reaction work-up. We furthermore found this reagent to be ideal for removing excess of electrophilic reagents like e.g. benzoyl chloride and toluenesulfonyl chloride.[12]

Inspired by the success of DMAPA (**1**) in our laboratory, we decided to investigate whether other common by-products in carbohydrate chemistry could be easily eliminated from the crude reaction mixture in a straightforward fashion during the common aqueous work-up. Given the nature of the typical glycosylation the glycosyl donor leaving group or a derivative thereof will unavoidably be present after the reaction. Other typical by-products originate from donor hydrolysis product (reducing sugar/lactol) and excess/unreacted acceptor. As our previous work with DMAPA (**1**),[12] our goal was to develop a protocol using inexpensive commercially available chemicals and simple procedures that could be used to remove the above mentioned by-products.

Purification and Discussion

The trichloroacetimidate[13] and the *N*-phenyl trifluoroacetimidate[14] donors are among the most popular glycosyl donor types in carbohydrate chemistry, due to their mild and catalytic activation. Glycosylation reactions using imidate donors, however, generates lipophilic amide by-products (**5** and **6**) originating from the leaving group (Figure 1). From time to time, these amide by-products

can be difficult to remove from the product mixture due to their physical properties. Furthermore, especially trichloroacetamide impurities can easily be overlooked since their detection by ^{1}H-NMR is compromised owing to the lack of protons. There are currently no reported procedures for removing these amide by-products by means other than column chromatography, which due to the compound's tailing tendency can be challenging.

Our first objective was to investigate if trichloroacetamide (**5**) and *N*-phenyl-trifluoroacetamide (**6**) could be removed from organic solvents by basic extraction since the amide protons are slightly acidic due to the electron withdrawing trichloromethyl and trifluoromethyl groups.[15] Previously, there has been an interest in having different substituents on the phenyl group of *N*-phenyl-trifluoroimidate leaving groups.[16] For that reason we also decided to investigate the basic extraction of *N*-phenyl-trifluoroacetamide having electron withdrawing *p*-chloro, *p*-cyano and *p*-nitro groups.

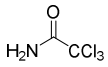
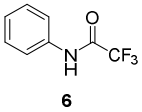
Four different aqueous solutions with varying alkalinity and demineralized water itself were explored for their ability to extract (or wash out) the amides **5** and **6** from CH_2Cl_2 (sat. $NaHCO_3$, 10% Na_2CO_3, 10% Na_3PO_4 and 1 M NaOH). As seen from Table 1, the base strength of the solution is crucial for the effectiveness of the extractions. Only 1 M NaOH (one extraction) and 10% aq. Na_3PO_4 (five extractions) were efficient for extracting trichloroacetamide and *N*-phenyl-trifluoroacetamide. In the case of *N*-(*p*-cyanophenyl)trifluoroacetamide and *N*-(*p*-nitrophenyl)trifluoroacetamide three extractions were sufficient with the milder base 10% aq. Na_2CO_3. (For the complete extraction table; see supporting information).

One could speculate whether base labile functionalities like the acetyl protecting group would be stable under the conditions used to remove amides **5** and **6**. Accordingly, extraction of amides from a CH_2Cl_2 solution also containing glucose pentaacetate (**7**, Figure 1) was successfully conducted without losing the carbohydrate to degradation and/or the aqueous layer (For complete list see supporting information). Furthermore, it was also investigated whether the amides could be recovered from the aqueous phase by acidification and three times back extraction with CH_2Cl_2 and thereby potentially be recycled by converting amides to imidoyl chlorides that can be used to synthesize new glycosyl donor.[17] As listed in

Table *1* especially *N*-phenyl-trifluoroacetamide (**6**) was nearly fully recovered.

Table 1. Extractions of amides (200 mg) from CH_2Cl_2 (20 mL) extracted by aqueous solution (20 mL) over 30 seconds.

