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A NEW REDUCTIVE PROCEDURE FOR THE PREPARATION OF VICINAL DIAMINES AND MONOAMINES[1]

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Summary: Selective reductive procedures for the preparation of vicinal diamines and monomines from alkyl bromocyanamides are described.

The frequent occurrence of the vicinal diamine functionality (1) in important naturally occurring compounds and medicinal agents renders this group a worthy synthetic target. Currently, few general methods exist for the preparation of vicinal diamines.[3] Recently we reported[4] a novel diamination procedure which utilized unactivated olefins (2), cyanamide (3), and N-bromosuccinimide (Scheme 1). The overall reaction was stereospecific and permitted access to diamines unsubstituted on nitrogen (1) in 51-71% yields. Keys steps included the addition of ethanol to the bromocyanamide adduct 4 to give the isourea salt 5a, the cyclization of the free base of 5a to produce the aziridine 7a and/or imidazoline 6a, and the hydrolytic cleavage of the O-ethyl imidazoline 6a to yield the vicinal diamine 1.

Although this procedure proved satisfactory for a variety of alkenes, significant improvement would be attained if less stringent conditions were required for both the cyclization and the final ring cleavage steps. We have found that both these limitations could be circumvented if the formamidine derivatives 5b were employed in place of 5a.[5] Moreover, by simple control of the initial reduction conditions, a new monoamination procedure has also been developed.

The synthetic strategy outlined in Scheme 1 demanded that selective reduction of the cyanamide group in 4 occur without concomitant hydrogenolysis of the carbon-bromine bond. Examination of the literature suggested that catalytic hydrogenation using palladium on charcoal under acidic conditions might be ideally suited to this task. These conditions have proven highly effective for the reduction of cyanamide to formamidine.[9] Moreover, reduction of 4 under acidic conditions should prevent unwanted hydrogenolysis of the carbon-bromine bond.[10]

Treatment of the bromocyanamide 4 with 1% palladium on charcoal in acetic acid-methanol (1:3) (1h) led to reduction of the cyanamide group to give the bromoformamidine 5b.[11] Formation of 5b was verified by IR, ^{1}H and ^{13}C NMR spectroscopy. After removal of the excess acetic acid under reduced pressure, the residue was dissolved in methanol and treated with sodium methoxide to yield the imidazoline 6b after workup. The reaction proved successful for

