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SYNTHESIS OF 3-SUBSTITUTED ISOINDOLIN-1-ONES BY REGIO-SELECTIVE CYCLIZATION OF NITRILE WITH A STYRYL DOUBLE BOND

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Abstract- An efficient preparation of 3-substituted isoindolin-1-one was established *via* basic condensation of aromatic or aliphatic aldehyde with 6-alkoxy-3-methylbenzene-1,2,4-tricarbonitrile (**1**) in a one-pot reaction. The key step involved regioselective either hydrolysis or nucleophilic attack of the hydroxide anion to the 2-cyano group followed by 5-exo-trig cyclization with the involvement of the styryl double bond. The structure of isoindolinone and regiochemistry of the cyclization products were proved by spectroscopic methods.

INTRODUCTION

Isoindolin-1-one, 1-oxoisoindoline and its derivatives have become an intriguing research area of medicinal chemistry.[1] Isoindolin-1-one ring system is common in many biologically active compounds.[2] The effective method for the synthesis of isoindolin-1-one ring systems has been reported.[3] Moreover, the condensation of tolunitriles with benzaldehyde derivatives under basic conditions to produce stilbenes offers a very convenient route to a styryl carbon-carbon double.[4] Such condensation provided the formation of PPV (*para*-phenylenevinylene) oligomer or polymer for the study of organic luminescent materials.[5] During our study of organic light emitting diodes, we observed that the

condensation of aldehyde with tolunitrile derivatives gave isoindolin-1-one in the presence of water. Herein, an efficient method for the synthesis of 3-substituted isoindolin-1-one in a one-pot reaction is reported. Regioselective hydrolysis of the cyano group or nucleophilic attack of the hydroxide anion to the 2-cyano group followed by cyclization with the carbon-carbon double bond of stilbene are key steps responsible for this reaction.

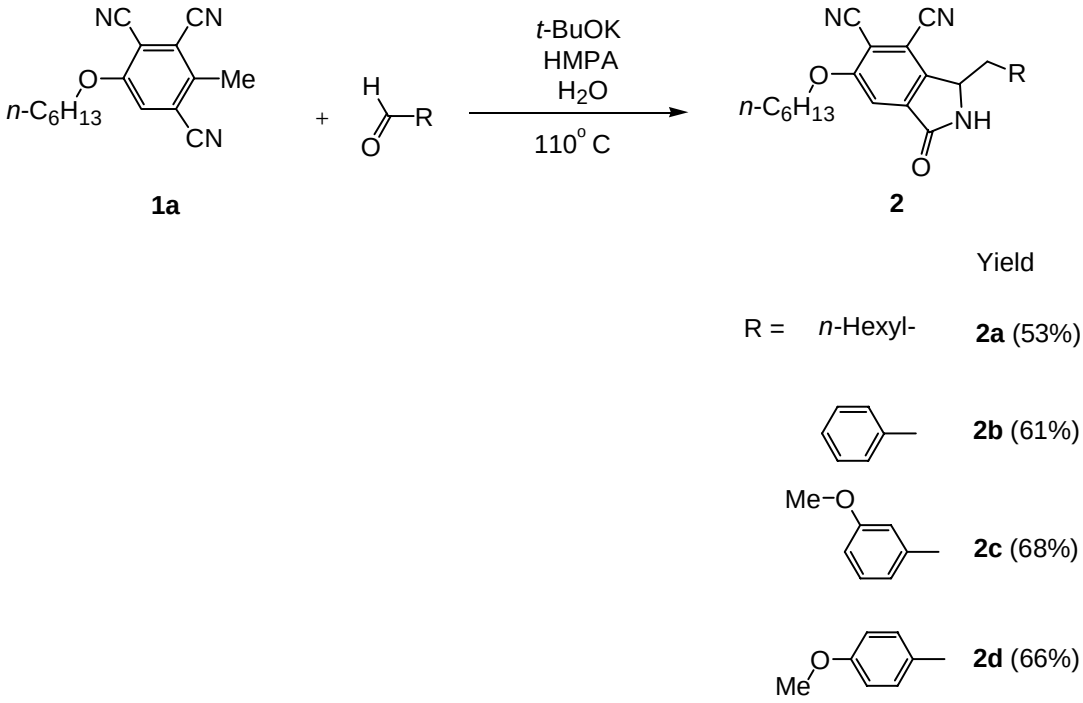
RESULTS AND DISCUSSION

Scheme 1 illustrates the synthesis of 3-substituted isoindolin-1-ones (**2**) from aldehyde and 6-hexyloxy-3-methylbenzene-1,2,4-tricarbonitrile (**1a**) in the presence of potassium *t*-butoxide and water in HMPA. Tricarbonitrile (**1a**) was prepared in good yield (78-84%) in the Rosenmund-von Braun reaction of 1,2,4,5-tetrabromo-6-hexyloxy-3-methylbenzene (**3a**) with cupric cyanide in NMP.[6] Treatment of **1a** with potassium *t*-butoxide, water, and aldehydes in HMPA gave **2** with moderate yields (53-68%). Under the absence of water, only the styryl carbon-carbon double bond was formed without its subsequent cyclization as evidenced by the ^{1}H-NMR spectral analysis. With reactions conducted in such solvents as DMF, DMSO, THF, or diethyl ether, only traces of products of cyclization were formed as shown in the crude ^{1}H-NMR spectral analysis. It was shown that apart from aromatic aldehydes but also aliphatic aldehydes cyclized under similar conditions. It should be emphasized that tetrabenzaldehyde (**4**), prepared from pentaerythrityl tetrabromide[7] and *p*-hydroxybenzaldehyde, reacted with **1** and four equivalents of water to give a dendrite compound (**5**) (**Scheme 2**). The yields were reasonable (62-69%). The temperature of the reaction is an essential parameter. The reaction required a temperature above 60°C. 2-Tolunitrile reacted with aromatic aldehyde under identical conditions to produce only stilbenes (**6**) with *trans* configuration product prevailing (*trans*/*cis* = 8/1) (**Scheme 3**). Stilbenes were not cyclized further in the presence of water or by prolonging the reaction time.

