

An Efficient Scalable Synthesis of 2,3-Epoxypropyl Phenylhydrazones

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Received: 3 January 2005; in revised form: 16 December 2005 / Accepted: 17 December 2005 /
Published: 31 January 2006

Abstract: A series of mono and di-*N*-2,3-epoxypropyl *N*-phenylhydrazones have been prepared on a large scale by reaction of the corresponding *N*-phenylhydrazones of 9-ethyl-3-carbazolecarbaldehyde, 9-ethyl-3,6-carbazoledicarbaldehyde, 4-dimethyl-amino-, 4-diethylamino-, 4-benzylethylamino-, 4-(diphenylamino)-, 4-(4,4'-dimethyl-diphenylamino)-, 4-(4-formyldiphenylamino)- and 4-(4-formyl-4'-methyldiphenyl-amino)benzaldehyde with epichlorohydrin in the presence of KOH and anhydrous Na₂SO₄.

Keywords: Heterocycles, epichlorohydrin, hydrazones, charge transport.

Introduction

Epoxides are versatile intermediates in organic synthesis; and a large variety of reagents are known for the ring opening of these compounds to yield products with important biological activities and pharmacological properties [1, 2]. On the other hand, hydrazine derivatives are nowadays of considerable technical and commercial importance [3]. Particularly hydrazones are often mentioned among the most effective charge transporting low-molecular-weight materials used in electrophotography, due to their excellent hole-transporting properties and relatively simple synthesis [4-7].

Recently, we have reported the synthesis and properties of new hole transporting materials consisting of two hydrazone branches. These materials were synthesized by connecting two *N*-2,3-

epoxypropyl *N*-phenylhydrazones with various difunctional nucleophilic compounds. The molecular structure of these transporting materials makes crystallization in the solid state difficult, so these materials are able to form glasses. Another peculiarity of the branched hydrazones is the presence of two hydroxyl groups in the molecule that improves their adhesion to some substrates and compatibility with some polymers, such as polyvinylbutyraldehyde. A variety of these branched hydrazones, involving *N*-ethylcarbazole, *N,N*-diethylaniline, *N,N*-benzylethylaniline and triphenylamine moieties have been generated [8,9]. Moreover, a new class of polymeric hydrazones was reported [10]. They ensure rapid charge transporting ability, high photosensitivity and durability of EPL, however until now there was no data concerning the synthesis of the epoxypropyl phenylhydrazones of arylaldehydes, which are the starting materials for preparation of above described novel electronactive molecules.

