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Indirect Monoalkylation of Primary and Secondary Amines by Reductive Decyanation of α-Aminonitriles with Sodium Cyanoborohydride-Mercury Bis(Trifluoroacetate)

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Abstract: Secondary and tertiary amines are prepared from α-aminonitriles by selective reductive cleavage of the cyanide moiety. The α-aminonitriles in this case, function as "masked" imine or iminium ions and are "unmasked" by mercury (II) in the presence of sodium cyanoborohydride to obtain the reduced product. Secondary amines may be prepared indirectly from primary amines in good yield without danger of over alkylation. Published by Elsevier Science Ltd

The "retro-Strecker" decomposition of α-aminonitriles to form imines or iminium ions by loss of cyanide or HCN occurs under a variety of conditions such as mass spectrometry, vacuum flash thermolysis, and gas-phase pyrolysis.[1] Occasionally, this has been used for synthetic advantage, as in the preparation of phencyclidine (see Figure 1), where the net replacement of cyanide by phenyl Grignard reagent apparently proceeds via attack on a transient tertiary iminium species.[2]

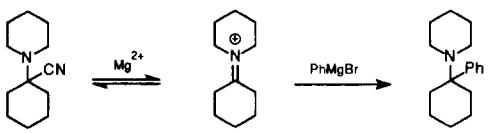


FIGURE 1

α-Aminonitriles, may then be considered to be "masked" imines or iminium ions and if "unmasked" in the presence of a suitable reducing agent, could provide a means for monoalkylation of amines. This is particularly important in the conversion of primary to secondary amines since it is not possible to stop at that stage by conventional methods of alkylation.

Sodium cyanoborohydride, which has been shown to reduce charged species in preference to neutral ones,[3] proved to be ideal for this purpose. Attempted cyanide abstraction with magnesium bromide, chosen by analogy to Grignard reactions, produced large amounts of insoluble gum, presumably due to coordination with the amino (or imino) nitrogen. Mercury (II), on the other hand, was expected to display a more specific soft-soft acid-base interaction with cyanide to the exclusion of the amino nitrogen, and gave excellent results as depicted in Figure 2.

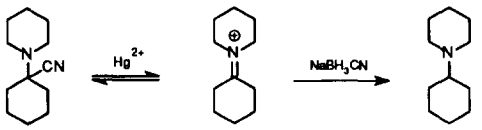


FIGURE 2

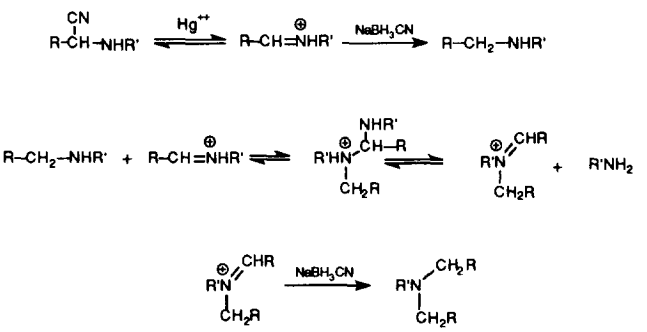
The reduction proceeds with the apparent stoichiometry shown in Figure 3. In practice, however, it is convenient to use excess reagents to insure complete conversion to product (see Table 1). During the course of the reaction, mercury (II) is reduced to mercury (0). The *ultimate* success of the reaction is due to the faster rate of reduction of the iminium intermediate than for mercury.

$$R_2NCH(CN)R' + Hg(O_2CCF_3)_2 + NaBH_3CN + 3\,MeOH \longrightarrow$$

$$R_2NCH_2R' + HO_2CCF_3 + \underline{Hg^0} + H_2\uparrow + 2\,HCN + NaO_2CCF_3 + B(OMe)_3$$