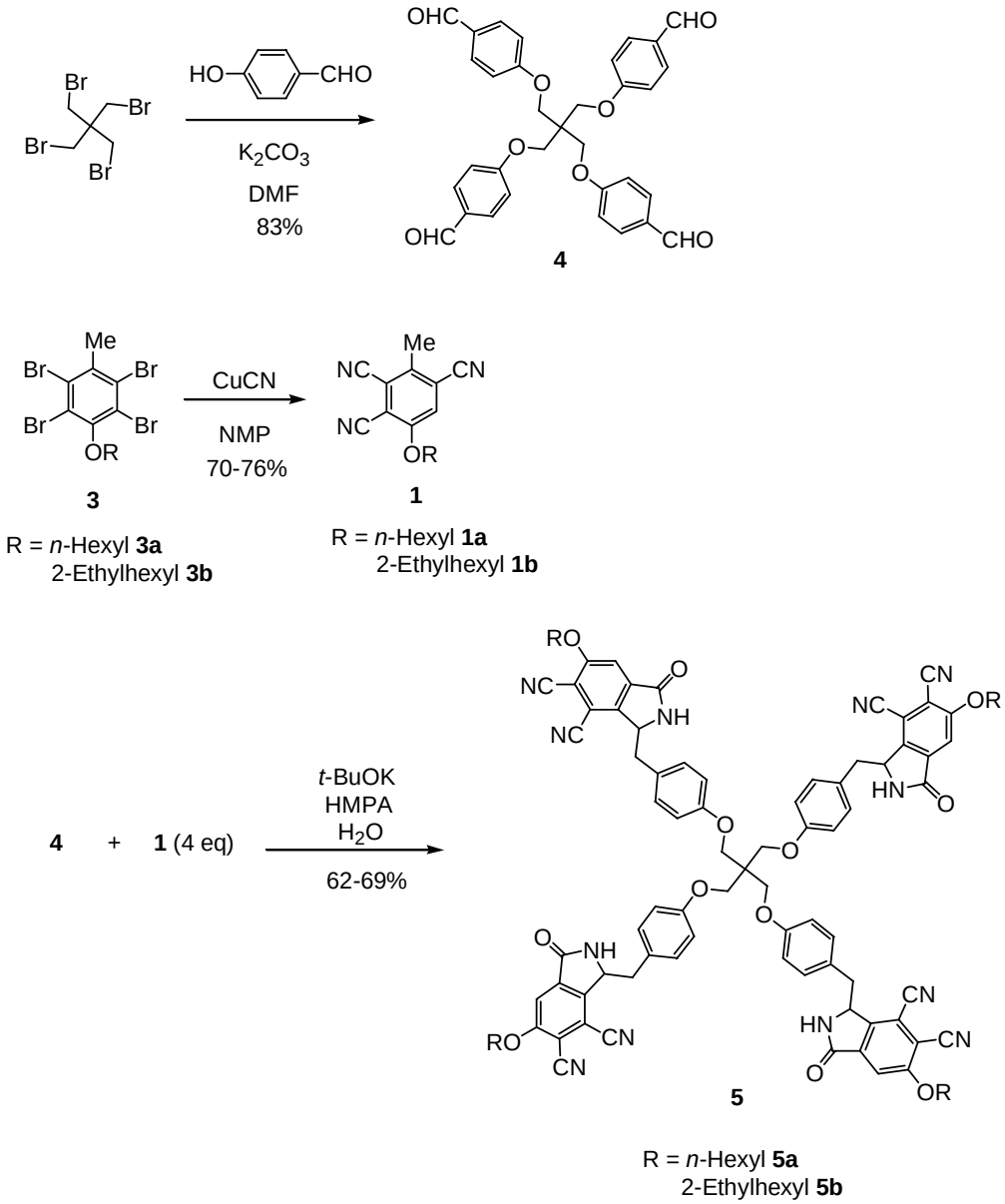
The structures of **2**, **5**, and **6** were elucidated based on MS, ^{1}H-NMR, ^{13}C-NMR, 2D NOESY, 2D COSY, HMQC, HMBC, and elemental analyses. The presence of only one hydrolyzed cyano group in the reaction was indicated by the additional 18 amu in the M^{+} of **2** in the MS spectra instead of the expected

M^+ for non-hydrolyzed product.[4] When **1** reacted with **4** to form **5**, an additional 72 amu instead of M^+ for the non-hydrolyzed product was observed in the MS spectral analysis. The ^{1}H-NMR spectrum of **2c,** a representative structure of the cyclization products, exhibits an ABX pattern for the protons at δ 3.25 (dd, *J* = 16, 11 Hz, 1 H), 3.42 (dd, *J* = 16, 5 Hz, 1 H), and 4.86 (dd, *J* = 11, 5 Hz, 1 H) ppm. This ABX pattern points to a chiral center located vicinally to two benzylic hydrogen atoms. No cyclizations of the *ortho* cyano group with the vinylic carbon-carbon double bond of stilbene are known. Thus, hydrolysis of one of the two cyano groups was assumed to form an amide group which was responsible for the following cyclization. On the other hand, a hydroxide nucleophile, formed from potassium *t*-butoxide and water, might attack the *sp*-carbon of one of the two cyano groups *ortho* to the vinylic carbon-carbon double bond and induce a 5-exo-trig ring closure process.[8] It rationalized the presence of isoindolin-1-one among reaction products. Either hydrolysis or nucleophilic attack to the cyano groups at position 2 or 4 in **1** would lead to two different regioisomers, **2c** and **7** (**Figure 1**). In fact, in all condensation and cyclization with **1**, only one regioisomer of the cyclized product was observed. It indicated a high level of regioselectivity in the above reaction (>99%).

Scheme 1. Synthesis of 3-Substituted Isoindolin-1-ones from Aldehyde and **1a**.



Scheme 2. Synthesis of Dendrite Compound (**5**) from **1** and **4** under Basic Conditions.



Scheme 3. The Reaction of 2-Tolunitrile with Aldehydes under Basic Conditions.

