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One-pot synthesis of D-glucosamine and chitobiosyl building blocks catalyzed by triflic acid on molecular sieves†

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Combining triflic acid-catalyzed acetalation, benzylation, reductive ring opening of benzylidene acetal and glycosylation in one-pot transformations leads to a wide range of D-glucosamine building blocks for assembling oligomers.

The construction of complex carbohydrate oligomers is a challenging task as it often requires high degrees of functionalization.[1] Synthesis of both glycosyl donors and acceptors may be readily achieved by means of one-pot processes, decreasing the number of synthetic and purification steps.[2] One-pot Lewis acid catalyzed reactions were developed by our group[3] ($Cu(OTf)_2$, $FeCl_3{\cdot}6H_2O$) and by Hung and coworkers[4] (TMSOTf). These protocols have been successfully applied to persilylated monosaccharides (glucose, mannose, galactose),[3,5] disaccharides (trehalose, maltose),[3b] and unprotected glucosides.[6]

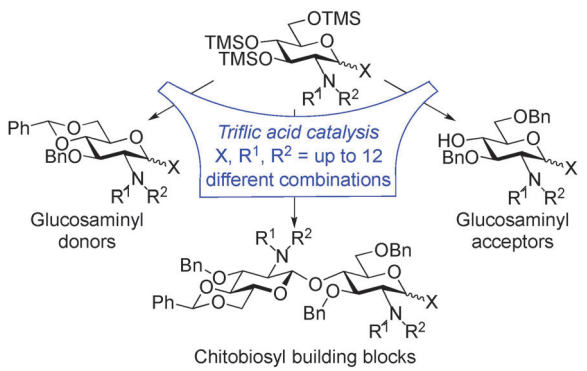
Glucosamine containing oligosaccharides are in high demand because of their wide biological properties.[7] The above procedures, promoted by TMSOTf, are however presently limited.[8] Our preliminary attempts using $Cu(OTf)_2$ or $FeCl_3{\cdot}6H_2O$ as a catalyst on various *N*-protected substrates were either heterogeneous, depending on the *N*-protecting group [$Cu(OTf)_2$],[3c] or inefficient ($FeCl_3{\cdot}6H_2O$).[3b] The major problem associated with these substrates is that the catalysts are sequestrated by some of the *N*-containing functionalities on carbohydrates, making the catalysis unproductive. In our effort to explore complementary catalysts, we report here a solution using trifluoromethanesulfonic acid as a catalyst, associated with molecular sieves (Scheme 1).

Electrophilic activation of organic substrates by protic acids, including triflic acid (TfOH), has been extensively studied.[9] In carbohydrate chemistry, TfOH was notably used in glycosylations[10] or with alkylsilanes to promote 4,6-*O*-benzylidene reductive ring opening to the C-4 alcohol.[10b,11]

Our study started with thiophenylglycosides, attractive building blocks as both glycosyl donors or acceptors,[12] with the participating amino protecting halogen acetamides **1** and **2** and carbamates **3**[13] and **4** (Fig. 1).

It was completed by the *N*-protected β-thioarylglycosides **5–9** prepared from odorless 2-methyl-5-*tert*-butylthiophenol,[14,15] as well as by α-methyl glycoside **10**[16] and β-*O*-silyl compounds **11** and **12**. The *O*-silylated substrates **1a–12a** were obtained in high yield (89–97%) from the triols **1–12** by treatment with hexamethyldisilazane (HMDS, 2 equiv.) and TMSOTf (10 mol%) in CH_2Cl_2 at rt.[8b]

The acetalation–etherification procedure, initially examined on *O*-silylated trichloroacetamide **6a** with benzaldehyde (3 equiv.) and triethylsilane (1.1 equiv.) in the presence of 1 mol% of $Cu(OTf)_2$ under the previously optimized solvent conditions (CH_2Cl_2 : CH_3CN, ratio of 4 : 1),[3a] afforded the expected 3-*O*-benzyl-4,6-*O*-benzylidene **6b** (66%) together with the 4,6-*O*-benzylidene **6c** (33%, entry 1, Table 1). This result is representative of the limitation observed with these *N*-protected derivatives of glucosamine. The same loading of TfOH (1 mol%) in CH_2Cl_2 provided similar results (entry 2). Increasing the amount of TfOH to 5 mol% (entry 3) enhanced significantly the



Scheme 1 Selective one-pot transformations of glucosamine derivatives catalyzed by triflic acid.

