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Sulfonylation-Induced *N*- to *O*-Acetyl Migration in 2-Acetamidoethanol Derivatives

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Abstract



The first example of sulfonylation-induced *N*- to *O*-acetyl migration of 2-acetamidoethanol derivatives is described. This type of reaction could happen with any 2-acetamidoethanol derivatives under typical sulfonylation conditions (TsCl or MsCl, pyridine) and might be a common side reaction of significance. Furthermore, the results reveal that 2-acetamidoethanol derivatives with sterically encumbered hydroxyl group result in the migration products in high yields. The mechanism of the migration reaction is discussed.

Sulfonylation of alcohols is a common transformation in numerous synthetic processes. This derivatization is generally performed by utilizing sulfonyl chlorides in the presence of a base (typically, pyridine, triethylamine, DABCO and the like), and gives the desired products in high yield. However, during the course of our efforts to synthesize 3-*O*-tosyl glucosamine derivative **2a**, we identified a significant byproduct (Scheme 1). The byproduct was found to have the same mass as **2a**, and the resonances of both the acetyl and tosyl groups were seen in the ¹H NMR spectrum. After full characterization, the byproduct was assigned the structure **3a**, which disclosed an unusual *N*- to *O*-acetyl migration. Our follow up on this reaction revealed that this type of acetyl migration could happen with facility with any number of 2-acetamidoethanol derivatives under typical sulfonylation conditions.

For tosylation of **1a**,¹ we initially used a mild condition (TsCl, pyridine, CH₂Cl₂, room temperature). However, the starting material was fully recovered. When heated under reflux in pyridine for a longer duration, two compounds were obtained, as outlined in Scheme 1, with the major component identified as the product of acetyl migration **3a**. The products **2a** and **3a** showed similar ¹H and ¹³C NMR spectra, and had the same mass. Thus, the differentiation of each compound was difficult.

In the ¹H NMR spectra (Figure 1), the H-2 resonance of **3a** (δ 3.53 ppm) appeared at higher field than that of **2a** (δ 4.46 ppm). The H-3 resonance of **3a** appeared at δ 5.24 ppm, and the

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 Supporting Information Available: General experimental procedures, characterization data for all new compounds, including copies of 1D NMR spectra (¹H, ¹³C NMR, and DEPT) and 2D NMR spectra (H-H COSY and C-H HETCOR), and crystallographic information file (CIF) of compound **2f**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

axial orientation for the hydrogen was confirmed by the coupling constants ($J_{2,3} = J_{3,4} = 10$ Hz). Confirmatory evidence for the structure of **3a** was the ester carbonyl stretch at 1734 cm^{-1} in the IR spectrum. The IR resonances of the amide carbonyl groups of **1a** and **2a** were seen at 1651 and 1656 cm^{-1} , respectively.

A similar observation for acetyl migration in compound **1a** was reported by Calvo-Mateo *et al.* (Scheme 2).² They obtained the product **6** by heating of the unstable triflate **4** in a mixture of pyridine, water, and DMF (Scheme 2a). It is interesting that an inversion at the C-3 position was observed in their reaction, in contrast to our result. They proposed the transient formation of the oxazoline intermediate **5**, with the attendant inversion of configuration at C-3, which then underwent hydrolysis to give **6**. The authors indicated that a rearrangement product **9** also formed as a byproduct in small yield after the treatment of **8** with NaN_3 (Scheme 2b). To our knowledge, this is the only example that approaches the reaction that we report here.³

We carried out a series of additional reactions to gain insight into the mechanism of this acetyl migration reaction. Initially, we wondered whether the acetyl group could migrate to the hydroxyl group before the *N*-tosylation event (Scheme 3, route A). In order to examine this possibility, compound **1a** was heated under reflux in pyridine for 48 h. However, in the absence of TsCl, no transformation took place and the starting compound **1a** was recovered as the only compound. It is also conceivable that the migration product **3a** might be generated from **2a** (route D). To confirm this, compound **2a** was heated under reflux in pyridine with and without TsCl for 48 h. Again, under these conditions starting **2a** was fully recovered. These results, thus, ruled out routes A and D.