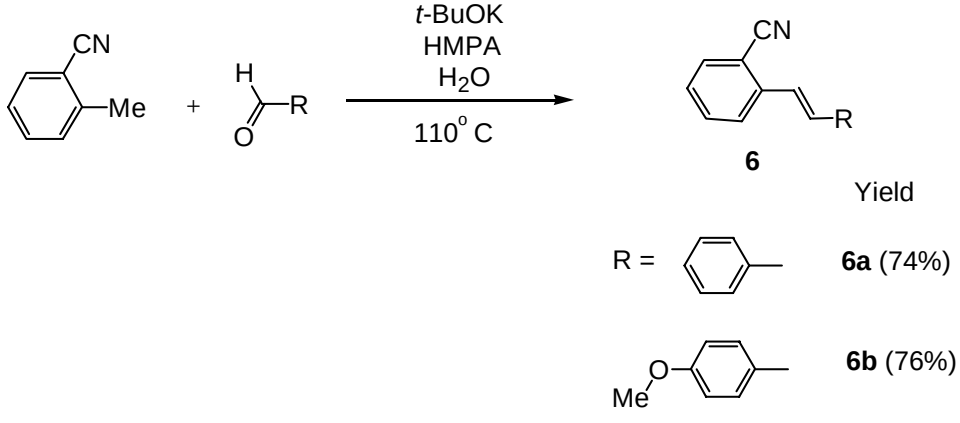
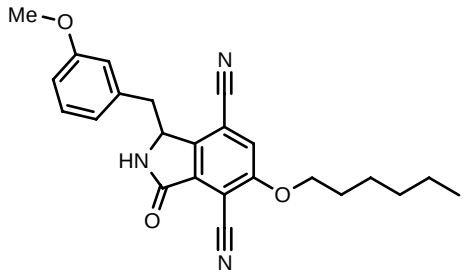


Figure 1. One of the Regioisomers of **2c.**



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The 2D NOESY spectrum of **2c** shows a coupling of hydrogen atom at δ 7.97 ppm with hydrogen atoms at δ 4.21 ppm. It indicates the hydrogen atom at C-8, appearing as a singlet at δ 7.97 ppm, is close to the methylene hydrogen atoms at C-6, appearing as a triplet at δ 4.21 ppm. The 2D COSY spectrum of **2c** also shows a long range coupling of the hydrogen atom at C-8 in the benzene ring with two benzylic hydrogen atoms at C-17. This is a very rare long range coupling through *six* bonds. Probably, the "W" shape of bonding configuration facilitates such long range coupling. The HMBC spectrum (**Figure 2**) revealed a coupling between the hydrogen atom at C-8 in the benzene ring and the carbonyl carbon (C-15), appeared at δ 162.81 ppm. It clearly indicates that C-15 is in the *ortho* position to the hydrogen atom at C-8 and not in the *para* position typical for the other regioisomer **7**. Moreover, the HMQC spectrum (**Figure 3**) showed that the carbon at 8-position (C-8), appeared at δ 115.89 ppm, coupled with the hydrogen atom in the benzene ring. The carbon at 17-position, appeared at δ 34.79 ppm, coupled with two benzylic hydrogen atoms. The coupling of two benzylic hydrogen atoms at C-17 and C-8 in its HMBC spectrum indicated a long distance coupling through *five* bonds. Probably, the "W" shape of bonding conformation between these two hetero nucleus is responsible for such coupling in the HMBC spectrum. It should be noted that the long range coupling shown in HMBC is asymmetric because a strong coupling appeared between the two benzylic hydrogen atoms at C-17 and C-8, but there is no coupling between the hydrogen atom at C-8 and the benzylic carbon at the 17-position. It is also important that the coupling through three bonds produces more intensive peaks than coupling across two bonds in the benzene ring. For example, H-22 of **2c** has coupling with C-18 and C-20 in HMBC, but H-22 has no coupling with C-21 and C-23. While H-23 of **2c** has coupling with C-19 and C-21 in

Figure 2. HMBC Spectrum and Assignment of Carbon and Hydrogen Atoms of **2c**.

