Preparation of some nitrogen-containing 2,5-dialkoxystyrene derivatives

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Dedicated to Professor Benito Alcaide on the occasion of his 60th anniversary

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Abstract

The synthesis of 2,5-dialkoxystyrene derivatives starting from 2,5-dihydroxybenzaldehyde is described. The key steps in the synthesis are the alkylation of the phenolic hydroxyl groups and subsequent Wittig olefination of the aldehyde moiety. The ether side-chains of the products display several nitrogen-containing functional groups, including phthalimido, *tert*-butoxycarbonylamino, cyano and aminotriazines.

Keywords: Styrene derivatives, triazine derivatives, Wittig reaction

Introduction

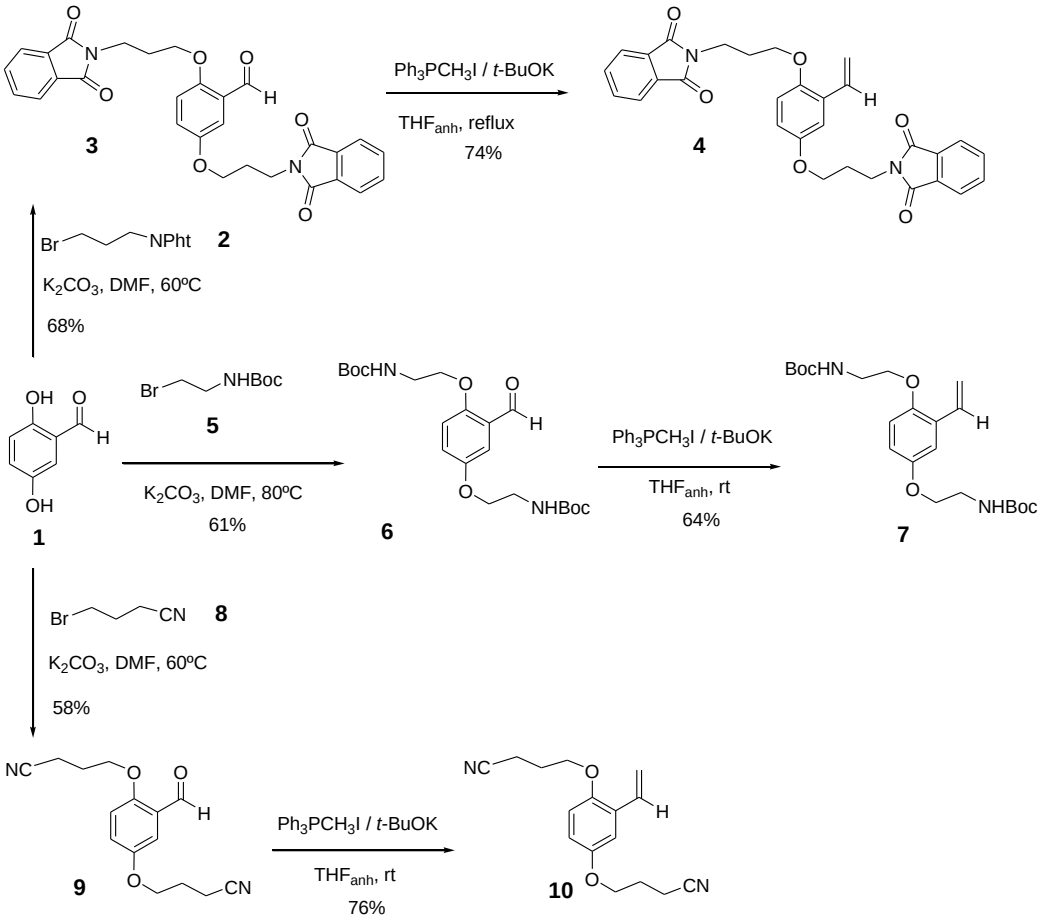
Styrene[1] and styrene derivatives[2] have been widely used for the preparation of a broad range of homo- and copolymers under free-radical, anionic, cationic and metal initiator catalyst conditions. Styrenic compounds are also suitable substrates for a number of synthetically useful organic processes, such as hydroformylation, hydrocarboxylation/hydroesterification, epoxidation, aziridination, cyclopropanation, hydroboration, dihydroxylation, and Wacker-type oxidations. In addition to their use as synthetic precursors, α-alkoxystyrenes were introduced by the Hoveyda group as chelating ligands in the development of ruthenium alkylidene complexes (known as the Hoveyda-Grubbs catalysts) which display high catalytic activity and good air-stability in metathesis reactions.[3] The influence of steric and electronic factors in modified styrene ethers has been investigated and improved versions of the metathesis catalysts were

obtained by modifying the chelating arm with suitable substituents.[4] Thus, substituted α-alkoxystyrenes are organic intermediates which may be useful for a number of purposes.

In the course of an ongoing research project directed towards the incorporation of α-alkoxystyrene groups within an inorganic silica-based matrix, we were faced with the task of preparing the 2,5-dialkoxystyrenes bearing various nitrogen-containing moieties on the ether side chains. These would then serve as precursors to the silylated urea derivatives necessary for the subsequent gel formation. We report herein the synthetic approaches leading to these derivatives starting from the commercial 2,5-dihydroxybenzaldehyde.

