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Regioselective S_N2 reactions for rapid syntheses of azido-inositols by one-pot sequence-specific nucleophilyses

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Arthi Ravi, Syed Zahid Hassan, A. N. Vanikrishna and Kana M. Sureshan*

Triflates of *myo*-inositol undergo facile solvolysis in DMSO and DMF giving S_N2 products substituted with *O*-nucleophiles; DMF showed slower kinetics. Axial *O*-triflate undergoes faster substitution than equatorial *O*-triflate. By exploiting this difference in kinetics, solvent-tuning and by sequence-controlled nucleophilyses, rapid synthesis of three azido-inositols of *myo*-configuration from *myo*-inositol itself have been achieved.

Nature uses inositol scaffold for making a combinatorial library of molecules by phosphorylation, glycosylation and lipidation, for cellular signalling and other vital cellular processes.[1] Azide being a bio-orthogonal functional group,[2] azido-inositols are of great interest for metabolic labelling to understand these complex cellular processes. Some of the azido-inositols are known to inhibit cellular proliferation[3] show glycosidase inhibition,[4a,b] *etc*. Azido-inositols are also precursors for the synthesis of aminocyclitols,[4c] which are essential pharmacophores for many antibiotics[5] and other bioactive natural products.[6] Various azido-cyclitols have been synthesized from various starting materials *via* multistep synthetic transformations.[4,5,7] The most common method for azido-inositol synthesis involves the azidolysis of appropriately protected sulfonates of cheap and abundant *myo*-inositol.[4] However, for the synthesis of mono-azido derivatives of *myo*-configuration, by this strategy, it is necessary to start with an expensive inositol, whose hydroxyl protection-deprotection strategies are not known.[8] As inversion of both C2 and C5 stereocenters of *myo*-inositol provide a product with *myo*-configuration, it is in principle possible to get monoazido-*myo*-inositols from protected 2,5-disulfonyl-*myo*-inositol by successive inversion (S_N2 reaction) with azide and an oxygen nucleophile. We herein report the synthesis of 2-azido and 5-azido inositol of *myo*- configuration by sequentially and temporally controlled regioselective azidolysis/solvolysis of *myo*-inositol 2,5-di-sulfonates.

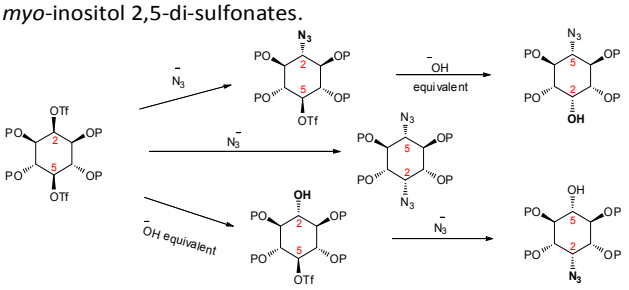

Fig. 1 Stepwise inversion of 2,5-di-*O*-sulfonyl-*myo*-inositol derivative with azide and O-nucleophile giving 2-azido and 5-azido *myo*-inositol derivatives.

In view of exploiting the difference in reactivities of the nucleophilysis of axial and equatorial sulfonates, we have chosen sulfonates of diol **1**, whose *trans*- fused butane-2,3-diacetal (BDA)-protection locks the inositol ring in the penta-equatorial-mono-axial disposition of O-substituents. During the synthesis of *neo*-azido-inositol **3** from the triflate **2**, we have noticed a time-dependent solvolysis of the triflate **2** when dissolved in DMSO-d_6. The nucleophilic action of DMSO (ESI) gives an oxosulfonium intermediate, which upon hydrolysis gives the diol **4** of *neo*-configuration (Fig. 2A). This suggests that the solvolysis proceeds *via* S_N2 mechanism. Though solvolytic effect of DMSO on mesylates and triflates[9] has been reported, the stereochemical course of the solvolysis was unclear. Similarly, formolysis of sulfonates in DMF has been known to occur *via* an iminium intermediate which on hydrolysis gives the ester (Fig. 2B).[10] We could reproduce the solvolysis of triflate **2** by both DMF and DMA (dimethylacetamide) in high yields (ESI).