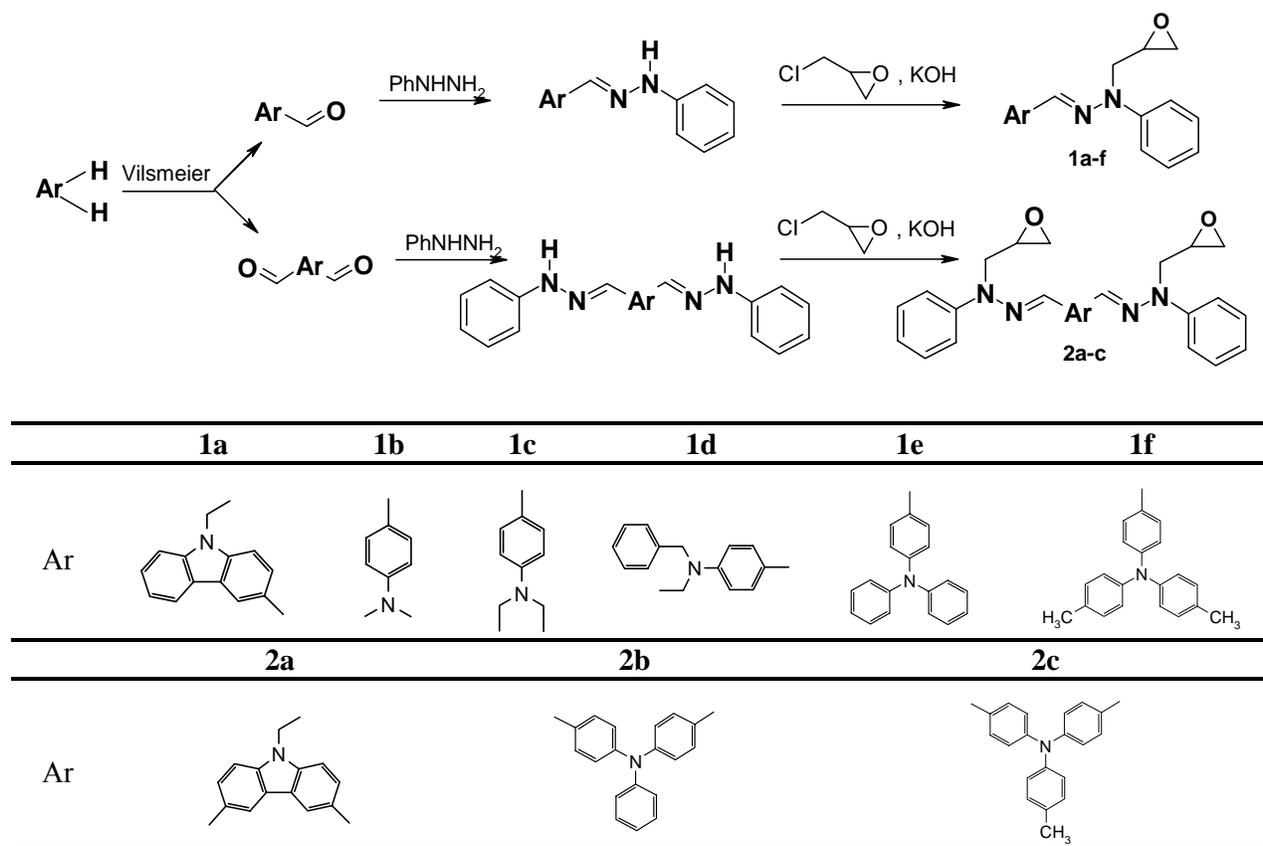
In this paper we report a synthetic method for large scale preparations of 2,3-epoxypropyl-*N*-phenyl-hydrazones and their bis-analogues containing 9-ethylcarbazole, diethylaniline, benzylethylaniline, triphenylamine, methyltriphenylamine, dimethyltriphenylamine moieties, which have been recently mentioned among the most usable organic photoconductors [11-14].

Results and Discussion

At first the reaction of phenylhydrazones with epichlorohydrin was carried out at room temperature in the presence of potassium hydroxide and anhydrous K_2CO_3 and lasted for 3 days. More attractive seemed the alkylation at 55-60 °C which allows to obtain various *N*-2,3-epoxypropylated hydrazones. At the elevated temperature the reaction time was reduced to 1.5-2 h, and high yields (57-81 %) were observed.

The experiments carried out revealed that this method was not suitable for bigger than preparative scale synthesis. At 55-60 °C in the presence of KOH and anhydrous K_2CO_3 the reaction often slipped out of control due to the polymerization of epichlorohydrin. Some changes to this method were made: the reaction was carried out at 35-40 °C by adding KOH and dewatering material in three portions with prior cooling of the reaction mixture to 20-25°C, the anhydrous K_2CO_3 was replaced by anhydrous Na_2SO_4 . These changes enabled to decrease the amount of the water adsorbent used, reduce the amount of poly(epichlorohydrin) formed and ensure better reaction control.

Based on the developed method, by interaction of *N*-phenylhydrazones of 9-ethyl-3-carbazole-carbaldehyde, 4-dimethylamino-, 4-diethylamino-, 4-benzylethylamino-, 4-(diphenylamino)-, 4-(4,4'-dimethyldiphenylamino)benzaldehydes with epichlorohydrin (Scheme 1) a series of *N*-2,3-epoxypropyl hydrazones were synthesized on large scale with 78-90 % yields. This series included 1-(9-ethyl-carbazol-3-ylmethylene)-2-(2,3-epoxypropyl)-2-phenylhydrazine (**1a**), 2-(2,3-epoxypropyl)-1-(4-dimethylaminophenylmethylene)-2-phenylhydrazine (**1b**), 2-(2,3-epoxypropyl)-1-(4-diethylamino-phenylmethylene)-2-phenylhydrazine (**1c**), 1-(4-benzylethylaminophenylmethylene)-2-(2,3-epoxy-propyl)-2-phenylhydrazine (**1d**), 1-[4-(diphenylamino)phenylmethylene]-2-(2,3-epoxypropyl)-2-phenylhydrazine (**1e**) and 2-(2,3-epoxypropyl)-1-[4-(4,4'-dimethyldiphenylaminophenylmethylene)]-2-phenylhydrazine (**1f**).