Results and Discussion

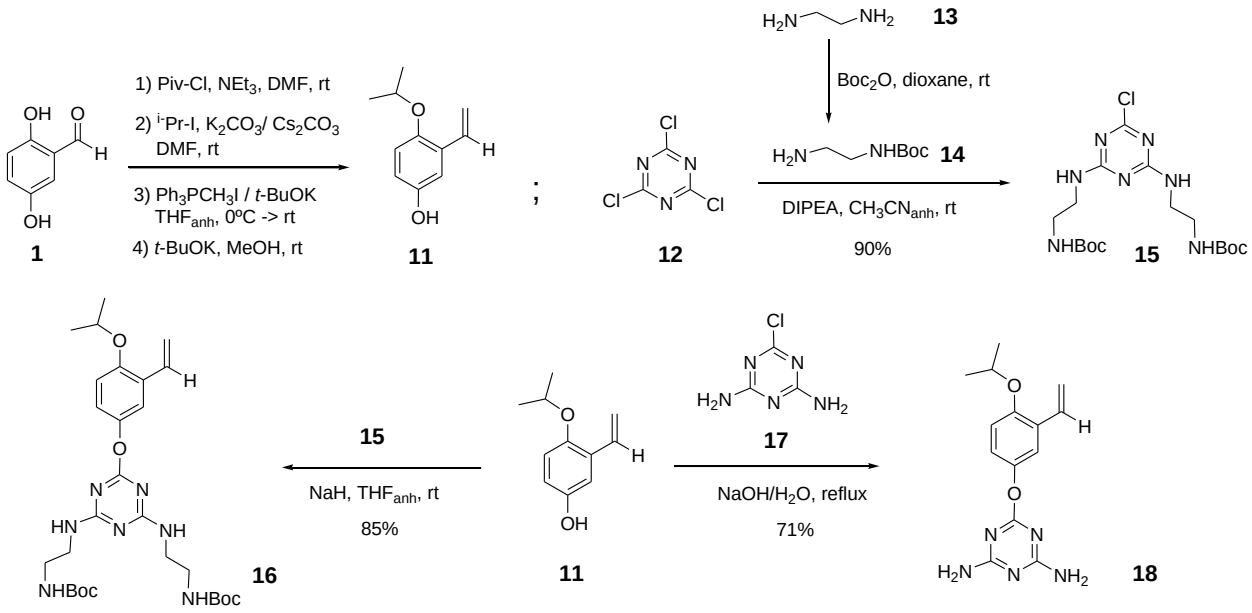
We were interested in introducing the cyano and N-protected amino groups in the ether side chains of the 2,5-dialkoxystyrenes. The synthetic route starting with 2,5-dihydroxybenzaldehyde, **1**, and leading to compounds **4**, **7** and **10,** bearing 3-(1,3-dioxoisoindolin-2-yl)propoxy, 2-(*tert*-butoxycarbonylamino)ethoxy and 3-cyanopropoxy groups, respectively, is outlined in Scheme 1. The dialkylation of **1** with two equivalents of commercial bromo derivatives **2**, **5** and **8** was performed in *N*,*N*-dimethylformamide at 60-80ºC in the presence of potassium carbonate as a base, affording the corresponding aldehydes **3**, **6** and **9**. The subsequent Wittig olefination of these aldehydes with the ylide generated from methyltriphenylphosphonium iodide and potassium *tert*-butoxide was achieved in tetrahydrofuran under reflux or at room temperature, to give the desired styrenes **4**, **7** and **10**, which were isolated in good yields after column chromatography.



Scheme 1

During the subsequent studies of this class of compounds, we were also interested in the preparation of some advanced triazine intermediates with a dialkoxystyrene appendage**.** In Scheme 2, we summarize the synthesis of styrenes **16** and **18** from commercially available compounds **1, 12, 13** and **17**. 4-Isopropoxy-3-vinylphenol, **11,** was obtained from **1** as previously reported,[5] introducing a slight modification in the Wittig olefination step, which involved the use of potassium *tert*-butoxide as base instead of lithium bis(trimethylsilyl)imide. The triazine derivative **15** was prepared by treatment of cyanuryl chloride, **12**, with two equivalents of *tert*-butyl *N*-(2-aminoethyl)carbamic acid *tert*-butyl ester,[6] **14**, in anhydrous acetonitrile at room temperature, in the presence of *N*,*N*-diisopropylethylamine as base. The S_NAr-type reaction of phenol **11** with the chlorotriazine **15** in the presence of sodium hydride, in anhydrous tetrahydrofuran at room temperature, afforded the styrene **16** in 85% yield. The use of an excess of NaH (2 equiv. or more) should be avoided, otherwise secondary products were formed. The same conditions were not found appropriate for the reaction of **11** with chlorotriazine **17**. After some experimentation, styrene **18** could be obtained in 71% yield by an overnight reflux of a

mixture of reagents in aqueous sodium hydroxide. The desired compound precipitated from the reaction medium.



