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Metal Catalyzed Diazo Transfer for the Synthesis of Azides From Amines

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Abstract: An improved method for the synthesis of azides is described. Diazo transfer from triflyl azide occurs effectively with Cu^{++}, Ni^{++} or Zn^{++} as a catalyst. The process is amenable to scaleup, can be carried out using commercially available reagents and does not require anhydrous conditions. When metals are scavenged from the reaction, the rate drops by many orders of magnitude. Copyright © 1996 Elsevier Science Ltd

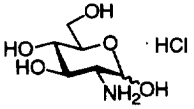
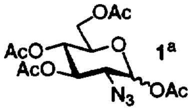
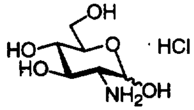
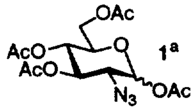
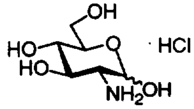
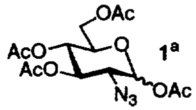
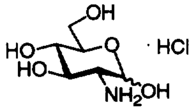
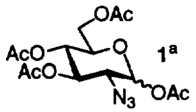
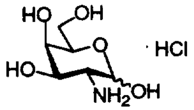
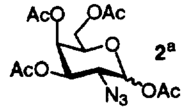
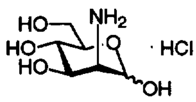
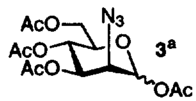
The choice of method for the protection of the amine functionality in amino sugar synthesis is of utmost importance. For various reasons, the azide has emerged as an important and desirable masking agent. The introduction of azido groups via azide ion S_N2 reaction has been a difficult undertaking due to the notorious problems associated with nucleophilic displacement in glycosides. Non nucleophilic methods have been developed but in general involve long reaction sequences and / or low yields.[1]

Triflyl azide was first described by Ruff[2] and subsequently shown to react with primary amines to give azides under mild conditions (WARNING: TfN_3 has been reported to be explosive when not in solvent and should always be used as a solution).[3] The methodology has been used to make azides out of aliphatic amines,[3] amino acids[4] and amino sugars.[5-7] This reaction is of tremendous potential interest due to its apparent ease of operation and high yield. In our synthetic studies on the amino glycoside antibiotics, we envisioned to use this reaction to mask the many amine functionalities to obtain intermediates which exhibited both good solubility properties as well as clean and sharp NMR spectra.

However, in our hands, the reaction between TfN_3 and amino sugars proved to be unpredictable. The reaction would only occur effectively when Tf_2O was distilled before the TfN_3 reagent was made and the yields were not as high as previously reported.[5] It was noted that when EDTA was introduced into the reaction, the rate dropped severely.

It was then observed that the diazo transfer reaction was subject to catalysis by divalent Cu ions. In conditions where the reaction mixture is homogenous (CH_2Cl_2, H_2O and MeOH), the addition of approximately 1 mol % concentrations of $CuSO_4$ is enough to cause the reaction to go to completion within several minutes in the case of mono amine substrates, as opposed to the 20 hours reported in the literature.[5] Since the distillation of Tf_2O can be a somewhat hazardous operation, the reaction was performed with commercially available reagent and addition of exogenous $CuSO_4$ in an attempt to override the deleterious effects exhibited by the impurities. This proved to be successful and Table 1 below summarizes the results on several substrates:

Table 1. Diazo transfer reaction of representative amino sugars

Substrate	Scale	Tf_2O distilled	Conditions	Time	Pdct. after acetylation	Yield
	100 mg	Yes	A	20 h	 1[a]	78%
	100 mg	Yes	A + 10 mol % EDTA + 20 mol % DMAP	20 h	 1[a]	29%
	100 mg	Yes	B	15 min	 1[a]	82%
	2g	No	B	18 h	 1[a]	79%
	200 mg	No	B	18 h	 2[a]	72%
	200 mg	No	B	18 h	 3[a]	72%

[a]All compounds gave spectral data in agreement with the reported values.[5] A: Sugar·HCl, MeOH, NaOMe, DMAP, 0.4 M TfN_3 solution in CH_2Cl_2, as reprted in the literature.[5] B: Sugar·HCl, H_2O, K_2CO_3, 1 mol % $CuSO_4$, MeOH, TfN_3 solution in CH_2Cl_2 made using 2 eq of Tf_2O.

