Syntheses of β-Diamines and β-Amino Alcohols from α,β-Unsaturated Ketones and Aldehyde, Methylamine, and Borohydride Reducing Agents

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Received June 18, 1976

The reduction of three α,β-unsaturated ketones and one aldehyde by sodium borohydride and/or sodium cyanoborohydride in the presence of methylamine produced β-diamines and β-amino alcohols in variable yields. Thus, the maximum yields obtained follow: from crotonaldehyde, 40% *N,N'*-dimethyl-1,3-butanediamine (**1**) and 5% 3-methylamino-1-butanol (**4**); from methyl vinyl ketone, 15% **1** and 5% 4-methylamino-2-butanol (**5**); from 3-penten-2-one, 50% *N,N'*-dimethyl-2,4-pentanediamine (**2**) and 60% 4-methylamino-2-pentanol (**6**); and from mesityl oxide, less than 5% *N,N'*-dimethyl-2-methyl-2,4-pentanediamine (**3**) and 70% 4-methylamino-2-methyl-4-pentanol (**7**). A reaction mechanism of initial addition of amine followed by reduction of one or both of the carbonyl–imine (or iminium ion) equilibrium species is discussed.

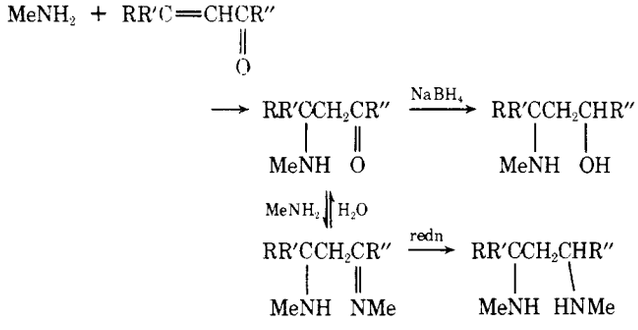
During the pursuit of our research we found that the availability of β-disubstituted secondary amines such as **1–3** (see Table I) would be highly desirable. Although procedures for the preparations of primary amine analogues have been established,[1] the same techniques are not always applicable for the secondary amines. Only compound **1** of **1–3** has been reported and it was obtained as a by-product in less than 15% yield.[2] The development of reliable syntheses for these types of compounds was therefore undertaken.

This paper reports the procedures and results obtained employing four α,β-unsaturated carbonyl compounds (crotonaldehyde, methyl vinyl ketone, 3-penten-2-one, and mesityl oxide), two borohydride reducing agents ($NaBH_4$ and $NaBH_3CN$), and methylamine. In addition to obtaining the desired secondary diamines (although in highly variable yields), proper control of reaction conditions resulted in the preparation of β-amino alcohols.

Results and Discussion

The results of these and previously reported syntheses are summarized in Table I. In none of the reactions reported here were by-products readily identifiable, although NMR spectra and elemental analyses were consistent with the formation of some triamines. The majority of the by-products (30% and more of the total product weight, depending on the starting material) were viscous, polymeric materils.

It is proposed that the reactions to produce compounds **1–7** proceed by the mechanism depicted below (where R, R', and R'' are H or Me as defined in Table I). The addition of methylamine was likely the first step followed by reduction of one or more of the carbonyl–imine equilibrium species. This mechanism is consistent with the experimental results. (Although imines are depicted above as being the species reduced to amines by both reagents, Borch, Bernstein, and Durst have reported that iminium ions are the actual species reduced by sodium cyanoborohydride.[3])



Reduction of crotonaldehyde, methyl vinyl ketone, and mesityl oxide with sodium borohydride by procedures 3 and/or 4 (see Experimental Section) gave the amino alcohols **4, 5,** and **7,** respectively. In each case the hydroxyl function was attached to the carbon atom that was formerly a part of the carbonyl group. This suggests that the initial step in each of the reactions was addition of amine to form the Mannich base. The preparations of compounds **8** and **9** substantiate this.

8 **9**

When crotonaldehyde, dimethylamine hydrochloride, and sodium cyanoborohydride were sequentially added to a solution of ammonia in methanol, 1-dimethylamino-3-aminobutane (**8**) was obtained. The reverse deployment of amine reagents, addition of crotonaldehyde to dimethylamine followed by ammonium chloride and sodium cyanoborohydride, produced 1-amino-3-dimethylaminobutane (**9**). In neither case was the other compound obtained.

