

TETRAALKYLHYDRAZINE PREPARATION BY REDUCTIVE ALKYLATION WITH SODIUM
CYANOBOROHYDRIDE

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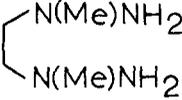
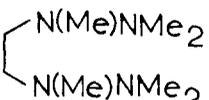
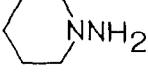
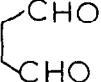
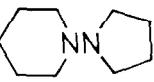
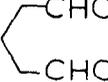
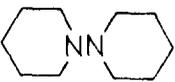
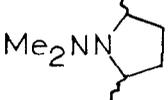
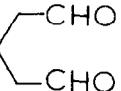
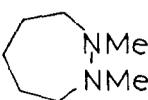
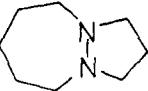
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Borch and coworkers have reported the effective use of alkalai cyanoborohydrides for reductive alkylation of amines with aldehydes and ketones¹⁻³. Our interest in tetraalkylhydrazines⁴ led us to explore the use of cyanoborohydride for synthesis of these compounds. Hydrazines are conveniently methylated using formalin and sodium cyanoborohydride in acetonitrile (Table 1, entry 1-3), and yields remain reasonable even when four methyls are introduced in a single synthetic step. The yields quoted in Table 1 are based on weight of distilled product using 5-10 mm of starting hydrazine, so they should be minimum yields as significant amounts of material are undoubtedly lost in distillation. Most products were obtained in greater than 90% purity (by vpc). It is not surprising that hydrazones may be used as starting material (entries 4,5), and the reasonable yield of triisopropylmethyl hydrazine demonstrates that fairly hindered compounds may be synthesized. We were unsuccessful in attempts to prepare tetra-isopropylhydrazine under these conditions, however. The major product from acetone and hydrazine proved to be N,N'-diisopropylhydrazine, and from acetone diisopropylhydrazone, triisopropylhydrazine. N-Nitrosoamines are not reduced under our conditions, and aldazines appear to reduce only slowly, for complex product mixtures were obtained.

By use of dicarbonyls, N,N cyclizations to piperidine and pyrrolidine derivatives are conveniently conducted. Thus N-aminopiperidine was converted to 1,1'-dipiperidiny1 (entry 8) and 1,1'-piperidiny1pyrrolidine (entry 7), using glutaraldehyde and succinaldehyde respectively, and dimethylhydrazine gave

Table 1. Representative Tetraalkylhydrazine Preparations.

| Entry | Hydrazine | Aldehyde | Product | Isolated Yield |
|-------|---|---|---|------------------|
| 1 |  | CH ₂ O |  | 59% |
| 2 |  | " |  | 40% |
| 3 |  | " |  | 52% |
| 4 | Me ₂ NN=CMe ₂ | " | Me ₂ NN(Me)i-Pr | 44% |
| 5 | i-Pr ₂ NN=CMe ₂ | " | i-Pr ₂ NN(Me)i-Pr | 52% |
| 6 |  | MeCHO |  | 30% ^a |
| 7 | " |  |  | 36% |
| 8 | " |  |  | 29% |
| 9 | Me ₂ NNH ₂ |  |  | 45% ^b |
| 10 | MeNHNHMe |  |  | 27% |
| 11 |  | " |  | 32% |

a. also 30% 1-ethylaminopiperidine

b. 3:1 ratio of trans:cis isomers

1-dimethylamino-2,5-dimethylpyrrolidine (entry 9). It is not necessary to remove the water from commercial glutaraldehyde to conduct cyanoborohydride reductions, as Borch and coworkers² did. Since 1:1 molar ratios of hydrazine to dialdehyde were employed, the great selectivity of cyanoborohydride for reduction of imines over carbonyls is apparent. Both dipiperidiny1 and piperidiny1pyrrolidine have been prepared by alkylation of hydrazines with dibromides⁵, but much purer product is obtained by reductive alkylation.⁶

The technique is also effective for cyclizing N,N', as illustrated by seven-membered ring closure to 1,2-dimethyl-hexahydro-1H-1,2-diazepine (entry 10) and 1,7-diazabicyclo[5.3.0]decane (entry 11), using aqueous glutaraldehyde. Conditions for these seven-membered ring closures were the same as the other cases. The bis-carbamate related to the entry 10 product was prepared in 15% yield by alkylation⁷, but reductive alkylation is clearly far superior for tetraalkylhydrazine preparation.

The following general method was employed for the reactions reported in Table 1: Hydrazine or hydrazone (5-10 mM), 15-25 ml of acetonitrile, pure or aqueous solution of the aldehyde or ketone (3-5 fold excess of monoaldehyde per NH bond to be substituted, but 1:1 molar ratio of bis-carbonyl to hydrazine), and 0.33 mM NaBH₃CN per mM aldehyde plus imine unsaturation present were magnetically stirred. In contrast to the observation of Borch and Hassid³, heat was not evolved until acetic acid was added, a few drops at a time over a one hour period. The reaction mixture remained basic (pH about 8 on wet pH paper). After 2-4 hr, 5 ml conc. HCl was gradually added, the mixture evaporated to a residue, dissolved in water, basicified with KOH, extracted with ether, and the organic layer dried (MgSO₄) and distilled (Kontes "short path" column). Products were identified by spectral techniques, and empirical formulas established by high resolution mass spectroscopy.

References

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2. R. E. Borch, M. D. Bernstein, and H. D. Durst, ibid., 93, 2897 (1971).

3. R. F. Borch and A. I. Hassid, J. Org. Chem., 37, 1673 (1972).
4. S. F. Nelsen and P. J. Hintz, J. Amer. Chem. Soc., 94, 7198 (1972).
5. M. Mehta and R. Lux, Arch. Pharm., 294, 640 (1961).
6. In our hands, preparation of 1,1'-dipiperidiny1 by alkylation⁵ gave a product (b (20 mm) 110-114°, lit³ b(13) 104-105°) consisting of a mixture of at least five compounds in significant amounts (VPC).
7. G. Zinner and W. Deucker, Arch. Pharm., 295, 526 (1962).