Scheme 2

The ^{1}H NMR spectrum of triazine derivative **15** showed, as expected, a singlet corresponding to the *tert*-butyl groups and two multiplets at 3.14 and 3.32 (500 MHz, DMSO-d_6) corresponding to the two different methylene groups present in the molecule. However, the NH region of the spectrum was more complex, displaying two sets of resonances, one at 6.3-6.9 and another at 7.5-7.9, each set of signals integrating 1H with respect to 9H of the *tert*-butyl group (Figure 1a). To shed light on this phenomenon and to ensure that we were dealing with a pure compound, a more detailed NMR study was undertaken. Heating the sample to 50 ºC resulted in the signals being broadened and shifted to higher fields (Figure 1b). However, coalescence was not yet achieved in this temperature. A simplification of the NMR spectrum was obtained at 100 ºC (360 MHz, DMSO-d_6), indicating a rapid interconversion of the different isomers at this temperature (Figure 1c).

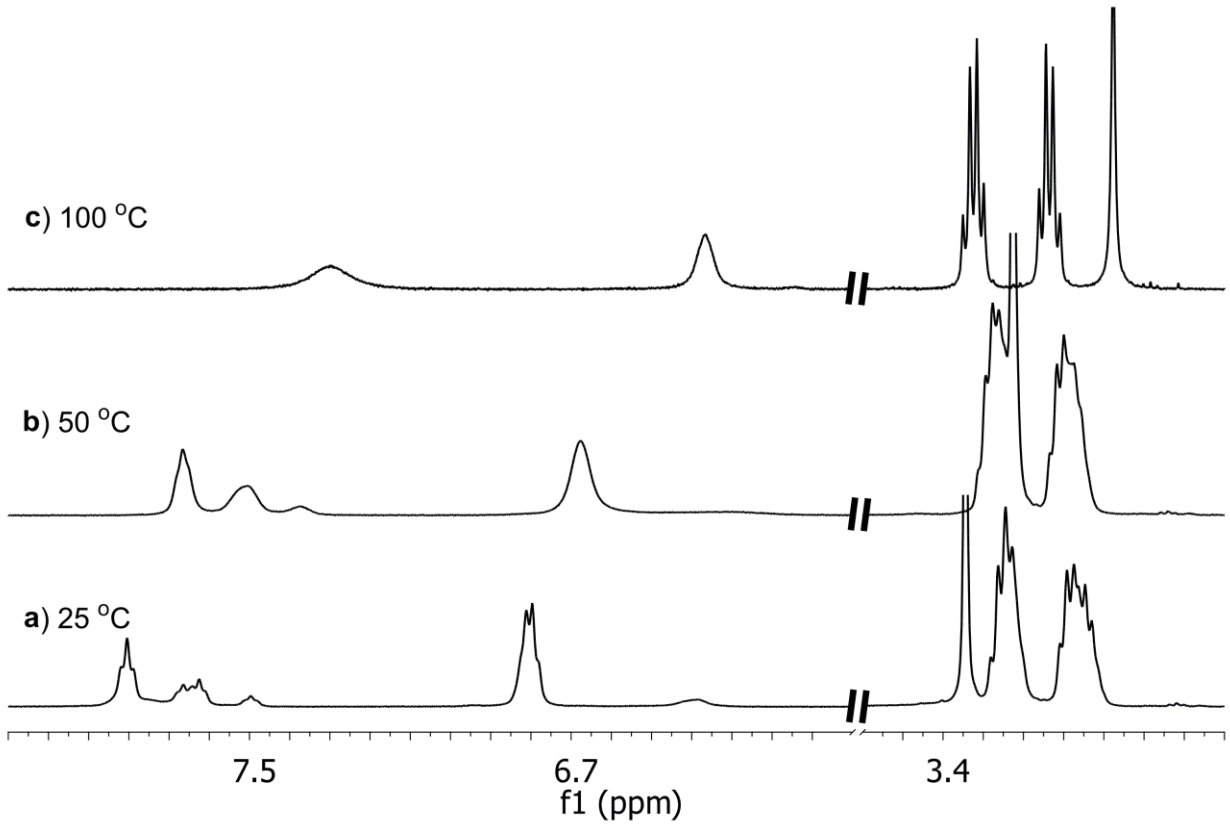


Figure 1. ^{1}H-NMR spectrum (360 MHz, DMSO-d_6) of **15** at a) 25 °C, b) 50 °C and c) 100 °C.

In the room temperature ^{13}C NMR spectrum of **15** the signals of the methylene carbons were masked by the solvent and in the region of 150-170 ppm we observed more absorptions than expected, 6 signals distributed in three groups of two signals, with one of the absorptions in each group being more intense than the other one (Figure 2).