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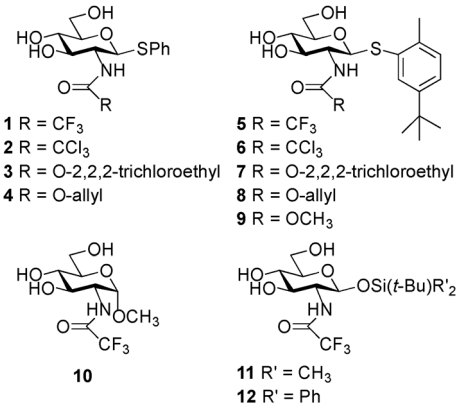
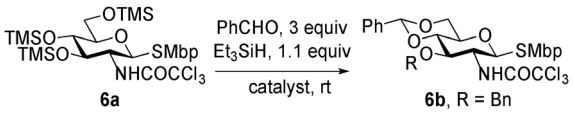


Fig. 1 Starting sugars for the one-pot regioselective protection of the *N*-protected glycosides.

Table 1 Copper triflate *versus* triflic acid-catalyzed transformation of *O*-silylated trichloroacetamide **6a**



Entry	Catalyst	Solvent	Time	**6b**[a] (%)	**6c**[a] (%)
1	$Cu(OTf)_2$[b], 1 mol%	CH_2Cl_2 : CH_3CN, 4 : 1	16 h	66	33
2	TfOH, 1 mol%	CH_2Cl_2	16 h	62	30
3	TfOH, 5 mol%	CH_2Cl_2	15 min	76	23
4[c]	TfOH, 5 mol%	CH_2Cl_2	10 min	98	—

[a] Yields were determined by NMR spectroscopy with 4-nitrobenzaldehyde as standard. [b] Catalyst was added in solution in acetonitrile. [c] With 3 Å molecular sieves. Mbp = 2-methyl-5-*tert*-butylphenyl.

conversion rate into **6b** (15 min *versus* 16 h) but with a similar **6b**/**6c** ratio. Adding powdered 3 Å molecular sieves (3 Å MS, 1 g per g of substrate) induced a remarkable improvement with the quick formation (10 min) of only **6b** (98%, entry 4).

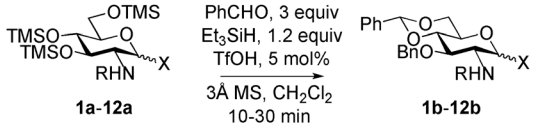
This drastic change in the reaction course could be understood as the *in situ* formation of an active solid-like catalyst.[17] This was confirmed by the ^{1}H- and ^{19}F-NMR spectra of a TfOH solution in CD_2Cl_2 at the catalyst concentration (10 mM). The ^{1}H-signal at 10.58 ppm and the ^{19}F-signal at −79.9 ppm completely disappeared after adding 3 Å MS to the NMR tube (see ESI†).[18] This qualitatively demonstrated that TfOH has been adsorbed at the surface of the solid to provide an apparently better performing solid acid catalyst.

The transformation of the *O*-silylated substrates **1a–12a** under these optimized conditions proceeded fast and cleanly to the target products (Table 2, entries 1–12).[19] The silyl anomeric substituents in **11b** (92%) and **12b** (72%) were notably stable (entries 4 and 5), showing the mildness of the reaction conditions.‡

Finally, persilylated α-methyl glucose[3a] subjected to this procedure (20 min at 0 °C) provided the 3-*O*-benzyl-4,6-*O*-benzylidene product[3a] in good yield (76%). This result underlines the ability of the triflic acid–molecular sieves system to catalyze the one-pot transformation, which could be applied to other carbohydrate series or polyol compounds.