Two additional possibilities, routes B and C, can be envisioned. That is to say that product **3a** could be formed via an intermediate ortho amide, **12**, which would be generated from tosylation of **10** (route B) or through *N*-tosylation of the acetamido group of **1a** (route C). However, *N*-tosylation of an amide moiety (as in route C) generally requires a strong base such as *n*-BuLi or LiHMDS.⁴ Tosylation of a simple acetamido group in a compound such as **14** under the same condition as Scheme 1 resulted only in the recovery of the starting material (Scheme 4). For this reason, route C might be ruled out. The most probable mechanism would then be through route B.

To explore the scope of this transformation, we investigated tosylations of several additional examples (Table 1). Substrates **1b**, **1d** and **1g** were prepared from the corresponding commercially available amines (see Supporting Information). Tosylation of **1b**, with the flexible cyclohexane skeleton, also afforded the acetyl migration compound **3b** as the major product, and *O*-tosyl product **2b** was present in smaller yield at 9% (entry 1). Unexpectedly, *N*-tosyl cyclohexanol **15b** and *N,O*-diacetyl product **16b** were present in 25% and 19%, respectively. We believe that the activated acetyl group of **18** probably migrated via an intermolecular reaction to afford compounds **15b** and **16b** (Scheme 5). The structures of products **3b**, **15b** and **16b** were confirmed by comparison to the reported data.⁵ In contrast to this result, tosylation of **1g** gave *O*-tosyl compound **2g** as the major product, and the migration product **3g** was not seen, as to be expected (entry 6). This result supports that the migration products **3a** and **3b** are produced by intramolecular acetyl migration. The case of the simple 2-acetamidoethanol (**1c**) is of interest (entry 2), as this too gave the migration product **3c**, in the highest yield among the three products, whereas *O*-tosyl product **2c** was not obtained. We conclude that acetyl migration can happen with any kind of 2-acetamidoethanol derivatives under typical tosylation condition. Compound **1d**, with a hindered hydroxyl group, afforded the migration product **3d** in 52% yield (entry 3, condition A). Moreover, under condition B, **3d** was obtained in 96% yield. It is possible that the tertiary alcohol in this example might have played an entropic role as the intramolecular nucleophile. 1-Deoxy-*N*-acetylglucosamine **1e**, prepared from an oxazoline derivative,⁶ was also allowed to react with TsCl (entry 4). In this

case, the migration product **3e** was produced in 94%. Compared to compound **1a** having the α -benzyloxy group at C-1, the less-hindered **1e** gave the migration product in higher yield. Meanwhile, tosylation of 2-acetamidophenol (**1f**) gave *O*-tosyl product **2f** exclusively in 98% yield (entry 5, conditions A or B). This result might be due to different reactivity of phenol **1f** compared to alcohols. The structure of **2f** was confirmed by X-ray structure analysis (see Supporting Information).

We also tested the scope of this type of acetyl migration in a mesylation reaction. As shown in Scheme 6, mesylation of compound **1d** efficiently afforded migration product **19**. Therefore, the mesylation reaction also can afford the *N*- to *O*-acetyl migration.

In summary, we have demonstrated sulfonylation-induced *N*- to *O*-acetyl migration of 2-acetamidoethanol derivatives. The acetyl migration proceeds even in a simple compound such as 2-acetamidoethanol (**1c**), although the sterically hindered hydroxyl group is found to be an excellent substrate for acetyl migration. Furthermore, it is also noteworthy that the unusual “*N*- to *O*-acetyl migration” proceeds under typical sulfonylation conditions in 2-acetamidoethanol. Since the 2-acetamidoethanol motif is common in both natural products and synthetic samples, this type of acetyl migration might be generally useful. Also significantly, the type of acetyl (acyl) migration could be happening as a side product of consequence in reactions of this type.

Experimental Section

General procedures for the tosylation of 2- acetamidoethanol derivatives

Condition A: *p*-Toluenesulfonyl chloride (1.05 equiv) and pyridine (3.0 equiv) were added to a solution of substrate in CH_2Cl_2 at 0 °C, and the mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography. Condition B: *p*-Toluenesulfonyl chloride (2.0 equiv) was added to a solution of substrate in pyridine, and the mixture was heated under reflux for 30 h. The mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography.