Entry	Amide	Aqueous solution	Extracted from organic phase (number of extractions)	Recovered from aq. phase by back extraction with CH_2Cl_2

1	 **5**	H_2O	66% (5)	
2		Saturated $NaHCO_3$	47% (3)	
3		10% Na_2CO_3	42% (3)	
5		10% Na_3PO_4	96% (3)	
5		10% Na_3PO_4	99% (5)	16%
6		1M NaOH	>99% (1)	22%
7	 **6**	H_2O	5% (3)	
8		Saturated $NaHCO_3$	7% (3)	
9		10% Na_2CO_3	34% (3)	
10		10% Na_3PO_4	94% (3)	
11		10% Na_3PO_4	>99% (5)	85%
12		1M NaOH	>99% (1)	89%

Having established a protocol for eliminating trichloroacetamide (**5**) and *N*-phenyl-trifluoroacetamide (**6**) from a CH_2Cl_2 layer by extraction/washing, we moved on to investigate the possibility of removing sugar alcohols (excess glycosyl acceptors) and lactols (hydrolyzed glycosyl donors) by aqueous work-up. First, the commercially available glycine derivative dimethylaminoacetyl chloride hydrochloride (DMAACl (**2**), Figure 1) was explored as an acylating reagent, which in itself has an amine tail available for protonation. The tagging procedure was tested on different substrates with varying lipophilicity and nature of the OH functional group (primary, secondary and lactol). In presence of Et_3N and 4-dimethylaminopyridine (DMAP), DMAACl (**2**) reacted fully with **7**-**11** as judged by TLC analysis within hours at ambient temperature. Other tagging procedures were also tested; first reaction between alcohol or lactol with either $POCl_3$ or acryloyl chloride (**3**) followed by reaction of the installed electrophilic site with either DMAPA (**1**) or *N*-methyl-piperazine (**4**) (Scheme 1).

After complete reaction of the amine as judged by TLC analysis, the reaction mixture was transferred to a separatory funnel. First, dilution with diethyl ether to give good separation of the

two resulting phases and then washing of the organic layer three times with an aqueous 1 M HCl solution generally removed the tagged saccharides.

Scheme 1. Removal of sugar alcohol by derivatization by reagents $POCl_3$, 1, 2, 3 or 4 and washing with hydrochloric acid.