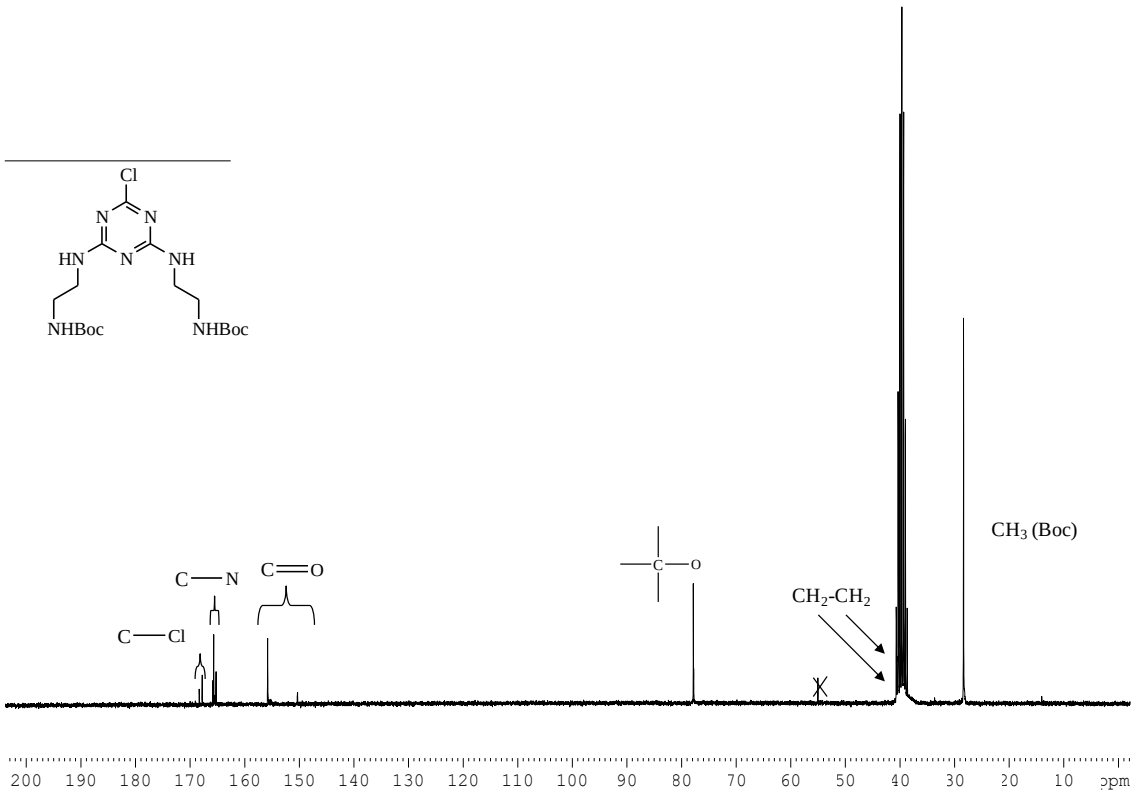


Figure 2. ^{13}C-NMR spectrum (62.5 MHz, DMSO-d_6) of **15** at 25 ºC.

A complete signal assignment was made by means of two-dimensional NMR experiments (^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC). A ^{1}H-^{1}H NOESY spectrum of **15** (Figure 3) showed that the several absorptions at 6.3-6.9 ppm correspond to the same NH proton (chemical exchange cross-signals are observed; in red in Figure 3) in different conformational isomers, and the same is occurring for the NH signals at 7.5-7.9 ppm. Compound **15** has two alkylamino groups linked to the triazine moiety and a restricted rotation about the C-N(exo) bonds has been envisaged to explain this dynamic process. It has been previously described[7] that two set of signals appear for the aromatic protons of 2-alkylamino-1,3,5-triazines, three different absorptions being observed for the three aromatic carbons of the ring. These facts are indicative of a conjugation of the alkylamino group with the triazine ring and the subsequent hindered rotation around the C(2)-N(exo) bond. Some precedents also exist[8] about di(alkylamino)-1,3,5-triazine derivatives presenting different absorptions for the NH protons due to conformational isomers. Compound **16** also presents complex ^{1}H NMR and ^{13}C NMR spectra with more signals than expected, probably due to the same dynamic processes mentioned before for its precursor **15**.