Sample procedure and data for **2a** and **3a**

Condition B was used for compound **1a** (100 mg, 0.25 mmol), and the crude product was purified by silica gel column chromatography (AcOEt/hexane, 1:3) to afford **2a** (46 mg, 33%) and **3a** (74 mg, 53%) as white solids. **2a**: ^1H NMR (500 MHz, CDCl_3) δ 2.02 (s, 3H, CH_3CO), 2.28 (s, 3H, CH_3Ph), 3.68 (dd, $J = 9.6, 9.6$ Hz, 1H, H-4), 3.72 (dd, $J = 10.7, 10.7$ Hz, 1H, H-6a), 3.88 (ddd, $J = 4.8, 9.8, 9.8$ Hz, 1H, H-5), 4.21 (dd, $J = 5.0, 10.4$ Hz, 1H, H-6b), 4.46 (ddd, $J = 3.6, 9.2, 10.4$ Hz, 1H, H-2), 4.53 and 4.73 (AB, $J = 11.9$ Hz, 2H, OCH_2Ph), 4.92 (dd, $J = 10.0, 10.0$ Hz, 1H, H-3), 5.02 (d, $J = 3.8$ Hz, 1H, H-1), 5.37 (s, 1H, CHPh), 6.00 (d, $J = 9.0$ Hz, 1H, NH), 6.97 (d, $J = 8.0$ Hz, 2H, Ts), 7.19–7.44 (m, 10H), 7.67 (d, $J = 8.4$ Hz, 2H, Ts); ^{13}C NMR (126 MHz, CDCl_3) δ 21.9 (CH_3Ph), 23.4 (CH_3CO), 52.5 (C-2), 63.6 (C-5), 68.9 (C-6), 70.6 (OCH_2Ph), 78.4 (C-3), 79.2 (C-4), 98.0 (C-1), 101.8 (CHPh), 126.4, 128.1, 128.3, 128.4, 128.6, 128.9, 129.2, 129.5, 133.9, 136.7, 136.8, 144.6, 170.6 (C=O); IR 3324, 1656, 1547, 1362, 1182, 1123, 1097 cm^{-1} ; HRMS (FAB) calcd for $\text{C}_{29}\text{H}_{32}\text{NO}_8\text{S}$ ($\text{M} + \text{H}^+$), 554.1849, found 554.1848. **3a**: ^1H NMR (500 MHz, CDCl_3) δ 1.72 (s, 3H, CH_3CO), 2.37 (s, 3H, CH_3Ph), 3.53 (ddd, $J = 3.8, 10.2, 10.2$ Hz, 1H, H-2), 3.56 (dd, $J = 9.7, 9.7$ Hz, 1H, H-4), 3.67 (dd, $J = 10.3, 10.3$ Hz, 1H, H-6a), 3.83 (ddd, $J = 4.8, 9.8, 9.8$ Hz, 1H, H-5), 4.15 (dd, $J = 4.8, 10.4$ Hz, 1H, H-6b), 4.37 and 4.62 (AB, $J = 11.6$ Hz, 2H, OCH_2Ph), 4.71 (d, $J = 3.8$ Hz, 1H, H-1), 5.00 (d, $J = 10.2$ Hz, 1H, NH), 5.24 (dd, $J = 10.1, 10.1$ Hz, 1H, H-3), 5.42 (s, 1H, CHPh), 7.21 (d, $J = 8.4$ Hz, 2H, Ts), 7.26–7.39 (m, 10H), 7.62 (d, $J = 8.4$ Hz, 2H, Ts); ^{13}C NMR (126 MHz, CDCl_3) δ 20.8 (CH_3CO), 21.7 (CH_3Ph), 56.8 (C-2), 63.1 (C-5), 68.9 (C-6), 69.4 (C-3), 70.5 (OCH_2Ph),