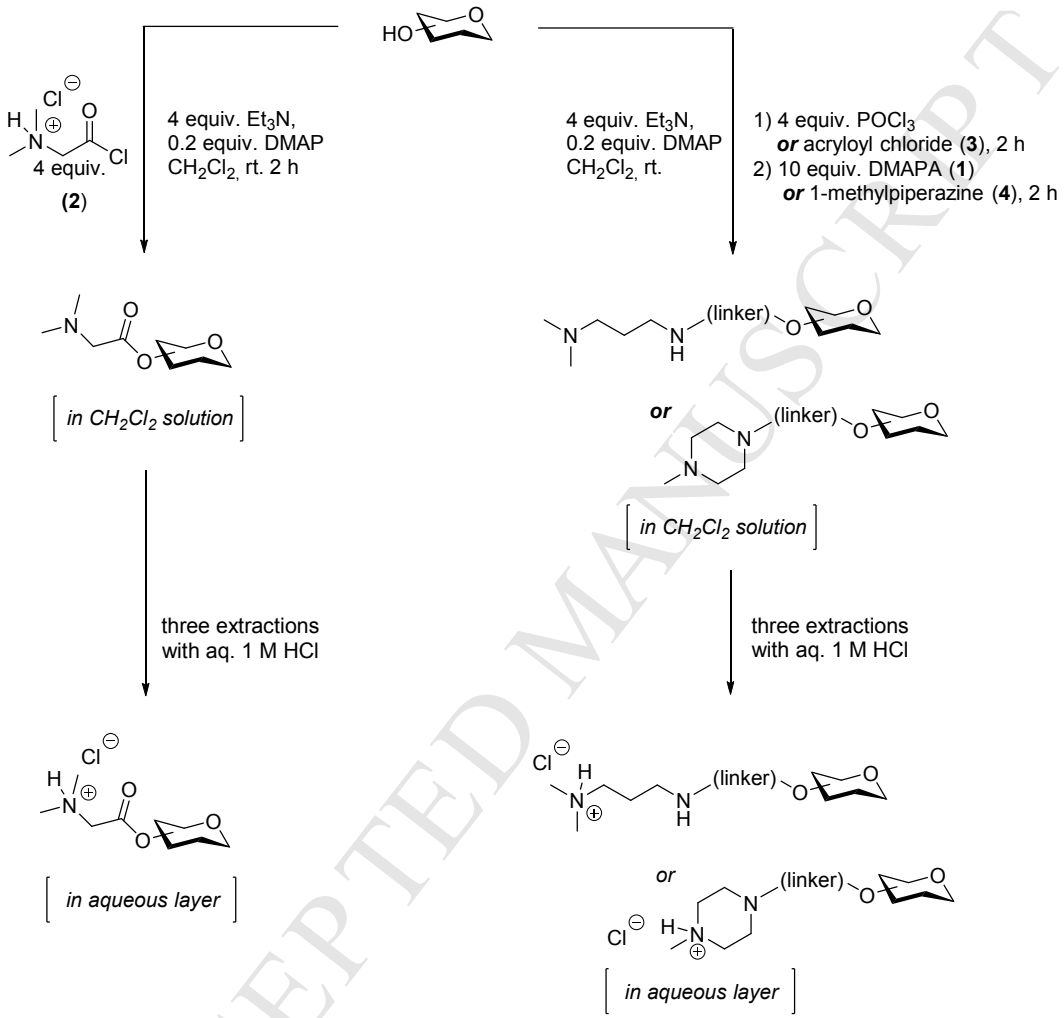
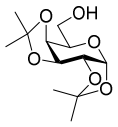
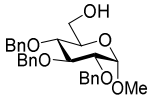
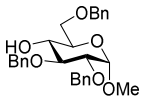
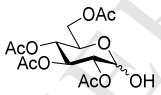
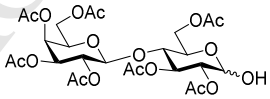
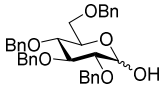
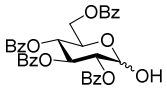


Table 2. Extraction (3 times with 1 M aq. HCl) of sugar alcohols and lactols from an organic layer by amine tagging.

Entry	Sugar alcohol or lactol	Tagging reagents	Extracted from organic phase*
1	 **8**	DMAACl (**2**) Et_3N, DMAP	>99%
2		1) $POCl_3$, Et_3N, DMAP 2) 1-Methylpiperazine (**4**)	>99%
3		1) Acryloyl chloride (**3**), Et_3N, DMAP 2) 1-Methylpiperazine (**4**)	>99%
4	 **9**	DMAACl (**2**) Et_3N, DMAP	>99%
5		1) $POCl_3$, Et_3N, DMAP 2) DMAPA (**1**)	>91%
6		1) Acryloyl chloride (**3**), Et_3N, DMAP 2) DMAPA (**1**)	>99%
7	 **10**	DMAACl (**2**) Et_3N, DMAP	>99%
8		1) $POCl_3$, Et_3N, DMAP 2) DMAPA	>96%
9		1) Acryloyl chloride (**3**) Et_3N, DMAP 2) DMAPA (**1**)	>99%
10	 **11**	DMAACl (**2**) Et_3N, DMAP	>99%
11		1) Acryloyl chloride (**3**) Et_3N, DMAP 2) 1-Methylpiperazine (**4**)	>99%
12	 **12**	DMAACl (**2**) Et_3N, DMAP	>99%
13		1) Acryloyl chloride (**3**) Et_3N, DMAP 2) 1-Methylpiperazine (**4**)	>99%
14	 **13**	1) Acryloyl chloride (**3**) Et_3N, DMAP 2) 1-Methylpiperazine (**4**)	>99%

15	 **14**	1) Acryloyl chloride (**3**) Et_3N, DMAP 2) 1-Methylpiperazine (**4**)	94%

