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Augusto Rivera^a, Rodolfo Quevedo^a, Miguel A. Navarro^a & Mauricio Maldonado^a

^a Departamento de Química, Universidad Nacional de Colombia, Apartado Aéreo 14490, Ciudad Universitaria, Bogotá, Colombia Published online: 10 Jan 2011.

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Efficient Tetrahydrosalen Synthesis from Mannich-Type Bases

Augusto Rivera,* Rodolfo Quevedo, Miguel A. Navarro, and Mauricio Maldonado

Departamento de Química, Universidad Nacional de Colombia, Ciudad Universitaria, Bogotá, Colombia

ABSTRACT

Synthesizing a variety of tetrahydrosalens from hydrolyzing 1,3-*bis* (2'-hydroxy-5'-substituted-benzyl)imidazolidines with hydrochloric acid is described. Further reaction of such tetrahydrosalens with alde-hydes yielded 2-substituted-1,3-*bis*(2'-hydroxy-5'-substituted-benzyl) imidazolidines.

Key Words: Tetrahydrosalen; Mannich-type bases; Ethylenediamine; Formaldehyde.

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^{*}Correspondence: Augusto Rivera, Departamento de Química, Universidad Nacional de Colombia, Apartado Aéreo 14490, Ciudad Universitaria, Bogotá, Colombia; E-mail: ariverau@unal.edu.co.

INTRODUCTION

The continuing search for new ligand systems for transition metals has drawn considerable interest to chelating amino and hydroxy compounds. Compounds from the salen family have been extensively studied for many purposes and applied mostly in catalysis.^[11] Tetrahydrosalens have also been investigated for the potential use as achiral ligand that can adopt asymmetric conformations and can participate in enantioselective catalysis transferring asymmetry from the catalyst to the substrate.^[2–5] Previous syntheses of N,N'-bis(2-hydroxybenzyl)ethylenediamine compounds (tetrahydrosalens) have involved isolation of the salen intermediate and reduction with NaBH₄ or LiAlH₄, resulting in lower yields.^[6] Other procedures employ the reductive amination of N-N'-dimethylethylenediamine with NaBH₃(CN).^[7] Tshuva et al. recently published a new method for synthesizing tetrahydrosalens in a single stage via Mannich condensation from primary or secondary diamine, formaldehyde, and a substituted phenol.^[11]

In a previous paper,^[8] we reported that 1,3-bis(2'-hydroxy-5'-substitutedbenzyl)imidazolidines reacted with benzaldehyde and p-methoxybenzaldehyde affording 2t-substituted-1r.3c-bis(2'-hydroxy-5'-substituted-benzyl)imidazolidines as the main reaction product and proposed a mechanism which involves the possible formation of N,N'-bis(5-substituted-2-hydroxybenzyl) ethylenediamine as intermediate. It should be mentioned that the aforementioned reaction failed when *m*-nitrobenzaldehyde and salicyaldehyde were used and no transformation was observed; thus reaction with other aldehydes or a ketone was chosen as the basis for the work reported in this article. These results encouraged us to develop a general method for synthesizing N, N'-bis(2-hydroxybenzyl)ethylenediamine tetrahydrosalens. To test this method, we prepared 2a-e from imidazolidines 1a-e and carried out reactions to obtain substituted tetrahydrosalens not only with *m*-nitrobenzaldehyde, salicylaldehyde, benzaldehyde, and *p*-methoxybenzaldehyde but also with other carbonyl compounds such as furfural and acetone. In all cases, 2-substituted-1,3-bis-(2'-hydroxy-5'-substituted-benzyl) imidazolidines 3a-f were obtained with excellent yield.

EXPERIMENTAL

¹H NMR spectra were measured on a Brucker AC-500 spectrometer operating at 500 MHz. In all cases, CDCl₃ was used with TMS as the internal standard. Melting points were determined with a electrothermal 9100 melting point apparatus and are uncorrected. The 1,3-*bis*(2'-hydroxybenzyl)imidazolidines were prepared as described^[9] from phenols and 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]

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dodecane (TATD), which was prepared as described^[10] from ethylenediamine and formaldehyde and was further purified by recrystallisation from benzene. All new compounds gave satisfactory elemental analysis.