The second step of the mechanism, establishment and reduction of a ketone–imine or aldehyde–imine (or iminium ion) equilibrium, has precedence.[4] Indeed, it is the selective reduction of such equilibrium species that has led to the use of sodium cyanoborohydride for reductive amination. Although at pH values of 4 or less aldehydes and ketones are reduced to alcohols by sodium cyanoborohydride, they are reduced only slowly at values of 6 and above.[3] At the higher pH values sodium cyanoborohydride thus functions selectively by reducing the iminium ions of the carbonyl–iminium ion equilibrium.[3] The fact that diamines were obtained in the reactions reported here indicates that such equilibria also exist in this system. The reactions of 3-penten-2-one with sodium borohydride to produce **2** and **6** exemplify the presence and importance of these equilibria. The ratio of amino alcohol (**6**) to diamine (**2**) obtained (see Table I) was substantially increased when the relative amount of methylamine was reduced (procedure 2 vs. 3) and when additional quantities of water were introduced prior to reduction (procedure 3 vs. 4).

The mechanism involved in the reactions to form diamines and amino alcohols thus appears to be unambiguous, but the large variations in yields among the three diamines and four amino alcohols cannot be rationalized with certainty since the compositions of the by-products and the mechanisms of their formation are not known. Based on the results for **2** and **6** discussed above, however, the carbonyl–imine equilibrium appears to be an important consideration. From the mesityl oxide reductions, for example, the consistently poor yields of diamine **3** compared to those of amino alcohol **7** suggest that the ketone–imine equilibrium lay far to the ketone side under all of the conditions employed. Thus, in contrast to the 3-

Table I. Table of Compounds and Yields

$$RR'CCH_2CHR''$$
$$\quad\quad|\quad\quad|$$
$$\quad MeNH\ X$$

Compd	R	R'	R''	X	Yield, % 1[a]	2[a]	3[a]	4[a]	Lit.
1	Me	H	H	HNMe	40[b]	35[b]	0[b]	c	<15[d]
					15[e]	5[e]	0[e]	0[e]	
2	Me	H	Me	HNMe	20	50	30	5	
3	Me	Me	Me	HNMe	<5	0	0	0	
4	Me	H	H	OH	0	0	5	c	64,[f] <30[d]
5	H	H	Me	OH	0	0	5	5	
6	Me	H	Me	OH	0	5	35	60	35[g]
7	Me	Me	Me	OH	0	60	70	70	80[h]

[a] See Experimental Section for description of procedures 1, 2, 3, and 4. [b] From crotonaldehyde as starting material. [c] Crotonaldehyde is incompatible with procedure 4. [d] From crotonaldehyde, methylamine, and sodium amalgam (ref 2). [e] From methyl vinyl ketone as starting material. [f] From methyl crotonate, methylamine, and $LiAlH_4$: H. Schonenberg, H. Vogel, and E. Bamann, *Arch. Pharm. (Weinheim, Ger.)*, **298**, 371 (1965). [g] From 3-penten-2-one, methylamine, and sodium amalgam (ref 7). [h] From mesityl oxide, methylamine, and sodium amalgam (ref 7 and 9).

penten-2-one and sodium borohydride system (vide supra), variations in the relative methylamine quantities and the presence of additional water did not greatly affect the product distributions when mesityl oxide was reduced with sodium borohydride. In fact, the diamine was observed only when sodium cyanoborohydride was employed (procedure 1) and then it was obtained in very poor yield. An equilibrium lying far to the ketone side can be rationalized in terms of the greater steric requirements of the additional methyl group in mesityl oxide compared to 3-penten-2-one.

Experimental Section

Chemicals. With the exception of crotonaldehyde, obtained from Eastman Chemical, reagents were obtained from Aldrich Chemical and were used without further purification.

Analyses. Microanalyses were obtained from Midwest Microlabs, Inc., Indianapolis, Ind.

Syntheses of Secondary Amino Compounds. The general preparative procedures are described below. Yields of the individual compounds are summarized in Table I. NMR, analytical, and derivative data for the individual compounds follow the general procedures.

1. Procedure 1. Reduction of a 2:1 mole ratio of amine to α,β-unsaturated ketone or aldehyde with sodium cyanoborohydride.

