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1,3-Dioxonium cation facilitated Ritter-type reaction: facile synthesis of protected aminopolyols

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Abstract—A unique 1,3-dioxonium cation facilitated Ritter-type reaction was discovered when glycerol dipivaloates were treated with strong acid in acetonitrile. The stereoselectivity and regioselectivity of this new Ritter-type reaction were further explored by using erythritol tripivaloate and 1,2,4-butanetriol dipivaloate as the substrates. Several protected aminopolyols were generated as important chiral building blocks. This reaction was employed to synthesize a protected aminosugar lactone.

Ritter-type reaction has been known for many years as an important methodology for amide synthesis.[1–3] Presumably due to its harsh reaction conditions and difficulty with stereochemistry control, the synthetic applications of Ritter-type reaction, on the other hand, have been relatively scarce. Fraser-Reid and co-workers[4–7] synthesized a series of glycosylamine derivatives from *n*-pentenyl glycosides by generating a positive charge at the anomeric position with mild conditions. The following Ritter-type reaction occurs in a stereoselective fashion, favoring β-glycosylamide generally. Epoxide opening by Ritter reaction condition has also been explored and applied in synthetic work.[8–11] Both *trans*-[8,9] and *cis*-[10,11] opening have been detected, respectively, and ascribed to different mechanisms.

Inspired from our previous work on the *N*-bromo succinimide (NBS) initiated pivaloyl rearrangement and bromination,[12] we envisioned that *tert*-butyl-1,3-dioxonium cation could act as a good electrophile. The stabilization effect from electron-donating *tert*-butyl group could be enough for Ritter-type reaction to occur. As the simplest acyclic polyols, glycerol **1** was selected to test our hypothesis. It was treated with 2.0 equivalent pivaloyl chloride to protect two hydroxyl groups. Two regio-isomers were obtained, which were assigned to be 1,3-di-*O*-pivaloyl glycerol **2a** and (±)-1,2-di-*O*-pivaloyl glycerol **2b**, respectively, with a ratio of 2:1. Without separation, the mixture was treated with 3:1 (v/v) acetonitrile and methanesulfonic acid at room temperature for 3 days. The protected aminodiol (±)-**4** was obtained in about 80% yield as a single product (Scheme 1). Under treatment with strong acid, both of the two glycerol dipivaloates **2a** and **2b** would form the same *tert*-butyl-1,3-dioxonium cation species **3**. This species was subsequently attacked by the acetonitrile in the primary position. Following hydrolysis of the nitrilinium ion afforded (±)-**4**.

Usually, for a Ritter-type reaction, the carbocation has to be substantially stabilized and then attacked by a nitrile group. The nitrile group usually attacks the most positively charged position. In our case, the possible reactive sites partially positively charged were the dioxonium cation, the secondary C-2 and the primary C-1 in decreasing order (Fig. 1). The nucleophilic attack to these positively charged positions would generate different species. As a result, the regioselectivity of this *tert*-butyl-1,3-dioxonium cation was mainly based on the steric hindrance. This is different from the traditional Ritter reaction, in which the most stabilized charged position is the reactive site. As a result, a protected (±)-aminopropanediol **4** was successfully synthesized as a racemic mixture, which could serve as a useful building block for some synthetic work.

Besides the regioselectivity, the reaction mechanism for the dioxonium cation facilitated amidation suggested

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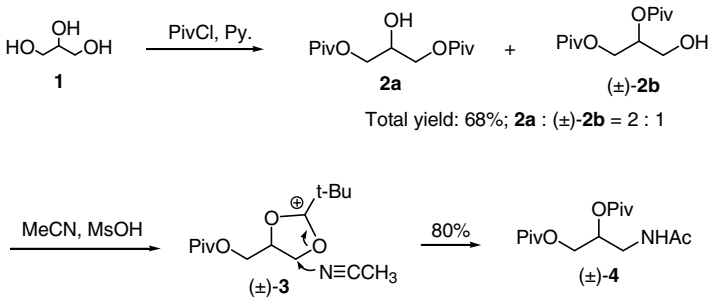


Scheme 1. The synthesis of (±)-3-*N*-acetylamino-3-deoxy-1,2-di-*O*-pivaloyl-glycerol **4**.