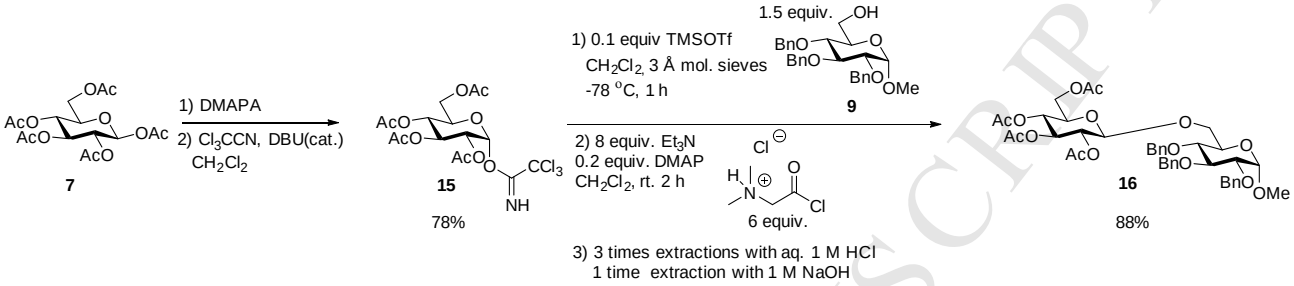
As seen from Table 2 the amine tagging by e.g. acylation and subsequent acidic aqueous work-up offers effective approach for removing both primary, secondary sugar alcohols and lactols from the organic phase, this also brings the opportunity to recycle unreacted acceptor by subsequent back extraction and deacylation. When having primary alcohols or lactols, the best results were achieved by using the secondary amine 1-methylpiperazine (**4**) since the primary amine DMAPA (**1**) in some cases cleaved the linker on the alcohol or lactol. Glycine derivative DMAACl (**2**) possessing only one amine group was effective in removing most sugar alcohols and acetylated lactols, but going to lactols with four benzyl (**13**) or benzoyl groups (**14**) (compared to acceptors with 3 benzyl groups, **9** and **10**), then DMAACl (**2**) was not effective enough to transfer all material to the aqueous phase.

The electrophilic reagent $POCl_3$ worked well with sugar alcohols of all kinds, but $POCl_3$ was not a good choice as a linker in the case of some lactols. We ascribe this to glycosyl chloride formation, which was observed in some cases by TLC analysis. Instead acryloyl chloride (**3**) in combination with 1-methylpiperazine (**4**) was capable of transferring lactols with four benzyl or benzoyl groups (**13** and **14**, respectively) into the aqueous phase (See Table 2, entry 14 and 15).

Next, it was decided to explore the tagging/washing efficiency of excess/by-product sugar alcohols and lactols in a sequence of reactions involving a glycosylation reaction. First, glucose pentaacetate (**7**) was easily converted to the imidate donor (**15**) over two steps using our previously published one-pot procedure.[12] The glucosyl imidate (**15**) was then activated under standard conditions with a catalytic amount of TMSOTf at -78 °C in CH_2Cl_2 in presence of the acceptor **9** (Scheme 2). TLC analysis of the reaction mixture after 1 hour showed no formation of a major new spot, which would indicate either that no glycosylation had taken place, or that acceptor and disaccharide were co-polar in the used eluent system. The tagging reagent DMAACl (**2**) was then added and the reaction was stirred for another 2 hours at ambient temperature before then reaction mixture eventually underwent aqueous work-up. ^1H and ^{13}C-NMR spectra of the crude reaction outcome can be seen in Figure 2 both before and after the acidic washing step. The reaction resulted in isolation of the disaccharide **16**[18] in good purity and in 88% yield after the acidic washing step of the organic layer. In this particular case, the presented technique is especially powerful since excess acceptor

and disaccharide product would be difficult to separate by column chromatography due to their similar level of polarity (see result of TLC analysis in Supporting Information).

Scheme 2. Reaction sequence of glucosyl imidate formation, glycosylation, tagging and aqueous work-up.



