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A Simplified Synthesis of (±)-1,2-Diphenyl-1,2-diaminoethane (1) from Benzaldehyde and Ammonia. Revision of the Structures of the Long-Known Intermediates "Hydrobenzamide" and "Amarine"

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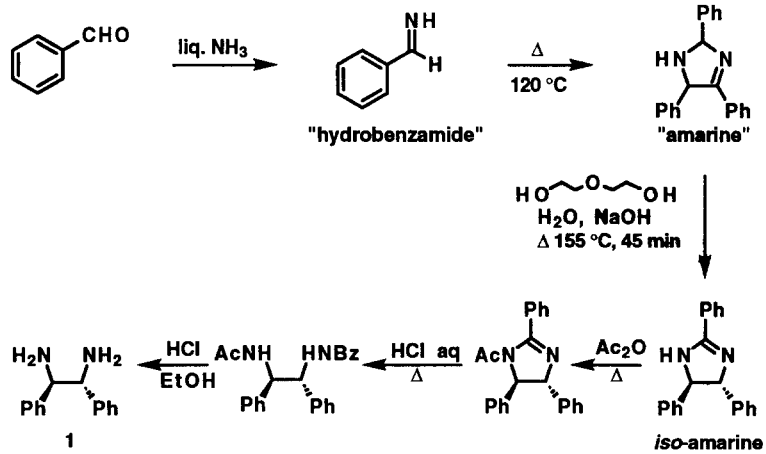
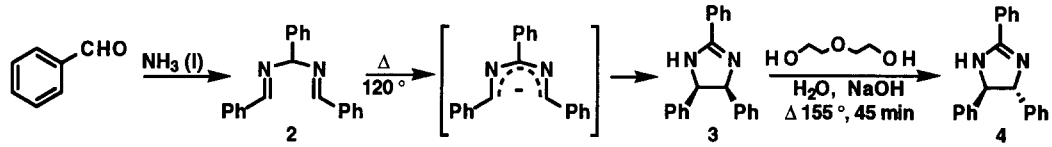
Summary: *A new pathway for the simple, stereocontrolled and economical synthesis of (±)-1 from benzaldehyde is described. The structures of two intermediates (Scheme 1) have been revised to those shown in Scheme 2.* © 1997 Elsevier Science Ltd.

1,2-Diphenyl-1,2-diaminoethane (**1**) (stilbenediamine) has long been used as a ligand ("*stien*") in the study of metal chelates because of it's C_2-symmetric structure.[1] More recently, the enantiomers of this diamine have been employed extensively in new reagents and catalysts for enantioselective synthesis. For example, highly enantioselective versions have been described for the following reactions: Diels-Alder,[2] aldol,[2a,3] carbonyl allylation[4] and propargylation,[5] dihydroxylation[6] and epoxidation[7] of olefins, electrophilic attack on enolates.[8,9] The utility of the (*R*,*R*) and (*S*,*S*) enantiomers of **1** in asymmetric synthesis has stimulated the development of a

Scheme 1. Synthesis of Racemic **1** via "Hydrobenzamide", "Amarine, and *iso*-Amarine, (Structures According to Saigo *et. al*)[11]



Scheme 2. Corrected Reaction Sequence for the Synthesis of *iso*-Amarine (**4**).



number of new processes for their preparation.[10] Since the resolution of (±)-**1** can be carried out efficiently to provide the two pure enantiomers,[1,10,11] the principal need is for a very simple and cheap synthesis of racemic **1** on a commercial scale. In principle, a reductive coupling process starting with benzaldehyde imine would seem attractive. However, that imine is not available, since the reaction of benzaldehyde with ammonia leads to the long-known substance "hydrobenzamide" instead.[1,11,12] In addition, numerous studies of the reductive coupling of *N*-protected imines of aromatic aldehydes offer little promise because such couplings have produced diastereomeric mixtures of the racemic and meso *N*-protected 1,2-diamines, and also have involved expensive or impractical reagents.[13-17] The original route to (±)-**1** starting from benzaldehyde and ammonia[1,11,12] is definitely usuable, although it suffers from excessive length and inconvenient procedures.[18] That old process includes two intermediates "hydrobenzamide" and "amarine" the structures of which have remained questionable,[1,11,12] even after so many years; it is outlined in the previously accepted version[11] in Scheme 1. The purpose of this paper is to clarify the structures of "hydrobenzamide" and "amarine" and to show how these intermediates can be used in a shorter and more effective synthesis of (±)-**1**.

