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# Reductive Amination of Nitroimidazole Aldehyde with Diamines Using Sodium Triacetoxyborohydride

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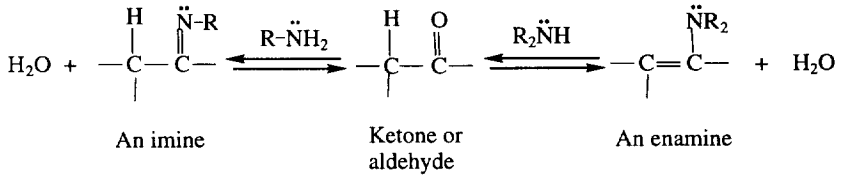
**Abstract:** Nitroimidazole Aldehyde reacts with various diamines under a nitrogen atmosphere at room temperature, using sodium triacetoxyborohydride as a reducing agent, to give the corresponding tertiary amines.

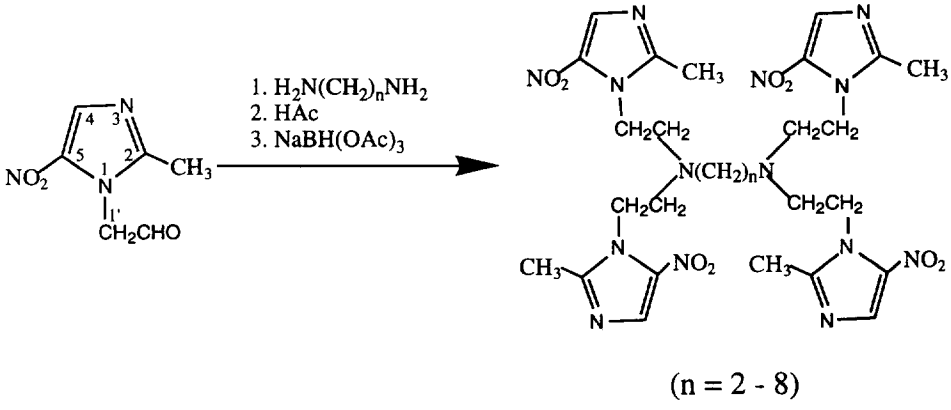

Many reductive amination procedures for the synthesis of amines have been reported in the literature,[1 - 6] but few have dealt with nitroheterocyclic aldehydes and diamines. Since nitro groups are easily reduced under catalytic hydrogenation conditions, only very mild reducing agents can be used for reductive amination of nitro containing aldehydes. A test of the Borch reduction which employs sodium cyanoborohydride [$NaBH_3CN$] as the reducing agent yielded negative results[7]. However, successful reductive amination was achieved with sodium triacetoxyborohydride [$NaBH(OAc)_3$], an agent that had previously been used by Abdel-Magid et al. and Gribble et al. for reductive amination of aliphatic, cyclic saturated, and aromatic aldehydes and ketones.[1 - 6] The results reported here demonstrate that $NaBH(OAc)_3$ is a reagent of choice in the reductive amination of nitroimidazole aldehydes (2-methyl-5-nitroimidazol-1-yl-acetaldehyde) with diamines.




Scheme 1

It is well known that primary and secondary amines react with aldehydes and ketones to yield imines and enamines, respectively (Scheme 1). These intermediates can then be reduced to the corresponding amines by appropriate reducing agents (Scheme 1).

The two reactions are quite similar. Theoretically, in the presence of excess of carbonyl compounds, tertiary amines could be obtained in a one pot reaction by reductive amination of aldehyde with primary amines. The newly formed secondary amines existing in reaction mixtures should react with aldehyde to form tertiary amines under reductive amination conditions. However, the aldehyde remaining in the reaction mixture may compete with imines and enamines for the hydrides in reduction step, causing significant reduction to the alcohol form. As a result, only a few procedures for the synthesis of tertiary amines from primary amines in one reaction vessel have been described in the literature;[6] most reports deal with the synthesis of mono-amines, rather than tertiary diamines. In this study, we report a one-step synthesis procedure for tertiary diamines which extends the application of $NaBH(OAc)_3$ to the reductive amination of 2-methyl-5-nitroimidazol-1-yl-acetaldehyde with various primary diamines (Scheme 2).




Scheme 2

Using reaction scheme 2, four nitroimidazole groups were attached to diamines of different length (2 - 8 carbons). The reaction mixture consisted of 4 molar equivalents of 2-methyl-5-nitroimidazol-1-yl-acetaldehyde, 1 molar equivalent of diamines, 4 molar equivalents of acetic acid, and 4.8 molar equivalents of $NaBH(OAc)_3$ in 1, 2-diachloroethane (DCE). The reaction was allowed to proceed at room temperature for 48 hours. Under these mild conditions the reaction rates were low, but produced good isolated yields (Table 1). If the reaction time was extended beyond 48 hours, more side reactions occurred and the reaction yields decreased.

