Stereoselective synthesis of 1,2-diamino-1,2-diarylethane derivatives

I. V. Bessonov, N. A. Lozinskaya, V. R. Katashova, M. V. Proskurnina, and N. S. Zefirov*

Department of Chemistry, M. V. Lomonosov Moscow State University,
1 Leninskie Gory, 119992 Moscow, Russian Federation.
Fax: +7 (095) 939 0290. E-mail: natalylozinskaya@mail.ru

A procedure was developed for selective opening of the *cis*-2,4,5-triarylimidazoline ring to form *erythro*-1,2-diamino-1,2-diarylethane derivatives. These ring-opening products, *erythro*-ethylenediamine derivatives, can undergo quantitative isomerization to *threo*-ethylenediamine derivatives in the presence of strong bases in DMSO.

Key words: vicinal diamines; stereoselective synthesis; isomerization; *cis*-imidazolines.

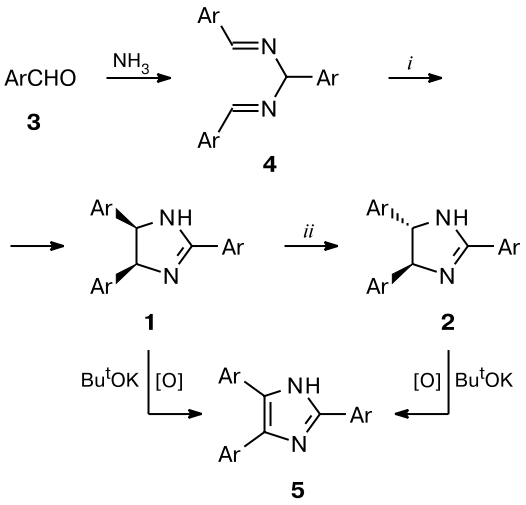
The design of catalysts providing higher stereoselectivity of reactions is a promising field of modern organic chemistry. For this purpose, researchers are carrying out an extensive search for new complex-forming ligands, which are rather sterically crowded and can easily be modified. From this point of view, 1,2-ethylenediamine derivatives are of considerable interest. However, the range of vicinal diamines is presently limited to 1,2-diphenylethylene-1,2-diamine, 1,2-diaminocyclohexane, and their derivatives. The reason is that a simple procedure has been devised in detail only for the synthesis of these compounds, whereas a convenient and universal method for the synthesis of vicinal diamines is lacking. The development of a simple and stereoselective procedure for the synthesis of 1,2-diamines, which would allow one to perform successive modifications of each amino group, could substantially facilitate the solution of many synthetic problems.

As part of our continuing studies aimed at devising a method for the synthesis of 1,2-diarylethylenediamines,[1,2] we examined the possibility of ring opening in *cis*- and *trans*-imidazolines to produce derivatives of vicinal diamines. One can easily and stereoselectively prepare *cis*- and *trans*-imidazolines **1** and **2** from the corresponding aromatic aldehydes **3** and ammonia (Scheme 1).[2]

The ring closure in the anion derived from aldehyde ammonia **4** occurs strictly disrotatory in accordance with electronic control over the reaction. However, *trans*-imidazolines containing electron-withdrawing substituents in the aromatic ring are difficult to synthesize, because such imidazolines undergo predominantly oxidation to the corresponding imidazoles **5** (Scheme 1).

The 2,4,5-triarylimidazoline ring opening is a more complicated problem than the opening of rings containing aliphatic substituents because the former ring is more inert due, apparently, to conjugation of the C=N double bond with the aryl group. For example, refluxing of

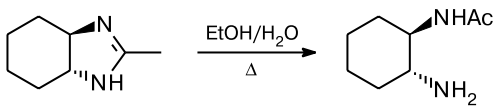
Scheme 1



i. Bu^tOK/THF, −10 °C, 1—10 min. *ii*. Bu^tOK/Bu^tOH, 60 °C.