General Procedure for the Synthesis of *N*,*N'-bis* (2-Hydroxybenzyl)ethylenediamines 2a-e

A 10% hydrochloric acid (10 mL) was added to a 1,3-*bis*(2'-hydroxy-5'substituted-benzyl)imidazolidine **1** (3.0 mmol) in 1,4-dioxane (2 mL) solution; the resulting mixture was stirred until a precipitate appeared. The product was filtered off and washed with 1,4-dioxane. The N,N'-bis(2-hydroxybenzyl)ethylenediamine hydrochloride obtained from the foregoing was dissolved in methanol (5 mL). A 10% aqueous ammonia solution (10 mL) was added and the mixture was stirred until a precipitate appeared. The N,N'-bis(2-hydroxybenzyl)ethylenediamine **2** was filtered and washed with water. Melting points and yields are given in Table 1.

¹H NMR: *N*,*N*'-*bis*(2-hydroxy-5-chlorobenzyl)ethylenediamine **2a** δ: 2.95 (s, 4H, CH₂), 3.97 (s, 4H, Ar-CH₂), 6.79 (d, 2H, H-C3'), 6.95 (d, 2H, H-C5'), 7.14 (dd, 2H, H-C4'); Anal. Calcd for $C_{16}H_{18}Cl_2N_2O_2$: C, 56.26; N, 8.20; H, 5.27; Cl, 20.78. Found: C, 56.30; N, 8.28; H, 5.20; Cl, 20.82. *N*,*N*'-*bis*(2-Hydroxy-benzyl)ethylenediamine **2b** δ: 2.85 (s, 4H, CH₂), 3.99 (s, 4H, Ar-CH₂), 6.78 (td, 2H, H-C5'), 6.83 (dd, 2H, H-C3'), 6.98 (dd, 2H, H-C6'), 7.17 (td, 2H, H-C4'). *N*,*N*'-*bis*(2-Hydroxy-3-methylbenzyl)ethylenediamine **2c** δ: 2.21 (s, 6H, CH₃), 2.84 (s, 4H, CH₂), 3.97 (s, 4H, Ar-CH₂), 6.70 (t, 2H, H-C5'), 6.83 (dd, 2H, H-C6'), 7.05 (dd, 2H, H-C4'); Anal. Calcd for C₁₈H₂₄N₂O₂: C, 71.90; N, 9.32; H, 7.98. Found: C, 71.96; N, 9.37; H, 7.93. *N*,*N*'-*bis*(2-Hydroxy-4-methylbenzyl)ethylenediamine **2d**: 2.27 (s, 6H, CH₃), 2.90 (s, 4H, CH₂), 3.60 (s, 4H, Ar-CH₂), 6.70 (d, 2H, H-C3'), 6.60 (d, 2H, H-C5'); Anal. Calc. for C₁₈H₂₄N₂O₂: C, 71.90; N, 9.32; H, 7.94; N, 9.34; H, 7.97. *N*,*N*'-*bis*(2-Hydroxy-4-methylenediamine **2d**: 2.77. *N*,*N*'-*bis*(2-Hydroxy-4-methylenzyl)ethylenediamine **2d**: 2.27 (s, 6H, CH₃), 2.90 (s, 4H, CH₂), 3.60 (s, 4H, Ar-CH₂), 6.70 (d, 2H, H-C3'), 6.60 (d, 2H, H-C6'); Anal. Calc. for C₁₈H₂₄N₂O₂: C, 71.90; N, 9.32; H, 7.98. Found: C, 71.94; N, 9.34; H, 7.97. *N*,*N*'-*bis*(2-Hydroxy-4-methylenzyl)ethylenediamine **2**H; 4.79.