79.4 (C-4), 98.0 (C-1), 101.7 (CHPh), 126.3, 127.1, 128.4, 128.6, 128.6, 128.9, 129.3, 129.9, 136.4, 137.0, 138.4, 143.7, 170.8 (C=O); IR 3356, 1734, 1498, 1337, 1234, 1163, 1090 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{31}\text{NNaO}_8\text{S}$ ($\text{M} + \text{Na}^+$), 576.1659, found 576.1662.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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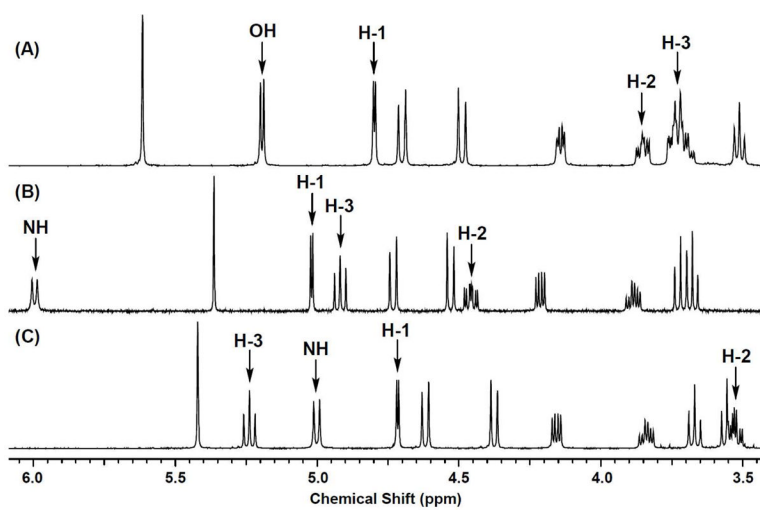
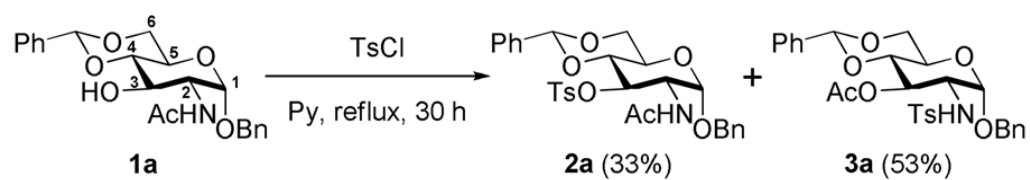
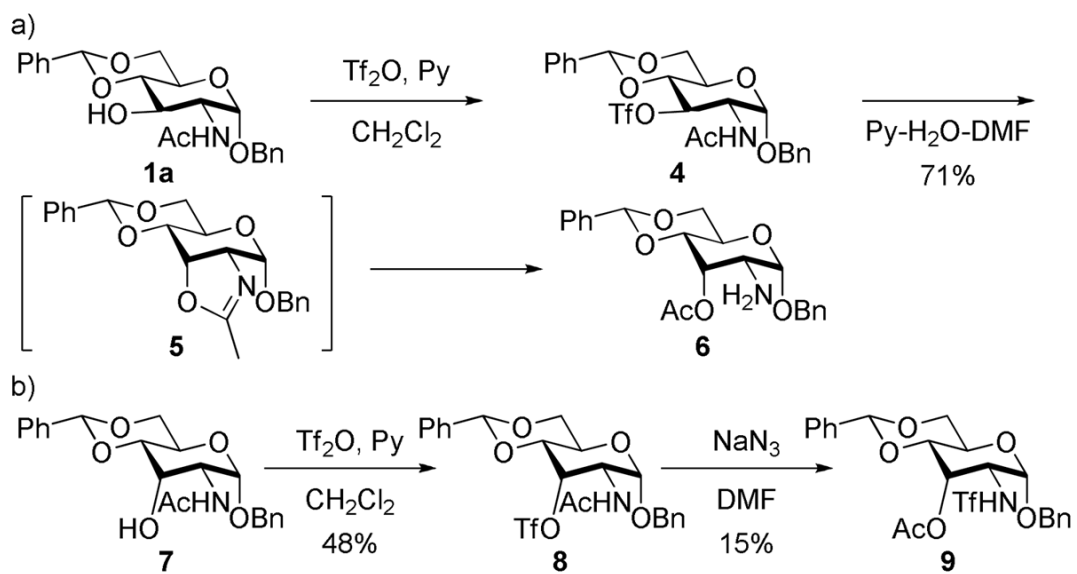
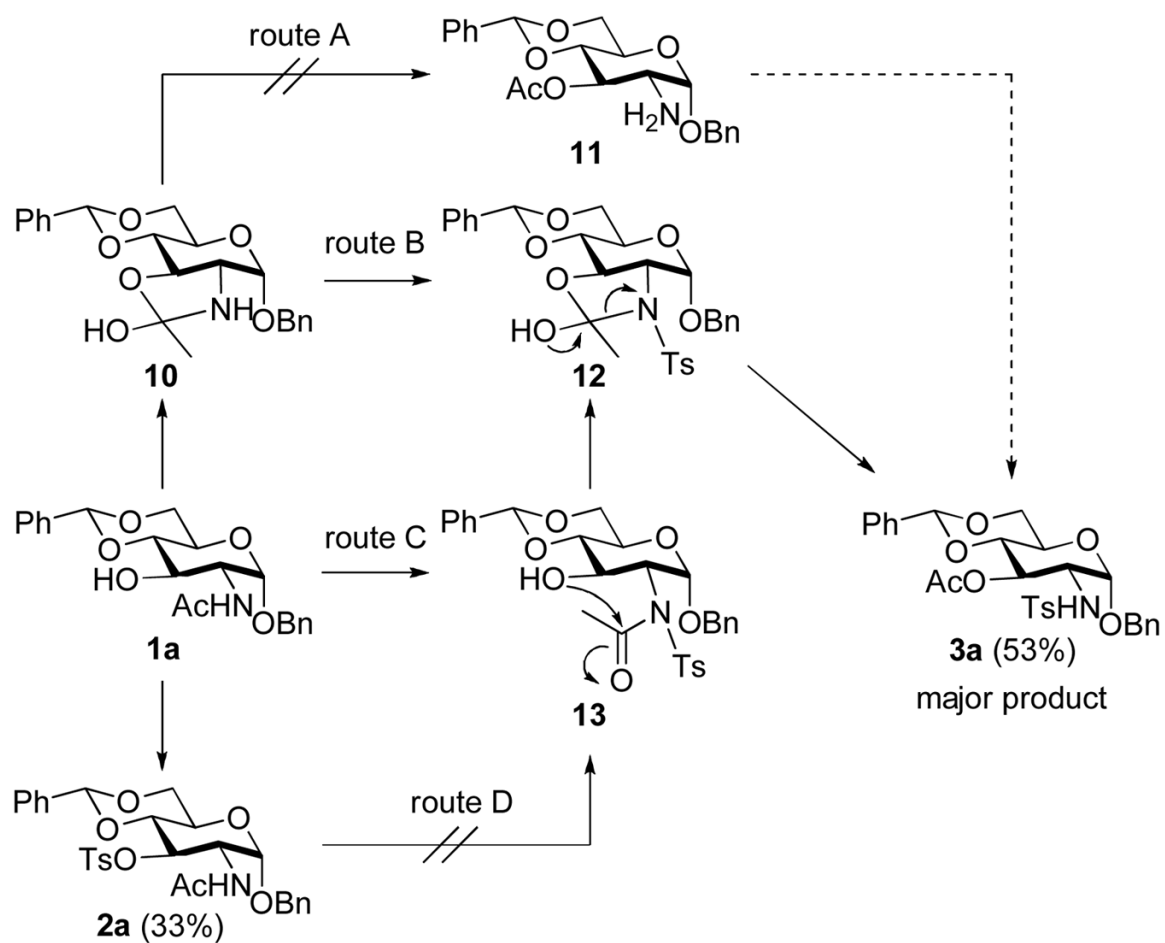