2-methyl-4,5-tetramethyleneimidazoline in aqueous alcohol is sufficient to perform ring opening (Scheme 2),[3] whereas the 2,4,5-triarylimidazoline ring opening requires more drastic conditions, such as refluxing with acetic anhydride giving rise to *N*-acetyl-*N*′-aroyl-substituted vicinal diamine[4,5] or reduction with aluminum amalgam to form unsubstituted diamine.[6]

Scheme 2



Earlier,[1] we have studied the reactions of aromatic aldehydes with ammonium acetate yielding *N*′-aroyl-

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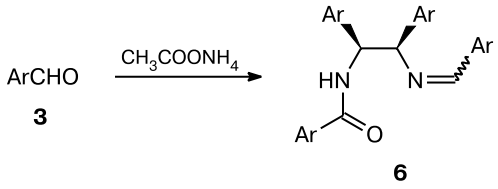
N-arylidene derivatives **6** (Scheme 3), which should proceed through the formation of *cis*-imidazoline.

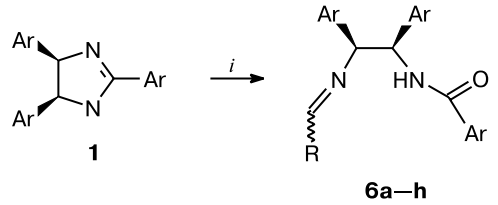
Scheme 3



Ar = Ph, 2-thienyl, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 3-$NO_2C_6H_4$

In the present study, we found that *cis*-imidazolines can react with aromatic aldehydes in the presence of catalytic amounts of acetic acid to give derivatives **6** (Scheme 4). It is of fundamental importance that *trans*-2,4,5-triarylimidazolines are not involved in this reaction.

Scheme 4



i. RCHO, dioxane, AcOH, Δ.

6	Ar	R
a	Ph	Ph
b	4-MeO—C_6H_4	4-MeO—C_6H_4
c	3-NO_2—C_6H_4	3-NO_2—C_6H_4
d	Ph	4-Br—C_6H_4
e	Ph	4-MeO-C_6H_4
f	Ph	2-OH—C_6H_4
g	4-MeO—C_6H_4	Ph
h	Bu^t—C_6H_4	3-NO_2—C_6H_4

We found the optimal conditions for this reaction. The highest yield was obtained with the use of either DMF or dioxane as the solvent. However, dioxane makes isolation of the product easier. The reactions with the use of other solvents, such as THF, dichloromethane, alcohol, toluene, or xylene, afford products in substantially lower yields and require longer time. We also found that mineral acids, *viz.*, HCl or H_2SO_4, do not catalyze this reaction, whereas the presence of catalytic amounts of acetic or trifluoroacetic acids (the molar ratio imidazoline : AcOH = 5 : 1) leads to a decrease in the reaction time. In the presence of a stoichiometric amount of the acid, the reaction is completely suppressed. Aromatic aldehydes containing electron-withdrawing substituents in the ring more readily react with *cis*-imidazolines (the reaction time decreases). An attempt to use aliphatic aldehydes for the imidazoline ring opening failed (Table 1).

Table 1. Reactions of imidazolines **1** with aldehydes*

Ar	RCHO	Yield of product **6** (%)
Ph	PhCHO	98 (**6a**)
4-MeO—C_6H_4	4-MeO—C_6H_4CHO	76 (**6b**)
3-NO_2—C_6H_4	3-NO_2—C_6H_4CHO	80 (**6c**)
Ph	4-BrC_6H_4CHO	87 (**6d**)
Ph	4-$MeOC_6H_4$CHO	91 (**6e**)
Ph	2-HOC_6H_4CHO	76 (**6f**)
4-$MeOC_6H_4$	PhCHO	87 (**6g**)
Ph	Paraformaldehyde	—
Ph	*n*-Propanal	**
4-$Bu^tC_6H_4$	3-NO_2—C_6H_4CHO	76 (**6h**)

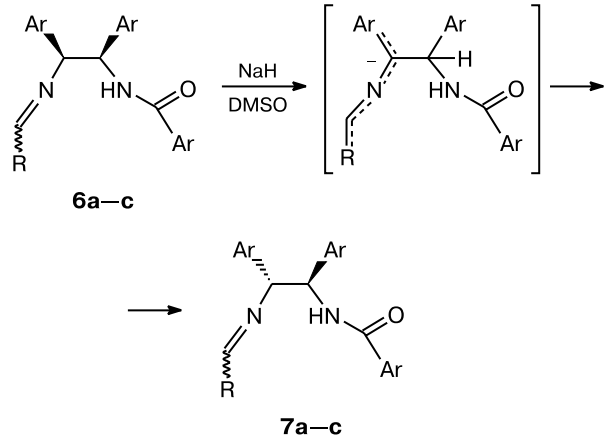
* Dioxane, AcOH catal., Δ.