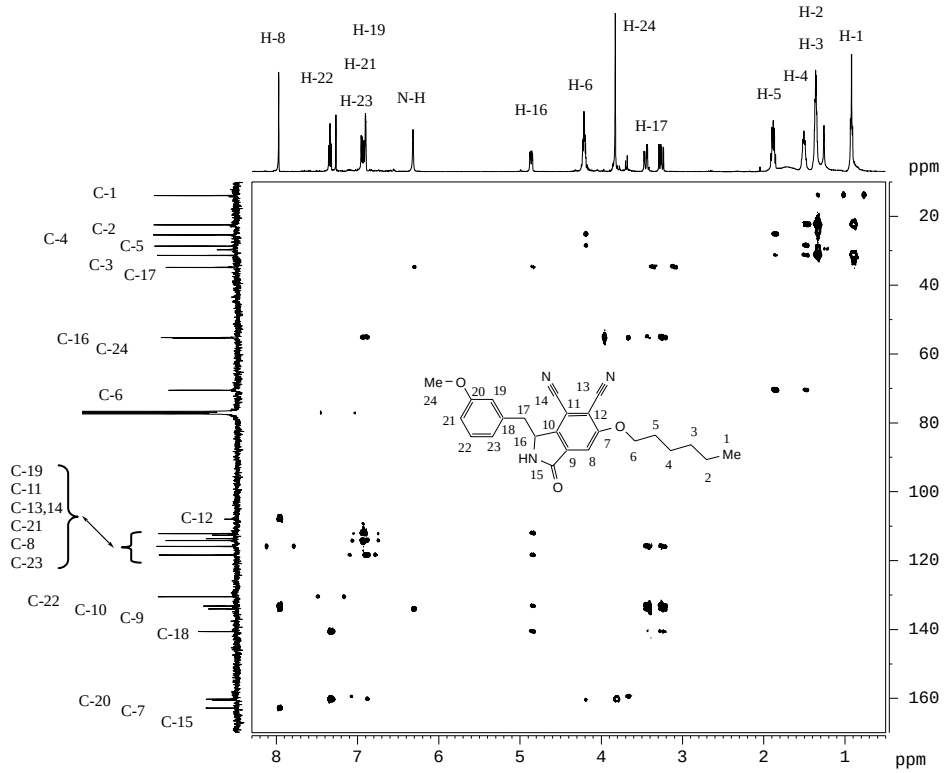
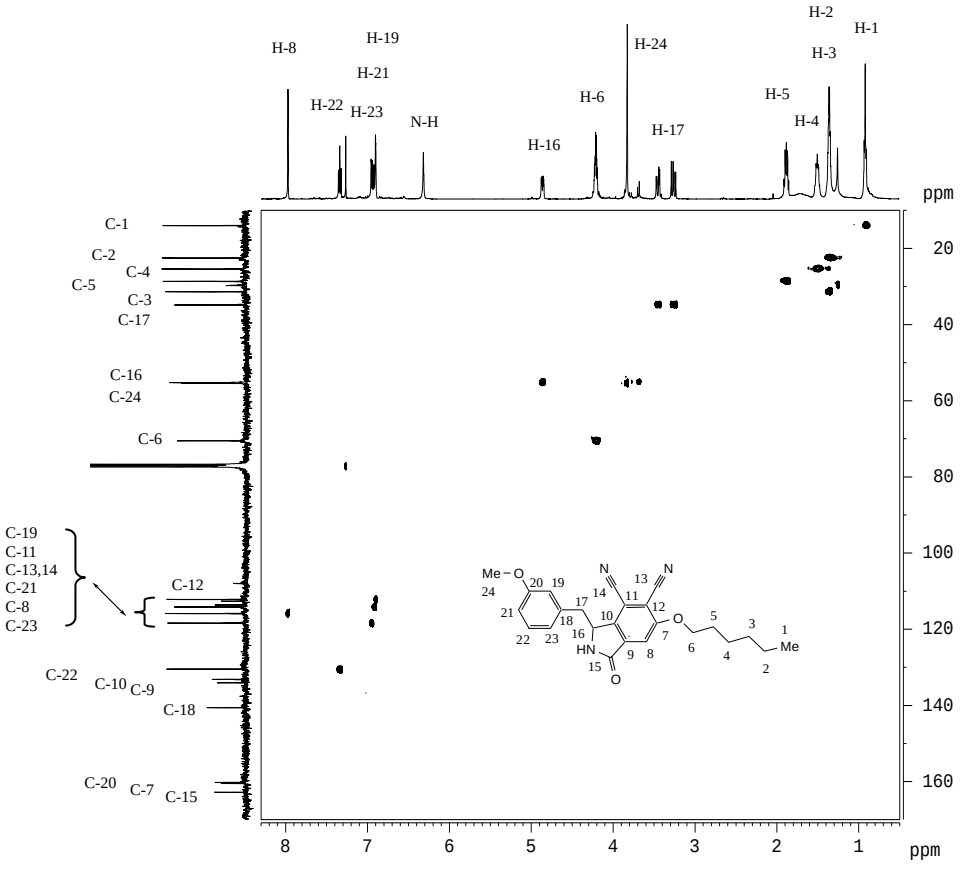


Figure 3. HMQC Spectrum and Assignment of Carbon and Hydrogen Atoms of **2c**.



HMBC, but H-23 has no coupling with C-18 and C-22.

The mechanism of the reaction may involve the regioselective hydrolysis of one of the two *ortho* cyano groups at the positions of 2 or 4 of **1** to form an amide group. This may occur prior to the cyclization. However, the hydroxide nucleophile may attack the carbon of one of the two cyano groups *ortho* to the vinylic carbon-carbon double bond to induce a 5-exo-trig ring closure (**Scheme 4**). The reason for such high regioselective cyclization is poorly understood. However, molecular calculation (SPARTAN) pointed to a higher Mulliken charge on the nitrogen atom of the cyano group *ortho* to the hydrogen atom in the benzene ring of **1** than on the nitrogen atoms on the two other cyano groups (**Figure 4**). A higher charge on the nitrogen atom may facilitate either hydrolysis of the cyano group or the nucleophilic attack of the hydroxide anion.[9] The molecular modeling study indicates that the relative energy of **2c** (-14.0441 kcal/mol) is lower than that of the regioisomer (**7**) (-12.9374 kcal/mol).

EXPERIMENTAL

Precoated silica gel 60F-254 on aluminum plates made by EM chemical company was used for thin-layer chromatography. Purification by column chromatography was carried out with EM silica gel 60 (70-230 mesh ASTM). HPLC separation was performed at a flow rate of 0.7 mL/min by the use of two Chemco-Pak 10 x 250 columns packed with Chemcosorb 5-ODS-H. GLC analysis was performed

Scheme 4. Plausible Mechanism for the Formation of **2** from **1**.

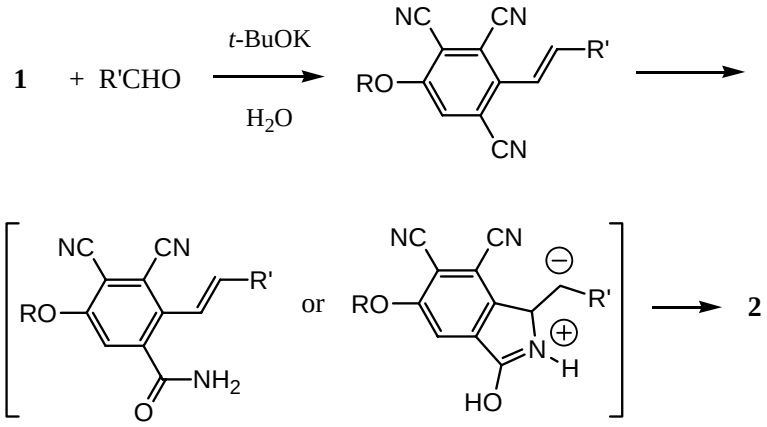
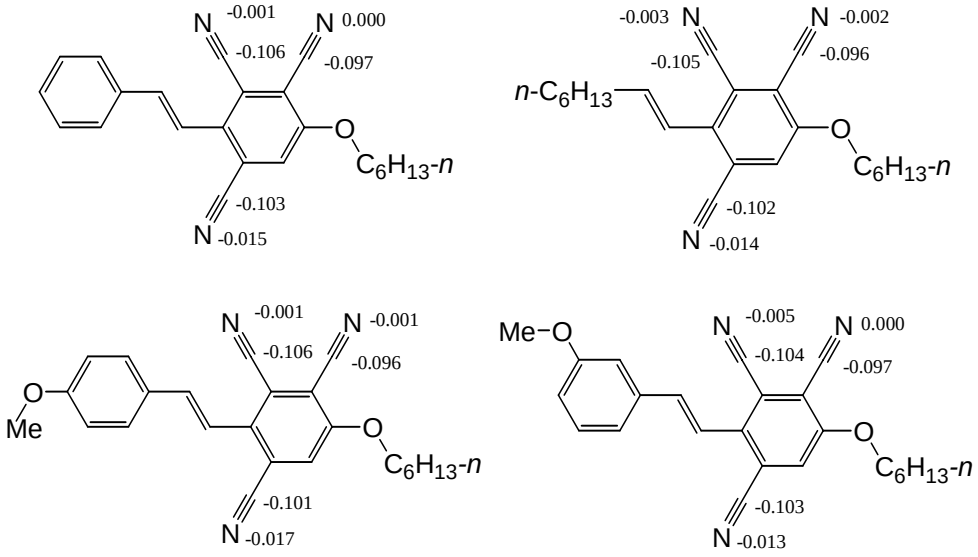