The following procedure was modeled after that of Borch.[5] To a solution of 33.3 g (0.50 mol) of $MeNH_2$·HCl and 200 ml of MeOH contained in a 500-ml round-bottom flask equipped with a magnetic stirring system, ice bath, addition funnel, and nitrogen inlet was added all at once 11.2 g (0.20 mol) of KOH. Although KCl precipitated, it caused no interference. When the KOH had completely reacted, 0.20 mol of α,β-unsaturated ketone or aldehyde dissolved in 40 ml of methanol was added dropwise. After completion of addition, the suspension was stirred for 0.5 h and a solution of 5.23 g (25% excess of 0.067 mol) of $NaBH_3CN$ dissolved in 40 ml of MeOH was added dropwise. (This procedure using crotonaldehyde required the immediate addition of the reducing agent rather than allowing the solution of crotonaldehyde, $MeNH_2$, and $MeNH_2$·HCl to stir for 0.5 h. Failure to begin the addition immediately resulted in discoloration of the solution and eventual formation of a brown oil.) The suspension was stirred overnight and allowed to warm to room temperature. The KCl was removed by filtration, and 16.8 g (0.30 mol) of KOH was added to the filtrate. After the KOH had completely dissolved and reacted, the suspension was filtered again. It was found that these two filtrations were more efficient than a single filtration after the latter portion of KOH had been added to the original suspension. The MeOH was then removed by rotary evaporation until about 50 ml of solution was left. The remaining solvent was distilled at atmospheric pressure. The product was removed from the viscous material remaining by crude vacuum distillation (0.8–0.1 mm) requiring pot temperatures of up to 100 °C, and a heat lamp on exposed pot and distillation head glassware. The receiving flask was kept in a dry ice-2-propanol bath. These drastic conditions were necessary to remove the product from the increasingly viscous residue. Any water in the product was removed by benzene azeotrope employing a Dean-Stark apparatus. The benzene was then removed by distillation and the product was distilled at either atmospheric pressure or under vacuum.

2. Procedure 2. Reduction of a 2:1 mole ratio of amine to α,β-unsaturated ketone or aldehyde with sodium borohydride.

The same general procedures were employed as in 1 above with the exception that 4.4 g of $NaBH_4$ dissolved in a solution of 3–4 pellets of KOH and 40 ml of water was used instead of $NaBH_3CN$ in methanol.

3. Procedure 3. Reduction of a 1:1 mole ratio of amine to α,β-unsaturated ketone or aldehyde with sodium borohydride.

The procedures were similar to 2 above. Only 16.2 g (0.25 mol) of $MeNH_2$·HCl and 13.6 g (0.24 mol) of KOH were used for 0.2 mol of aldehyde or ketone. After stirring overnight the KCl was filtered, but no further addition of KOH was necessary.

4. Procedure 4. Reduction of a 1:1 mole ratio of amine to α,β-unsaturated ketone with sodium borohydride in the presence of additional water.

The procedure differed from 3 above only in that an additional 50 ml of water was added after the ketone-containing solution, and the suspension was allowed to stir 0.5 h before addition of the reducing agent. This procedure is $_2$·HCl discolored and eventually formed a brown oil unless the reducing agent addition was begun immediately.

***N,N'*-Dimethyl-1,3-butanediamine (1):** bp 61 °C (10 mm), 152 °C (740 mm); NMR ($CDCl_3$) δ 1.12 (d, 3, CH_3), 1.30 (m, 4, CH_2), 1.67 (s, 2, NH), 2.45 (s, 3, NCH_3), 2.48 (s, 3, NCH_3) and 2.7 (m, 3, CH and CH_2). The dioxalate derivative had mp 192–192.5 °C dec (lit.[2] mp 193 °C dec).

***meso*- and *dl*-*N,N'*-Dimethyl-2,4-pentanediamine (2).** Two points in the preparation should be mentioned. It was found during the crude distillation that when a yellow, higher boiling, more viscous compound began to distill, the desired product was completely removed and the distillation could be stopped. In those preparations where the amino alcohol 6 was also obtained (procedures 2, 3, and 4), the two compounds could be separated by vacuum distillation through a 10-cm Vigreux column: bp 52 °C (6 mm); NMR ($CDCl_3$) δ 0.88 (d, 6, CH_3), 1.1 (m, 2, CH_2), 1.29 (s, 2, NH), 2.22 (s, 6, NCH_3), and 2.45 (m, 2, CH). The dipicrate derivative of the isomeric mixture had mp 210 °C.

