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# The Use of Tetramethylguanidinium Azide in Non-halogenated Solvents Avoids Potential Explosion Hazards

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***Abstract:*** Tetramethylguanidinium azide was used in the quantitative conversion of glycosyl halides **1** - **5** to the corresponding glycosyl azides **10** - **14**. The stereoselective reactions occurred with complete inversion at the anomeric centers. The titled reagent was also employed in the selective synthesis of pseudoglycosyl azide **16** and two steroidal azides **17** and **18**. All reactions were carried out in non-halogenated solvents to avoid potential explosion hazards.

Glycosyl azides are synthetic precursors to biologically important substances such as glycopeptides.[1] We have recently reported an efficient procedure for the stereoselective synthesis of glycosyl azides using tetramethylguanidinium azide (TMGA; $[(Me_2N)_2CNH_2]N_3$).[1] **These reactions were carried out in dichloromethane.** However, two laboratories have recently issued warnings on the explosive nature of sodium azide in dichloromethane, with diazidomethane being blamed as the culprit.[2] Although TMGA in $CH_2Cl_2$ has been routinely used in our laboratory for the past three years without incident,[1,3] the safety concerns over any azide reagent in halogenated solvents have prompted us to re-investigate the synthesis of glycosyl azides using TMGA in non-halogenated solvents (i.e., $CH_3CN$ or $CH_3NO_2$) obtaining comparable results with equal efficiency (Table).[4] Mannosyl chloride **6** was largely unreactive under the conditions employed. We have also extended this revised procedure to non-carbohydrate substrates. When the dibromide **7** was heated at 78°C with 1 equivalent of TMGA in $CH_3CN$, the monoazide **16** was obtained quantitatively after three hours, in comparison with only 50% conversion after 15 hours at room temperature. Most interestingly, when steroidal bromide **8** was treated with two equivalents of TMGA at room temperature in $CH_3CN$, the corresponding azide **17** was obtained in a remarkable 95% yield, without complication from the α-aminoenone formation.[3a] This yield was 46% better than the previously reported method using TMGA in dichloromethane at reflux.[3a] It should be noted that the products **10** - **13** and **16** - **17** were homogeneous by TLC and $^1H$ NMR after workup, no further purification being necessary. The application of TMGA in the synthesis of cephalostatin precursor **18** highlights the broader application of this revised procedure.

In conclusion, this revised procedure avoids the use any halogenated solvents, thereby providing a safe alternative for the efficient synthesis of glycosyl azides and steroidal azides.

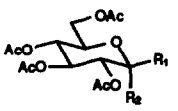
**Procedure A** To glycosyl halides in dry $CH_3CN$ or $CH_3NO_2$ was added TMGA (1.5 equiv.) in one batch. The homogeneous solutions were stirred at room temperature until TLC indicated total consumption of the halides. $Et_2O$ was then added and stirred for a few minutes to produce a precipitate, which was filtered and washed with $Et_2O$. The filtrate was washed once with $H_2O$ and dried (anhyd. $Na_2SO_4$). Concentration *in vacuo* afforded glycosyl azides in quantitative yields. The products were chromatographed to obtain analytical purity. The purified yields are reported in the Table.

**Procedure B** Same as A except upon finishing the reaction, $Et_2O$:EtOAc (2:1 by volume) was added and stirred for a few minutes to produce a precipitate, which was filtered and washed with $Et_2O$. The filtrate was concentrated and followed by chromatography via a short pad of silica gel.