FIGURE 3

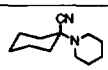
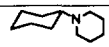
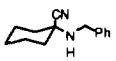
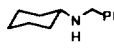
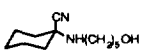
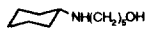
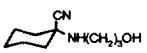
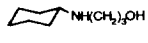
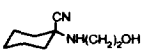
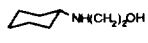
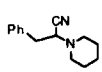
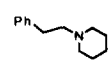
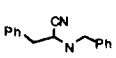
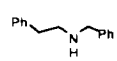
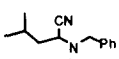
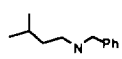
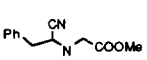
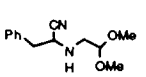
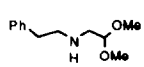
In some cases, particularly where the intermediate species is a protonated secondary imine, mercury (II) is consumed (reduced) prior to complete abstraction of cyanide. The addition of 1,4-diazobicyclo[2.2.2]octane (DABCO), as a nonoxidizable organic base, retards the rate of mercury (II) reduction, presumably by raising the pH, and allows the reaction to proceed cleanly. A second complication, polyalkylation by attack of an amine on an intermediate iminium ion (see Scheme), is also avoided by the use of DABCO.



SCHEME

Neither triethylamine or pyridine were successful alternatives to DABCO in depressing the rate of mercury (II) reduction or in preventing polyalkylation. The results of reductive decyanations of α-aminonitriles are shown in Table 1.

TABLE 1. Reductive Decyanation of α-Aminonitriles

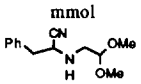
Entry	α-Aminonitrile	(mmol)	mmol $Hg(TFA)_2$	mmol $NaBH_3CN$	mmol DABCO	Product	Yield (%)
1		5.00	6.00	5.00	0.00		93 [a]
2		5.00	6.00	7.50	7.50		96 [a]
3		5.00	5.00	10.0	10.0		82 [a]
4		5.00	5.00	10.0	10.0		41 [a]
5		5.00	7.50	15.0	15.0		52 [a,b]
6		5.00	10.0	10.0	10.0		88 [a]
7		0.25	0.25	0.50	0.50		100 [c]
8		5.00	10.0	12.0	12.0		59 [a,d]
9		5.00	5.00	10.0	10.0	---	0
10		5.00	5.50	11.0	11.0		30 [c]

a Isolated yield. b Contains 2.5% spirocyclic hemiaminal. c Conversion determined by GC/MS. d Isolated as the HCl salt

Structures which contained geminal oxygens positioned proximal to the amino portion of the molecule, gave low or no conversion (entries 9 and 10, Table 1). While this appears to be due to the formation of a 1,3,2-oxazamercurolidine[4] chelate, a *single* oxygen at the same proximity provided no interference (entry 5, Table 1).[5]

The effects of solvents which could coordinate strongly with mercury and potentially destroy any chelation were studied using 2-[(2,2-dimethoxyethyl)amino]-3-phenylpropanenitrile (entry 10, Table 1) as the substrate (see Table 2). When reactions were run in THF, THF/MeOH, or when DMSO was added to THF/MeOH, no reductive decyanation occurred and all mercury (II) was reduced to mercury (0) in a short period of time. Powerful coordination by the solvent evidently prohibits any productive interaction between the metal ion and cyanide and reduction of the metal becomes the preferred avenue for consumption of hydride. In either case, coordination of mercury (II) by solvent or by some internal structural element, is a limiting factor in reductive decyanations.