** Traces of a mixture containing *N*-benzoyl-*N*′-propylidene-1,2-diamino-1,2-diphenylethane, which we failed to separate from by-products.

This scheme has advantages over many other methods because it provides a way of removing symmetry of vicinal diamines due to the presence of differently protected amino groups. Each amino group can be independently modified by successive hydrolysis. In addition, due to the fact that *trans*-imidazolines are not involved in this reaction, the method can be used to separate a mixture of *cis*- and *trans*-2,4,5-triarylimidazolines.

We also demonstrated for the first time that *erythro* compound **6a** can undergo quantitative isomerization to *threo* compound **7a** in the presence of strong bases (such as NaH, Bu^tOK) in DMSO. This substantially extends the synthetic scope of the reaction because it allows one

Scheme 5

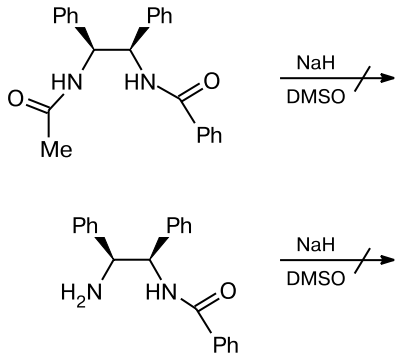


Substituents	**a**	**b**	**c**
	Ph	4-MeO—C_6H_4	3-NO_2—C_6H_4

to obviate the synthesis of *trans*-imidazolines, which often involves problems associated with the preparation of *threo* derivatives of vicinal diamines.

It appeared that the presence of the arylidene fragment is necessary for isomerization to occur. For example, isomerization of monoacylated and completely acylated *cis*-diamine, which was prepared by the reaction of **3a** with acetic anhydride,[4] did not occur (Scheme 6).

Scheme 6



The presence of electron-withdrawing substituents in the aromatic ring of compound **6** facilitates isomerization. For example, isomerization of a compound with Ar = 3-NO_2-C_6H_4 occurs in the presence of KOH in DMSO, whereas isomerization of a compound with 4-MeO-C_6H_4 takes place only in the presence of sodium hydride.

Experimental

The reactions were monitored and the purities of the products were checked by TLC on a fixed layer of silica gel (Silufol plates). The NMR spectra were recorded on Bruker AC-300, Bruker AC-200, and Varian VXR-400 instruments. The chemical shifts are given on the δ scale with respect to Me_4Si as the internal standard. The melting points were determined on a hot-stage apparatus in an open capillary tube. All melting points are uncorrected. Elemental analysis was carried out on a CarloErba CHN-analyzer.

All solvents were purified and dehydrated according to standard procedures.

Acid-catalyzed imidazoline ring opening in aldehydes (general procedure). Glacial acetic acid (0.1 mL) and aldehyde (3.3 mmol) were added to a solution of imidazoline **1** (3.3 mmol) in dioxane (20 mL). The resulting mixture was refluxed. The reaction was monitored by TLC (ethyl acetate as the eluent). After completion of the reaction, the solution was poured into water (100 mL). The precipitate that formed was recrystallized from ethanol and analyzed. This method was used to prepare compounds **6a—h.**

***erythro*-*N*-Benzoyl-*N*′-phenylmethylidene-1,2-diamino-1,2-diphenylethane (6a).** Refluxing of a mixture of *cis*-2,4,5-triphenylimidazoline (**1a**) (1 g, 3.3 mmol) and benzaldehyde (0.5 g, 4.7 mmol) for 18 h afforded product **6a** in a yield of 1.3 g (3.2 mmol, 98%), m.p. 257 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6), δ: 4.80 (d, 1 H, CH—N=, $J_1 = J_2 = 8$ Hz); 5.65 (dd, 1 H, CH—NH, $J_1 = J_2 = 8$ Hz); 7.05—7.70 (m, 20 H); 8.00 (s, 1 H, CH=N); 8.80 (d, 1 H, NH, $J = 8$ Hz). Found (%): C, 83.01; H, 5.91; N, 6.72. $C_{28}H_{24}N_2O$. Calculated (%): C, 83.14; H, 5.98; N, 6.93.

