Preparation of Morpholine-2-one and 1,4-Oxazepan-2-one Derivatives by Cyclization Reaction between *N*-Bts Amino Alcohol and Chloroacetyl Chloride

Ji-ah Choi, Jong Ook Lee, Man Soo Kim, Jeong E. Nam Shin, and Keun Ho Chun*

*Department of Chemistry, Soongsil University, Seoul 156-743, Korea. *E-mail: kchun@ssu.ac.kr*
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Sulfonamide is one of the most stable nitrogen protective group, and various sulfonamides have been developed and applied for organic synthesis. However, deprotection of most sulfonamides has drawbacks due to harsh reaction conditions.[1]

Benzothiazole-2-sulfonyl (Bts) was first reported as an amine protective group in amino acid synthesis.[2,3] Compared to other sulfonyl groups, Bts is an attractive choice because it requires milder deprotection conditions. Initially, Bts chloride, the reagent for Bts protection for simple amines, was prepared using Cl_2 gas, which is toxic and inconvenient. Recently, an improved methodology using aqueous sodium hypochlorite instead of toxic Cl_2 was reported and making Bts protection much easier.[4-6]

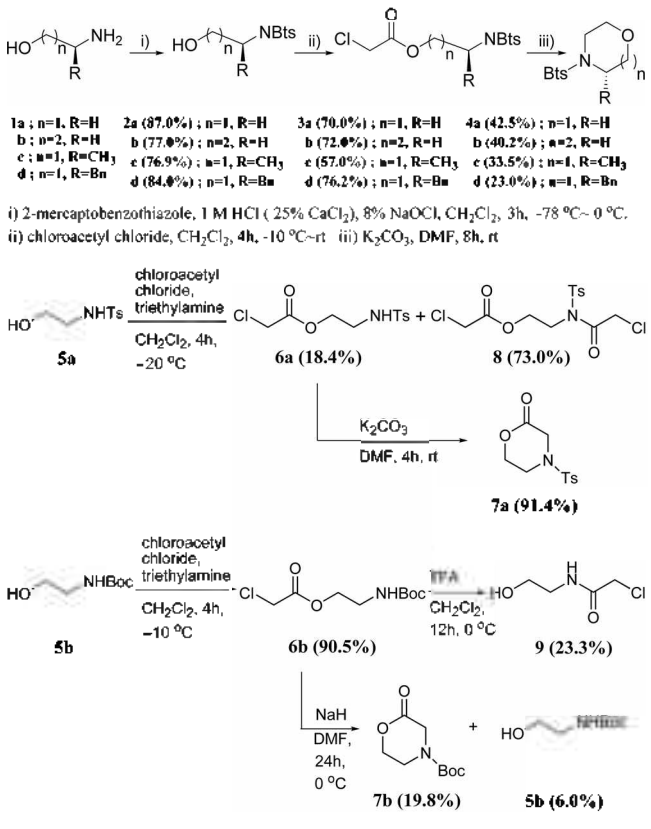
The Bts group is known to have an electron withdrawing property, and Bts protected amide shows a different reactivity compared to other *N*-protected amide derivatives. Although usual amide bond is strong enough not to be easily hydrolyzed or aminolized, *N*-Bts amide linkage can be broken by attack of simple amine nucleophiles. This is another benefit of Bts protection, and the ring opening reaction of 1-Bts piperazin-2-one derivative as a peptide nucleic acid (PNA) monomer with a PNA oligomer anchored on solid phase has been usefully applied for solid phase PNA synthesis.[7]

In this paper, a facile cyclization reaction of *N*-Bts amino alcohol with chloroacetyl chloride is described. We speculated that if the Bts group could effectively withdraw electrons from nitrogen, nucleophilicity of Bts attached amine would be reduced, and a different reactivity toward electrophiles would be observed compared to normal amine derivatives. These subtle reactivity differences could be an effective means of obtaining different regioselectivity. Detailed data pertaining to change of nucleophilicity due to Bts protection has not been reported thus far.

To investigate this hypothesis, Bts, Ts (toluensulfonyl), and Boc (*t*-butyl carbamate) protected amino alcohols were prepared, and reactions with chloroacetyl chloride were performed (Scheme 1). Between two chlorides in chloroacetyl chloride, acyl chloride is known to be more reactive toward usual nucleophiles. In the case of unprotected amino alcohol, the amine should react with acyl chloride prior to OH, and OH can subsequently attack α-carbon to produce a morpholine-3-one.[8] However, for *N*-protected amino alcohol, OH should be acylated prior to the acylation of *N*-protected amine. If the *N*-protected amine has sufficient reactivity to perform intramolecular cyclization to attack α-carbon, a morpholine-2-one derivative can be prepared.

In the reaction of *N*-Bts amino alcohol (**2a, b**), The OH group reacted with acyl chloride to form ester **3a, b**. After workup to remove remaining chloroacetyl chloride, and stirring in DMF with K_2CO_3, it was found that *N*-Bts amine could substitute a chloride at α-carbon, and morpholine-2-one (**4a**) or 1,4-oxazepan-2-one (**4b**) derivative was produced.

When *N*-Ts amino ethanol (**5a**) was reacted with chloroacetyl chloride dropwise, a different outcome was obtained. A mixture of *O*-acylated (**6a**) and diacylated compound **8** was produced in 1:4 ratios. The production of diacylated compound **8** as a major product means that *N*-Ts amine has enough nucleophilicity to react with acyl chloride, and its reactivity is higher than *N*-Bts amine. When *O*-acylated product (**6a**) was separated and stirred with K_2CO_3, morpholine-2-one derivative (**7a**) was obtained.