TABLE 2. The Effects of Solvents on Reductive Decyanation of 2-[(2,2-Dimethoxyethyl)amino]-3-phenylpropanenitrile

Entry	mmol 	mmol $Hg(TFA)_2$	mmol $NaBH_3CN$	mmol DABCO	Solvent	Time	Conversion [a,b]
1	5.00	5.50	11.0	5.50	MeOH	4.5 hr	30%
2	1.07	1.18	2.36	1.18	THF	3.0 hr [c]	0%
3	2.50	5.50	5.50	2.75	MeOH/THF 1:1 (v:v)	3.0 hr [c]	0%
4	1.00	1.10	2.20	2.20	MeOH/THF 1:1 (v:v) DMSO (2.20 mmol)	3.0 hr [c]	0%
5	1.00	1.10	2.20		2-PrOH	24 hr	30%
6	1.00	1.10	2.20		EtOH	24 hr	50%
7	1.00	1.10	2.20		EtOH	36 hr	60%

a Conversions determined by GC/MS. b Reaction mixture contained only product and/or starting material. c All Hg(II) reduced to Hg(0) during this time period.

Higher alcohols were effective as solvents (entries 5, 6, and 7, Table 2), but required longer reaction times. Conversions were higher but they remained incomplete. The equilibria between internal chelation, solvation, and cyanide abstraction, and the effects on rates of competing processes are, no doubt, quite complex, but the trends are evident. Methanol remains the best solvent for general purposes and as a participant in the reaction according to the stoichiometry in Figure 3.

Reductive decyanation of α-aminonitriles offers a method of preparing amines from carbonyl compounds via a formal reductive alkylation process. Tertiary α-aminonitriles have been reductively decyanated with sodium in liquid ammonia[6] and by various metal hydrides.[6,7] By intentionally "unmasking" a reactive iminium intermediate with mercury (II) in the presence of $NaBH_3CN$ and DABCO, the reduction of secondary α-aminonitriles to secondary amines is also feasible (entries 2, 3, 4, 5, 7, and 8, Table 1). This "unmasking" strategy obviates the existence of free carbonyl compound, which would ordinarily react with secondary amines faster than with primary ones, and give tertiary products. The potential problem of over-alkylation via the mechanism shown in the Scheme, has been bypassed by the addition of DABCO to the reaction medium.

Experimental Section

α–Aminonitriles were prepared from commercially available material by modification[8] of known methods[1] and used without purification. All reagents and solvents were purchased from Aldrich. ^{13}C and ^1H NMR data were obtained at 50 and 200 MHz, respectively. Chemical shifts are reported in ppm (δ) downfield of tetramethylsilane and coupling constants are given in Hertz. Spectra were obtained in $CDCl_3$ unless otherwise indicated. Mass spectra were obtained by GC/MS analysis, using a 12.0 meter HP-5 capillary (5% diphenyl/95% dimethylpolysiloxane). Identification numbers of the compounds correspond to entry numbers in Table 1. Changes in molar ratios from the "General Procedure" are notated in Table 1. *Caution! Both sodium cyanoborohydride and mercury (II) trifluoroacetate, as well as their by-products, are extremely toxic and should be handled with extreme care in a fume hood with gloves.*

General Procedure. The α-aminonitrile (5.00 mmol), DABCO (5.00 mmol), and sodium cyanoborohydride (10.0 mmol) are dissolved in 10 mL MeOH and a solution of mercury (II) trifluoroacetate in 10 mL MeOH is added dropwise over 10 min, under argon. A complex of mercury (II) trifluoroacetate and sodium cyanoborohydride appears immediately as a fine grey precipitate and hydrogen is evolved midway through the addition. After stirring 24 h at room temperature, mercury (0) and any remaining grey precipitate are removed by filtration through a thin pad of Celite and rinsed with 15 mL MeOH. Volatiles are removed from the combined filtrate and rinse and the residue partitioned between 10 mL 1N NaOH and 30 mL EtOAc. Layers are separated and the organic portion washed with H_2O (3 x 10 mL), brine (1 x 10 mL), and dried over Na_2SO_4. The product is obtained by evaporation of the solvent under reduced pressure.

Generally, there is no need for further purification. Compound 5 contained 2.5% impurity[5] (see Table 1 and spectral data below); compound 8 was purified by conversion to the hydrochloride; the remainder showed less than 0.5% impurity by GC/MS and/or NMR. The reduced isolated yields for compounds 4 and 5 are due to the products' solubility in water and consequent loss during workup.