***erythro*-*N*-(4-Methoxybenzoyl)-*N*′-(4-methoxyphenyl)methylidene-1,2-diamino-1,2-di(4-methoxyphenyl)ethane (6b).** Refluxing of a mixture of *cis*-2,4,5-tri(4-methoxyphenyl)imidazoline (**1b**) (1 g, 2.5 mmol) and anisaldehyde (0.5 g, 4.7 mmol) for 24 h produced compound **6b** in a yield of 1 g (1.9 mmol, 76%), m.p. 218 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6), δ: 3.69 and 3.70 (both s, 3 H each, OMe); 3.80 (s, 6 H, OMe); 4.66 (d, 1 H, CH—N=, $J = 8$ Hz); 5.45 (dd, 1 H, CH—NH, $J_1 = J_2 = 8$ Hz); 6.70—6.90 (m, 8 H); 7.35, 7.45, 7.55, and 7.65 (all d, 2 H each); 7.90 (s, 1 H, CH=N); 8.19 (d, 1 H, NH, $J = 8$ Hz). Found (%): C, 73.30; H, 5.99; N, 5.28. $C_{32}H_{32}N_2O_5$. Calculated (%): C, 73.26; H, 6.15; N, 5.34.

***erythro*-*N*-(3-Nitrobenzoyl)-*N*′-(3-nitrophenyl)methylidene-1,2-diamino-1,2-di(3-nitrophenyl)ethane (6c).** Refluxing of a mixture of *cis*-2,4,5-tri(3-nitrophenyl)imidazoline (**1c**) (4 g, 9.2 mmol) and 3-nitrobenzaldehyde (1.4 g, 9.2 mmol) for 7 h afforded compound **6c** in a yield of 4.2 g (7.2 mmol, 78%), m.p. 256 °C. ^{1}H NMR (400.13 MHz, 25.6 °C, DMSO-d_6), δ: 5.14 (d, 1 H, CH—N=, $J = 9.6$ Hz); 5.86 (dd, 1 H, CH—NH, $J = 9.4$ Hz, $J = 9.6$ Hz); 7.52 (dd, 1 H, $J = 7.8$ Hz, $J = 8.1$ Hz); 7.67 (m, 2 H); 7.87 (m, 1 H); 8.11 (m, 5 H); 8.26 (m, 2 H); 8.33 (m, 1 H); 8.49 (s, 2 H); 8.57 and 8.60 (both s, 1 H each); 9.53 (d, 1 H, NH, $J = 9.4$ Hz).

***erythro*-*N*-Benzoyl-*N*′-(4-bromophenyl)methylidene-1,2-diamino-1,2-diphenylethane (6d).** Refluxing of a mixture of *cis*-2,4,5-triphenylimidazoline (**1a**) (1 g, 3.3 mmol) and 4-bromobenzaldehyde (0.6 g, 3.3 mmol) for 18 h gave compound **6d** in a yield of 1.4 g (2.9 mmol, 88%), m.p. 232—233 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6), δ: 4.45 (d, 1 H, $J = 5$ Hz); 5.00 (dd, 1 H, $J = 5$ Hz, $J = 5$ Hz); 7.10—7.90 (m, 19 H); 8.00 (s, 1 H); 8.70 (d, 1 H, $J = 7$ Hz). Found (%): C, 69.68; H, 4.83; N, 5.98. $C_{28}H_{23}BrN_2O$. Calculated (%): C, 69.57; H, 4.80; N, 5.80.

***erythro*-*N*-Benzoyl-*N*′-(4-methoxyphenyl)methylidene-1,2-diamino-1,2-diphenylethane (6e).** Refluxing of a mixture of *cis*-2,4,5-triphenylimidazoline (**1a**) (0.5 g, 1.65 mmol) and 4-methoxybenzaldehyde (0.2 g, 1.65 mmol) for 18 h afforded compound **6e** in a yield of 0.66 g (1.52 mmol, 92%), m.p. 210—215 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6), δ: 3.90 (s, 3 H, MeO); 4.72 (d, 1 H, CH—N, $J = 8.8$ Hz); 5.45 (dd, 1 H, CH—NH, $J = 8.8$ Hz, $J = 8.8$ Hz); 7.05 (d, 2 H, $J = 8$ Hz); 7.10—7.60 (m, 15 H); 7.80 (d, 2 H, $J = 8$ Hz); 7.90 (s, 1 H, CH=N); 8.70 (d, 1 H, NH, $J = 8$ Hz). Found (%): C, 80.10; H, 6.03; N, 6.40. $C_{29}H_{26}N_2O_2$. Calculated (%): C, 80.16; H, 6.03; N, 6.45.