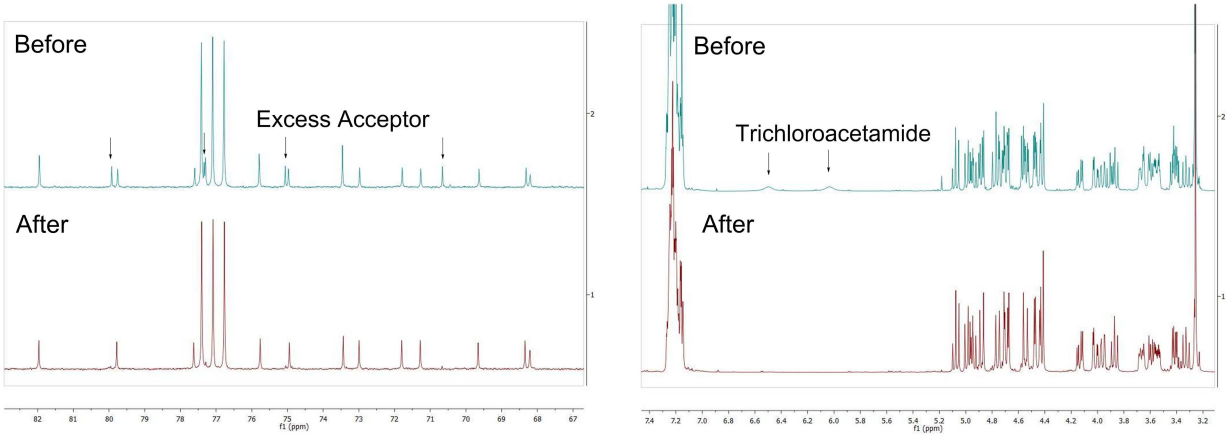


Figure 2. ^{13}C-NMR (left) and ^{1}H-NMR (right) of the crude reaction mixture shown in Scheme 1 before tagging and aqueous work-up and after tagging and aqueous work-up. No chromatography was used at any point.

Conclusion

In conclusion, we have described a new protocol for removing amide by-products from glycosylation reactions with trichloroacetimidate- and *N*-phenyltrifluoroacetimidate donors. We have furthermore shown that cheap and commercial amines can be used for tagging either directly or via an electrophilic linker to lactols and sugar alcohols. Despite having large lipophilic groups, the amine tagged sugar molecules can be removed from the organic layer during reaction work-up by washing with a hydrochloric acid solution. Contrary to the solid phase approach the present protocol is easily scalable and could in principle be used in general organic chemistry.

Experimental Section

General Remarks

All reagents were used as purchased without further purification. Dry solvents were taken from a solvent purification system. Glassware used for water-free reactions were dried for 12 h at 120 °C before use. Columns were packed with silica gel 60 (230–400 mesh) as the stationary phase. TLC plates were visualized by 10% H_2SO_4 in EtOH and heating until spots appeared. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a 400/100 MHz spectrometer, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal. High-resolution mass spectral (HRMS) data were obtained on an electrospray (ES) mass spectrometer analyzing time-of-flight.

Extraction studies

Extraction of amides

The amide (200 mg) was dissolved in CH_2Cl_2 (20 mL) in a separatory funnel. The organic phase was washed thrice (3x30 seconds) or once (1x30 seconds), with base (20 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue in the flask was weighed to evaluate the effect of the extraction.

Recovery of amide

The amide (200 mg) was dissolved in CH_2Cl_2 (20 mL) in a separatory funnel. The organic phase was washed five times (5x30 seconds) or once (1x30 seconds), with base (20 mL). The basic aqueous fractions were immediately added to a flask containing enough 1M HCl to neutralize the base. The combined aqueous fraction was extracted thrice with CH_2Cl_2 (20 mL, 3x30 seconds). The

combined organic fractions were dried over $MgSO_4$, filtered and evaporated. The residue in the flask was weighed to evaluate the effect of the extraction.

Extraction of amides from a solution containing β-D-glucose pentaacetate.