We next examined a subsequent one-pot reductive ring opening of the 4,6-*O*-benzylidene acetal. The triflic acid–triethylsilane system

Table 2 Triflic acid-catalyzed one-pot regioselective protection of *O*-silylated **1a–12a**



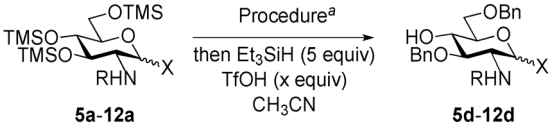
Entry	Substrate, R, X	*T*	Product, yield[a] (%)
1	**1a**, TFA, β-SPh	rt	**1b**, 92
2	**5a**, TFA, β-SMbp	0 °C	**5b**, 85
3	**10a**, TFA, α-OMe	0 °C	**10b**, 80
4	**11a**, TFA, β-OTBDMS	0 °C	**11b**, 92[b]
5	**12a**, TFA, β-OTBDPS	rt	**12b**, 72
6	**2a**, TCA, β-SPh	0 °C	**2b**, 78
7	**6a**, TCA, β-SMbp	rt	**6b**, 83
8	**3a**, Troc, β-SPh	rt	**3b**, 85
9	**7a**, Troc, β-SMbp	rt	**7b**, 90
10	**4a**, Alloc, β-SPh	rt	**4b**, 83
11	**8a**, Alloc, β-SMbp	rt	**8b**, 93
12	**9a**, CO_2Me, β-SMbp	rt	**9b**, 79

[a] **11a** and **11b** were isolated after silica gel chromatography; other products were isolated by precipitation in hexanes. [b] The reaction was carried out at a gram scale. Mbp = 2-methyl-5-*tert*-butylphenyl.

is well known for achieving this reaction,[10b,11] with, however, no example reporting catalytic amounts of the acid. The above "heterogeneous" acid catalysis was not favorable to effect this transformation as seen with the silylated substrate **10a**. Treatment with the above procedure (entry 1, Table 3), followed by further addition in the same pot of Et_3SiH (5 equiv.) and TfOH (10 mol%), induced only partial opening of the 4,6-*O*-benzylidene, giving a mixture of **10b** (28%) and C4-alcohol **10d** (24%) (entry 1, Table 3).

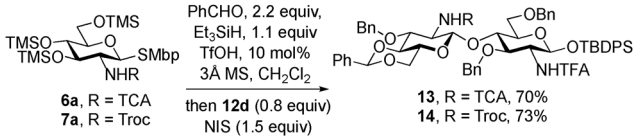
Clear improvement occurred by adding CH_3CN as a co-solvent and using acid washed molecular sieves AW300.[20] Under these conditions, the reductive ring opening to **10d** (67% yield, entry 2)

Table 3 Regioselective one-pot transformations to 4-alcohol glucosamine derivatives



Entry	Substrate, R, X	Added TfOH (mol%)	Time	Product, yield[b] (%)
1	**10a**, TFA, α-OMe	10	4 h 30 min[c]	**10d**, 24[d]
2	**10a**, TFA, α-OMe	5	2 h[e]	**10d**, 67
3	**5a**, TFA, β-SMbp	10	2 h[e]	**5d**, 72
4	**6a**, TCA, β-SMbp	10	2 h 30 min[e]	**6d**, 72
5	**7a**, Troc, β-SMbp	10	4 h 30 min[f]	**7d**, 67
6	**8a**, Alloc, β-SMbp	15	3 h 30 min[g]	**8d**, 60
7	**9a**, CO_2Me, β-SMbp	15	5 h[g]	**9d**, 49
8	**12a**, TFA, β-OTBDPS	10	1 h 45 min[g]	**12d**, 21
9	**12a**, TFA, β-OTBDPS	—	1 h 10 min[h,i]	**12d**, 56
10	**12a**, TFA, β-OTBDPS	—	0.8 h[i,j]	**12d**, 68