Figure 4. The Calculated Mulliken Charges of the Carbon and Nitrogen Atoms on the Cyano Groups of the Plausible Intermediates of **2a**-**2d**.



by a 3.2 x 3.1 column packed with SE-30 (5% on Chemcosorb W). The purity of each compound was judged to be > 95% by GLC, ^{1}H-NMR or ^{13}C-NMR spectral analyses. Reactions of organometallic compounds were undertaken in oven- and/or flame-dried glassware. All other materials were used without further purification. IR spectra were recorded on a Perkin-Elmer Paragon 1000 or 882 infrared spectrophotometer. 1D and 2D NMR spectra were recorded on a Bruker AC200, AC300P, AMX400, or DRX500 spectrometer, and chemical shifts were reported in ppm down field from TMS. MS spectra were obtained on HP 5971, Fisons MD800 GC/MS or VG 70-250S spectrometers. HRMS was recorded on VG 70-250S or VG Autospec double focusing high-resolution mass spectrometer. Elemental analyses were performed on a Perkin Elmer EA-2400.

4-{2,2-Bis[(4-formylphenoxy)methyl]-3-(4-formylphenoxy)propoxy}benzaldehyde (**4**). To a solution of 4-hydroxybenzaldehyde (3.90 g, 32 mmol) in 40 mL of dry DMF were added anhydrous potassium carbonate (4.42 g, 32 mmol) and pentaerythrityl tetrabromide (1.55 g, 4 mmol). The reaction was stirred at 120°C for 18 h, then the mixture was cooled and the solvent was removed under reduced pressure. The residue was treated with 15 mL of water and extracted with ethyl acetate. The combined organic phases were washed with water, brine and dried over anhydrous magnesium sulfate and evaporated in

vacum. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 15/1) to give a pale yellow solid (1.83 g, 83 %): mp 179-180 °C; ^{1}H NMR ($CDCl_3$, TMS) δ 4.48 (s, 8 H), 7.05 (d, *J* = 8.6 Hz, 8 H), 7.83 (d, *J* = 8.6 Hz, 8 H), 9.89 (s, 4 H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 44.64, 66.41, 114.80, 130.51, 131.90, 163.11, 190.55 ppm; IR ν 2742 (w), 1691 (s), 1600 (s), 1578 (m), 1508 (m), 1467 (w), 1427 (w), 1392 (w), 1312 (m), 1248 (s), 1214 (w), 1158 (s), 1048 (w), 1029 (w), 859 (w), 831 (m), 754 (w) cm^{-1}; MS *m/z* 552 (M^+), 307, 289, 219, 154. HRMS calcd for $C_{33}H_{28}O_8$ 552.1784; found 552.1786. Anal. Calcd for $C_{33}H_{28}O_8$: C, 71.73; H, 5.11. Found: C, 71.82; H, 5.21.

1,2,4,5-Tetrabromo-6-hexyloxy-3-methylbenzene (**3a**). This compound was prepared in 89% yield by a procedure similar to that for the preparation of **4** using 2.12 g (5 mmol) of 2,3,5,6-tetrabromo-4-methylphenol,[10] 1.04 g (7.5 mmol) of potassium carbonate, 1.24 g (7.5 mmol) of *n*-hexyl bromide, and 15 mL of dry DMF: white solid; mp 38-39 °C; ^{1}H NMR ($CDCl_3$, TMS) δ 0.90 (t, J = 7 Hz, 3 H), 1.34–1.38 (m, 4 H), 1.52–1.54 (m, 2 H), 1.85–1.89 (m, 2 H), 2.77 (s, 3 H), 3.97 (t, *J* = 7 Hz, 2 H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 14.06, 22.59, 25.48, 27.93, 29.68, 29.86, 31.63, 73.45, 121.76, 127.03, 136.85, 153.41 ppm; IR ν 1537 (w), 1465 (w), 1411 (s), 1364 (s), 1329 (s), 1253 (m), 1114 (w), 993 (s), 907 (w), 629 (m) cm^{-1}; MS *m/z* 512 (M^+ + 8), 510 (M^+ + 6), 508 (M^+ + 4), 506 (M^+ + 2), 504 (M^+), 428, 426, 424, 422, 420, 344. HRMS calcd for $C_{13}H_{16}OBr_4$ 503.7935; found 503.7936. Anal. Calcd for $C_{13}H_{16}OBr_4$: C, 30.74; H, 3.18. Found: C, 30.86; H, 3.23.