FIGURE 1. ¹H NMR spectra of the compounds (A) 1a in DMSO-*d*₆, (B) 2a in CDCl₃ and (C) 3a in CDCl₃. Compound 1a was not soluble in CDCl₃.

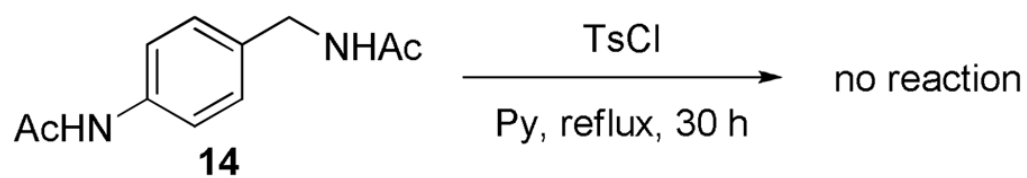


SCHEME 1.
Tosylation of *N*-acetylglucosamine derivative 1a

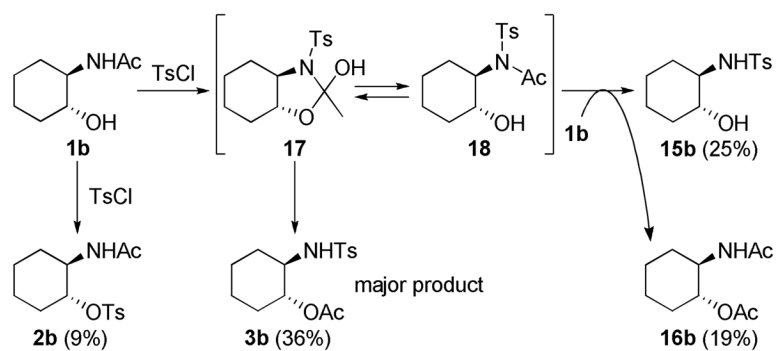
**SCHEME 2.**The acetyl migration reactions of 2-acetamidoethanol derivatives²



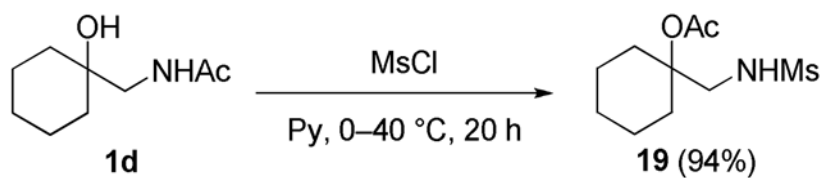
SCHEME 3.
Mechanistic possibilities of *N*- to *O*-acetyl migration of 1a