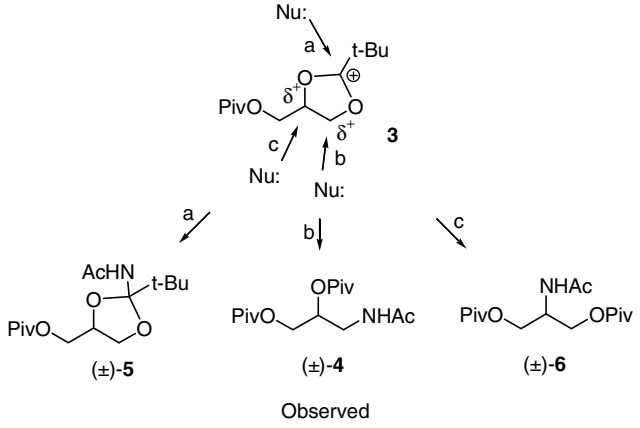


Figure 1. The preference of nucleophilic attack of *tert*-butyl-1,3-dioxonium cation **3** to (a) the dioxonium cation; (b) the secondary C-2; and (c) the primary C-1.

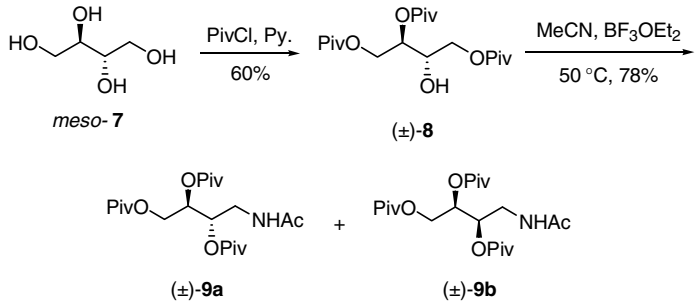
that this reaction to be highly stereoselective since no apparent epimerization was involved in the substitution site. To clarify this issue, we further explored these reactions employing *meso*-erythritol **7** as our starting material. Theoretically, by looking at the relative chirality change between the two existing chiral centers, the mechanism could be further clarified and confirmed.

meso-Erythritol **7** was partially protected by treatment with 3.0 equivalent pivaloyl chloride in pyridine. When (±)-1,2,4-tri-*O*-pivaloyl-erythritol **8** was subjected to the same Ritter reaction condition described above, a complicated mixture was obtained. Increasing the temperature did not improve the reaction. NMR analysis of the mixture showed only small amount of Ritter-type product, characterized by the signals of the *N*-acetylamino group. Interestingly, some methanesulfonyl groups were introduced into the polyol structure. Presumably, under strong acidic conditions, the acid itself served as a competitive nucleophile and attacked the *tert*-butyl-1,3-dioxonium cation instead of acetonitrile. As a result, only a small amount of Ritter-type product was formed. Substituting the protic acid with Lewis acid solved this problem successfully. When we treated (±)-1,2,4-tri-*O*-pivaloyl-erythritol **8** with 3:1 (v/v) acetonitrile and boron trifluoride etherate at 50 °C for 5 h, the Ritter-type products (±)-4-*N*-acetylamino-4-deoxy-1,2,3-tri-*O*-pivaloyl-erythritol **9a** and (±)-4-*N*-acetylamino-4-deoxy-1,2,3-tri-*O*-pivaloyl-threitol **9b** were obtained in 78% total yield (Scheme 2). The ratio of *erythro*-:*threo*-configuration was about 4:1. No 3-*N*-acetylamino product was detected. Although formation of the dioxonium by a unimolecular process could be a reason for loss of stereospecificity, this is more likely due to the participation of other ester groups at 1- and 2-positions. This would lead to competing pathways that involve inversions at chiral centers.