Interestingly, reaction of triflate **2** in DMSO with excess of NaN_3 yielded a mixture of azide **3** and the diol **4**, (Scheme 1) suggesting that DMSO can compete with highly nucleophilic azide ion. The azidolysis of the triflate **2** in DMF gave the azide **3** and the formate **6** (7:2 ratio) suggesting that though DMF competes with azide, its nucleophilicity is lower than that of DMSO. The azidolysis of triflate **2** in acetonitrile yielded the azide **3** as the exclusive product without any competing

School of Chemistry, Indian Institute of Science Education and Research Thiruvananthapuram, CET Campus, Thiruvananthapuram-695016, India.

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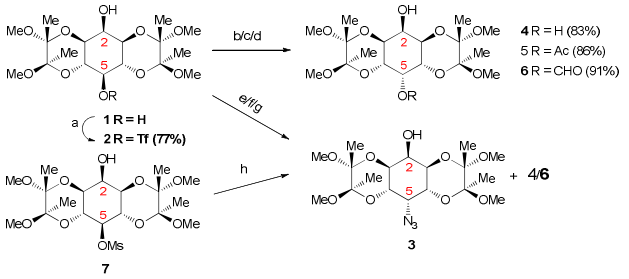
solvolysis. The mesylate **7** was unaffected in DMSO at room temperature and its reaction with NaN_3 in DMSO yielded azide **3** almost quantitatively (ESI). Having established the solvents that can solvolyse sulfonates (to introduce oxygen nucleophile) and their relative reactivities, we set out to explore the regioselective solvolysis of ditriflate **8**.



Scheme 1 Solvolysis and azidolysis of triflate **2** and mesylate **7**. a) Tf_2O, pyridine, DCM, 12 h, **2**; b) DMSO, rt, 2.5h, **4**; c) DMF, rt, 17h, **6**; d) DMA, 50 °C, 3h, **5**; e) DMSO, NaN_3, rt, 2h, **3** (42%) + **4** (51%); f) DMF, NaN_3, rt, 3h, **3** (58%) + **6** (15%); g) Acetonitrile, NaN_3, 60 °C, 12h, **3** (73%); (h) NaN_3, DMSO, rt, 12 h, **3** (90%).

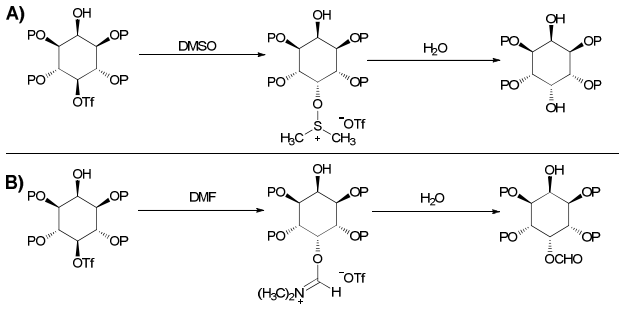
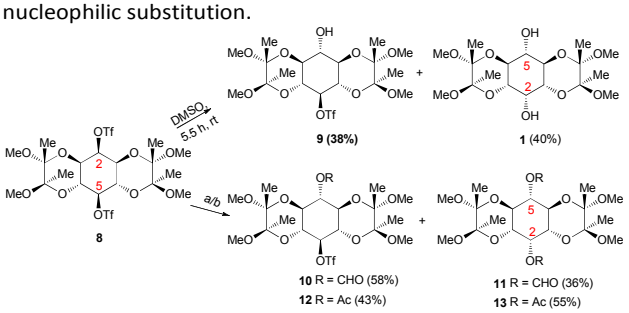


Fig. 2 Solvolysis of triflate: A) in DMSO *via* oxosulfonium ion intermediate; B) in DMF *via* iminium ion intermediate.

The ^{19}F NMR spectrum of ditriflate **8** in DMSO-d_6 showed two distinct signals at -73.76 ppm and -74.47 ppm corresponding to two triflate groups (ESI). As the time progressed, the relative intensities of these signals varied with the concomitant appearance of a new signal at -77.75 ppm corresponding to the triflate anion.[11] By 5.5 h, the signal at -73.76 ppm completely disappeared, suggesting that one of the triflates has been cleaved completely. By 17 h, the other signal also disappeared, suggesting a clear difference in the kinetics of the solvolysis of two triflates. The solvolytic effect of DMF and DMA on ditriflate **8** was also studied by recording time-dependent ^{19}F NMR (ESI). In these cases also, one of the triflates underwent faster solvolysis compared to the other but the rate of solvolysis was much slower compared to DMSO (ESI). It took several days for the solvolyses of both the triflates in DMF (11 days) and DMA (7 days). When a solution of ditriflate **8** in DMSO was quenched at 5.5 h, a mixture of triflate **9** and diol **1** (Scheme 2) were obtained. But quenching after 17h, yielded diol **1** in high yield (85%). Addition of water to a solution of ditriflate **8** in DMF after 22 h gave a mixture of triflate **10** (58%) and the diformate **11** (36%). Though same selectivity was observed in the solvolysis of compound **8** in DMA, the yield of diacetate **13** (55%) was more than that of trilfate **12** (43%), suggesting that DMA is more reactive than DMF. It is very clear that, DMSO, DMA and DMF preferentially solvolyze the triflate group at the 2-position than that at 5-position. This difference in reactivity could be due to the less hindered approach of the incoming nucleophile at C2 than at C5. It is to be noted that triflates **10** and **12** can offer easy access to 2-OH mutated *myo*-inositol analogues *via* simple nucleophilic substitution.