The amide (0.51 mmol) and β-D-glucose pentaacetate (0.51 mmol) were dissolved in CH_2Cl_2 (20 mL) in a separatory funnel. The organic phase was washed 5 times (5x30 seconds) or once (1x30 seconds), with base (20 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue in the flask was weighed to evaluate the effect of the extraction.

Tagging and extractions with dimethylaminoacetyl chloride (DMAACl)

The sugar alcohol (0.1 mmol) and DMAP (0.02mmol) were dissolved in CH_2Cl_2 (2 mL), then triethylamine (0.4 mmol) and DMAACl (0.4 mmol) were added. The reaction mixture was stirred for 2 hours and then transferred to a separatory funnel using Et_2O (20 mL). The organic layer was extracted thrice with 1 M HCl (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue in the flask was weighed to evaluate the effect of the tagging and extraction.

Tagging and extractions with $POCl_3$ and DMAPA/1-methylpiperazine

The sugar alcohol (0.1 mmol) and DMAP (0.02mmol) were dissolved in CH_2Cl_2 (2 mL), then triethylamine (0.4 mmol) and $POCl_3$ (0.4 mmol) were added. The reaction mixture was stirred for 2 hours and then added the amine (1 mmol). The reaction mixture was stirred for additional 2 hours and the mixture was then transferred to a separatory funnel using Et_2O (20 mL). The organic layer was extracted thrice with 1 M HCl (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue in the flask was weighed to evaluate the effect of the tagging and extraction.

Tagging and extractions with acryloyl chloride and DMAPA/1-methylpiperazine

The sugar alcohol (0.1 mmol) and DMAP (0.02mmol) were dissolved in CH_2Cl_2 (2 mL), then triethylamine (0.4 mmol) and acryloyl chloride (0.4 mmol) were added. The reaction mixture was stirred for 2 hours and then added the amine (1 mmol). The reaction mixture was stirred for additional 2 hours and the mixture was then transferred to a separatory funnel using Et_2O (20 mL). The organic layer was extracted thrice with 1 M HCl (20 mL). The organic layer was dried over

$MgSO_4$, filtered and evaporated. The residue in the flask was weighed to evaluate the effect of the tagging and extraction.

One pot anomeric deacetylation and imidate formation.

A solution of glucose pentaacetate (0.5 mmol) and DMAPA (2.5 mmol) in CH_2Cl_2 (2.5 mL) was stirred at room temperature. After 3 hours CCl_3CN (5 mmol) and DBU (0.01 mmol) were added to the reaction mixture. The reaction was stirred for another 45 minutes. The reaction was diluted with CH_2Cl_2 and washed once with 1 M HCl (aq.) and saturated $NaHCO_3$ (aq.). The organic phase was dried over Na_2SO_4, filtered and evaporated. The crude product was purified by elution trough a short silica plug. (pentane/EtOAc 1:1) giving the product.

Glycosylation, tagging and extraction

A mixture of glycosyl donor (0.10 mmol), glycosyl acceptor (0.15 mmol), and freshly activated molecular sieves (3 Å, 100 mg) in CH_2Cl_2 (2 mL) was stirred under argon for ½ h. The solution was cooled to – 78 °C using a dry ice/acetone bath. TMSOTf (0.1 mL of a 0.1 M solution of TMSOTf in CH_2Cl_2) were added. The reaction was stirred for 1 hour at – 78 °C. Upon completion the reaction mixture was added Et_3N (0.8 mmol), DMAP (0.02 mmol) and DMAACl (0.6 mmol). The flask was removed from the cooling bath and stirred for 2 hours at rt. The reactions mixture was then transferred to a separatory funnel using Et_2O (20 mL). The organic layer was extracted thrice with 1 M HCl (20 mL), once with 1 M NaOH (20 ml) and finally with brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated, giving the glycosylation product.