1,2,4,5-Tetrabromo-6-(2-ethylhexyloxy)-3-methylbenzene (**3b**). This compound was prepared in 81% yield (2.17 g) by a procedure similar to that for the preparation of **4** using 2.12 g (5 mmol) of 2,3,5,6-tetrabromo-4-methylphenol, 1.04 g (7.5 mmol) of potassium carbonate, 1.45 g (7.5 mmol) of 2-ethylhexyl bromide, and 10 mL of dry DMF: white solid; mp 45-46 °C; ^{1}H NMR ($CDCl_3$, TMS) δ 0.89–1.00 (m, 6 H), 1.33–1.62 (m, 8 H), 1.83–1.87 (m, 1 H), 2.77 (s, 3 H), 3.85 (d, *J* = 6 Hz, 2 H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 11.24, 14.15, 23.06, 23.53, 27.97, 29.14, 30.03, 40.34, 75.87, 121.76, 127.08, 136.82, 153.43 ppm; IR ν 1460 (w), 1411 (s), 1362 (s), 1329 (s), 1254 (m), 1115 (w), 1006 (s), 629 (m) cm^{-1}; MS *m/z* 540 (M^+ + 8), 538 (M^+ + 6), 536 (M^+ + 4), 534 (M^+ + 2), 532 (M^+), 428, 426, 424, 422, 420, 344. HRMS calcd for $C_{15}H_{20}OBr_4$ 531.8248; found 531.8248. Anal. Calcd for $C_{15}H_{20}OBr_4$: C,

33.62; H, 3.76. Found: C, 33.68; H, 3.82.

6-Hexyloxy-3-methylbenzene-1,2,4-tricarbonitrile (**1a**). To a mixture of cupric cyanide (1.61 g, 18 mmol) in 10 mL of NMP was added a solution of **3a** (1.52 g, 3 mmol) in 20 mL of dry NMP. The reaction was stirred at 120°C for 16 h, then the mixture was cooled and the solvent was removed under reduced pressure. The residue was treated with 15 mL of water and extracted with ethyl acetate. The combined organic phases were washed with water, brine and dried over anhydrous magnesium sulfate and evaporated in vacum. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 15/1) to give a white solid (0.61 g, 76 %): mp 97-98 °C; ^{1}H NMR ($CDCl_3$, TMS) δ 0.91 (t, *J* = 7 Hz, 3 H), 1.34–1.37 (m, 4 H), 1.45–1.55 (m, 2 H), 1.82–1.90 (m, 2 H), 2.72 (s, 3 H), 4.14 (t, *J* = 7 Hz, 2 H), 7.40 (s, 1 H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 13.90, 18.81, 22.43, 25.30, 28.49, 31.25, 70.81, 109.28, 111.97, 113.35, 115.19, 118.73, 119.13, 119.77, 137.58, 159.14 ppm; IR ν 2236 (m), 1692 (m), 1461 (m), 1320 (s), 1203 (s), 1097 (s), 903 (m) cm^{-1}; MS *m/z* 267 (M^+), 183, 154, 127. HRMS calcd for $C_{16}H_{17}N_3O$ 267.1372; found 267.1373. Anal. Calcd for $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41. Found: C, 71.98; H, 6.53.

6-(2-Ethylhexyloxy)-3-methylbenzene-1,2,4-tricarbonitrile (**1b**). This compound was prepared in 70% yield by a procedure similar to that for the preparation of **1a** using 1.61 g (3 mmol) of **3b**, 1.62 g (18 mmol) of cupric cyanide, and 30 mL of dry NMP: pale yellow solid; mp 48-49 °C; ^{1}H NMR ($CDCl_3$, TMS) δ 0.89-0.97 (m, 6 H), 1.31–1.34 (m, 4 H), 1.43–1.61 (m, 4 H), 1.81–1.86 (m, 1 H), 2.72 (s, 3 H), 4.02 (d, *J* = 5.5 Hz, 2 H), 7.43 (s, 1 H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 11.00, 13.98, 18.82, 22.86, 23.56, 28.88, 30.10, 39.00, , 73.06, 109.23, 111.94, 113.36, 115.20, 118.64, 119.11, 119.74, 137.55, 159.30 ppm; IR ν 2235 (m), 1592 (m), 1466 (s), 1322 (s), 1283 (s), 1261 (m), 1224 (w), 1095 (s), 1014 (m), 889 (w), 799 (s) cm^{-1}; MS *m/z* 295 (M^+), 183, 182, 154, 139. HRMS calcd for $C_{18}H_{21}N_3O$ 295.1685; found 295.1687. Anal. Calcd for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17. Found: C, 73.30; H, 7.26.

Preparation of 6-hexyloxy-3-[(3-methoxyphenyl)methyl]-1-oxoisoindoline-4,5-dicarbonitrile (**2c**) **as the representative procedure for the synthesis of isoindolin-1-ones**: Under nitrogen atmosphere, **1a** (0.53 g, 2 mmol), *m*-anisaldehyde (0.27 g, 2 mmol), and water (36 μL, 2 mmol) were sequentially

added to a mixture containing potassium *t*-butoxide (0.23 g, 2 mmol) and 2 mL of dry HMPA. The reaction mixture was stirred at rt for 24 h, then the reaction mixture was treated with 10 mL of water and extracted with ethyl acetate. The combined organic phases were washed with water, brine and dried over anhydrous magnesium sulfate and evaporated in vacum. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 1/3) to give a pale yellow solid (0.55 g, 68 %): mp 121-122 °C; ^{1}H NMR ($CDCl_3$, TMS) δ 0.92 (t, *J* = 7 Hz, 3 H, H-1), 1.34–1.37 (m, 4 H, H-2 and H-3), 1.46–1.53 (m, 2 H, H-4), 1.83–1.88 (m, 2 H, H-5), 3.25 (dd, *J* = 16, 11 Hz, 1 H, H-17), 3.42 (dd, *J* = 16, 5 Hz, 1 H, H-17), 3.82 (s, 3 H, H-24), 4.21 (t, *J* = 7 Hz, 2 H, H-6), 4.86 (dd, *J* = 11, 5 Hz, 1 H, H-16), 6.35 (s, 1 H, N-H), 6.89 (s, 1 H, H-19), 6.91 (d, *J* = 7.5 Hz, 1 H, H-21), 6.94 (d, *J* = 7.5 Hz, 1 H, H-23), 7.34 (t, *J* = 7.5 Hz, 1 H, H-22), 7.97 (s, 1 H, H-8) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 13.95 (C-1), 22.48 (C-2), 25.36 (C-4), 28.61 (C-5), 31.32 (C-3), 34.79 (C-17), 55.18 (C-16), 55.33 (C-24), 70.50 (C-6), 107.98 (C-12), 112.18 (C-19), 112.64 (C-11), 113.63 (C-13 and C-14), 114.16 (C-21), 115.89 (C-8), 118.38 (C-23), 130.48 (C-22), 133.21 (C-10), 134.08 (C-9), 140.63 (C-18), 160.26 (C-20), 160.48 (C-7), 162.81 (C-15) ppm; IR ν 1677 (m), 1596 (w), 1458 (m), 1083 (w) cm^{-1}; MS *m/z* 404 (M^+ + 1), 303. HRMS calcd for $C_{24}H_{25}N_3O_3$ 403.1896; found 403.1897. Anal. Calcd for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25. Found: C, 71.56; H, 6.36.