Scheme 1. Synthetic route to the epoxides **1a-i** containing hydrazone moieties

This method was slightly modified in the case of bis(*N*-2,3-epoxypropyl-*N*-phenyl)hydrazones **2a-c**; the amounts of epichlorohydrin, KOH and anhydrous Na₂SO₄ were increased, as well as the reaction times. 9-Ethyl-3,6-carbazoledicarbaldehyde bis(*N*-2,3-epoxypropyl-*N*-phenyl)hydrazone (**2a**), 4-(4-formyldiphenylamino)benzaldehyde bis(*N*-2,3-epoxypropyl-*N*-phenyl)hydrazone (**2b**) and 4-(4'-formylmethyldiphenylamino)benzaldehyde bis(*N*-2,3-epoxypropyl-*N*-phenyl)hydrazone (**2c**) were thus synthesized on a large scale in 50-60 % yields.

The structures of **1a-i** were confirmed by their ¹H-NMR spectra and elemental analysis data. A typical set of lines for the epoxypropyl group appears in the 4.40-2.50 ppm region of the ¹H-NMR spectra of **1a-f** and **2a-c**. In the ¹H-NMR spectrum of **1e** (shown in Figure 1) we observed the most clearly defined ABX systems of the non-equivalent geminal protons of NCH₂ and CH₂O. Thus the CH₂O appeared as a doublet of doublets at 2.62 ppm (H_A with J_{AB}=4.8 Hz, J_{AX}=2.7 Hz) and as a doublet of doublets at 2.84 ppm (H_B with J_{BX}=4.1 Hz) due to the coupling with CH, while protons of NCH₂ respectively gave dd at 4.35 ppm (H_{A'} with J_{A'B'}=16.4 Hz, J_{A'X}=2.4 Hz) and dd at 3.99 ppm (H_{B'} with J_{B'X}=4.1 Hz).

General method for the preparation of aldehyde mono- and diphenylhydrazones

Phenylhydrazine (0.1 mol for monohydrazones or 0.25 mol in case of dihydrazones) and the corresponding aldehyde (0.1 mol) were dissolved in 2-propanol (100 mL) in case of hydrazones or THF (100 mL) in the case of dihydrazones. The mixture was refluxed until the aldehyde disappeared (10 min). At the end of the reaction, the mixture was cooled to room temperature. The crystals formed upon standing were filtered off and washed with 2-propanol to give corresponding phenylhydrazones, which were subjected to the reaction with epichlorohydrin without further purification.

General method of the preparation of N-2,3-epoxypropylated phenylhydrazones 1a-f

To the mixture of phenylhydrazone of the corresponding aldehyde (1 mol) and epichlorohydrin (1.5 mol), powdered 85 % potassium hydroxide (3 mol) and anhydrous Na₂SO₄ (0.4 mol) were added in three portions with prior cooling of the reaction mixture to 20-25 °C (1st portion – 1/2 of Na₂SO₄ and 1/3 of KOH; 2nd portion – 1/4 of Na₂SO₄ and 1/3 of KOH after 1h from the beginning of the reaction; 3rd – 1/4 of Na₂SO₄ and 1/3 of KOH after 2h from the beginning of the reaction). The reaction mixture was stirred vigorously at 35-40 °C until the starting hydrazone disappeared (3-4 h). After termination of the reaction, the mixture was cooled to RT and filtered off. The organic layer was washed with distilled water until the wash water was neutral. The organic layer was dried over anhydrous magnesium sulfate, treated with activated charcoal, filtered and excess of epichlorohydrin was removed. In the case of **1a-d** the obtained residue was dissolved in a 1:1 mixture of toluene and 2-propanol. The crystals formed upon standing were filtered off and washed with 2-propanol. Compounds **1e,f** were purified by column chromatography.