Table 1. Tetrahydrosalen yield from 1,3-*bis*(2'-hydroxybenzyl) imidazolidines **1**.

| M.p. found/lit. ($^{\circ}$ C) | Yield (%) | |
|---------------------------------|--|--|
| 146 | 90 | |
| 118/117 ^[5] | 87 | |
| 129 | 71 | |
| 151 | 83 | |
| 140 | 89 | |
| | M.p. found/lit. (°C) 146 118/117 ^[5] 129 151 140 | |

(2-Hydroxy-5-methylbenzyl)ethylenediamine **2e**: 2.23 (s, 6H, CH₃), 2.96 (s, 4H, CH₂), 3.87 (s, 4H, Ar-CH₂), 6.75 (d, 2H, H-C3'), 6.99 (dd, 2H, H-C4'), 6.77 (d, 2H, H-C6'); Anal. Calc. for $C_{18}H_{24}N_2O_2$: C, 71.90; N, 9.32; H, 7.98. Found: C, 71.96; N, 9.35; H, 7.95.

General Procedure for the Synthesis of 2-Substituted-1,3-bis (2'-hydroxy-5'-chlorobenzyl)imidazolidines 3a-f

As stated in Section 1, either an aldehyde or a ketone (2.9 mmol) was added to an ethylenediamine 2 (1.0 g, 2.9 mmol) in benzene (5 mL) solution (in a well-ventilated fume cupboard). The reaction mixture was heated until reflux occurred, product forming at different times depending on reagent used; reaction was monitored by TLC. A resinous solid was obtained after removing solvent at reduced pressure (20 mm Hg). The product was purified by column chromatography on silica gel eluted with benzene : ethyl acetate (8:2) mixture. Table 2 shows melting points, reaction time, and yields.

¹H NMR: 2*t*-phenyl-1*r*,3*c*-*bis*(2'-hydroxy-5'-chlorobenzyl)imidazolidine **3a** δ: 2.68 (td, 2H, H-C4, H-C5), 3.34 (td, 2H, H-C4, H-C5), 3.30 (d, 2H, Ar-CH₂), 3.96 (d, 2H, Ar-CH₂), 3.80 (s, 1H, H-C2), 6.70 (d, 2H, H-C3'), 6.92 (d, 2H, H-C6'), 7.08 (dd, 2H, H-C4'), 7.46 (s, SH, H-C2", 3", 4", 5", 6"); 2*t*-(2"-hydroxyphenyl)-1*r*,3*c*-*bis*(2'-hydroxy-5'-chlorobenzyl)imidazolidine **3b** δ: 2.65 (td, 2H, H-C4, H-C5), 3.27 (td, 2H, H-C4, H-C5), 3.35 (d, 2H, Ar-CH₂), 4.06 (d, 2H, Ar-CH₂), 3.95 (s, 1H, H-C2), 6.76 (d, 2H, H-C3'), 6.89 (m, 2H, H-C5", H-C6"), 6.99 (d, 2H, H-C6'), 7.09 (dd, 2H, H-C4'), 7.16 (dd, 1H, H-C3"), 7.22 (dd, 1H, H-C4"); Anal. Calcd for C₂₃H₂₂Cl₂N₂O₃: C, 62.02; N, 6.29; H, 4.94; Cl, 15.92. Found: C, 62.13; N, 6.33; H, 4.91; Cl, 15.96. 2*t*-(3"-Nitrophenyl)-1*r*,3*c*-*bis*(2'-hydroxy-5'-chlorobenzyl)imidazolidine **3c** δ: 2.75 (td, 2H, H-C4, H-C5), 3.40 (td, 2H, H-C4, H-C5), 3.47 (d, 2H,

Table 2. Reaction of N,N'-bis(2-hydroxy-5-chlorobenzyl)ethylenediamine 2 with aldehydes and ketones.

| Carbonyl compound | Product | M.p. found/ lit. (°C) | Time (hr) | Yield (%) |
|-------------------------------|------------|----------------------------|--------------|--------------|
| Benzaldehyde | 3 a | 175/173-175 ^[8] | 6 | 91 |
| Salicylaldehyde | 3b | 169 | 14 | 78 |
| <i>m</i> -Nitrobenzaldehyde | 3c | 161 | 36 | 63 |
| <i>p</i> -Methoxybenzaldehyde | 3d | 187/187-189 ^[8] | 2 | 93 |
| Furfural | 3e | 178 | 48 | 755 |
| Acetone | 3f | 181 | 0.5 | 94 |