[a] Procedure: PhCHO (3 equiv.), Et_3SiH (1.2 equiv.), TfOH (5 mol%), AW300 molecular sieves, CH_2Cl_2, 20 min. After completion of the acetalation–etherification, CH_3CN was added to give a final CH_2Cl_2/CH_3CN solvent ratio of 4/1. [b] Yields obtained after silica gel chromatography. [c] Conditions: PhCHO (3 equiv.), Et_3SiH (1.2 equiv.), TfOH (5 mol%), 3 Å molecular sieves, CH_2Cl_2, 4 h 30 min at 0 °C to rt. [d] 28% of the benzylidene **10b** was also isolated. [e] At 0 °C. [f] At rt. [g] At 0 °C to rt. [h] The reaction was performed with 2.2 equiv. of benzaldehyde. [i] Without CH_3CN at 0 °C. [j] Reductive ring opening was carried out with 2 equiv. of CF_3CO_2H.



Scheme 2 One-pot synthesis of chitobiosyl building blocks **13** and **14** catalyzed by triflic acid.

was complete. As seen with 3 Å MS, the ^{1}H- and ^{19}F-signals of TfOH in solution in CD_2Cl_2 also disappeared in the presence of AW300 MS.[18] These conditions, applied to the silylated 2-methyl-5-*tert*-butylphenyl thioglycosides **5a–8a**, gave good results but not with the methyl carbamate **9a** (entries 3–7).[21] The anomeric *O*-TBDPS product **12d** was isolated in poor yield (21%, entry 8) due to the competing cleavage of the anomeric silyl ether. However, without additional TfOH, this conversion of **12a** to **12d** was increased to a 56% yield (entry 9) or by replacing TfOH by an excess of CF_3CO_2H[22] (68% yield, entry 10).

In a further step, this could be combined, in a modular approach, with an acid catalyzed glycosylation step, to prepare *N*-differentiated chitobiosyl building blocks. Thus, silylated **6a** and **7a** were transformed to donors **6b** and **7b** under the optimized conditions (Table 2) in CH_2Cl_2 at rt, after which acceptor **12d** (Table 3, 0.8 equiv.) and promoter *N*-iodosuccinimide (1.5 equiv.) were added to the reaction mixture (Scheme 2). This gave the disaccharides **13** and **14** (70–73% yield) with, as expected, only the β-linkage due to the *N*-neighboring group participants.

In summary, it has been demonstrated that different transformations, combined in one-pot procedures catalyzed by triflic acid on molecular sieves,[23] furnish various glucosamine building blocks useful in oligosaccharide synthesis. This includes the one-pot synthesis of *N*-differentiated chito-disaccharides and the methodology can be further extended to other oligomers of interest. Triflic acid in catalytic amounts combines with molecular sieves providing *in situ* a valuable "solid" acid catalyst. It is to be expected that, in large scale preparation, this procedure can be amenable to the design of a continuous flow process.

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Notes and references

‡ Representative procedure (synthesis of compound **11b**): to a 0.2 M solution of **11a** (1.0 g, 1.65 mmol) in dry CH_2Cl_2, under an inert atmosphere, benzaldehyde (500 μL, 4.97 mmol, 3 equiv.) and freshly activated 3 Å molecular sieves (1 g per g of substrate) were added. The mixture was stirred at rt for 15 min, then TfOH (7.5 μL, 0.083 mmol, 5 mol%) and Et_3SiH (315 μL, 1.96 mmol, 1.2 equiv.) were added. After stirring for 10 min, the solution was neutralized with triethylamine (1 mL), filtered through a celite pad and concentrated. The residue was purified by flash chromatography (cyclohexane/AcOEt 9 : 1 to 4 : 1) to afford **11b** (0.866 g, 92%) as a white foam.