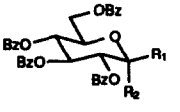
**Procedure C** Same as A except upon finishing the reaction, $Et_2O$:EtOAc (5:1 by volume) was added to produce a precipitate, which was filtered and washed with $Et_2O$:EtOAc (5:1 by volume). The filtrate was washed with $H_2O$ and brine, then dried over $MgSO_4$. Purification of **18** by chromatography was required.

| Substrate | Product | in $CH_3CN$ Yield (%)* | in $CH_3NO_2$ Yield (%)* | Mole Equiv. of TMGA | Conc. (M) | Reaction Time | Reaction Temp | Workup Procedure |
|---|---|---|---|---|---|---|---|---|
| 1 | 10 | 97 | 100 | 1.5 | 0.2 | 2-2.5 hrs | 25°C | A |
| 2 | 11 | 97 | 96 | 1.5 | 0.2 | 2 hrs | 25°C | A |
| 3 | 12 | 96 | 99 | 1.5 | 0.2-0.3 | 3-4 hrs | 25°C | A |
| 4 | 13 | 99 | 99 | 1.5 | 0.1 | 2 hrs | 25°C | A |
| 5 | 14 | 95 | 95 | 1.5 | 0.2 | 1 hr | 25°C | B |
| 6 | 15 | No reaction | No reaction | 1.5 | 0.2 | 1 day | 25°C | A |
| 7 | 16 | 95 | ----- | 1.0 | 0.13 | 3 hrs | 78°C | A |
| 8 | 17 | 92 | ----- | 2.0 | 0.05 | 4 hrs | 25°C | C |
| 9 | 18 | 83 | ----- | 2.0 | 0.05 | 4 hrs | 25°C | C |

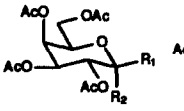
* After purification by column chromatography.



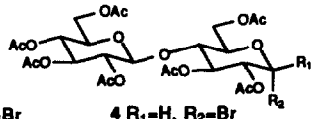

1 $R_1$=H, $R_2$=Br
10 $R_1$=$N_3$, $R_2$=H



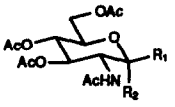

2 $R_1$=H, $R_2$=Br
11 $R_1$=$N_3$, $R_2$=H



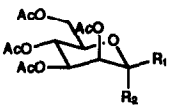

3 $R_1$=H, $R_2$=Br
12 $R_1$=$N_3$, $R_2$=H



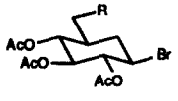

4 $R_1$=H, $R_2$=Br
13 $R_1$=$N_3$, $R_2$=H



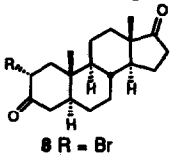

5 $R_1$=H, $R_2$=Cl
14 $R_1$=$N_3$, $R_2$=H



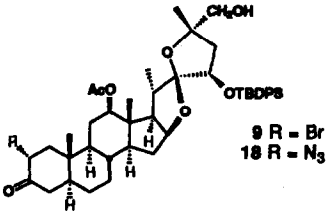

6 $R_1$=H, $R_2$=Br
15 $R_1$=$N_3$, $R_2$=H




7 R = Br
16 R = $N_3$




8 R = Br
17 R = $N_3$




9 R = Br
18 R = $N_3$

## References and Notes


1 Li, C.; Arasappan, A.; Fuchs, P. L. *Tetrahedron Lett.* **1993**, 3535, and references cited therein.

2 a) Peet, N. P.; Weintraube, P. M. *Chem. & Engr. News* April 9, 1993, page 4; b) Hruby, V. J.; Boteju, L.; Li, G. *Chem. & Engr. News* Oct. 11, 1993, page 2; c) for the synthesis and explosive nature of di- and triazidomethane, see: Hassner, A.; Stern, M.; Gottlieb, H. E.; Frolow, F. *J. Org. Chem.* **1990**, *55*, 2304.

3 a) Pan, Y.; Merriman, R. L.; Tanzer, L. R.; Fuchs, P. L. *Biomed. Chem. Lett.* **1992**, *2*, 967; b) Jeong, J.; Fuchs, P. L. *J. Am. Chem. Soc.* submitted for publication.

4 TMGA is soluble in $CH_3CN$, $CH_3NO_2$ and MeOH. When $Et_2O$ was added to these solutions, TMGA precipitated. This observation led to the revised procedure.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