Ar-CH₂), 3.92 (d, 2H, Ar-CH₂), 3.97 (s, 1H, H-C2), 6.65 (d, 2H, H-C3'), 6.92 (d, 2H, H-C6'), 7.65 (t, 1H, H-C5'), 7.88 (d, 1H, H-C6"), 8.25 (m, 2H, H-C4", H-C2"), 9.48 (s, 2H, OH). 2t-(4''-Methoxyphenyl-1r, 3c-bis(2'-hydroxy-5'-chlorobenzyl)imidazolidine 3d δ: 2.65 (td, 2H, H-C4, H-C5), 3.32 (td, 2H, H-C4, H-C5), 3.27 (d, 2H, Ar-CH₂), 3.98 (d, 2H, Ar-CH₂), 3.75 (s, 1H,H-C2), 6.71 (d, 2H, H-C3'), 6.92 (d, 2H, H-C6'), 6.97 (d, 2H, H-C3", 5"), 7.08 (dd, 2H, H-C4'), 7.41 (d, 2H, H-C2", 6"), 3.80 (s, 3H, O-CH₃). 2t-furyl- $1r_{,3c-bis}(2'-Hydroxy-5'-chlorobenzyl)$ imidazolidine **3e** δ : 2.78 (td, 2H, H-C4, H-C5), 3.25 (td, 2H, H-C4, H-C5), 3.42 (d, 2H, Ar-CH2), 4.00 (d, 2H, Ar-CH₂), 4.20 (s, 1H, H-C2), 6.38 (s, 1H, H-C4"), 6.50 (s, 1H, H-C3"), 6.75 (d, 2H, H-C3'), 6.92 (d, 2H, H-C6'), 7.15 (dd, 2H, H-C4'), 7.55 (s, 1H, H-C5"), 9.8 (s, 2H, OH); Anal. Calcd for C₂₁H₂₀Cl₂N₂O₃: C, 60.10; N, 6.67; H, 4.77; Cl, 16.91. Found: C, 60.07; N, 6.68; H, 4.75; Cl, 16.94. 2,2-Dimethyl-1,3-bis(2'-hydroxy-5'-chlorobenzyl)imidazolidine 3f δ: 1.35 (s, 6H, H-Cl", H-C2"), 2.85 (s, 4H, H-C4, H-C5), 3.82 (s, 4H, Ar-CH₂), 6.75 (d, 2H, H-C3'), 6.98 (d, 2H, H-C6'), 7.12 (dd, 2H, H-C4'). Anal. Calcd for C₁₉H₂₂Cl₂N₂O₂: C, 59.80; N, 7.34; H, 5.76; Cl, 18.59. Found: C, 59.77; N, 7.33; H, 5.79; Cl, 18.61.

RESULTS AND DISCUSSION

As mentioned above, acid hydrolysis of Mannich type bases such as 1,3-*bis*(2'-hydroxybenzyl)-imidazolidine **1a**–e synthesized according to the cited methodology,^[9] leads to tetrahydrosalens **2a**–e, respectively (Sch. 1). These results show that the nature and position of substituents in the aromatic ring do not influence the course of the reaction, making this a very versatile method for producing unsubstituted tetrahydrosalens with good yield (Table 1). 1,3-*bis*(2'-Hydroxy-5'-chlorobenzyl)imidazolidines **1** and



Scheme 1.

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N,*N'-bis*(2-hydroxy-5-chlorobenzyl)ethylenediamines **2** form complexes and can be theoretically directly used as tetradented ligands or serve as base materials for synthesizing new ligands.^[11] As an example of their use as base materials in synthesizing new ligands, a new family of 2-substituted-1, 3-*bis*(2'-hydroxy-5'-substituted-benzyl)imidazolidine **3a–f** tetrahydrosalens was synthesized by the reaction of **2** with some aldehydes or ketones (Sch. 2) which also form complexes whose structure is being currently studied by our research group. This represents a new, convenient asymmetrical tetrahydrosalen synthetic route having good yield (Table 2) for simple reactions and can be done using commercially available reagents.

In conclusion, our protocol provides an expedient approach to unsubstituted tetrahydrosalens and substituted tetrahydrosalens derived from a variety of phenols and aromatic aldehydes or aliphatic ketones. The main advantages of this method over previous ones are the ready availability of reagents, high yields for various carbonyl compounds, and operational simplicity.

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