1 (*a*) H. Paulsen, *Angew. Chem., Int. Ed.*, 1982, **21**, 155; (*b*) T. K. Linhorst, *Essentials of Carbohydrate Chemistry and Biochemistry*, Wiley –VCH, Weinheim, 2nd edn, 2003; (*c*) T. J. Boltje, T. Buskas and G.-J. Boons, *Nat. Chem.*, 2009, **1**, 611; (*d*) X. Zhu and R. R. Schmidt, *Angew. Chem., Int. Ed.*, 2009, **48**, 1900.
2 (*a*) C.-H. Hsu, S.-C. Hung, C.-Y. Wu and C.-H. Wong, *Angew. Chem., Int. Ed.*, 2011, **50**, 11872; (*b*) M. Filice, J. M. Guisan, M. Terreni and J. M. Palomo, *Nat. Protocols*, 2012, **7**, 1783; (*c*) D. Lee and M. S. Taylor, *Synthesis*, 2012, 3421M. Emmadi and S. S. Kulkarni, *Nat. Protocols*, 2013, **8**, 1870.
3 (*a*) A. Français, D. Urban and J.-M. Beau, *Angew. Chem., Int. Ed.*, 2007, **46**, 8662; (*b*) Y. Bourdreux, A. Lemetais, D. Urban and J.-M. Beau, *Chem. Commun.*, 2011, **47**, 2146; (*c*) G. San Jose, PhD thesis, University of Paris Sud, Orsay, France, 2009.
4 C.-C. Wang, J.-C. Lee, S.-Y. Luo, S. S. Kulkarni, Y.-W. Huang, C.-C. Lee, K.-L. Chang and S.-C. Hung, *Nature*, 2007, **446**, 896.
5 (*a*) S. Serna, B. Kardak, N.-C. Reichardt and M. Martin-Lomas, *Tetrahedron: Asymmetry*, 2009, **20**, 851; (*b*) E. Kaji, T. Komori, M. Yokoyama, T. Kato, T. Nishino and T. Shirahata, *Tetrahedron*, 2010, **66**, 4089; (*c*) B. C. Milgram, B. B. Liau and M. D. Shair, *Org. Lett.*, 2011, **13**, 6436.
6 A.-T. Tran, R. A. Jones, J. Pastor, J. Boisson, N. Smith and M. C. Galan, *Adv. Synth. Catal.*, 2011, **353**, 2593.
7 (*a*) A. F. G. Bongat and A. V. Demchenko, *Carbohydr. Res.*, 2007, **342**, 374; (*b*) S. H. El Ashry and M. R. E. Aly, *Pure Appl. Chem.*, 2007, **79**, 2229; (*c*) J.-M. Beau, *Chimia*, 2011, **65**, 45.
8 (*a*) R. Enugala, L. C. R. Carvalho and M. M. B. Marques, *Synlett*, 2010, 2711; (*b*) A. A. Joseph, V. P. Verma, X.-Y. Liu, C.-H. Wu, V. M. Dhurandhare and C.-C. Wang, *Eur. J. Org. Chem.*, 2012, 744.
9 (*a*) *Superacids*, ed. G. A. Olah, G. K. S. Prakash and J. Sommer, J. Wiley and Sons, New York, 1985; (*b*) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744.
10 Trichloroacetimidates: (*a*) R. R. Schmidt and J. Michel, *J. Carbohydr. Chem.*, 1985, **4**, 141. Glycosylations combined with reductive opening: (*b*) Y. Vohra, M. Vasan, A. Venot and G. J. Boons, *Org. Lett.*, 2008, **10**, 3247. Acetates: (*c*) K. Sasaki, S. Matsumura and K. Toshima, *Tetrahedron Lett.*, 2006, **47**, 9039. Thioglycosides: (*d*) G. H. Veeneman, S. H. van Leeuwen and J. H. van Boom, *Tetrahedron Lett.*, 1990, **31**, 1331; (*e*) P. Konradsson, U. E. Udodong and B. Fraser-Reid, *Tetrahedron Lett.*, 1990, **31**, 4313.
11 (*a*) M. Sakagami and H. Hamana, *Tetrahedron Lett.*, 2000, **41**, 5547; (*b*) K.-F. Mo, X. Li, H. Li, L. Y. Low, C. P. Quinn and G.-J. Boons, *J. Am. Chem. Soc.*, 2012, **134**, 15556.