3-Heptyl-6-hexyloxy-1-oxoisoindoline-4,5-dicarbonitrile (**2a**). This compound was prepared in 53% yield by a procedure similar to that for the preparation of **2c** using 0.53 g (2 mmol) of **1a**, 0.23 g (2 mmol) of heptanal, 36 μL (2 mmol) of water, 0.23 g (2 mmol) of potassium *t*-butoxide, and 2 mL of dry HMPA: white solid; mp 139-140 °C; ^{1}H NMR ($CDCl_3$, TMS) δ 0.90 (t, *J* = 7 Hz, 6 H), 1.31–1.70 (m, 16 H), 1.82–1.89 (m, 2 H), 2.90 (dd, *J* = 16, 10 Hz, 1 H), 3.25 (dd, *J* = 16, 4 Hz, 1 H), 3.71–3.74 (m, 1 H), 4.19 (t, *J*= 6.5 Hz, 2 H), 6.06 (s, 1 H), 7.91 (s, 1 H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 13.98, 22.49, 25.23, 25.36, 28.60, 28.92, 31.32, 31.54, 31.96, 35.27, 50.82, 70.43, 112.24, 113.69, 115.77, 116.41, 133.85, 134.33, 160.32, 162.56 ppm; IR ν 2363 (w), 2234 (w), 1677 (s), 1595 (w), 1452 (m), 1303 (w), 1086 (w) cm^{-1}; MS *m/z* 382 (M^+ + 1), 298, 213. HRMS calcd for $C_{23}H_{31}N_3O_2$ 381.2416; found 381.2417. Anal. Calcd for $C_{23}H_{31}N_3O_3$: C, 72.41; H, 8.19. Found: C, 72.56; H, 8.26.

6-Hexyloxy-1-oxo-3-benzylisoindoline-4,5-dicarbonitrile (**2b**). This compound was prepared in 61% yield by a procedure similar to that for the preparation of **2c** using 0.53 g (2 mmol) of **1a**, 0.21 g (2 mmol) of benzaldehyde, 36 μL (2 mmol) of water, 0.23 g (2 mmol) of potassium *t*-butoxide, and 2 mL of dry HMPA: yellow solid; mp 114-115 °C; ^{1}H NMR ($CDCl_3$, TMS) δ 0.90 (t, *J* = 7 Hz, 3 H), 1.33–1.38 (m, 4 H), 1.48–1.52 (m, 2 H), 1.85–1.90 (m, 2 H), 3.27 (dd, *J* = 16, 11 Hz, 1 H), 3.46 (dd, *J* = 16, 4 Hz, 1 H), 4.20 (t, *J* = 6.5 Hz, 2 H), 4.89 (dd, *J* = 11, 4 Hz, 1 H), 6.22 (s, 1 H), 7.36–7.45 (m, 5 H), 7.98 (s, 1 H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 13.95, 22.48, 25.37, 28.62, 31.33, 34.87, 55.32, 70.52, 108.02, 112.64, 113.64, 115.91, 126.27, 129.16, 129.39, 133.24, 134.09, 139.03, 160.50, 162.81 ppm; IR ν 2234 (w), 1670 (m), 1527 (s), 1455 (m), 1351 (s), 1202 (m), 1044 (m), 803 (m), 732 (m), 670 (w) cm^{-1}; MS *m/z* 374 (M^+ + 1), 307, 289, 176, 154. HRMS calcd for $C_{23}H_{23}N_3O_2$ 373.1790; found 373.1791. Anal. Calcd for $C_{23}H_{23}N_3O_2$: C, 73.97; H, 6.21. Found: C, 73.82; H, 6.34.

6-Hexyloxy-3-[(4-methoxyphenyl)methyl]-1-oxoisoindoline-4,5-dicarbonitrile (**2d**). This compound was prepared in 66% yield by a procedure similar to that for the preparation of **2c** using 0.53 g (2 mmol) of **1a**, 0.27 g (2 mmol) of *p*-anisaldehyde, 36 μL (2 mmol) of water, 0.23 g (2 mmol) of potassium *t*-butoxide, and 2 mL of dry HMPA: yellow solid; mp 142-143 °C; ^{1}H NMR ($CDCl_3$, TMS) δ 0.89 (t, *J* = 7 Hz, 3 H), 1.25–1.56 (m, 6 H), 1.84–1.93 (m, 2 H), 3.23 (dd, *J* = 16, 11 Hz, 1 H), 3.38 (dd, *J* = 16, 4 Hz, 1 H), 3.83 (s, 3 H), 4.21 (t, *J* = 7 Hz, 2 H), 4.83 (dd, *J* = 11, 4 Hz, 1 H), 6.11 (s, 1 H), 6.94 (d, *J* = 8.5 Hz, 2 H), 7.29 (d, *J* = 8.5 Hz, 2 H), 7.97 (s, 1 H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 13.96, 22.49, 25.38, 28.63, 31.34, 34.98, 54.83, 55.40, 70.50, 107.96, 112.67, 113.67, 114.69, 115.90, 127.57, 130.93, 133.43, 134.15, 160.12, 160.47, 162.78 ppm; IR ν 2363 (w), 2335 (w), 2234 (w), 1670 (m), 1527 (s), 1455 (m), 1351 (s), 1033 (m), 803 (m), 732 (m), 670 (w) cm^{-1}; MS *m/z* 404 (M^+ + 1), 307, 289, 176, 154. HRMS calcd for $C_{24}H_{25}N_3O_3$ 403.1896; found 403.1897. Anal. Calcd for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25. Found: C, 71.54; H, 6.34.

