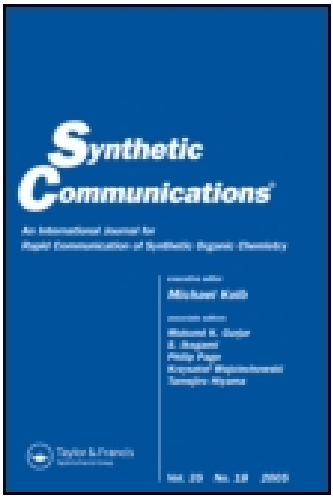

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Novel Process for the Synthesis of Class I Antiarrhythmic Agent (±)-Cibenzoline and Its Analogs

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Novel Process for the Synthesis of Class I Antiarrhythmic Agent (±)-Cibenzoline and Its Analogs

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Abstract: Synthesis of (±)-cibenzoline and its analogs has been achieved by a simple sequence of reactions. The diaryl cyanoolefin intermediate **3** could be prepared by Knoevenagel condensation of benzophenone with ethylcyanoacetate to form the tetra-substituted olefin intermediate **2** followed by Krapcho deethoxycarbonylation or from β-hydroxynitrile intermediate **2′** followed by the elimination of hydroxyl group respectively. The 2,2-diphenylcyclopropanecarbonitrile **4** was synthesized from intermediate **3** by cyclopropanation, which was converted to (±)-2-(2,2-diphenylcyclopropyl)-2-imidazoline **5** by reaction with ethylenediamine in the presence of a catalytic amount of sulfur. Moreover, the obtained 2-imidazolines were smoothly oxidized to the corresponding imidazoles **6** in good to moderate yields.

Keywords: Benzophenone, cibenzoline, cyclopropanation, diaryl cyanoolefin

INTRODUCTION

Atrial fibrillation represents an important medical problem,[1] because not only of increased incidence in the elderly population, but also it is a major cause of embolic stroke. Atrial fibrillation is the most commonly sustained cardiac arrhythmia and is a frequent reason for antiarrhythmic therapy.[2] Numerous antiarrhythmic drugs have been developed and used to treat arrhythmia, but clinical efficacy is often less than satisfactory.

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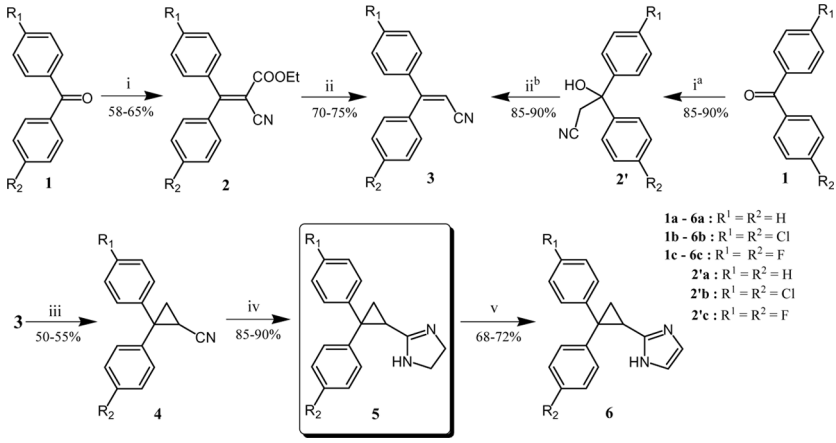


Scheme 1. Synthesis of cibenzoline and its analogs: reagents and conditions: (i) $CNCH_2COOEt$, $HOAc/C_6H_6$, β-alanine at reflux, 90 (i[a]) CH_3CN, n-BuLi, dry THF, $-80°C$, 2 h; (ii) NaCl, H_2O, DMSO, 160–170°C, 4 h; (ii[b]) $SOCl_2$, dry pyridine, dry DCM, 0°C to rt, 3 h; (iii) $Me_3S(O)I$, NaH, DMSO, rt, 24 h; (iv) sulfur, ethylenediamine, reflux, 4 h; (v) (diacetoxyiodo) benzene, K_2CO_3, DMSO, rt, 48 h.