***N*-phenyl-2,2,2-trifluoroacetimidate (6)**

Aniline (5 mL, 0.055 mol) and Et_3N (7.7 mL, 0.055mol) was dissolved in dry CH_2Cl_2 (20mL). The mixture was cooled to 0 °C and then was TFAA (7.6 mL, 0.055 mol) slowly added. The reaction was allowed to reach rt. and stirred for 2 hours. The CH_2Cl_2 was evaporated and the mixture dissolved in EtOAc and transferred to a separatory funnel. The organic phase was washed thrice with 1M HCl solution, then saturated sodium bicarbonate solution and brine. The organic phase was dried over $MgSO_4$ and evaporated to dryness. The solid was recrystallized from pentane/Et_2O giving white fluffy crystals. 7.02 g, 68%, R_f 0.32 (pentane/EtOAc 10:1) M_p 86.2-89.2 °C, lit. 87.7 °C.[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.85 (s, 1H, N*H*), 7.45 (d, *J* 7.7 Hz, 2H), 7.28 (t, *J* 8.0 Hz, 2H), 7.14 (t, *J* 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 155.3 (q, $J_{C\text{-}F}$ 37.5 Hz, C=O), 135.2,

129.4, 126.5, 120.9, 115.9 (q, $J_{C\text{-}F}$ 288.4 Hz, *C*F_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -75.7. HRMS (ES): calcd. for $C_8H_6F_3NONa^+$ 212.0294; found 212.0288. Spectral values were in accordance with those reported in ref. 19.

_N_-(4-chlorophenyl)-2,2,2-trifluoroacetimidate

4-chloroaniline (5 g, 0.039 mol) and Et_3N (5.5 mL, 0.039 mol) was dissolved in dry CH_2Cl_2 (20 mL). The mixture was cooled to 0°C and then was TFAA (5.5 mL, 0.039 mol) slowly added. The reaction was allowed to reach rt. and stirred for 2 hours. The CH_2Cl_2 was evaporated and the mixture dissolved in EtOAc and transferred to a separatory funnel. The organic phase was washed thrice with 1M HCl solution, then saturated sodium bicarbonate solution and brine. The organic phase was dried with $MgSO_4$ and evaporated to dryness. The solid was recrystallized from pentane/EtOAc giving white fluffy crystals. 7.8 g, 88%, R_f 0.30 (pentane/EtOAc 10:1) M_p 123.5-125 °C, lit. 123-124 °C.[15] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.43 (s, 1H, N*H*), 7.77 (d, *J* 8.6 Hz, 1H), 7.70 (d, *J* 8.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 154.6 (q, $J_{C\text{-}F}$ 37.1 Hz, C=O), 135.4, 129.5, 128.9, 122.6, 115.8 (q, $J_{C\text{-}F}$ 288.6 Hz, *C*F_3).^{19}F NMR (376 MHz, $CDCl_3$) δ_F -75.7. HRMS (ES): calcd. for $C_8H_5ClF_3NONa^+$ 245.9904; found 245.9887. Spectral values were in accordance with those reported in ref. 20.

_N_-(4-cyanophenyl)-2,2,2-trifluoroacetimidate

4-cyanoaniline (5 g, 0.042 mol) and Et_3N (5.9 mL, 0.042 mol) was dissolved in dry CH_2Cl_2 (20 mL). The mixture was cooled to 0°C and then was TFAA (5.9 mL, 0.042 mol) slowly added. The reaction was allowed to reach rt. and stirred for 2 hours. The CH_2Cl_2 was evaporated and the mixture was dissolved in EtOAc and transferred to a separatory funnel. The organic phase was washed thrice with 1M HCl solution, then saturated sodium bicarbonate solution and brine. The organic phase was dried over $MgSO_4$ and evaporated to dryness. The solid was recrystallized from pentane/Et_2O giving white fluffy crystals. 6.4 g, 70%, R_f 0.63 (pentane/EtOAc 10:1) M_p 165-168 °C, lit. 166-167 °C [21]. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.47 (s, 1H, N*H*), 7.78 (d, *J* 8.9 Hz, 2H), 7.70 (d, *J* 8.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 154.9 (q, $J_{C\text{-}F}$ 37.6 Hz, C=O), 140.7, 133.4, 121.1, 118.6(*C*N) 115.5 (q, $J_{C\text{-}F}$ 288.7 Hz, *C*F_3), 107.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ_F -75.6. HRMS (ES): calcd. for $C_9H_5F_3N_2OH^+$ 215.0427; found 215.0426. Spectral values were in accordance with those reported in ref. 22.