1-(9-ethylcarbazol-3-ylmethylene)-2-(2,3-epoxypropyl)-2-phenylhydrazine (1a): Yield 78.5 %, m.p. 136-137 °C (recrystallized from toluene); ¹H-NMR spectrum (CDCl₃, δ, 250 MHz): 8.35 (s, 1H, 4-H_{Ht}); 8.14 (d, *J*=7,8 Hz, 1H, 1-H_{Ht}); 7.93 (d, *J*=7,6 Hz, 1H, 2-H_{Ht}); 7.90 (s, 1H, CH=N); 7.54-7.20 (m, 8H, Ph, H_t); 6.96 (t, *J*=7.2 Hz, 1H, 4-H_{Ph}); 4.37 (m, 3H, CH₂CH₃, one of the NCH₂ protons); 4.04 (dd, *J*₁=4.3 Hz, *J*₂=16.4 Hz, 1H, next of the NCH₂ protons); 3.32 (m, 1H, CH); 2.88 (dd, 1H, part of the ABX system, *cis*-H_A of CH₂O, *J*_{AX}=2.6 Hz, *J*_{AB}=4.9 Hz); 2.69 (dd, 1H, part of the ABX system, *trans*-H_B of CH₂O, *J*_{BX}=4.0 Hz); 1.44 (t, *J*=7.2 Hz, 3H, CH₃) ppm; Anal. Calcd. for C₂₄H₂₃N₃O: C, 78.02; H, 6.27; N, 11.37. Found: C, 78.12; H, 6.18; N, 11.38.

2-(2,3-epoxypropyl)-1-(4-dimethylaminophenyl-methylene)-2-phenylhydrazine (1b): Yield 86.4 %; m.p. 123.5-124.5 °C (recrystallized from 2-propanol); ¹H-NMR (CDCl₃, δ, 80 MHz): 7.7-6.8 (m, 8H, CH=N, Ar); 6.7 (d, 2H, part of AB system, *p*-Ph); 4.5-3.7 (m, 2H, NCH₂); 3.4-3.1 (m, 1H, CH); 2.9 (s, 6H, CH₃); 2.9-2.7 (m, 1H, *cis*-H of CH₂O); 2.7-2.5 (m, 1H, *trans*-H of CH₂O) ppm; Anal. Calcd. for C₁₈H₂₁N₃O: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.15; H, 7.19; N, 14.31.

2-(2,3-epoxypropyl)-1-(4-diethylaminophenylmethylene)-2-phenylhydrazine (1c): Yield 80.4 %; m.p. 79-80.5 °C (recrystallized from ethyl ether); ¹H-NMR (CDCl₃, δ, 250 MHz): 7.7-6.7 (m, 8H, Ar, CH=N); 6.6 (d, 2H, 2-H, 6-H of *p*-Ph); 4.4-3.6 (m, 2H, NCH₂CH); 3.6-3.0 (m, 5H, CH₂CH₃,

CH₂CHCH₂); 2.75 (m, 1H, ABX, *cis*-H_A of CH₂O); 2.55 (m, ABX, *trans*-H_B of CH₂O); 1.1 (t, *J*=7.0 Hz, 6H, CH₃) ppm; Anal. Calcd. for C₂₀H₂₅N₃O: C, 74.27; H, 7.79; N, 12.99. Found: C, 74.21; H, 7.70; N, 12.91.