"Hydrobenzamide" and "amarine" can be synthesized easily and in high yield as previously described.[1] Suitable single crystals of each were readily obtained and analyzed by X-ray diffraction. The structure of

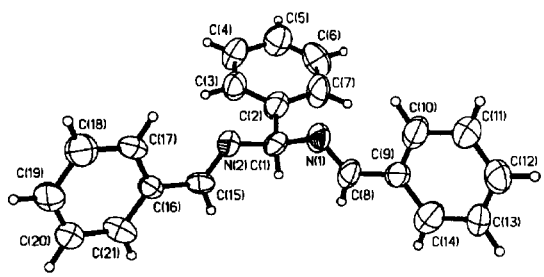


Figure 1. ORTEP representation of the crystal structure of hydrobenzamide **2**.

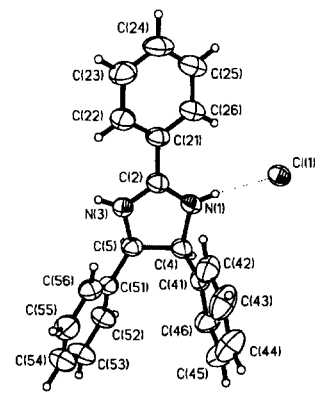
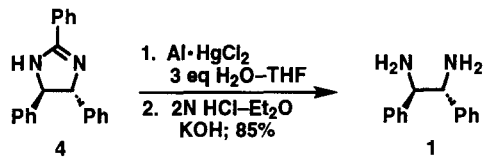


Figure 2. ORTEP representation of the crystal structure of amarine hydrochloride **3**•HCl.

"hydrobenzamide" was thereby shown to be **2** (Figure 1 and Scheme 2) and that of amarine hydrochloride to be **3**•HCl (Figure 2 and Scheme 2). The stereospecific formation of **3** from **2** can readily be accounted for as a well-precedented disrotatory pericyclic closure of an intermediate 2,4-diazapentadienyl anion. The conversion of **3** to **4** under vigorous basic conditions is also simply explained in terms of equilibration via deprotonation of **3** to form a delocalized benzylic anion and subsequent protonation to give **4**, with reversibility at each step.

Because of the ready availability of **4** from benzaldehyde and ammonia via intermediates **2** and **3**, we sought a simple method for conversion of **4** into (±)-1,2-diphenyl-1,2-diaminoethane (**1**). As expected for a cyclic amidine, **4** is resistant to acid-catalyzed hydrolysis even at reflux, because of the stability of the conjugate acid. The amidinium ion derived from **4** also resists reduction by borohydride-type reagents. However, reduction of **4** by aluminum amalgam in moist THF occurred readily to give the corresponding imidazolidine which upon treatment with aqueous acid and subsequent workup provided (±)-**1** in 85% yield. The specific procedure follows.



Reduction of 4 to 1. Aluminum foil (450 mg, 16.8 mmol, cut into 20 x 20 mm strips) was immersed with agitation for 30 seconds successively in Et_2O, EtOH, 2% aqueous mercuric chloride, EtOH, and Et_2O. The pieces were immediately cut into smaller strips (6 x 2 mm) and covered with THF under N_2 in a 50 ml round-bottom flask. Imidazoline **4** (1 g, 3.35 mmol) dissolved in THF (20 ml) containing 10 mmole of H_2O was added dropwise with stirring. The mixture was stirred at 23 °C for 2 h, and filtered. The alumina was washed thoroughly with THF and concentrated to yield 995 mg of a colorless solid. This solid product was suspended in Et_2O and 2*N* HCl (25 ml of each), and the suspension was treated gradually with 20 ml of H_2O with stirring until all the solid had dissolved. The phases were separated, and the aqueous phase was adjusted to pH 12 by addition of 2*N* KOH and extracted with CH_2Cl_2 (5 x 50 ml). The extract was dried (Na_2SO_4) and concentrated *in vacuo* to give the racemic diamine **1** as a colorless solid (604 mg, 85% of the theory). The diamine so obtained was identical with an authentic sample[10] in all respects and pure by ^1H NMR analysis. The product had a melting point of 81-82 °C, R_f 0.1 (30% EtOAc–hexanes) and the following spectral properties: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.59 (bs, 4 H), 4.10 (s, 2 H), 7.2 - 7.3 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 61.9, 126.9, 127.0, 128.2, 143.4; mass spectrum (CI) *m/z* (rel intensity) 230 (15) $[M + NH_4]^+$, 213 (100) $[M + H]^+$, 139 (4), 106 (5).[19,20]

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19. The coordinates of **2** and **3** can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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