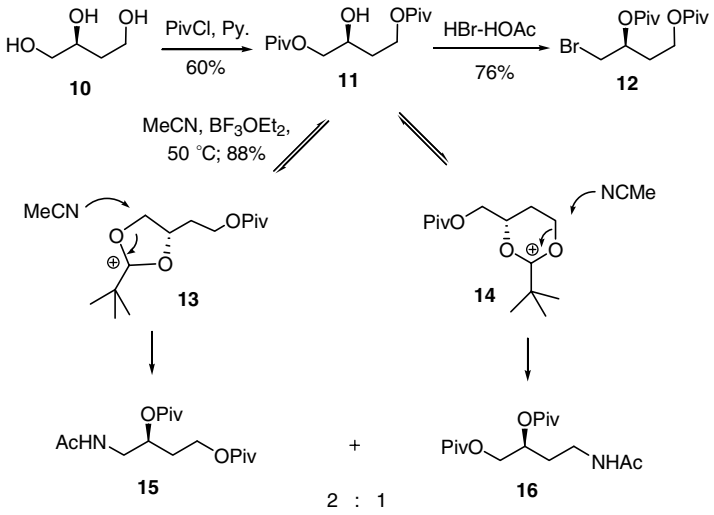
This reaction suggested that this *tert*-butyl-1,3-dioxonium cation facilitated Ritter-reaction was not only highly regioselective, but also stereoselective. Due to its carbocation intermediate mechanism, Ritter-type reaction often suffers from the poor stereocontrol. This has greatly limited its application in synthetic organic chemistry. In our dioxonium cation facilitated Ritter-type reaction, the carbocation was generated from an achiral protecting group. This carbocation in turn activated the carbon chain without scrambling its chirality. After nucleophile introduction, this carbocation was transformed back to the protecting group. This strategy successfully improved the stereoselectivity and could be very useful in future synthetic work.

Besides regioselectivity and stereoselectivity, there remained one issue about the intermediate dioxoniun cation to be addressed. Was the five-membered ring or the six-membered ring dioxonium cation the real active intermediate? Although generally the five-membered ring has been suggested as the active intermediate because of the kinetic effect, there has been no direct evidence excluding the six-membered carboxonium cation intermediate. We therefore reasoned that by employing (*S*)-1,2,4-butanetriol **10** as the starting material, this issue could be easily addressed. (*S*)-1,2,4-Butanetriol **10** is a commercially available chiral building block. Its simple chiral structure has made it a perfect platform for synthesis of complex chiral molecules. The functional group transformations of this molecule, which would generate new diverse chiral building blocks, are of great practical interest.

(*S*)-1,2,4-Butanetriol was treated with 2 equivalent pivaloyl chloride in pyridine to afford (*S*)-1,4-di-*O*-pivaloyl-1,2,4-butanetriol **11** in 60% yield. As a comparable experiment, we treated **11** with hydrogen bromide in acetic acid, a single regioisomer was obtained. NMR analysis showed the structure to be 4-bromo-1,3-di-*O*-pivaloyl-butanediol **12** (Scheme 3). The product sug-



Scheme 2. Synthesis of protected chiral *N*-acetylaminobutanetriol (±)-**9a** and (±)-**9b**.



Scheme 3. Synthesis of protected chiral *N*-acetylaminobutanediol **15** and **16**.

gested that the reaction went through a five-membered ring dioxonium cation intermediate **13**, which was attacked by bromide at the primary position to yield the product. The six-membered ring dioxonium cation **14** could only be formed between 2-OH and 4-*O*-pivaloyl group. If this was the active intermediate, the bromide would attack the 4-position to yield 4-bromo-1,2-di-*O*-pivaloyl-butanediol. The absence of this compound indicated that under this reaction condition, five-membered ring dioxonium cation intermediate was the active intermediate. Furthermore, the selectively protected and functionalized product 4-bromo-1,3-di-*O*-pivaloyl-butanediol **12** could serve as a good chiral synthon.

We then treated (*S*)-1,4-di-*O*-pivaloyl-1,2,4-butanetriol **11** with 3:1 acetonitrile and boron trifluoride etherate at 50 °C for 5 h, after which all the starting material was consumed. NMR analysis showed a mixture of two isomers, namely 4-*N*-acetylamino-1,3-di-*O*-pivaloyl-1,3-butanediol **15** and 4-*N*-acetylamino-1,2-di-*O*-pivaloyl-1,2-butanediol **16** in a ratio of 2:1.

Undoubtedly, the Lewis acid promoted Ritter-type reaction was through two active intermediates, the five-membered ring 1,2-*tert*-butyl-1,3-dioxonium cation **13** and the six-membered ring 2,4-*tert*-butyl-1,3-dioxonium cation **14**. Being attacked by acetonitrile in the 1- or 4-primary positions, respectively, they generated **15** and **16**, respectively. The 2:1 ratio showed that the five-membered ring intermediate was favored. To exclude the temperature effect, we also tried this reaction at room temperature. The Ritter-type reaction proceeded slowly under room temperature. After several days, the reaction was worked up and separated. It also yielded two isomers **15** and **16** with essentially the same ratio.