SCHEME 4.
Tosylation of the compound 14

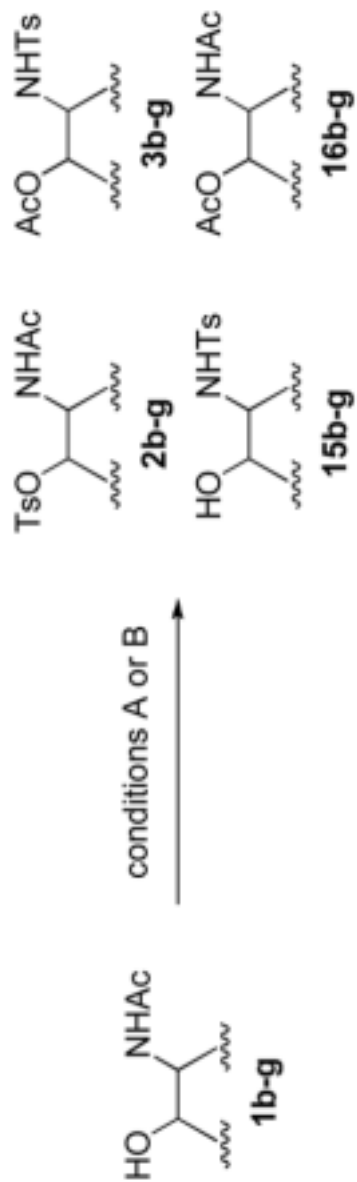
**SCHEME 5.**

The proposed mechanistic outcome for transformations of 1b

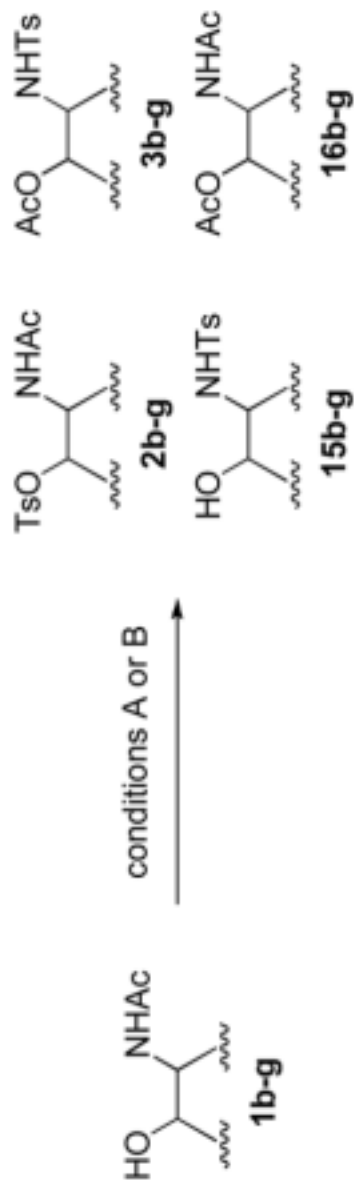


SCHEME 6.
Mesylation of the compound **1d**

TABLE 1

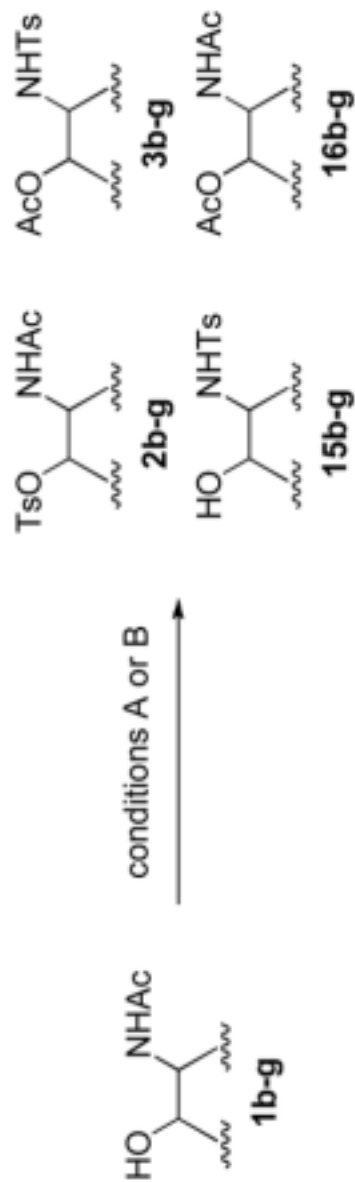
Tosylation of various 2-acetamidoethanol derivatives^a

entry	substrates	conditions	products (yield, %)					
			2b-g	3b-g	15b-g	16b-g	1b-g ^b	—
1	 1b	A	9	36	25	19	—	—
2	 1c	A	—	36	32	29	—	—



entry	substrates	conditions	products (yield, %)				
			2b-g	3b-g	15b-g	16b-g	1b-g ^b
3		A	—	52	—	—	46
		B	—	96	—	—	—

1d



entry	substrates	conditions	products (yield, %)					
			2b-g	3b-g	15b-g	16b-g	1b-g ^a	1b-g ^b
4	 1e	B	—	94	—	—	—	—
5	 1f	A	98	—	—	—	—	
		B	98	—	—	—	—	
6 ^c	 1g	A	41	—	9	8	39	

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^a The tosylation was performed under condition A or B. Condition A: TsCl (1.05 equiv) and pyridine (3 equiv) were added to a solution of substrate in CH₂Cl₂ at 0 °C, and the mixture was stirred at room temperature for 24 h. Condition B: TsCl (2 equiv) was added to a solution of substrate in pyridine at room temperature, and the mixture was heated under reflux for 30 h.

^b Recovery of starting substrate.

^c 4-(Acetamidocyclohexanol was used as a substrate in this case.