1-Cyclohexylpiperidine (1).[9] ^1H NMR δ 1.08-1.86 (m, 16H), 2.18-2.29 (m, 1H), 2.50 (pseudo t, 4H); ^{13}C NMR δ 24.8, 26.0, 26.3, 28.4, 28.6, 49.9, 64.2; EIMS *m/z* 167 (M^+), 124 (base).

N-Phenylmethylcyclohexaneamine (2).[10] ^1H NMR δ 1.01-1.30 (m, 6H), 1.60-1.91 (m, 5H), 2.40-2.51 (m, 1H) 3.78 (s, 2H), 7.17-7.30 (m, 5H); ^{13}C NMR δ 24.8, 26.0, 33.3, 50.8, 55.9, 126.5, 127.8, 128.1, 140.8; EIMS m/z 189 (M+), 91 (base).

5-Cyclohexylaminopentan-1-ol (3).[11] 1H NMR δ 0.95-1.90 (m, 16H), 2.33-2.73 (3 overlapping signals including t @ 2.61, J=6.8 and bs @ 2.73, 5H), 3.57 (t, J=6.1, 2H); ^{13}C NMR δ 23.4, 24.9, 25.9, 29.8, 32.4, 33.2, 46.6, 56.7, 61.6; EIMS *m/z* 185 (M^+), 142 (base).

3-Cyclohexylaminopropan-1-ol (4).[12] ^{1}H NMR δ 0.95-1.36 (m, 5H), 1.51-1.92 (overlapping m's, 7H) 2.35-2.48 (m, 1H) 2.85 (t, J=6.1, 2H), 3.40 (bs, 2H), 3.75 (t, J=5.5, 2H); EIMS *m/z* 157 (M^+), 114 (base).

2-Cyclohexylaminoethanol (5).[13] (Contains 2.5% spirocyclic hemiaminal by GC/MS analysis) ^{13}C NMR δ 25.0, 26.0, 33.5, 48.2, 56.6, 61.0 (hemiaminal: 45.7, 50.7, 95.4); EIMS *m/z* 143 (M+), 112 (base) [hemiaminal 142 ($M + H^+$), 112 (base)].

1-(2-Phenylethyl)piperidine (6).[14] ^{1}H NMR δ 1.38-1.49 (m, 2H), 1.55-1.66 (m, 4H), 2.42-2.58 (m, 6H), 2.76-2.84 (m, 2H), 7.11-7.30 (m, 5H); ^{13}C NMR δ 24.4, 26.0, 33.6, 54.5, 61.3, 125.8, 128.2, 128.6, 140.6; EIMS *m/z* 190 ($M + H^+$), 189 (M^+), 98 (base).

N-Phenylmethyl-N-3-methylbutaneamine (8).[15] Hydrochloride: ^{1}H NMR (DMSO-d_6) δ 0.86 (d, J=5.9, 6H), 1.56-1.62 (m, 3H), 2.84 (m, 2H), 4.10 (bs, 2H), 7.38-7.64 (m, 5H), 9.55 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 22.0, 25.3, 33.8, 44.7, 49.7, 128.4, 128.6, 130.0, 132.0; Free base: EIMS *m/z* 177 (M^+), 91 (base).

References and Notes

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5. Conversion was complete, although 2.5% of the isolated product was the spirocyclic hemiaminal (oxazolidine) by attack of the oxygen on the iminium intermediate.
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8. In a typical experiment, 20.0 mmol of the carbonyl-sodium bisulfite addition complex, 25.0 mmol potassium cyanide, and 25.0 mmol amine were suspended in 5 mL H_2O/20 mL MeOH and kept at reflux 60 min. After cooling to room temperature and filtering, volatiles were removed and the product extracted into ethyl acetate.
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