Table 1. Reductive amination of 2-methyl-5-nitroimidazol-1-yl-acetaldehyde with diamines using sodium triacetoxyborohydride

| Entry | Diamines | Compounds | Product Yield(%) |
|---|---|---|---|
| 1 | Ethylenediamine | N, N, N', N'-tetra[2'-(2-methyl-5-nitro-1-imidazolyl)ethyl]-ethylenediamine | 75 |
| 2 | Propanediamine | N, N, N', N'-tetra[2'-(2-methyl-5-nitro-1-imidazolyl)ethyl]-1,3-propanediamine | 82 |
| 3 | 1,4-Butanediamine | N, N, N', N'-tetra[2'-(2-methyl-5-nitro-1-imidazolyl)ethyl]-1,4-butanediamine | 86 |
| 4 | 1,5-Pentanedimine | N, N, N', N'-tetra[2'-(2-methyl-5-nitro-1-imidazolyl)ethyl]-1,5-pentanediamine | 80 |
| 5 | 1,6-Hexanediamine | N, N, N', N'-tetra[2'-(2-methyl-5-nitro-1-imidazolyl)ethyl]-1,6-hexanediamine | 90 |
| 6 | 1,7-Heptanediamine | N, N, N', N'-tetra[2'-(2-methyl-5-nitro-1-imidazolyl)ethyl]-1,7heptanediamine | 89 |
| 7 | 1,8-Octanediamine | N, N, N', N'-tetra[2'-(2-methyl-5-nitro-1-imidazolyl)ethyl]-1,8-octanediamine | 94 |

The starting material for the above reaction, 2-methyl-5-nitroimidazol-1-yl-acetaldehyde, was synthesized in our laboratory as previously described.[8] Since nitroimidazole aldehyde was not very stable during long purification procedures, the freshly made reaction mixture containing the aldehyde was extracted with a liquid-liquid extraction method (water and ethyl acetate). The aldehyde (along with impurities such as DMSO and alcohol) was recovered in ethyl acetate, the ethyl acetate was evaporated, and the resulting oil was used for reductive amination. From the good reaction yields shown in Table 1 it is obvious that impurities such as DMSO and alcohol in the oily aldehyde mixture did not interfere with reductive amination.

Using the preparation of N, N, N', N'-tetra[2'(2-methyl-5-nitro-1-imidazolyl)ethyl]-1, 8-octanediamine (entry 7 in Table 1) as an example, the actual reaction procedure was as follows: A total of 3.52 g (19 mmol) of freshly prepared 2-methyl-5-nitroimidazol-1-yl-acetaldehyde was dissolved in 80 mL of 1, 2-dichloroethane, and 0.685 g (4.75 mmol) of 1,8-octanediamine was added. The reaction mixture was stirred for 30 min and then acidified with 1.08 mL (19 mmol) of acetic acid. After that 4.83 g (22.8 mmol) of sodium triacetoxyborohydride was added as a reducing agent and the solution was stirred for 48 h at room temperature. During the entire procedure the reaction vessel was gassed with nitrogen. The resulting mixture was diluted with 60 mL of ethyl acetate, and then washed with 85 mL of saturated aqueous $NaHCO_3$ and 30 mL of water. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated to leave residual oil which solidified when stored at 4 $^{o}C$ for 2 days. The

obtained solid was recrystallized from ethyl acetate/hexane to give N, N, N', N'-tetra[2'(2-methyl-5-nitro-1-imidazolyl)ethyl]-1,8-octanediamine (m.p. 157 - 158 $^{0}$C).

Chemical structure analysis was performed by $^{1}$H NMR ($CDCl_3$, 300 MHz) $\partial$ 7.93 (s, 4H, imidazole H4); 4.26 (t, J = 6.9 Hz, 8H, H2'); 2.81 (t, J = 6.6 Hz, 8H, H1'); 2.54-2.51 (m, 4H, H1, H8); 2.50 (s, 12H, imidazole Me2); 1.27-1.22 (m, 12H, H2, H3, H4, H5, H6, H7). Also, the number of carbon atoms present was evaluated by $^{13}$C NMR ($CDCl_3$, 75 MHz) $\partial$ 150.548 (imidazole C5); 138.908 (imidazole C2); 133.142 (imidazole C4); 54.759 (C2'); 54.045 (C1'); 44.257 (C1, C8); 29.051 (C2, C7); 26.744 (C3, C4, C5, C6); 13.951 (imidazole Me2).

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## REFERENCES

1. Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* 1990, *31*, 5595-5598.
2. Abdel-Magid, A. F.; Maryanoff, C. A. *Synlett.* 1990, 537-539.
3. Gribble, G. W.; Ferguson, D. C. *J. C. S. Chem. Commun.* 1975, 535-536
4. Gribble, G. W. *Eastman Organic Chemical Bulletin.* 1979, *51*, No. 1, 1-6.
5. Gribble, G. W.; Lord, P. D.; Skotnicki, J. T.; Dietz, S. E.; Eaton, J. T.; Johnson, J. L. *J. Am. Chem.Soc.* 1974, *96*, 7812-7814
6. Gribble, G. W.; Jasinski, J. M.; Pellicone, J. T.; Panetta, J. A. *Synthesis.* 1978, 766-768.
7. Borch, R. F.; Bernstein, M. D.; Durst, H. D. J. Am. Chem. Soc. 1971, *93*, 2897-2904.
8. Yang, L. -X.; Hofer, K. G. *Synthetic Commun.* (in press), 1996.

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