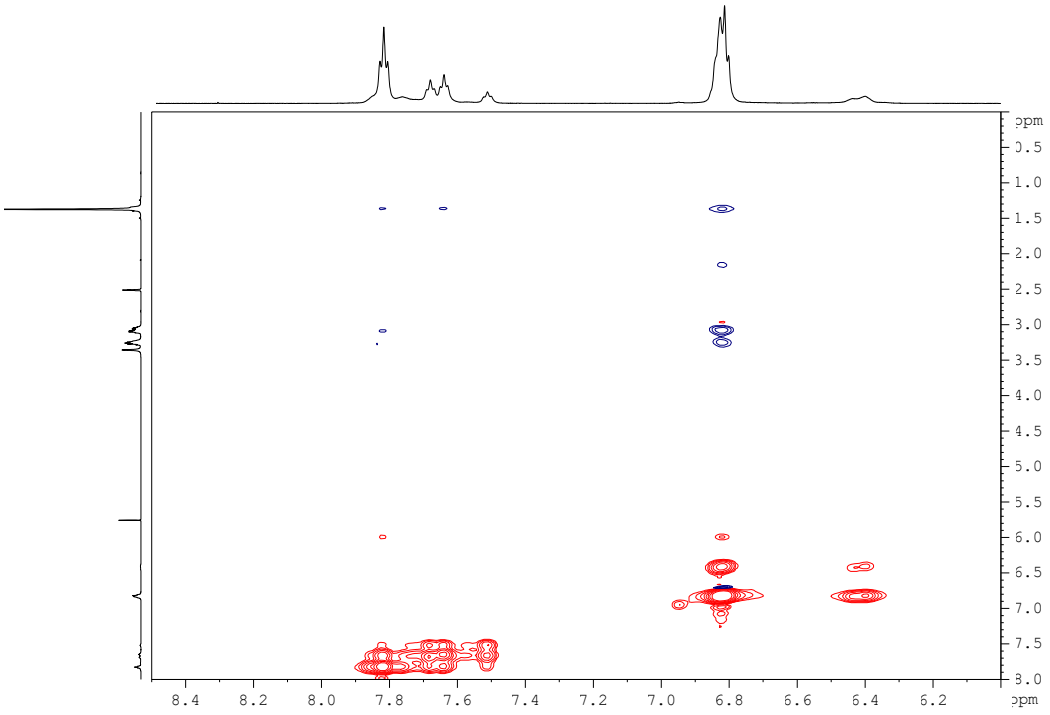


Figure 3. ^{1}H-^{1}H NOESY correlation spectrum (500MHz, DMSO-d_6) of **15** showing exchange cross-peaks between different NH resonances.

Conclusions

A synthesis of 2,5-dialkoxystyrenes bearing nitrogen-functionalized pendant ether chains is described starting from commercial-2,5-dihydroxybenzaldehyde. The route includes phenolic hydroxyl alkylation with the suitably functionalized alkyl halide derivative and a subsequent Wittig olefination. In this manner, 3-(1,3-dioxoisoindolin-2-yl)propoxy, 2-(*tert*-butoxycarbonylamino)ethoxy, 3-cyanopropoxy, 4,6-bis(2-*tert*-butoxycarbonylamino)ethyl-amino)-1,3,5-triazin-2-yloxy and 4,6-diamino-1,3,5-triazin-2-yloxy groups are efficiently introduced into the styrene moiety. The triazine derivatives present complex NMR spectra due to some dynamic processes in solution.

Experimental Section

General Procedures. Compounds **1**, **2**, **5**, **8**, **12**, **13** and **17** were purchased from Aldrich (**1**, **8**, **12**, **13**), Across Organics (**2**, **17**), and Fluka (**5**)**.** THF was dried by distillation from a Na-benzophenone ketyl. CH_3CN was distilled from P_4O_{10}. *N*,*N*-dimethylformamide was stored over activated 4 Å molecular sieves. Melting points were measured with a Kofler Reicherdt apparatus

and are uncorrected. IR data were obtained on a Bruker Tensor 27 spectrophotometer with ATR Golden Gate. ^{1}H NMR spectra (250 MHz) and ^{13}C NMR (62.5 MHz) were usually recorded on a Bruker DXP-250. However some experiments have been performed at 500 MHz on a Bruker AVANCE-500 or at 360 MHz on a Bruker AVANCE-360. Chemical shifts (δ, ppm) were referenced to TMS (^{1}H and ^{13}C). The abbreviations used are s for singlet, d for doublet, dd for double doublet, t for triplet, q for quartet, sept for septet and m for multiplet. Mass spectra (MS-ESI and HRMS-ESI) were recorded at the *Servei d'Anàlisi de la Universitat Autònoma de Barcelona* using an Esquire 3000 quadrupole instrument and a MicroTOFQ Bruker Daltonic operating in the positive ion mode (ES+) at a probe tip voltage of 3kV. Elemental analyses were performed at the *Servei d'Anàlisi de la Universitat Autònoma de Barcelona.*

2,5-Bis(3-(1,3-dioxoisoindolin-2-yl)propoxy)benzaldehyde (3). A mixture of **1** (1.002 g, 0.007 mol), *N*-(3-bromopropyl)phthalimide, **2** (3.842 g, 0.014 mol) and potassium carbonate (5.850 g, 0.042 mol) in anhydrous DMF (100 mL) was heated at 60ºC for 16 h with stirring under argon atmosphere. The hot mixture was filtered, and water (50 mL) was added to the filtrate. The resulting precipitate was collected by filtration, washed with water and dried at 60ºC under *vacuum* overnight to afford **3** as a white solid (2.445 g, 68%). A small quantity was recrystallized from ethyl acetate and was used for characterization: mp 182-183 ºC; IR (ATR, cm^{-1}) 2940, 2866, 1712, 1680, 1387, 1372, 1221, 1150, 722; ^{1}H NMR ($CDCl_3$) δ 2.11–2.29 (m, 4H), 3.91 (apparent q, J = 6.5 Hz, 4H), 4.00 (t, J = 5.8 Hz, 2H), 4.09 (t, J = 6.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 1H), 6.99 (dd, J = 9.0 and 3.0 Hz, 1H), 7.19 (d, J = 3.0 Hz, 1H), 7.70-7.86 (m, 8H), 10.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3, 28.5, 35.3, 35.5, 66.3, 66.8, 111.2, 114.3, 123.3, 123.4, 123.9, 125.1, 132.1, 132.2, 134.1, 134.2, 152.9, 155.9, 168.40, 168.45, 189.2; $C_{29}H_{24}N_2O_7$: calcd. C 67.96, H 4.72, N 5.47; found C 68.35, H 5.12, N 5.44.