(±)-2-(2,2-diphenylcyclopropyl)-2-imidazoline **5a** (Scheme 1) has been clinically used as one of the class I antiarrhythmic agents.[3,4] This drug relieves arrhythmia by restricting fast inward Na^+ current and blocking the slow inward Ca^{2+} channel in myocytes.[5] It was shown that micromolar concentrations of cibenzoline blocked the ATP-sensitive K^+(KATP) channel in excised membranes from rat heart and pancreatic β cells.[6–8] Cibenzoline is marketed under the trade names Cipralan (Glaxo) and Exacor (Monsanto).

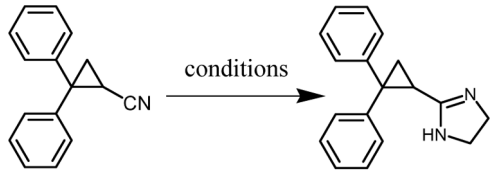
To our knowledge, literature cites only six reports so far, including four patents for the synthesis of cibenzoline from diphenyldiazomethane[9–13] and chiral cibenzoline from chiral 2,2-disubstituted cyclopropylmethanols.[14] In the patented method, the synthesis of diphenyldiazomethane has been carried out by the oxidation of benzophenone hydrazone with toxic reagents such as mercuric oxide or manganese dioxide, and a high temperature of about 200°C was needed for the final condensation process with ethylenediamine monotosylate. It is observed that all the reported methods are cumbersome and expensive for a process-scale preparation. They entail certain inconvenient reagents to handle, such as an unstable diphenyldiazomethane and HgO. This article describes our attempts to develop a novel and less hazardous synthetic route amenable for scale-up operations. Herein we report an improved

strategy for the synthesis of cibenzoline and its analogs from commercially available benzophenone as starting material. Toxic reagents such as mercuric oxide and high temperature in the final condensation process are avoided. The synthesis of the analogs has been carried out to create a more potent and well-tolerated therapeutic.

RESULTS AND DISCUSSION

The synthesis of imidazoles **6a–c** is outlined in Scheme 1. Thus benzophenone **1a** was converted to the tetra-substituted olefin **2a** with ethylcyanoacetate by Knoevenagel condensation.[15] The reported procedure, which makes use of ammonium acetate as a catalyst, failed to initiate the condensation of benzophenone and ethylcyanoacetate.[16] When a molar mixture of these components were heated to reflux in the presence of β-alanine in a mixture of glacial acetic acid and benzene for several hours, the formation of desired product **2a** was detected by gas chromatography (GC). The condensation reaction reached equilibrium after 90 h with continuous removal of water (Dean–Stark water trap). The rate of condensation was slow and was further retarded if higher boiling solvents such as toluene and xylene were used. The cyanoester **2** was isolated by column chromatography. The deethoxycarbonylation of 2-cyano-2-alkenoates **2** to the unsaturated nitriles **3** was carried out in good yields by Krapcho's protocol[17] using wet dimethyl sulfoxide (DMSO) containing sodium chloride. The synthesis of unsaturated nitriles **3** by the sequence of Knoevenagel condensation followed by deethoxycarbonylation was inconvenient because of the longer reaction time (90 h) and lower yields (58–65%). To achieve higher yields and short reaction time, synthesis of intermediate **3** was also carried out by an alternative route as shown in Scheme 1. The intermediate **3** can be prepared by starting from the substituted benzophenone. Acetonitrile was found to undergo mainly ionization of an α-hydrogen with n-butyl lithium in tetrahydrofuran, rather than an addition reaction involving the nitrile group. The ionization of acetonitrile with n-butyl lithium in tetrahydrofuran and its condensation with substituted benzophenone was carried out at $-80^{\circ}C$ to get the β-hydroxynitrile in just 2 h, followed by the elimination of the hydroxyl group using thionyl chloride and pyridine, which gave exclusively the compound **3**. The unsaturated nitrile **3** was cyclopropanated by the addition of trimethylsulfoxonium iodide and sodium hydride in dry DMSO at room temperature to afford the 2,2-diphenylcyclopropanecarbonitriles **4** as a mixture of diastereomers.