Anal. Calcd for dipicrate $C_{19}H_{24}N_8O_{14}$: C, 38.78; H, 4.11; N, 19.04. Found: C, 39.36; H, 4.20; N, 18.76.

***N,N'*-Dimethyl-2-methyl-2,4-pentanediamine (3):** bp 48 °C (10 mm); NMR ($CDCl_3$) δ 1.32 (s, 6, CH_3), 1.47 (d, 3, CH_3), 1.6 (m, 2, CH_2), 2.21 (s, 6, NCH_3), 2.3 (m, 1, CH), and 2.98 (s, 2, NH).

Anal. Calcd for $C_8H_{20}N_2$: C, 66.61; H, 13.97; N, 19.42. Found: C, 66.49; H, 13.90; N, 19.11.

3-Methylamino-1-butanol (4): bp 63 °C (13 mm) [lit.[6] 65 °C (14 mm)]; NMR ($CDCl_3$) δ 1.10 (d, 3, CH_3), 1.63 (m, 2, CH_2), 2.25 (s, 2, NH and OH), 2.48 (s, 3, NCH_3), 2.6 (m, 1, CH), 3.33 (m, 2, CH_2).

4-Methylamino-2-butanol (5): bp 78 °C (8 mm); NMR (D_2O) δ 1.23 (d, 3, CH_3), 1.70 (m, 2, CH_2), 2.32 (s, 3, NCH_3), 2.61 (m, 2, CH_2), 3.85 (m, 1, CH).

Anal. Calcd for $C_5H_{13}NO$: C, 58.21; H, 12.70; N, 13.58. Found: C, 58.31; H, 12.53; N, 13.65.

***erythro*- and *threo*-4-Methylamino-2-pentanol (6)** (see additional comments under 2 above): bp 63 °C (6 mm) [lit. 75.5–76 °C (14 mm),[7] 80–82 °C (17 mm)[8]]; NMR ($CDCl_3$) δ 1.04 (4 sets of d, 6, CH_3),

1.3 (m, 2, CH_2), 2.30 (s, 6, NCH_3), 2.53 (m, 1, CH), 3.1 (s, 2, NH and OH), and 3.83 (m, 1, CH). A picrate derivative of the isomeric mixture had mp 87–89 °C (lit.[7] threo mp 103.5–105 °C, erythro mp 86–87 °C).

Anal. Calcd for picrate $C_{12}H_{18}N_4O_8$: C, 41.62; H, 5.24; N, 16.18. Found: C, 41.76; H, 5.52; N, 16.20.

4-Methylamino-4-methyl-2-pentanol (7): bp 70 °C (10 mm) [lit. bp 115 °C (16 mm),[7] 184.5–185.5 °C (750 mm)[9]]; NMR (D_2O) δ 1.27 (s, 6, CH_3), 1.28 (d, 3, CH_3), 1.63 (m, 2, CH_2), 2.32 (s, 3, NCH_3), 4.07 (m, 1, CH). A picrate derivative had mp 154 °C (lit.[7,9] mp 156–158 °C).

1-Dimethylamino-3-aminobutane (8). The procedure was similar to procedure 1 above. Thus, 10.6 g (0.20 mol) of NH_4Cl was dissolved in 200 ml of methanol and cooled with ice, and 11.2 g (0.20 mol) of KOH was added all at once. After all of the KOH had reacted, 16.2 ml (0.20 mol) of crotonaldehyde dissolved in 40 ml of methanol was added dropwise. That addition was immediately followed by the addition of 16.2 g (0.20 mol) of Me_2NH·HCl and then the dropwise addition of a solution of 5.23 g (25% excess of 0.067 mol) of $NaBH_3CN$ in 40 ml of MeOH. The product was worked up in the manner described under 1 above except that no attempt was made to dry it. A yield of 40% was estimated by NMR after distillation through a 10-mm Vigreux column. Traces of water and MeOH remained in the product: bp of mixture 93 °C (740 mm) [lit.[10] bp 55 °C (16 mm)]; NMR ($CDCl_3$) δ 1.21 (d, 3, CH_3), 1.68 (m, 2, CH_2), 2.32 (s, 6, NCH_3), 2.4 (m, 3, CH_2 and CH), and 3.37 (s, 2, NH_2). A picrate had mp 180 °C (lit.[10] mp 181 °C).