_N_-(4-nitrophenyl)-2,2,2-trifluoroacetimidate

4-nitroaniline (5 g, 0.036 mol) and Et_3N (5.1 mL, 0.036mol) was dissolved in dry CH_2Cl_2 (20mL). The mixture was cooled to 0°C and then was TFAA (5.0 mL, 0.036 mol) slowly added. The reaction was allowed to reach rt. and stirred for 2 hours. The CH_2Cl_2 was evaporated and the mixture dissolved in EtOAc and transferred to a separatory funnel. The organic phase was washed trice with 1M HCl solution, then saturated sodium bicarbonate solution and brine. The organic phase was dried over $MgSO_4$ and evaporated to dryness. The solid was recrystallized from pentane/Et_2O giving brown-yellow fluffy crystals. 7.43 g, 88%, R_f 0.38 (pentane/EtOAc 5:1) M_p 148.5-152.5 °C, lit. 151.5-152 °C[22]. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.30 (d, *J* 9.2 Hz, 2H), 8.26 (s, 1H), 7.82 (d, *J* 9.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C155.02 (q, $J_{C\text{-}F}$ 37.8 Hz, C=O), 144.04 , 142.43 , 124.85 , 121.05 , 115.48 (q, $J_{C\text{-}F}$ 288.6 Hz, CF_3). ^{19}F NMR (376 MHz, DMSO-d_6) δ_F -74.0. HRMS (ES): calcd. for $C_8H_5F_3N_2O_3H^+$ 235.0325; found 235.0327. Spectral values were in accordance with those reported in ref. 23.

Methyl 6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (16)

Yield: 70 mg, 88%, R_f: 0.47 (pentane/EtOAc 3:2), $[\alpha]_D^{RT}$ 7.2 (*c* 1, $CHCl_3$), lit. 8.7 (*c* 1, $CHCl_3$),[24] ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.30 – 7.12 (m, 15H), 5.11 – 5.05 (m, 1H), 5.01 – 4.92 (m, 2H), 4.88 (d, *J* 10.9 Hz, 1H), 4.76 (d, *J* 10.8 Hz, 1H), 4.72 – 4.67 (m, 2H), 4.55 (d, *J* 12.1 Hz, 1H), 4.49 – 4.40 (m, 3H), 4.13 (dd, *J* 12.3, 4.7 Hz, 1H), 4.02 (dd, *J* 12.3, 2.4 Hz, 1H), 3.96 (dd, *J* 10.6, 1.5 Hz, 1H), 3.87 (t, *J* 9.3 Hz, 1H), 3.70 – 3.64 (m, 1H), 3.62 – 3.52 (m, 2H), 3.41 (dd, *J* 9.6, 3.5 Hz, 1H), 3.36 – 3.30 (m, 1H), 3.26 (s, 3H), 1.94 (s, 3H), 1.92 (s, 3H), 1.89 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.8, 170.4, 169.4, 169.1, 138.8, 138.2, 138.1, 128.6, 128.6, 128.5, 128.3, 128.0, 128.0, 128.0, 127.8, 127.7, 100.8, 98.1, 82.0, 79.9, 77.7, 75.8, 75.0, 73.5, 73.1, 71.9, 71.4, 69.7, 68.4, 68.3, 62.0, 55.3, 20.8, 20.8, 20.7, 20.7. HRMS (ES): calcd. for $C_{42}H_{50}O_{15}NH_4^+$ 812.3488; found 8123502. Spectral values were in accordance with those reported in ref. 18.

Associated Content

The Supporting Information is available free of charge on the publications website: General procedures and ^{1}H and ^{13}C spectra of compounds.

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The Authors declare no competing financial interest.

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A simpel way to remove trichloroacetamide during work-up after glycosylation with trichloroacetimidate glycosyl donors

Derivatization of lactols and excess acceptor with commercial reagent leads to their easy removal without using chromatographic purification