2,2'-(3,3'-(2-Vinyl-1,4-phenylene)bis(oxy)bis(propane-3,1-diyl))diisoindoline-1,3-dione (4). Potassium *tert*-butoxide (0.454 g, 3.97 mmol) was added to a stirred suspension of methyltriphenylphosphonium iodide (1.583 g, 3.92 mmol) in anhydrous THF (10 mL) under nitrogen atmosphere and the mixture was stirred at room temperature for 15 minutes. Then, a solution of **3** (1.015 g, 1.98 mmol) in anhydrous THF (20 mL) was added and the stirred mixture was brought to a reflux for 16 h under nitrogen atmosphere. The solvent was evaporated and the residue was partitioned between dichloromethane (40 mL) and water (60 mL). The aqueous phase was extracted with additional dichloromethane (2 x 10 mL). The combined organic phase was washed successively with water (2 x 15 mL) and with a saturated aqueous solution of sodium chloride, was dried with anhydrous sodium sulfate and the solvent was evaporated. The solid residue was subjected to column chromatography (silica gel, hexane/ethyl acetate 1:2). The eluted compound **4** was further purified by washing with methanol, affording a yellow solid (0.748 g, 74%). A small quantity was recrystallized from ethyl acetate and was used for characterization: mp 161-162 ºC; IR (ATR, cm^{-1}) 2949, 1705, 1497, 1391, 1373, 1218, 1061, 949, 811, 707; ^{1}H NMR ($CDCl_3$) δ 2.17 (m, 4H), 3.91 (t, J = 6.8 Hz, 4H), 3.98 (t, J = 6.0 Hz, 4H), 5.14 (dd, J = 11.3 and 1.3 Hz, 1H), 5.59 (dd, J = 17.8 and 1.3 Hz, 1H), 6.66 (dd, J = 9.0 and

3.0 Hz, 1H), 6.73 (d, J = 9.0 Hz, 1H), 6.88 (d, J = 3.0 Hz, 1H), 6.93 (dd, J = 17.8 and 11.3 Hz, 1H), 7.69-7.86 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 28.4, 28.7, 35.61, 35.64, 66.4, 66.9, 112.7, 113.5, 114.48, 114.53, 123.3, 127.8, 131.2, 132.2, 132.3, 134.0, 150.4, 153.0, 168.4, 168.5; HRMS (ESI) calcd. for $[C_{30}H_{26}N_2O_6Na]^+$: 533.1683, found: 533.1675.

Di-*tert*-butyl 2,2'-(2-formyl-1,4-phenylene)bis(oxy)bis(ethane-2,1-diyl)dicarbamate (6). A solution of **5** (1.601 g, 0.007 mol) in anhydrous DMF (30 mL) was added to a stirred mixture of **1** (0.315 g, 0.002 mol) and potassium carbonate (2.915 g, 0.020 mol) in anhydrous DMF (15 mL). The mixture was heated for 20 h at 80ºC under nitrogen atmosphere. Water was added (50 mL) and the solution was extracted with dichloromethane (3 x 50 mL). The combined organic phases were washed with a saturated aqueous solution of sodium chloride (2 x 40 mL), dried with anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography (silica gel, gradient: hexane -> hexane/ethyl acetate 2:1), affording **6** as a yellow oil (0.579 g, 61%); IR (ATR, cm^{-1}) 3339, 2976, 2932, 2873, 1682 (broad), 1493, 1391, 1365, 1271, 1250, 1159, 1058, 867, 755; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 18H), 3.46 (apparent q, J = 5.3 Hz, 2H), 3.53 (apparent q, J = 5.3 Hz, 2H), 3.95 (t, J = 5.3 Hz, 2H), 4.05 (t, J = 5.3 Hz, 2H), 5.12 (m, 2H), 6.87 (d, J = 9.3 Hz, 1H), 7.06 (dd, J = 9.3 and 3.3 Hz, 1H), 7.23 (d, J = 3.3 Hz, 1H), 10.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.6, 40.3, 68.0, 68.6, 79.8, 79.9, 112.2, 114.6, 123.7, 125.4, 153.0, 156.0, 156.1, 156.2, 189.4; HRMS (ESI) calcd. for $[C_{21}H_{32}N_2O_7Na]^+$: 447.2102, found: 447.2111.

Di-*tert*-butyl 2,2'-(2-vinyl-1,4-phenylene)bis(oxy)bis(ethane-2,1-diyl)dicarbamate (7). Potassium *tert*-butoxide (0.213 g, 1.86 mmol) was added to a stirred suspension of methyltriphenylphosphonium iodide (0.751 g, 1.86 mmol) in anhydrous THF (5 mL) under nitrogen atmosphere and the mixture was stirred at room temperature for 15 minutes. Then, a solution of **6** (0.393 g, 0.93 mmol) in anhydrous THF (9 mL) was added and the stirred mixture was left at room temperature for 3 hours under nitrogen atmosphere. The solvent was evaporated and the residue was partitioned between dichloromethane (10 mL) and water (15 mL). The aqueous phase was extracted with dichloromethane (2 x 10 mL). The combined organic phase was washed successively with water (2 x 15 mL) and with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate 2:1), affording **7** as an oil which crystallized as a white solid after drying in vacuum for 2 days (0.249 g, 64%); mp 82-83 ºC; IR (ATR, cm^{-1}) 3388, 2977, 2938, 2872, 1694, 1514, 1496, 1365, 1219, 1155, 1062, 804; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 18H), 3.51 (m, 4H), 3.98 (t, J = 5.1 Hz, 4H), 5.00 (m, 2H), 5.27 (dd, J = 11.0 and 1.3 Hz, 1H), 5.71 (dd, J = 17.8 and 1.3 Hz, 1H), 7.00 (dd, J = 17.8 and 11.0 Hz, 1H), 7.02 (d, J = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.5, 40.4, 67.9, 68.7, 79.6, 112.7, 114.0, 114.7, 115.1, 128.1, 131.3, 150.4, 153.1, 156.0; HRMS (ESI) calcd. for $[C_{22}H_{34}N_2O_6Na]^+$: 445.2309, found: 445.2305.