1-Amino-3-dimethylaminobutane (9). The preparation of 9 was the same as for 8 above except that the introductions of the NH_4Cl and Me_2NH·HCl were reversed. After the product had been crudely distilled, it was dried employing a benzene azeotrope as in procedure 1 above. A yield of 15% was obtained: bp 46 °C (10 mm) [lit.[11] bp 154–156 °C (pressure not given)]; NMR ($CDCl_3$) δ 1.03 (d, 3, CH_3), 1.63 (m, 2, CH_2), 1.08 (s, 2, NH_2), 2.30 (s, 6, NCH_3), 2.6 (m, 3, CH_2 and CH). A picrate derivative had mp 204 °C (lit.[11] mp 204 °C).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Ball State University Research Committee for support of this research. The authors thank Drs. T. L. Kruger and B. N. Storhoff for their discussions and suggestions.

Registry No.—**1**, 57757-16-1; *meso*-**2**, 60978-26-9; *dl*-**2**, 60978-27-0; *meso*-**2** dipicrate, 60978-28-1; *dl*-**2** dipicrate, 60978-29-2; **3**, 60978-30-5; **4**, 2704-55-4; **5**, 42142-55-2; *erythro*-**6**, 53019-16-2; *threo*-**6**, 53089-02-4; *erythro*-**6** picrate, 60978-31-6; *threo*-**6** picrate, 60978-32-7; **7**, 42142-50-7; **8**, 13022-87-2; **9**, 60978-33-8; crotonaldehyde, 4170-30-3; methyl vinyl ketone, 78-94-4; mesityl oxide, 141-79-7; dimethylamine HCl, 506-59-2; dimethylamine, 124-40-3; 3-penten-2-one, 625-33-2.

References and Notes

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Migration of Acyl Groups in *o*-Aminophenol. 1. The Acetyl–Benzoyl, Acetyl–*p*-Nitrobenzoyl, and Acetyl–Propionyl Systems

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Received July 19, 1976

The synthesis and characterization of six mixed diacyl derivatives of *o*-aminophenol is described. It is shown that the rearrangements which have created so much uncertainty in this area in the past are actually solvent-catalyzed isomerizations which were minimized in this work by the proper choice of reaction and recrystallization solvents. In pyridine and in ethanol, isomerization resulted in the formation of dynamic equilibrium mixtures in accord with the theoretical predictions of Le Rosen and Smith in 1949. The compositions of the equilibrium mixtures and of the mixtures of monoacyls obtained on saponification were also in general agreement with the theoretical predictions of these authors. However, the failure to obtain isomerization in acetone, ether, water, or acetic acid solvents appears to cast doubt on their assumption of a general acid–base catalyzed isomerization mechanism. Further work to test this mechanism was deferred because of inconsistencies in the isomerization rates which appear to be due to the presence of unknown trace impurities.

The rearrangements occurring in *N,O*-diacyl derivatives of *o*-aminophenol wherein the two acyl groups are different (mixed diacyls) have been studied extensively in the older literature.[1-4] A 1968 Russian review article lists 228 references dealing with these migrations and related phenomena.[5] As noted in this review, these reactions are of theoretical interest as well as being of considerable practical importance in organic synthesis. In general, the mechanism of these reactions has remained obscure because of the inability of these earlier workers to separate and analyze the labile product mixtures which they obtained.

Le Rosen and Smith were the first workers to provide quantitative results for one of these systems (acetyl–benzoyl) and their work strongly indicated that the rearrangements were actually isomerizations of the mixed diacyls caused by the catalytic influence of the solvents used in preparing and purifying these products.[6] They further showed that isomerization was rapid in alkaline medium so that saponification in dilute base gave a mixture of the two possible monoacyl products. A theoretical explanation of their findings was presented which seemed to clarify the reasons for the many conflicting results reported to that time. They suggested that the isomerizations were general acid or base catalyzed so that an equilibrium mixture of the mixed diacyls was formed in