Scheme 2 Solvolyses of ditriflate **8**. a) DMF, rt, 22 h, **10** + **11**; b) DMA, rt, 15 h, **12** + **13**.

Having established the relative reactivities of axial and equatorial sulfonates towards solvolysis, we set out to explore the regioselective nucleophilic substitution in ditriflate **8** to synthesize azides with *myo*-configuration. Ditriflate **8** on treatment with one equivalent of NaN_3 in DMF or DMA at rt yielded the azido-*scyllo*-triflate **14** in very good yields (Table 1, entries1 & 2). The mixture when heated after the formation of **14** at 60 °C for 8h yielded the formate **15** (in DMF) or the acetate **16** (in DMA) as exclusive products in good yields (Table 1, entries 3 & 4). Acidic hydrolysis of **15** and **16** yielded the 5-azido-*myo*-inositol in 91% and 95% yields respectively. It may be noted that triflate **14** can be used to access 5-azido *myo*-inositol analogs, having 2-OH mutation, *via* nucleophilic substitution.

To obtain the 2-azido-*myo*-inositol, it was decided to azidolyse after partial solvolysis of the ditriflate. Thus, a solution of ditriflate **8** in DMSO was stirred at rt for 5.5 h and was then subjected to azidolysis. However, the required product **17** was obtained only in 30% yield along with the diol **1** (49%) (Table 1, entry 5). Lowering the solvolysis time to 3h yielded a mixture of azides **17**-**19** along with diol **1** (Table 1, entry 6). The formation of 5-azide **18** and diazide **19** suggests incomplete solvolysis of the 2-*O*-triflate before the introduction of NaN_3. Direct azidolysis in DMSO yielded diazide **19** and 2-azide **17** suggesting that DMSO competes even with azide for the 2-*O*-triflate (Table 1, entry 7). The isolated *scyllo*-triflate **9** upon azidolysis in DMSO also gave a mixture of 2-azide **17** and diol **1** suggesting that DMSO competes even for the equatorial triflate (Scheme 3).

Azidolysis of **8** in DMF gave a mixture of diazide **19** and mono-azide **14** (Table 1, entry 8). But prolonged reaction gives diazide exclusively (Table 1, entry 9). Delayed addition of azide led to the formation of the azide **20** along with diformate **11** (Table 1, entry 10). Use of DMA as the solvent, gave the azide **21** along with diacetate **13** (Table 1, entry 11). It is to be noted that the byproducts diformate **11** and diacetate **13** formed during regioselective synthesis of 2-azido-*myo*-inositol derivatives **20** and **21**, can be recycled to the ditriflate **8**

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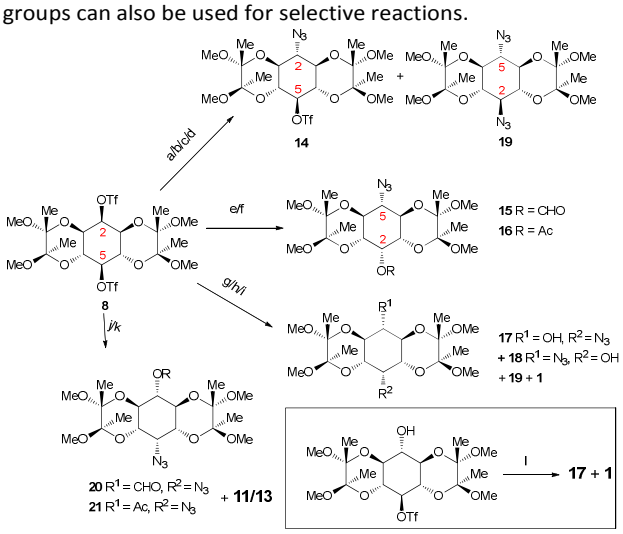
through hydrolysis and sulfonylation. Acidic hydrolysis of diazide **19** and formate **20** provided 2,5-diazido-*myo*-inositol and 2-azido-*myo*-inositol respectively in quantitative yields (ESI). Apart from 5-azido-*neo*-inositol and 2,5-diazido-*myo*-inositol, our methodology gave access to two mono-azido-*myo*-inositols by regioselective nucleophilic substitutions. Usual selective transformations in sugars and polyols exploit the nucleophilicity of hydroxyl groups.[12] Here we have shown that difference in electrophilicities of substituted hydroxy groups can also be used for selective reactions.