Scheme 1

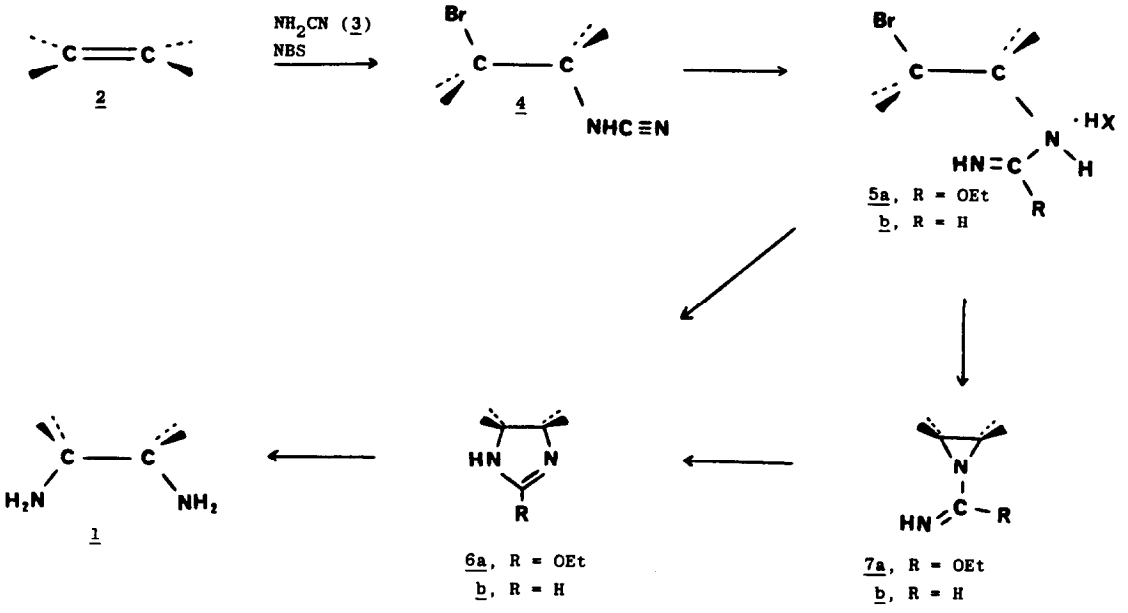


Table 1. Vicinal Diamination and Monoamination of Olefins

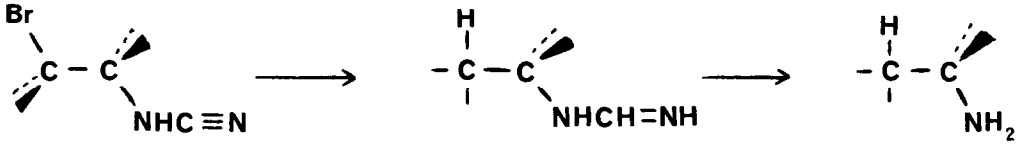
entry	olefin	vicinal diamine	yield,[a,b]%	monoamine	yield,[a]%
1	1-hexene	1,2-diaminohexane[c]	45	2-aminohexane[d](2) 1-aminohexane[d](1)	64
2	isobutylene	1,2-diamino-2-methyl-propane[c]	37	tert-butylamine[e]	34
3	trans-2-butene	dl-2,3-diaminobutane[c]	42	2-aminobutane[e]	54
4	trans-4-octene	dl-4,5-diaminooctane[c]	60	4-aminooctane[e]	71
5	cis-2-butene	-[f]	-	2-aminobutane[e]	53
6	cyclohexene	-[f]	-	cyclohexylamine[e]	48
7	2,3-dimethyl-2-butene	-[f]	-	2-amino-2,3-dimethyl butane[e,g]	61

[a]Purified yields. [b]The yields indicated are those obtained if imidazoline 6b is isolated and purified. [c]The diamine was characterized as the dihydrochloride salt. [d]Monoamines were verified as the hydrochloride salts by comparison of the ^{13}C NMR spectrum with that of authentic samples. [e]The monoamine was characterized as the N-benzoyl derivative. [f]Addition of base led to multiple products. [g]The monoamine was characterized as the picrate salt.

1-substituted alkenes, 1,1-disubstituted alkenes, and trans-disubstituted alkenes (Table 1). Attempted cyclization of the corresponding bromoformamidines 5b derived from cis-disubstituted alkenes with a variety of bases (i.e., $NaHCO_3$, NaOMe) led to mixture of products. Ring cleavage of the imidazoline 6b could be accomplished with aqueous methanolic NaOH (0.25M, reflux, 4h). In most cases, however, we have used more basic conditions (50% aqueous KOH) to facilitate isolation of the diamine. The overall yields for this reductive procedure from the alkene 2 are given in Table 1. Of note, the reaction was stereoselective and led to the formation of the unsubstituted diamine 1.

This procedure can be significantly streamlined by omitting the isolation of imidazoline 6b. A representative experimental protocol is given for the preparation of dl-2,3-diaminobutane. The bromocyanamide adduct of trans-2-butene[4] (2.00 g, 11.3 mmol) was dissolved in an acetic acid-methanol (1:3) solution (40 mL), and then 1% palladium on charcoal (2.00 g) added. Hydrogen gas was bubbled through the mixture (1h)[11] and the catalyst was filtered. The solution was then made strongly alkaline with sodium methoxide, allowed to stir overnight at room temperature, and heated to reflux (1h). An aqueous 10% NaOH solution (20 mL) was added, the reaction was heated (4h) and then distilled. The distillate was acidified with concentrated aqueous hydrochloric acid and evaporated to dryness. The white solid was washed with ethanol[12] and reprecipitated from methanol-ether to yield 1.10 g of dl-2,3-diaminobutane dihydrochloride (61%).

Omission of the acetic acid in the reduction of 4 led to the efficient production of formamidine 8. Addition of base to the reaction mixture (50% aqueous KOH, reflux, 6h) followed by extraction with ether gave monoamine 9.[14] In the case of the unsymmetrical alkene, 1-hexene, both 2-amino and 1-amino hexanes were formed in a 2:1 ratio. The overall yields for 9 from alkene 2 are reported in Table 1.



4 8 9

The results demonstrate that the reductive approach utilized in this study may be of significant value for the construction of vicinal diamines 1, 4,5-dihydroimidazoles 6b and monoamines 9. We are currently assessing the value of other reductive methods for the preparation of amines.

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References and Notes

(1) Presented, in part, at the 186th National Meeting of the American Chemical Society, Washington, D.C., August, 1983, Abstract ORGN 63.

(2) Camille and Henry Dreyfus Teacher-Scholar Grant Recipient, 1977-1982.

(3) For leading references to previous approaches, see reference 4.

(4) H. Kohn, and S.H. Jung, J. Am. Chem. Soc., 105, 4106-4108 (1983).

(5) Amidines (pKa ~ 12.5[6]) are considerably more basic than O-alkyl substituted isoureas (pKa ~ 9.1[7]). Moreover, formamidines readily cleave under basic conditions.[8]

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(9) K. Odo, E. Ichikawa, K. Shirai, and K. Sugino, J. Org. Chem., 22, 1715 (1957).

(10) R.L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, Inc., New York, N.Y., 1965, p. 125.

(11) Longer reduction times led to hydrogenolysis of the carbon-bromine bond.

(12) The ethanol layer contained erythro-3-chloro-2-amino butane hydrochloride[13] (0.30 g, 21%).

(13) A. Hassner, G.J. Matthews, and F.W. Fowler, J. Am. Chem. Soc., 91, 5046 (1969).

(14) For an excellent review on existing procedures for the preparation of monoamines from olefins, see: M.B. Gasc, A. Lattes, and J.J. Perie, Tetrahedron, 39, 703 (1983).

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