1-(4-benzylethylaminophenylmethylene)-2-(2,3-epoxypropyl)-2-phenylhydrazine (1d): Yield of oily **1d** 80.4 %; ¹H-NMR (CDCl₃, δ, 400 MHz): 7.70 (s, 1H, CH=N); 7.55 (d, 2H, *J*=8.8 Hz, 2,6-H_{p-Ph}); 7.16-7.41 (m, 4H, Ar); 6.93 (t, 1H, *J*=7.3 Hz, 4-H_{Ph}); 6.69 (d, 2H, *J*=8.8 Hz, 3,5-H_{p-Ph}); 4.58 (s, 2H, CH₂Ph); 4.37 (dd, 1H, ABX, *J*_{AB}=16.2, *J*_{AX}=2.4 Hz, H_A of NCH₂); 3.99 (dd, 1H, ABX, *J*_{BX}=4.1 Hz, H_B of NCH₂); 3.28 (m, 1H, CH_X); 3.53 (q, 2H, *J*=7.3 Hz, CH₂CH₃); 2.84 (dd, 1H, ABX, *J*_{AB}=4.8 Hz, *J*_{AX}=2.7 Hz, *cis*-H_A of CH₂O); 2.62 (dd, 1H, ABX, *J*_{BX}=4.0 Hz, *trans*-H_B of CH₂O); 1.24 (t, *J*=7.3 Hz, 3H, CH₂CH₃); Anal. Calcd. for C₂₅H₂₇N₃O: C, 77.89; H, 7.06; N, 10.90. Found: C, 77.91; H, 7.15; N, 10.81.

1-[4-(diphenylamino)phenylmethylene]-2-(2,3-epoxypropyl)-2-phenylhydrazine (1e): Yield 89.9 %; m.p. 141-142.5 °C (recrystallized from toluene); ¹H-NMR (CDCl₃, δ, 250 MHz 250): 7.65-6.98 (m, 19H, CH=N, Ar); 6.93 (t, *J*=7.2 Hz, 1H, 4-H_{Ph}); 4.35 (dd, 1H, part of the ABX system, H_A of NCH₂, *J*_{AX}=2.4 Hz, *J*_{AB}=16.4); 3.99 (dd, 1H, part of the ABX system, H_B of NCH₂, *J*_{BX}=4.1 Hz); 3.26 (m, 1H, CH); 2.84 (dd, 1H, part of the ABX system, *cis*-H_A of CH₂O, *J*_{AX}=2.7 Hz, *J*_{AB}=4.8 Hz); 2.62 (dd, 1H, part of the ABX system, *trans*-H_B of CH₂O, *J*_{BX}=4.1 Hz); Anal. Calcd. for C₂₈H₂₅N₃O: C, 80.16; H, 6.01; N, 10.02. Found: C, 80.19; H, 6.10; N, 10.09.

2-(2,3-epoxypropyl)-1-[4-(4,4'-dimethyldiphenylaminophenylmethylene)-2-phenylhydrazine (1f): Yield of oily **1f** 87.3 %; ¹H-NMR (CDCl₃, δ, 250 MHz): 7.62 (s, 1H, CH=N); 7.55-6.90 (m, 17H, Ar); 4.34 (dd, 1H, part of the ABX system, H_A of NCH₂, *J*_{AX}=2.2 Hz, *J*_{AB}=16.5); 3.98 (dd, 1H, part of the ABX system, H_B of NCH₂, *J*_{BX}=4.4 Hz); 3.27 (m, 1H, CH); 2.85 (dd, 1H, part of the ABX system, *cis*-H_A of CH₂O, *J*_{AX}=2.7 Hz, *J*_{AB}=4.9 Hz); 2.63 (dd, 1H, part of the ABX system, *trans*-H_B of CH₂O, *J*_{BX}=4.0 Hz). _{Ph}); 7.72 (s, 1H, CH=N); Anal. Calcd. for C₃₀H₂₉N₃O: C, 80.51; H, 6.53; N, 9.39. Found: C, 80.52; H, 6.48; N, 9.46.

General synthetic method of bis(*N*-2,3-epoxypropyl-*N*-phenyl)hydrazones **2a-c**

To the mixture of the diphenylhydrazone of the corresponding dialdehyde (1 mol) and epichlorohydrin (22.5 mol), powdered 85 % potassium hydroxide (4.5 mol) and anhydrous Na₂SO₄ (0.6 mol) were added in three portions with prior cooling of the reaction mixture to 20-25 °C (1st portion – 1/2 of Na₂SO₄ and 1/3 of KOH; 2nd portion – 1/4 of Na₂SO₄ and 1/3 of KOH after 1h from the beginning of the reaction; 3rd – 1/4 of Na₂SO₄ and 1/3 of KOH after 2h from the beginning of the reaction). The reaction mixture was stirred vigorously at 35-40 °C until the starting dihydrazone disappeared (7-8 h). After completion of the reaction, the mixture was cooled to RT and filtered off. The organic part was washed with distilled water until the wash water was neutral. The organic layer was dried over anhydrous magnesium sulfate, treated with activated charcoal, filtered and the excess of epichlorohydrin was removed. In the case of **2a,b** the residues obtained were recrystallized from

toluene and the crystals formed upon standing were filtered off and washed with 2-propanol. Compound **2c** was purified by column chromatography.