12 J. D. C. Codée, R. E. J. N. Litjens, L. J. van den Bos, H. S. Overkleeft and G. A. van der Marel, *Chem. Soc. Rev.*, 2005, **34**, 769.
13 (*a*) F. Yan, S. Mehta, E. Eichler, W. W. Wakarchuk, M. Gilbert, M. J. Schur and D. M. Whitfield, *J. Org. Chem.*, 2003, **68**, 2426; (*b*) K. Miyajima and K. Achiwa, *Chem. Pharm. Bull.*, 1997, **45**, 312.
14 (*a*) H. Weiss and C. Unverzagt, *Angew. Chem., Int. Ed.*, 2003, **42**, 4261; (*b*) M. Collot, J. Savreux and J.-M. Mallet, *Tetrahedron*, 2008, **64**, 1523; (*c*) G. Despras, R. Robert, B. Sendid, E. Machez, D. Poulain and J.-M. Mallet, *Bioorg. Med. Chem.*, 2012, **20**, 1817.
15 Thioarylglycosides **5–8** were prepared from α–β mixtures of the corresponding peracetylated derivatives (2-methyl-5-*tert*-butylthiophenol (1.2–1.5 equiv.), TMSOTf (1.2 equiv.), CH_2Cl_2, 0 °C to rt; 52–85%; NaOMe, MeOH, rt for **5**, **6**, **8** or NaOMe, MeOH/CH_2Cl_2, 0 °C for **7**, 87–98%). Alternatively, thioarylglycoside **9** was prepared from the acetylated, Troc-protected precursor of **7** (NaOMe, MeOH, rt, 95%).
16 B. Nilsson and S. Svensson, *Carbohydr. Res.*, 1978, **62**, 377.
17 For triflic acid supported on silica, see: (*a*) S. Yan, N. Ding, W. Zhang, P. Wang, Y. Li and M. Li, *Carbohydr. Res.*, 2012, **354**, 6; (*b*) P. N. Liu, F. Xia, Q. W. Wang, Y. J. Ren and J. Q. Chen, *Green Chem.*, 2010, **12**, 1049; (*c*) A. de Angelis, C. Flego, P. Ingallina, L. Montanari, M. G. Clerici, C. Carati and C. Perego, *Catal. Today*, 2001, **65**, 363.
18 ^{1}H and ^{19}F NMR spectra were recorded for 10 mM TfOH in CD_2Cl_2 without and with the molecular sieves; C_6F_6 was used as standard for the calibration of the ^{19}F experiment (see ESI†).
19 Most of the products were conveniently isolated by precipitation in hexanes in good to excellent yields (78 to 93%) with no contamination with benzaldehyde or benzyl alcohol.
20 Use of acid washed sieves AW300 in glycosylations: (*a*) M. Wilstermann and G. Magnusson, *Carbohydr. Res.*, 1995, **272**, 1; (*b*) M. Adinolfi, G. Barone, A. Iadonisi and M. Schiattarella, *Tetrahedron Lett.*, 2002, **43**, 5573; (*c*) M. Adinolfi, G. Barone, A. Iadonisi and M. Schiattarella, *Org. Lett.*, 2003, **5**, 987.
21 These conditions were not suitable for the phenyl thioglycosides because of their poor solubility in the solvent mixture.
22 M. P. DeNinno, J. B. Etienne and K. C. Duplantier, *Tetrahedron Lett.*, 1995, **36**, 669.
23 We prefer this expression to "adsorbed" or "supported" because we have no evidence that TfOH forms a stable solid acid catalyst with molecular sieves as shown previously with amorphous silica[17].