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An efficient and improved procedure for preparation of triflyl azide and application in catalytic diazotransfer reaction

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Abstract—An efficient and improved procedure for preparation of triflyl azide and application in catalytic diazotransfer reaction are described. The amount of highly toxic reagents NaN_3 and Tf_2O, is significantly reduced comparing with the previous protocol.

Azides play important roles in synthetic chemistry and chemical biology. For example, they can be used as protective groups for amines,[1] photoaffinity labeling reagents for biomolecules,[2] precursors in the 'click chemistry' to form linkages for various conjugates or to introduce heterocyclic structures,[3] and bioorthogonal chemical reporters or their reactive partners for tagging in biological system.[4] Preparation of azides from amines via diazotransfer reaction with triflyl azide (TfN_3) as a diazo donor,[5] has several advantages such as high yield, complete retention of configuration, mild reaction conditions, and good compatibility with most functional groups. This method was improved by the Wong's group[6] via the addition of metal catalyst and now has been applied in numerous works.[1,7,8] But the procedure employed still has some drawbacks. Firstly, two highly toxic reagents, NaN_3 and Tf_2O, have to be used with large excess. Secondly, in the diazotransferring step, three solvents, $H_2O/MeOH/CH_2Cl_2$, are used. The ratio of the solvents has to be balanced with particular caution, because it has a dramatic influence on the outcome of the reaction. Thirdly, the procedure seems to be still unpredictable and somewhat troublesome. In this report, the problems mentioned above are well solved.

Triflyl azide is a key reagent for this transformation. However, by searching the literatures, we found that the procedure for the preparation of triflyl azide had hardly gained any substantial improvement since the first application described by Shiner et al. over 30 years ago.[5,9] In the classical procedure, triflic anhydride was added to the biphasic mixture of dichloromethane and saturated NaN_3 aqueous directly while vigorous stirring. After extraction, a solution of triflyl azide in CH_2Cl_2 was then obtained. Obviously, there existed at least two drawbacks in this procedure. In the presence of water, triflic anhydride would be hydrolyzed inevitably. For minimizing the hydrolysis, a large excess of reagents, usually 6 equiv of NaN_3 and 3 equiv of Tf_2O, had to be employed. On the other hand, the resulting triflyl azide is distributed in CH_2Cl_2, which is not a versatile solvent for the subsequent diazotransfer reaction because of the poor solubility to many substrates. For the sake of a homogeneous phase, a complicated solvent system has to be used. Wong et. al. have developed a $H_2O/MeOH/CH_2Cl_2$ (v/v/v = 3:10:3) solvent system,[6b] but in our operations, cautious balance of the ratio is required especially when the solubility of substrates is not good and the yields are still unpredictable.

We reasoned that if a more polar solvent such as acetonitrile (CH_3CN) or pyridine (Py) instead of dichloromethane was used in the absence of water, the hydrolysis of Tf_2O would be effectively avoided. In fact, in our procedure, NaN_3 was soluble enough in CH_3CN or Py to ensure almost complete conversion of Tf_2O to TfN_3. In our practice, only 1.44 equiv of NaN_3 and 1.20 equiv of Tf_2O were needed for the diazotransfer reaction of per amine group. The resulting reaction mixture mainly contained TfN_3 and two salts, namely NaOTf and unreacted NaN_3. These two salts had

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Keywords: Diazotransfer reaction; Azide; Amine; Functional group transformation; Synthesis.

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considerable solubility in CH_3CN or Py but had no influence on the subsequent transfer reaction. Except a filtration if necessary, any other purification such as extraction required in the previous literature procedure was no longer needed.[10] Instead, the TfN_3-containing solution was directly added to the amine reactants. Because the amine substrates could easily dissolve in the resulting TfN_3 solution, the careful ratio balance of the multiple solvents for a homogeneous phase was thus avoided. The results of diazotransfer reaction on some representative substrates were summarized in Table 1.[11]

Simple amino sugars such as glucosamine and galactosamine underwent the reaction very smoothly to afford the desired products in good isolated yields (entries 1 and 2). When this method was extended to polyamine substrates (entries 5 and 6), good yields were also gained. It should be noted that when neamine was treated under the same conditions with Py as the solvent, 90% total isolated yield was obtained after reexamination by peracetylation.[12] The amino acid derivative reacted effectively, providing the diazotransferred product in excellent yield (entry 3). In the case of tryptamine containing both a primary aliphatic amino and a secondary aromatic amino group, the use of CH_3CN gave better yield than the use of Py (entry 4).[13]

In summary, a simple, efficient, and reliable procedure for preparation of triflyl azide and application in catalytic diazotransfer reaction were reported, the operations were more convenient. The disclosed procedure significantly reduced the amount of the reagents and large excessive usage of the highly toxic NaN_3 and Tf_2O was avoided. The yield of diazotransfer reaction by using our procedure was as good as that of the Wong's improved protocol. We anticipate that this improved protocol will be of broad interest and of wide use.