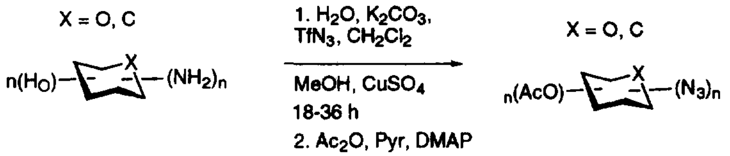
A typical experimental procedure is as follows: A solution of NaN_3 (595 mg, 9.15 mmol) in 1.5 mL of H_2O was cooled in an ice bath and treated with 2.5 mL of CH_2Cl_2. The resulting biphasic mixture was stirred vigorously and treated with Tf_2O (523 mg, 1.85 mmol) over a period of ~ 5 min. The reaction was stirred at ice bath temp. for 2 h, the organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2. The total volume of the reagent solution was ~ 5 mL. The organics were extracted once with saturated Na_2CO_3 solution and used without further purification.

Galactosamine hydrochloride (200 mg, 0.93 mmol) was dissolved in 3 mL of H_2O and treated with potassium carbonate (192 mg, 1.39 mmol) and $CuSO_4$ hydrate (1.4 mg., 8.8 μmol). To the sugar solution was added MeOH (6 mL) and the TfN_3 solution. Then, more MeOH was added to homogeneity. The reaction was allowed to stir for 18 h and the solvent was removed. The residue was acetylated using Ac_2O (3 mL) and pyridine

(5 mL) with catalytic DMAP and worked up by removal of solvent and extraction with water from EtOAc. Column chromatography of the organic phase over 50 mL of silica gel using a gradient of 30 to 35 to 40% EtOAc in hexane afforded the per acetylated 2-azido-2-deoxy-galactose as a colorless oil (250mg, 72% yield).

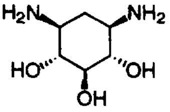
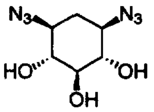
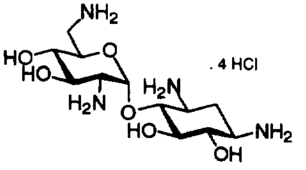
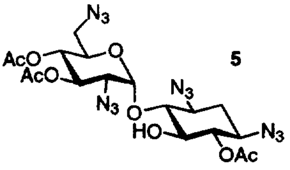
The optimized conditions for the reaction are summarized in Scheme 1:

Scheme 1



This methodology was also extended to poly amino substrates. In these cases, the TfN_3 reagent was not isolated, but was prepared *in situ* from commercially available Tf_2O. This could be accomplished because the product azides could be isolated away from the salts by extraction into organic solvent. Table 2 shows the results:

Table 2. Diazo transfer reaction of substrates with multiple amine groups.

Substrate	Scale	eq Tf_2O	Time	Product	Yield
	500 mg	6	18 h	 4[8]	69%
	3 g	14.6	3 d	 5	49 %[a]

[a]The product was isolated as a mixture of the per acetylated (18%)[9] and the tri-acetylated (31%)[10] adduct.

In these cases, the substrate was dissolved with 72 eq of NaN_3 and 10 eq of K_2CO_3 in enough H_2O so that the final azide conc. was 6.05 M. The solution was then treated with CH_2Cl_2 (half the volume of the water) and cooled to ice bath temp. The Tf_2O was then added *via* syringe in about 15 min and the solution was allowed to stir for 1.5 h. Then MeOH (half the volume of the water) and the $CuSO_4$ (15 mol % per amine for neamine and 5 mol % per amine for 2-deoxystreptamine) were added. After a certain period of time (see Table 2) the reaction was treated with 1 N NaOH to homogeneity and repeatedly extracted with EtOAc. The compounds were then purified by chromatography and crystallization or acetylation and chromatography.

The mechanism of the reaction was probed with several experiments. The counterion of Cu does not matter for the reaction since cuprous chloride and acetate exhibited a similar rate acceleration. Of the several metals tested in the homogenous reaction conditions (conditions B in Table 1), Rh^{II}, Pd^{II}, Os^{III}, Ru^{III}, Ca^{II} and Mg^{II} all failed to give a significant rate acceleration. However, the first row d-block metals Ni^{II} and Zn^{II} both showed a very significant rate acceleration (all metals tested as the chlorides except Mg, which was the sulfate). Moreover, the addition of a half mole equivalent of TEMPO or BHT failed to slow down the reaction when performed in the absense or the presence of copper. Taking these data together, it may be inferred that the metal is possibly acting as a Lewis acid catalyst to activate the TfN$_3$ toward reaction via the nucleophilic mechanism.[11]

In summary, this improved method for the transformation of aliphatic amines to azides has been shown to be reproducible and reliable and can be executed effectively in the presence of other reactive groups and reactive solvents using commercially available reagents. This method should allow for easier preparation of azido sugars. Work is in progress to determine the reaction mechanism.