Scheme 1

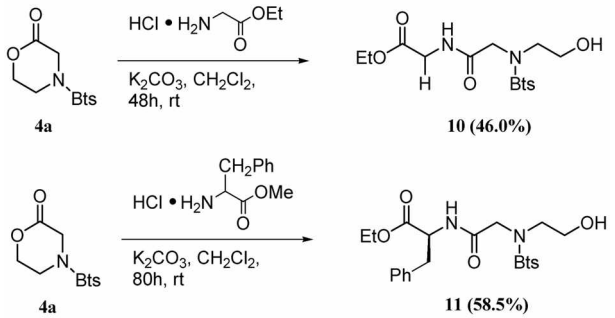
In the case of *N*-Boc amino ethanol (**5b**), *O*-acylated product **6b** was produced in a high yield. Compound **6b** failed to cyclize to form morpholin-2-one (**7b**) under the reaction condition with K_2CO_3 and stirring. This result tells that the nucleophilicity of Boc protected amine is lower than that of *N*-Bts amine. Although compound **6b** could be cyclized by treating strong base (NaH) in DMF, the reaction preceded much slowly. After 1-day reaction, morpholine-2-one (**7b**) was obtained in a low yield, and a hydrolysed product (**5b**) and unreacted starting material were also isolated. Raise of reaction temperature or increase the amount of base were ineffective.

When Boc of compound **6b** was removed by treating trifluoroacetic acid in order to facilitate intramolecular cyclization, surprisingly, a rearranged product **9** was isolated instead of compound **7b**.

These results indicate that the nucleophilicity of Bts protected amine lies between that of Ts and Boc protected amine. It is also clear that Bts protection is the best choice to prepare morpholine-2-one (**4a**) or 1,4-oxazepan-2-one (**4b**) derivatives through the intramolecular cyclization reaction with chloroacetyl chloride due to the slightly reduced nucleophilicity of the amine.

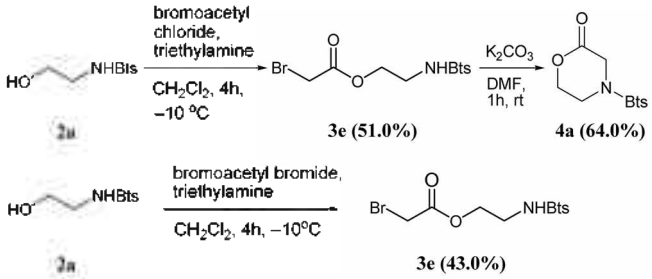
Chiral *N*-Bts aminoethanol derivatives (**2c**, **2d**) were reacted with chloroacetyl chloride, and chiral morpholin-2-one derivatives (**4c**, **4d**) were conveniently prepared. Chiral morpholin-2-one derivatives have been reported as a key intermediate in the synthesis of biological channel or receptor blockers.[9,10]

Ring opening of **4a** by amino acid was easily achived, and dipeptide **10** and **11** could be obtained by reaction with glycine ethyl ester and phenylalaine methyl ester, respectively (Scheme 2).



Scheme 2

We also attempted to replace chloroacetyl chloride with bromoacetyl chloride, or bromoacetyl bromide in the cyclization with *N*-Bts amino alcohol (Scheme 3).



Scheme 3

For the *O*-acylation step, chloroacetyl chloride was found to be more effective, and bromoacetyl group was more productive for the cyclization step. However, chloroacetyl chloride and bromoacetyl chloride showed a similar overall yield for the two steps, but bromoacetyl bromide was less efficient.

In conclusion, the cyclization reaction between *N*-Bts amino alcohols and chloroacetyl chloride were investigated, and regioselectively unusual morpholine-2-one and 1,4-oxazepan-2-one derivatives were produced in moderate yield. Other *N*-protective groups (Ts, Boc) were proved to be less effective for this purpose and produced side products. These results were attributed to the unusual reactivity of *N*-Bts amine. It is anticipated that this new methodology can be usefully applied for the facile synthesis of clinically important chiral morpholine-2-one and 1,4-oxazepan-2-one derivatives.

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References

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis, 4th* Ed., John Wiley & Sons, Inc.: 2007.
2. Vedejs, E.; Lin, S.; Klapars, A.; Wang, J. *J. Am. Chem. Soc.* **1996**, *118*, 9796.
3. Vedejs, E.; Kongkittingam, C. *J. Org. Chem.* **2000**, *65*, 2309.
4. Caldwell, W. T.; Kornfeld, E. C. *J. Am. Chem. Soc.* **1942**, *64*, 1695.
5. Roblin, R. O.; Clapp, J. W. *J. Am. Chem. Soc.* **1950**, *72*, 4890.
6. Stephen, W. W.; Kelly, N. H. *J. Org. Chem.* **2006**, *71*, 1080.
7. Lee, H.; Jeon, J. H.; Lim, C. J.; Choi, H.; Yoon, Y.; Kim, S. K. *Org. Lett.* **2007**, *9*, 3291.
8. Gerhard, S.; Glynn, M. *J. Agric. Food Chem.* **2001**, *49*, 138.
9. Ku, J. W.; Cho, S.; Doddareddy, M. R.; Jang, M. S.; Keum, G.; Lee, J. H.; Chung, B. Y.; Kim, Y.; Rhima, H.; Kanga, S. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5244.
10. Naveenkumar, K.; Chandrashekar, R. E.; Muthulingam, A.; Srinivas, G.; Pravinchandra, J. V.; Yerremilli, A.; Apurba, B.; Sundaram, V.; Vijayavitthal, T. M. *Org. Process Res. Dev.* **2007**, *11*, 455.