***erythro*-*N*-Benzoyl-*N*′-(2-hydroxyphenyl)methylidene-1,2-diamino-1,2-diphenylethane (6f).** Refluxing of a mixture of *cis*-2,4,5-triphenylimidazoline (**1a**) (1 g, 3.3 mmol) and salicylaldehyde (0.5 g, 4.0 mmol) for 18 h produced compound **6f** in a yield of 1 g (2.3 mmol, 72%), m.p. 248—250 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6), δ: 4.59 (d, 1 H, CH—N, $J = 8.8$ Hz); 5.70 (dd, 1 H, CH—NH, $J_1 = J_2 = 8.8$ Hz); 6.80—7.45 (m, 19 H); 7.90 (s, 1 H, CH=N); 8.70 (d, 1 H, NH, $J = 8$ Hz); 10.00 (br.s, 1 H, OH). Found (%): C, 79.70; H, 5.71; N, 6.85. $C_{29}H_{24}N_2O_2$. Calculated (%): C, 79.98; H, 5.75; N, 6.66.

***erythro*-*N*-(4-Methoxybenzoyl)-*N′*-phenylmethylidene-1,2-diamino-1,2-di(4-methoxyphenyl)ethane (6g).** Refluxing of a mixture of *cis*-2,4,5-tri(4-methoxyphenyl)imidazoline (**1b**) (1 g, 2.5 mmol) and benzaldehyde (0.5 g, 4.7 mmol) for 18 h afforded compound **6g** in a yield of 1.1 g (2.2 mmol, 87%), m.p. 215 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6), δ: 3.69, 3.71, and 3.80 (all s, 3 H each, MeO); 4.70 (d, 1 H, CH—N, J = 8.8 Hz); 5.48 (dd, 1 H, CH—NH, $J_1 = J_2$ = 8.8 Hz); 7.70—7.90 (m, 6 H); 7.25—7.45 (m, 7 H); 7.65 (d, 4 H, J = 8 Hz); 8.00 (s, 1 H, CH=N); 8.15 (br.s, 1 H, NH). Found (%): 75.59; H, 6.00; N, 5.99. $C_{31}H_{30}N_2O_4$. Calculated (%): C, 75.28; H, 6.11; N, 5.66.

***erythro*-*N*-(4-*tert*-Butylbenzoyl)-*N′*-(3-nitrophenyl)methylidene-1,2-diamino-1,2-di(4-*tert*-butylphenyl)ethane (6h).** Refluxing of a mixture of *cis*-2,4,5-tri(4-*tert*-butylphenyl)imidazoline (**1c**) (4 g, 8.6 mmol) and 3-nitrobenzaldehyde (1.3 g, 8.6 mmol) for 16 h gave compound **6h** in a yield of 4 g (6.5 mmol, 76%), m.p. 199 °C. ^{1}H NMR (400.13 MHz, DMSO-d_6), δ: 1.60 (s, 9 H, Bu^t); 1.23 (s, 9 H, Bu^t); 1.26 (s, 9 H, Bu^t); 4.82 (d, 1 H, CH—N, J = 10 Hz); 5.58 (dd, 1 H, CH—NH, J = 10 Hz, J = 10 Hz); 7.23—7.25 (d, 2 H, J = 8 Hz); 7.35—7.40 (m, 6 H); 7.51—7.54 (m, 4 H); 7.67 (dd, 1 H, 3-$NO_2C_6H_4$, $J_1 = J_2$ = 8 Hz); 7.99 (d, 1 H, 3-$NO_2C_6H_4$, J = 8 Hz); 8.09 (s, 1 H, 3-$NO_2C_6H_4$); 8.23 (d, 1 H, J = 8 Hz); 8.34 (s, 1 H, CH=N); 8.75 (d, 1 H, NH, J = 10 Hz). Found (%): C, 77.70; H, 7.70; N, 6.75. $C_{40}H_{43}N_3O_3$. Calculated (%): C, 77.76; H, 7.67; N, 6.80.