9-ethyl-3,6-carbazoledicarbaldehyde bis(N-2,3-epoxypropyl-N-phenyl)hydrazone (2a): Yield: 342 g (63 %), m.p. 119-120 °C; ¹H-NMR spectrum (300 MHz, CDCl₃), ppm: 8.38 (split s, 2H); 7.9-7.88 (m, 4H); 7.49-7.43 (m, 4H); 7.40-7.32 (m, 6H); 6.96 (t, 2H, *J*= 7.2 Hz); 4.42-4.29 (m, 6H); 4.06-3.97 (dd, 2H, (H_A), *J*_{AX}= 4.5 Hz, *J*_{AB}= 16.4 Hz); 3.31 (m, 2H); 2.90-2.85 (dd, 2H, (H_A), *J*_{AX}= 3.9 Hz); 2.70-2.65 (dd, 2H, (H_B), *J*_{BX}= 2.7 Hz; *J*_{AB}=5.1 Hz); 1.43 (t, *J*=7.2 Hz); Anal. Calcd for C₃₄H₃₃N₅O₂ %: C 75.11; H 6.12; N 12.88. Found, %: C 75.16; H 6.09; N 12.81.

4-(4-formyldiphenylamino)benzaldehyde bis(N-2,3-epoxypropyl-N-phenyl)hydrazone (2b): Yield: 312 g (52 %), m.p. 163.5-165 °C; ¹H-NMR spectrum (300 MHz, CDCl₃), ppm: 7.63 (s, 2H); 7.62-7.56 (m, 4H); 7.43-7.02 (m, 17H); 6.94 (t, 2H, *J*= 7.1 Hz); 4.40-4.30 (dd, 2H, (H_A), *J*_{AX}= 2.1 Hz, *J*_{AB}= 16.5 Hz); 4.02-3.92 (dd, 2H, (H_B), *J*_{BX}= 4.2 Hz); 3.26 (m, 2H); 2.84 (dd, 2H, (H_A), *J*_{AX}= 4.2 Hz, *J*_{AB}= 5.1 Hz); 2.65-2.60 (dd, (H_B), *J*_{BX}= 2.7 Hz); Anal. Calcd for C₃₈H₃₅N₅O₂ %: C 76.87; H 5.94; N 11.80. Found, %: C 76.71; H 5.91; N 11.70.

4-(4-formyl-4'-methyl-diphenylamino)benzaldehyde bis(N-2,3-epoxypropyl-N-phenyl)hydrazone (2c): Yield of amorphous **2c**: 332 g (55 %); ¹H-NMR spectrum (300 MHz, CDCl₃), ppm: 7.63 (s, 2H); 7.61-7.54 (m, 4H); 7.42-7.02 (m, 17H); 6.94 (t, 2H, *J*= 7.2 Hz); 4.40-4.28 (dd, 2H, (H_A), *J*_{AX}= 2.1 Hz, *J*_{AB}= 16.5 Hz); 4.02-3.90 (dd, 2H, (H_B), *J*_{BX}= 4.2 Hz); 3.26 (m, 2H); 2.84 (dd, 2H, (H_A), *J*_{AX}= 4.2 Hz, *J*_{AB}= 4.8 Hz); 2.66-2.60 (dd, (H_B), *J*_{BX}= 2.7 Hz); 2.33 (s, 3H); Anal. Calcd for C₃₉H₃₇N₅O₂ %: C 77.08; H 6.14; N 11.52. Found, %: C 77.14; H 6.10; N 11.58.

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Sample Availability: Available from the authors.

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