Acknowledgments

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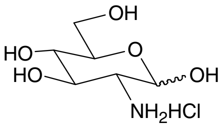
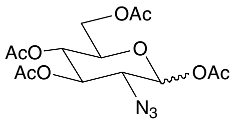
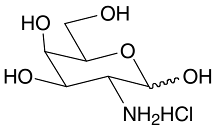
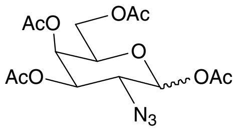
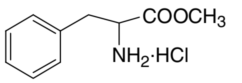
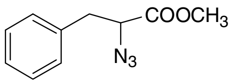
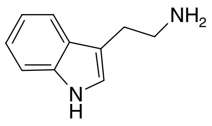
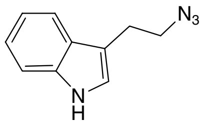
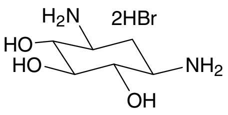
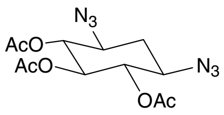
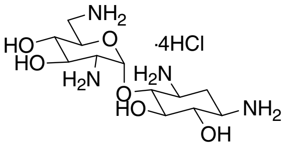
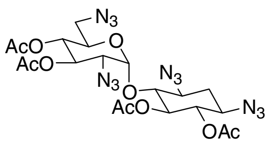
References and notes

1. For examples see: (a) Lohman, G. J. S.; Seeberger, P. H. *J. Org. Chem.* **2004**, *69*, 4081–4093; (b) Fridman, M.; Belakhov, V.; Lee, L. V.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 447–452.
2. For a review, see: Radominska, A.; Drake, R. R. *Methods Enzymol.* **1994**, *230*, 330–339.

Table 1. Diazotransfer reaction of representative amines

Entry	Amine	Azide	Isolated yield (%)	
			a	b
1			92	94
2			95	79
3			92	95
4			45	85
5			82	83
6			90	76

[a] Pyridine as solvent.

[b] Acetonitrile as solvent.

3. For reviews, see: (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021; (b) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–1137.
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8. Liu, Q.; Tor, Y. *Org. Lett.* **2003**, *5*, 2571–2572.
9. Ruff first reported the preparation of TfN_3 with NaN_3 and Tf_2O: Ruff, J. K. *Inorg. Chem.* **1965**, *4*, 567–570.
10. A typical experimental procedure for the preparation of triflyl azide was as following: A suspension of sodium azide (436 mg, 6.70 mmol) in 8 mL of acetonitrile (pyridine) was cooled in ice bath. Then triflic anhydride (1.57 g, 5.56 mmol) was added to the mixture by a syringe during 5 min while stirring. After the reaction was maintained for 2 h in ice bath, the TfN_3-containing solution (filtration of the salts can be done if necessary) was added directly to the amine solution for the subsequent diazotransfer reaction.
11. General procedure for the reaction of triflyl azide with amines. For organic soluble substrates, 1.0 g of substrate was dissolved in 5 mL of acetonitrile (pyridine). In case of saline substrates, water was employed instead. Then 1% equiv of $CuSO_4$ and 2 equiv of NEt_3 per substrate amine were added into the solution while stirring. The mixture was cooled in an ice bath for a while, acetonitrile (pyridine) solution of triflyl azide (1.2 equiv per amino group, based on the amount of triflic anhydride used in the preparation of TfN_3) was then added into the mixture dropwise. The reaction mixture was allowed to warm to room temperature. Generally speaking, a homogeneous solution could be obtained after the addition of triflyl azide, and the reaction normally went to completion within 12 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel or treated with Ac_2O/Py and catalytic amount of DMAP to gain the acetylated product.
12. Although the tetraazido neamine without being acetylated can be isolated on silicon gel column, it is occasionally contaminated by an unknown white solid, which cannot be stained with any stains.[6b] In result, the yield may sometimes be nearly quantitative. To examine the yield, peracetylation with Py/Ac_2O and DMAP was employed. The unknown white solid is probably triflamide.
13. With pyridine as solvent, the starting material was almost exhausted detected on TLC, as it did with CH_3CN as solvent. But the products were complicated. The reason of the reduced yield is undergoing further research.