Isomerization of an *erythro*-*N*-aroyl-*N′*-arylidene derivatives of vicinal diamines 6 to *threo* isomers 7 (general procedure). Anhydrous DMSO (30 mL) was placed in a 100-mL flask and then ice-cooled NaH (2.4 mmol, a 60% suspension in oil) was added. After 10 min, compound **6** (2.4 mmol) was added. The reaction mixture gradually turned dark-cherry. The mixture was stirred under argon at room temperature for 0.5—16 h, after which water (100 mL) was added. The precipitate that formed was separated, washed with ethanol, and dried. The ^{1}H NMR spectrum shows that compound **7** has no impurity of the starting *erythro* isomer.

***threo*-*N*-Benzoyl-*N′*-phenylmethylidene-1,2-diamino-1,2-diphenylethane (7a).** After 6 h, *threo* isomer **7a** was prepared from *erythro* isomer **6a** (1.3 g, 3.2 mmol) in a yield of 1.3 g (3.2 mmol, 98%), m.p. 210 °C. ^{1}H NMR (399.95 MHz, DMSO-d_6), δ: 5.23 (d, 1 H, CH—N=, J = 9 Hz); 5.60 (dd, 1 H, CH—NH, J = 9 Hz, J = 9 Hz); 7.10—7.70 (m, 20 H); 8.04 (s, 1 H, CH=N); 8.70 (d, 1 H, NH, J = 9 Hz). ^{13}C NMR (100.61 ppm, DMSO-d_6, T = 28 °C), δ: 59.99, 68.68, 127.06, 127.25, 127.43, 127.58, 128.08, 128.45, 128.59, 129.96, 131.47, 135.23, 140.97, 142.33, 142.86, 164.25, 165.97. MS, m/z (%): 297 (8), 208 (100), 193 (10), 167 (13), 152 (10), 105 (75), 77 (47). Found (%): C, 83.01; H, 5.91; N, 6.72. $C_{28}H_{24}N_2O$. Calculated (%): C, 83.15; H, 5.97; N, 6.93.

***threo*-*N*-(4-Methoxybenzoyl)-*N′*-(4-methoxyphenyl)methylidene-1,2-diamino-1,2-di(4-methoxyphenyl)ethane (7b).** After 16 h, *threo* isomer **7b** was synthesized from *erythro* isomer **6b** (2 g, 3.8 mmol) in a yield of 1.8 g (3.4 mmol, 90%), m.p. 212 °C. ^{1}H NMR (399.95 MHz, DMSO-d_6), δ: 3.36 and 3.66 (both s, 3 H each, OMe); 3.75 (s, 6 H, OMe); 5.10 (d, 1 H, CH—N=, J = 8 Hz); 5.44 (dd, 1 H, CH—NH, J = 8 Hz, J = 8 Hz); 6.70—6.90 (m, 8 H); 7.40 and 7.50 (both d, 2 H each, J = 6 Hz); 7.66 (m, 4 H); 8.23 (s, 1 H, CH=N); 8.55 (d, 1 H, NH, J = 8 Hz). ^{13}C NMR (100.61 ppm, DMSO-d_6, T = 27 °C), δ: 59.39, 55.37, 55.76, 67.77, 113.38, 113.81, 127.44, 128.56, 129.38, 133.65, 134.83, 135.29, 158.44, 160.85, 161.88, 162.71, 165.15. Found (%): C, 73.30; H, 5.99; N, 5.28. $C_{32}H_{32}N_2O_5$·, Calculated (%): C, 73.26; H, 6.15; N, 5.34.

***threo*-*N*-(3-Nitrobenzoyl)-*N′*-(3-nitrophenyl)methylidene-1,2-diamino-1,2-di-(3-nitrophenyl)ethane (7c).** After 30 min, *threo* isomer **7c** was prepared from *erythro* isomer **6c** (1.5 g, 2.6 mmol) in a yield of 1.4 g (2.4 mmol, 93%), m.p. 285 °C. ^{1}H NMR (399.95 MHz, DMSO-d_6), δ: 5.12 (d, 1 H, CH—N=, J = 9.23 Hz); 5.85 (dd, 1 H, CH—NH, J = 9.57 Hz, J = 9.57 Hz); 7.60—8.70 (m, 16 H); 9.03 (s, 1 H); 9.39 (d, 1 H, NH, J = 8 Hz). Found (%): C, 57.51; H, 3.47; N, 14.33. $C_{28}H_{20}N_6O_9$. Calculated (%): C, 57.54; H, 3.45; N, 14.38.

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