3-({4-2,2-Bis(4-[(6,7-dicyano-5-hexyloxy-3-oxoisoindolinyl)methyl]phenoxymethyl)-3-{4-[(6,7-dicyano-5-hexyloxy-3-oxoisoindolinyl)methyl]phenoxy}propoxyphenyl}methyl)-6-hexyloxy-1-oxoisoindoline-4,5-dicarbonitrile (**5a**). This compound was prepared in 62% yield by a procedure similar to

that for the preparation of **2c** using 0.27 g (1 mmol) of **1a**, 3.32 g (6 mmol) of **4**, 108 μL (6 mmol) of water, 0.67 g (6 mmol) of potassium *t*-butoxide, and 6 mL of dry HMPA: pale yellow oil; ^{1}H NMR ($CDCl_3$, TMS) δ 0.92 (t, *J* = 7 Hz, 12 H), 1.33–1.38 (m, 16 H), 1.45–1.63 (m, 8 H), 1.83–1.93 (m, 8 H), 3.20 (dd, *J* = 16, 10 Hz, 4 H), 3.39 (dd, *J* = 16, 4 Hz, 4 H), 4.21 (t, *J* = 6.4 Hz, 8 H), 4.35 (br s, 8 H), 4.82 (dd, *J* = 10, 4 Hz, 4 H), 6.17 (s, 4 H), 6.93 (d, *J* = 8.5 Hz, 8 H), 7.25 (d, *J* = 8.5 Hz, 8 H), 7.96 (s, 4 H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 13.95, 22.47, 25.36, 28.61, 31.32, 34.88, 45.38, 54.55, 66.57, 70.53, 107.94, 112.63, 113.68, 115.45, 115.92, 127.54, 131.79, 133.18, 134.08, 159.05, 160.50, 162.76 ppm; IR ν 2234 (w), 1724 (m), 1677 (m), 1588 (m), 1507 (m), 1459 (m), 1262 (s), 1106 (s), 1018 (s), 801 (s) cm^{-1}; MS *m/z* 1622 (M^+ + 1), 1538, 1355, 1233, 1071, 963, 831. Anal. Calcd for $C_{97}H_{96}N_{12}O_{12}$: C, 71.83; H, 5.97. Found: C, 71.98; H, 6.09.

3-[(4-{2,2-Bis[(4-[6,7-dicyano-5-(2-ethylhexyloxy)-3-oxoisoindolinyl]methylphenoxy)methyl]-3-(4-[6,7-dicyano-5-(2-ethylhexyloxy)-3-oxoisoindolinyl]methylphenoxy)propoxy}phenyl)methyl]-6-(2-ethylhexyloxy)-1-oxoisoindoline-4,5-dicarbonitrile (**5b**). This compound was prepared in 69% yield by a procedure similar to that for the preparation of **2c** using 0.30 g (1 mmol) of **1b**, 3.32 g (6 mmol) of **4**, 108 μL (6 mmol) of water, 0.67 g (3 mmol) of potassium *t*-butoxide, and 3 mL of dry HMPA: pale yellow oil; ^{1}H NMR ($CDCl_3$, TMS) δ 0.91 (t, *J* = 7 Hz, 12 H), 0.95 (t, *J* = 7 Hz, 12 H), 1.33–1.39 (m, 16 H), 1.44–1.56 (m, 16 H), 1.81–1.86 (m, 4 H), 3.20 (dd, *J* = 16, 10 Hz, 4 H), 3.39 (dd, *J* = 16, 4 Hz, 4 H), 4.06–4.13 (m, 8 H), 4.35 (br s, 8 H), 4.83 (br d, *J* = 6 Hz, 4 H), 6.30 (s, 4 H), 6.92 (d, *J* = 8 Hz, 8 H), 7.24 (d, *J* = 8 Hz, 8 H), 7.97 (s, 4 H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 11.00, 13.97, 22.86, 23.63, 28.88, 30.17, 34.80, 39.04, 45.27, 54.47, 66.56, 72.86, 107.89, 112.56, 113.66, 115.40, 115.80, 115.89, 127.51, 131.09, 133.15, 134.07, 158.99, 160.64, 162.77 ppm; IR ν 2234 (w), 1680 (s), 1595 (m), 1512 (m), 1452 (s), 1310 (m), 1241 (s) cm^{-1}; MS *m/z* 1733 (M^+), 1622, 1439. Anal. Calcd for $C_{105}H_{112}N_{12}O_{12}$: C, 72.73; H, 6.51. Found: C, 72.85; H, 6.63.

2-((1*E*)-2-Phenylvinyl)benzenecarbonitrile (**6a**).[11] This compound was prepared in 74% yield by a procedure similar to that for the preparation of **2c** using 0.23 g (2 mmol) of *o*-tolunitrile, 0.21 g (2 mmol) of benzaldehyde, 36 μL (2 mmol) of water, 0.23 g (2 mmol) of potassium *t*-butoxide, and 2 mL of dry

HMPA: orange yellow oil; ^{1}H NMR ($CDCl_3$, TMS) δ 7.28 –7.45 (m, 6 H), 7.52–7.60 (m, 3 H), 7.64 (d, *J* = 8 Hz, 1 H), 7.78 (d, *J* = 8 Hz, 1 H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 111.23, 117.96, 124.05, 125.24, 127.09, 127.51, 128.76, 128.81, 132.72, 133.10, 133.40, 136.14, 140.54 ppm; IR ν 2220 (m), 1695 (m), 1635 (w), 1595 (w), 1576 (w), 1494 (m), 1476 (w), 1447 (m), 1292 (w), 1200 (w), 959 (m), 760 (s), 689 (s), 520 (m) cm^{-1}; MS *m/z* 205 (M^+), 204, 203, 176, 175, 164, 151.

2-[(1*E*)-2-(4-Methoxyphenyl)vinyl]benzenecarbonitrile (**6b**). This compound was prepared in 76% yield by a procedure similar to that for the preparation of **2c** using 0.23 g (2 mmol) of *o*-tolunitrile, 0.27 g (2 mmol) of *p*-anisaldehyde, 36 μL (2 mmol) of water, 0.23 g (2 mmol) of potassium *t*-butoxide, and 2 mL of dry HMPA: white solid; mp 107-108 °C (lit.,[4d] mp 108-109 °C).

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hydrogen atom in the benzene ring, but, there is no coupling between the benzylic hydrogen atoms and the hydrogen in the benzene ring.

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