4,4'-(2-Formyl-1,4-phenylene)bis(oxy)dibutanenitrile (9). A stirred mixture of **1** (0.310 g, 2.2 mmol), potassium carbonate (1.80 g, 12.87 mmol), 4-bromobutanenitrile, **8** (0.5 mL, 0.745 g, 4.88 mmol) and anhydrous DMF (20 mL) was heated at 60ºC for 16 h under nitrogen

atmosphere. Water was added (30 mL) and the solution was extracted with dichloromethane (3 x 25 mL). The combined organic phases were washed with a saturated aqueous solution of sodium chloride and dried with anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate 1:2), affording **9** as a white solid (0.346 g, 58%). Further purification was achieved by washing with diethyl ether; mp 63-64 ºC; IR (ATR, cm^{-1}) 3064, 2947, 2887, 2241, 1674, 1498, 1428, 1392, 1219, 1170, 1048, 820, 729; ^{1}H NMR ($CDCl_3$) δ 2.12 (quint, J = 6.5 Hz, 2H), 2.20 (quint, J = 6.4 Hz, 2H), 2.58 (t, J = 7.6 Hz, 2H), 2.62 (t, J = 7.2 Hz, 2H), 4.06 (t, J = 5.8 Hz, 2H), 4.17 (t, J = 5.8 Hz, 2H), 6.94 (d, J = 9.0 Hz, 1H), 7.13 (dd, J = 9.0 and 3.0 Hz, 1H), 7.31 (d, J = 3.2 Hz, 1H), 10.42 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 25.4, 66.1, 66.6, 111.9, 114.4, 119.0, 119.2, 123.7, 125.3, 152.9, 155.6, 188.9; HRMS (ESI) calcd. for $[C_{15}H_{16}N_2O_3Na]^+$: 295.1053, found: 295.1050.

4,4'-(2-Vinyl-1,4-phenylene)bis(oxy)dibutanenitrile (10). Potassium *tert*-butoxide (0.337 g, 2.94 mmol) was added to a stirred suspension of methyltriphenylphosphonium iodide (1.190 g, 2.95 mmol) in anhydrous THF (9 mL) under nitrogen atmosphere and the mixture was stirred at room temperature for 15 minutes. Then, a solution of **9** (0.400 g, 1.47 mmol) in anhydrous THF (12 mL) was added and the stirred mixture was left at room temperature overnight under nitrogen atmosphere. The solvent was evaporated and the residue was partitioned between dichloromethane (20 mL) and water (30 mL). The aqueous phase was extracted with dichloromethane (2 x 20 mL). The combined organic phases were washed successively with water (2 x 15 mL) and with a saturated aqueous solution of sodium chloride, dried with anhydrous sodium sulfate and the solvent was evaporated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate 1:2), affording **10** as an oil (0.303 g, 76%); IR (ATR, cm^{-1}) 2942, 2876, 2247, 1625, 1579, 1494, 1470, 1426, 1214, 1058, 805, 726; ^{1}H NMR ($CDCl_3$) δ 2.07–2.16 (m, 4H), 2.57 (t, J = 7.2 Hz, 2H), 2.58 (t, J = 7.2 Hz, 2H), 4.03 (t, J = 5.7 Hz, 4H), 5.29 (dd, J = 11.0 and 1.1 Hz, 1H), 5.71 (dd, J = 17.6 and 1.1 Hz, 1H), 6.74-6.80 (m, 2H), 6.95-7.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 25.5, 25.6, 66.0, 66.7, 112.6, 113.7, 114.7, 115.2, 119.28, 119.32, 128.1, 131.0, 150.2, 152.9; HRMS (ESI) calcd. for $[C_{16}H_{18}N_2O_2Na]^+$: 293.1260, found: 293.1259.

***N*-(2-Aminoethyl)carbamic acid *tert*-butyl ester (14).** A solution of ethylenediamine, **13** (23.3 mL, 0.899 g/mL, 0.345 mol) in dioxane (100 mL) was added dropwise during 2 hours to a stirred solution of di-*tert*-butyldicarbonate (13.040 g, 0.060 mol) in dioxane (10 mL). The stirred mixture was left at room temperature under nitrogen atmosphere for 16 h. The solvent was evaporated and distilled water was added (150 mL). The resulting white solid (BocNH-CH_2-CH_2-NHBoc) was removed by filtration and the filtrate was extracted with dichloromethane (4 x 40 mL). The combined organic phases were washed with a saturated aqueous solution of sodium chloride (20 mL), dried with anhydrous sodium sulfate and the solvent was evaporated affording **14**[6] as a colorless oil (4.332 g, 45%).