Compared with the dioxonium cation facilitated bromination and the Ritter-type reaction, a plausible explanation was suggested in Figure 2. Presumably, the five-membered ring 1,2-*tert*-butyl-1,3-dioxonium cation **13** was kinetically much more favored than the six-membered ring 2,4-*tert*-butyl-1,3-dioxonium cation **14** ($k_1 \gg k_2$), while the latter was thermodynamically slightly more favored than the former. In the bromination reaction, the bromide ion was a good nucleophile, which made the bromination process relatively fast ($k_3 > k_2$). The kinetic product 4-bromo-1,3-di-*O*-pivaloyl-1,3-butanediol **12** was formed. However, the acetonitrile was not a nucleophile as good as bromide ion. This made the Ritter-type reaction very slow

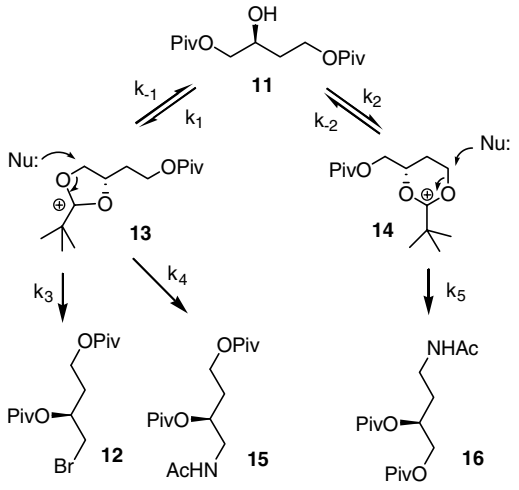
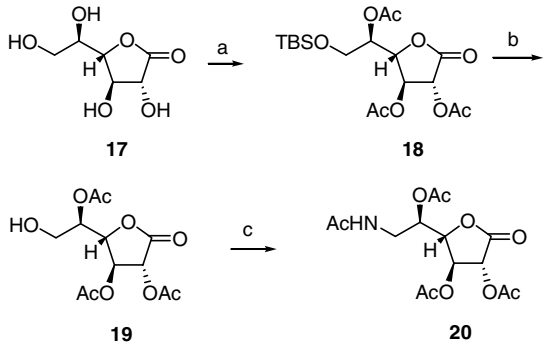


Figure 2. A explanation of the regioselectivities of acyloxonium cation facilitated bromination and the Ritter-type reaction.



Scheme 4. Synthesis of protected 6-aminogalactonolactone: (a) TBSCl, Py. then Ac_2O; (b) MeCN, BF_3OEt_2, rt; (c) MeCN, BF_3OEt_2, reflux, 3 h.

(k_4, $k_5 < k_1$, k_2). This step became the rate-limiting step. Under this circumstance, it was possible that the equilibrium between the five-membered ring *tert*-butyl-1,3-dioxonium cation **13** and the six-membered ring *tert*-butyl-1,3-dioxonium cation **14** was reached. Both of them then acted as the active intermediates to afford a mixture of two regioisomers. This analysis was further complicated by the fact that the rates of the dioxonium cation intermediates toward amidation were different for five-membered ring and six-membered ring. Presumably, the five-membered ring should have a faster rate toward amidation than the six-membered ring ($k_4 > k_5$) due to the higher ring strain. The 2:1 ratio of the two isomers reflected all the factors discussed above.

As a result, two regioisomers **15** and **16** of the Ritter-type reaction was obtained when (*S*)-1,4-di-*O*-pivaloyl-1,2,4-butanetriol **11** was treated with acetonitrile and Lewis acid. Both isomers could be employed as good chiral building blocks toward more complex structures.

To further demonstrate the synthetic utility of the regio- and stereoselective acetoxonium cation facilitated Ritter-type reaction, a simple synthesis of protected 6-amino-6-deoxy-D-galactono-1,4-lactone was carried out. Selective silylation of the primary hydroxyl group, peracetylation followed by easy deprotection of the primary group gave compound **19**, which is ready for Ritter-type reaction. Treatment of this compound with boron trifluoride etherate in acetonitrile gave the protected 6-amino sugar lactone **20** in 52% overall yield. Principally, this procedure could be generalized in the synthesis of other 6-aminosugars (Scheme 4).

As a summary, a stereoselective 1,3-dioxonium cation facilitated Ritter-type reaction was developed. Several chiral aminopolyols and a 6-aminosugar lactone were synthesized in their protected forms.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.149.

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