Scheme 3 Nucleophilyses of ditriflate **8**. a) DMF, NaN_3, rt, 4 h, **14** (83%); b) DMA, NaN_3, rt, 2 h, **14** (80%); c) DMF, NaN_3, (10 equiv), 4 h, **14** (42%), **19** (48%); d) DMF, NaN_3 (10 equiv), 24 h, **19** (75%); e) DMF, NaN_3 (1 equiv), rt 4 h, then 60 °C, 8 h, **15** (85%); f) DMA, NaN_3 (1 equiv), rt, 3 h, then 60 °C, 6 h, **16** (73%); g) DMSO, rt, 5.5 h then, NaN_3 (10 equiv), **17** (30%), 1 (49 %); h) DMSO, rt, 3 h, then NaN_3 (10 equiv), **17** (26 %), **18** (18 %), **1** (44%), **19** (10%); i) DMSO, NaN_3 (10 equiv), 1 h, **19** (65%), **17** (11%); j) DMF, 22 h, then NaN_3 (5 equiv), 2 h, **20** (58%), **11** (36 %); k) DMA, 15 h, then NaN_3 (5 equiv), 2 h **21** (49 %), **13** (40%); l) NaN_3 (10 equiv), DMSO, **17** (54%), **1** (36%).

Table 1 One-pot sequence-specific nucleophilyses of ditriflate **8**

Entry	Reagent and conditions	Products
1	DMF, NaN_3 (1 equiv), 4 h	**14** (83%)
2	DMA, NaN_3 (1 equiv), 3 h	**14** (80%)
3	DMF, NaN_3 (1 equiv), rt 4 h, then 60 °C, 8 h	**15** (85%)
4	DMA, NaN_3 (1 equiv), rt, 3 h, then 60 °C, 6 h	**16** (73%)
5	DMSO, 5.5 h then, NaN_3 (10 equiv),	**17** (30%), **1** (49%)
6	DMSO 3 h, then NaN_3 (10 equiv)	**17** (26%), **18** (18%), **1** (44%), **19** (10%)
7	DMSO, NaN_3 (10 equiv), 1 h	**19** (65%), **17** (11%)
8	DMF, NaN_3 (10 equiv), 4 h	**19** (48%), **14** (42%)
9	DMF, NaN_3 (10 equiv), 24 h	**19** (75%)
10	DMF, 22 h, then NaN_3 (5 equiv), 2 h	**20** (58%), **11** (36%)
11	DMA, 15 h, then NaN_3 (5 equiv), 2 h	**21** (49%), **13** (40%)

In conclusion, we have observed a remarkable selectivity in nucleophilic substitution of 2,5-di-sulfonates of *myo*-inositol. The C2 sulfonate (axial) underwent faster substitution than the C5 sulfonate (equatorial). The triflate underwent solvolysis in DMSO and DMF at room temperature, installing an oxygen nucleophile, the former showing higher reactivity. Azidolysis of the disulfonate in these solvents by modulating the time of addition of azide nucleophile, we could synthesize 2-azido-*myo*-inositol and 5-azido-*myo*-inositol which are otherwise difficult to synthesise from *myo*-inositol in one pot. We have also synthesized 5-azido-*neo*-inostiol and 2,5-diazido-*myo*-inositol from *myo*-inositol-derived triflates. During this study, we have also synthesized several intermediates that can be converted into OH-mutated *myo*-inositol analogs. This study on the selectivity between the nucleophilysis of axial-leaving group versus equatorially placed leaving group and the exploitation of the difference in kinetics to achieve different regioselectivities would be of general interest.

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