Di-*tert*-butyl 2,2'-(6-chloro-1,3,5-triazine-2,4-diyl)bis(azanediyl)bis(ethane-2,1-diyl)dicarbamate (15). A solution of **14** (8.559 g, 0.053 mol) in anhydrous acetonitrile (88 mL) was added under nitrogen atmosphere to a stirred suspension of cyanuryl chloride (3.940 g, 0.021 mol) in

anhydrous acetonitrile (63 mL). Then, diisopropylethylamine was added (34.6 mL, 0.742 g/mL, 0.197 mol) and the stirred mixture was left at room temperature overnight under inert atmosphere. The precipitate formed was collected by filtration, washed with acetonitrile and dried to give **15** as a white solid (8.335 g, 80%); mp 221-223 ºC; IR (ATR, cm^{-1}) 3249, 3102, 2976, 1703, 1636, 1557, 1510, 1407, 1271, 1241, 1168, 1097, 988, 962, 805; ^{1}H NMR (DMSO-d_6, 360 MHz, 100 ºC) δ 1.39 (s, 18H), 3.14 (apparent q, J = 6.2 Hz, 4H), 3.32 (apparent q, J = 6.2 Hz, 4H), 6.37 (m, 2H), 7.31 (m, 2H); ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ 28.4, 55.0, 77.8, 77.9, 150.3, 155.8, 165.2, 165.5, 165.7, 165.8, 167.8, 168.3; MS-ESI *m/z*: 456.1 (12), 454.2 $[M + Na]^+$ (36), 434.2 (33), 432.2 $[M + H]^+$ (100); HRMS (ESI) calcd. for $[C_{17}H_{30}N_7O_4ClNa]^+$: 454.1940, found: 454.1947.

Di-*tert*-butyl 2,2'-(6-(4-isopropoxy-3-vinylphenoxy)-1,3,5-triazine-2,4-diyl)bis(azanediyl)-bis(ethane-2,1-diyl)dicarbamate (16). A solution of **11**[5] (0.162 g, 0.91 mmol) in anhydrous THF (1 mL) was added under argon to a stirred suspension of NaH 60% (0.0421 g, 1.05 mmol) (previously washed with anhydrous hexane) in anhydrous THF (2 mL). The mixture was stirred under argon at room temperature for 30 minutes. Then, a solution of **15** (0.3505 g, 0.81 mmol) in anhydrous THF (4 mL) was added. The stirred mixture was left at room temperature under argon atmosphere for 2 days. The solvent was evaporated, the residue was taken in dichloromethane (20 mL) and the organic solution was washed successively with 1 M NaOH (4 x 5 mL) and with a saturated aqueous solution of sodium chloride (2 x 5 mL). Then it was dried with anhydrous sodium sulfate and the solvent was evaporated to yield **16** (0.397 g, 85%); mp 69-70 ºC; IR (ATR, cm^{-1}) 3367, 2975, 2932, 1696, 1589, 1522, 1356, 1270, 1251, 1161, 812; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.33 (d, J = 6.0 Hz, 6H), 1.40 (s, 18H), 3.20-3.31 (m, 4H), 3.36-3.49 (m, 4H), 4.47 (sept, J = 6.0 Hz, 1H), 5.23 (d, J = 11.6 Hz, 1H), 4.96-5.42 (m, 2H), 5.67 (d, J = 17.6 Hz, 1H), 6.17-6.31 (m, 2H), 6.83-7.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 62.5 Hz) δ 22.3, 28.5, 40.5, 41.0, 71.6, 71.7, 79.4, 114.7, 114.8, 114.9, 115.1, 119.5, 119.6, 121.9, 122.0, 128.7, 128.8, 131.4, 145.7, 146.0, 152.5, 152.6, 156.3, 156.4, 166.1, 167.7, 170.6; MS-ESI *m/z*: 596.3 $[M + Na]^+$ (100); HRMS (ESI) calcd. for $[C_{28}H_{43}N_7O_6Na]^+$: 596.3167, found: 596.3150.

2,4-Diamino-6-(4-isopropoxy-3-vinylphenoxy)-1,3,5-triazine (18). A stirred mixture of **17** (0.076 g, 0.506 mmol), **11** (0.090 g, 0.506 mmol) and sodium hydroxide (0.045 g, 1.125 mmol) in water (2 mL) was heated under reflux overnight. The precipitate formed was collected by filtration, it was washed with water and dried under *vacuum* to afford **18** as a white solid (0.104 g, 71%); mp 238-240 ºC; IR (ATR, cm^{-1}) 3510, 3396, 3134, 2978,1680, 1615, 1552, 1370, 1200, 1053, 813, 679; ^{1}H NMR (CD_3SOCD_3) δ 1.28 (d, J = 6.0 Hz, 6H), 4.66 (sept, J = 6.0 Hz, 1H), 5.25 (dd, J = 11.3 and 1.3 Hz, 1H), 5.81 (dd, J = 18.0 and 1.3 Hz, 1H), 6.73 (broad s, 4H), 6.95 (m, 3H), 7.26 (d, J = 2.3 Hz, 1H); ^{13}C NMR (CD_3SOCD_3) δ 22.0, 70.6, 115.0, 115.1, 119.3, 122.4, 127.5, 130.9, 146.0, 151.8, 168.5, 171.3; HRMS (ESI) calcd. for $C_{14}H_{17}N_5O_2Na$: 310.1274, found: 310.1266

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