Acknowledgments

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(8) ^{1}H NMR (CD$_3$OD, Bruker AMX-500): δ1.22 (ddd, J_1=25.5 Hz, J_2=12.5 Hz, 1H, H2 eq), δ2.08 (ddd, J_1=13 Hz, J_2=J_3=4.5 Hz, 1H, H2 ax), δ3.19-3.22 (m, 3H, H4, H5 and H6), δ3.27-3.30 (m, 2H, H1 and H3); ^{13}C NMR (CD$_3$OD, Bruker AMX-500): δ 33.4, 62.3, 76.9, 77.7; HRMS for $C_6H_{10}N_6O_3$ (M+Na): calcd, 237.0712; found, 237.0718.

(9) ^{1}H NMR (CDCl$_3$, Bruker AMX-500): δ1.62 (dd, J_1=J_2=J_3=12.5 Hz, 1H, H2 eq), δ2.06 (s, 3H, acetate methyl), δ2.08-2.10 (m, 9H, acetate methyls), δ2.46 (ddd, J_1=13.5 Hz, J_2=J_3=4.5 Hz, 1H, H2 ax), δ3.29-3.41 (m, 3H, H6'a, H6'b and H2'), δ3.48 (ddd, J_1=12.5 Hz, J_2=10 Hz, J_3=5 Hz, 1H, H3), δ3.67 (dd, J_1=J_2=10 Hz, 1H, H4), δ3.64-3.71 (m, 1H, H1), δ4.43-4.48 (m, 1H, H5'), δ3.67 (dd, J_1=J_2=10 Hz, 1H, H6), δ5.04 (dd, J_1=10 Hz, J_2=9.5 Hz, 1H, H4'), δ5.16 (dd, J_1=J_2=10 Hz, 1H, H5), δ5.21 (d, J=4 Hz, 1H, H1'), δ5.44 (dd, J_1=11 Hz, J_2=9 Hz, 1H, H3'); ^{13}C NMR (CDCl$_3$, Bruker AMX-500): δ 20.6, 20.6, 31.7, 50.6, 57.6, 58.3, 60.5, 69.3, 69.5, 69.7, 73.5, 74.1, 78.6, 98.8, 169.3, 169.7, 169.9, 169.9; HRMS for $C_{20}H_{26}N_{12}O_{10}$ (M+Cs): calcd, 727.0949; found, 727.0959.

(10) ^{1}H NMR (CDCl$_3$, Bruker AMX-500): δ1.62 (dd, J_1=J_2=J_3=13.5 Hz, 1H, H2 eq), δ2.06 (s, 3H, acetate methyl), δ2.10 (s, 3H, acetate methyl), δ2.18 (s, 3H, acetate methyl), δ2.40 (ddd, J_1=13.5 Hz, J_2=J_3=4.5 Hz, 1H, H2 ax), δ3.32 (dd, J_1=13.5 Hz, J_2=5 Hz, 1H, H6'a), δ3.35-3.46 (m, 3H, H3, H4, H6'b), δ3.51-3.58 (m, 1H, H1), δ3.64 (m, 1H, H5), δ3.67 (dd, J_1=10.5 Hz, J_2=3.5 Hz, 1H, H2'), δ4.32-4.37 (m, 1H, H5'), δ4.93 (dd, J_1=J_2=10 Hz, 1H, H6), δ5.05 (dd, J_1=J_2=10 Hz, 1H, H4'), δ5.35 (d, J=3.5 Hz, 1H, H1'), δ5.48 (dd, J_1=10.5 Hz, J_2=9.5 Hz, 1H, H3'); ^{13}C NMR (CDCl$_3$, Bruker AMX-500): δ 20.6, 20.7, 20.8, 31.9, 50.8, 57.9, 58.2, 61.7, 69.2, 69.5, 71.2, 74.4, 74.9, 83.7, 98.8, 169.7, 170.2, 170.5; HRMS for $C_{18}H_{24}N_{12}O_9$ (M+Cs): calcd, 685.0844; found, 685.0859.

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