Table 1. Method for conversion of nitrile to 2-imidazoline

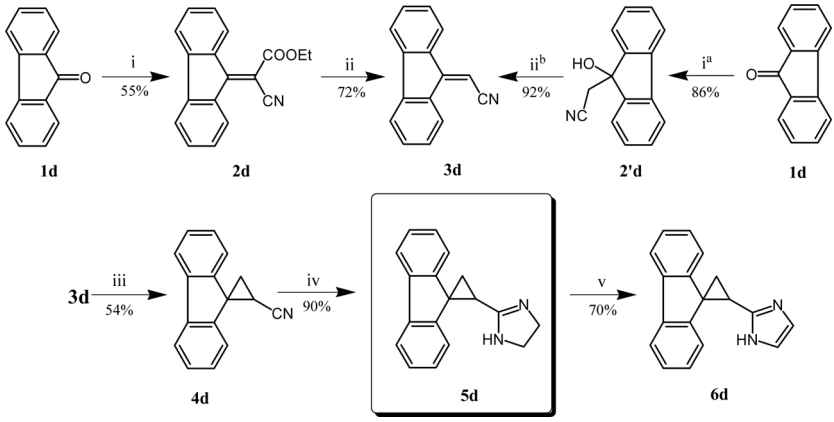


4a **5a**

Entry	Conditions	Time (h)	Results
1	(i) Dry HCl/EtOH, 0°C, (ii) Et_3N, ethylenediamine, MeOH, reflux[18]	12	No expected product
2	CuCl/MeOH, ethylenediamine, reflux[19]	24	No reaction
3	Ethylenediamine monotosylate 200°C[12]	10	No expected product
4	Ethylediamine, reflux	12	No reaction
5	Ethylediamine, sulfur, reflux[20]	4	88% isolated yield

Attempts were made synthesize 4,5-dihydro-2-(2,2-diphenylcyclopropyl)-1*H*-imidazole **5a** by the reaction of ethylenediamine with 2,2-diphenylcyclopropanecarbonitrile **4a** using reported methods in literature (Table 1).[18–20] Thus various methods (entries 1 to 4) as shown in Table 1 were tried, which failed to convert the nitrile to 2-imidazoline. Finally the conversion of the nitrile group to 2-imidazoline was achieved by refluxing **4a** with ethylenediamine in the presence of a catalytic amount of sulfur. The plausible explanation[21–23] is that sulfur reacts with the nitrile to produce a thioamide. The thioamide reacts with ethylenediamine, which upon elimination of hydrogen sulfide and ammonia produces the target molecule cibenzoline. The oxidation of imidazoline to imidazole[24] derivative was carried out smoothly in good yields using (diacetoxyiodo) benzene in the presence of K_2CO_3 in DMSO at room temperature.

Recently Miura et al.[14] failed to synthesize cibenzoline analog from 9-fluorenone. However, using the methodology of our present article, we have successfully synthesized the racemic analog of cibenzoline starting from 9-fluorenone as shown in Scheme 2. The sterically hindered two benzene rings of spiro (cyclopropane-1,9′-fluorene)-2-carbonitrile **4d** fixed in the same plane can stereochemically hinder the formation of the imidazoline ring. In our hands, however, **4d** was easily converted to the target molecule **5d** by heating with ethylenediamine in the presence of sulfur. Further, **5d** was oxidized to **6d**.



Scheme 2. Synthesis of cibenzoline analog: reagents and conditions: (i) $CNCH_2COOEt$, $HOAc/C_6H_6$, β-alanine at reflux, 90 h; (ia) CH_3CN, n-BuLi, dry THF, $-80^{\circ}C$, 2 h; (ii) NaCl, H_2O, DMSO, 160–170 °C, 4 h; (iib) $SOCl_2$, dry pyridine, dry DCM, 0°C to rt, 3 h; (iii) $Me_3S(O)I$, NaH, DMSO, rt, 24 h; (iv) sulfur, ethylenediamine reflux, 4 h; (v) (diacetoxyiodo) benzene, K_2CO_3, DMSO, rt, 48 h.

CONCLUSION

In summary, we have presented an efficient and simple four-step organic transformation for the synthesis of cibenzoline and its analogs. The synthesis of intermediate **3** via β-hydroxynitrile is more convenient with higher yields. The nitrile group of intermediate **4** was easily converted into the imidazoline ring in the presence of elemental sulfur as catalyst, which is relatively less toxic among the commercially available sulfur sources. We believe that this less hazardous and simple organic transformations makes the process amenable for scale-up operations.

EXPERIMENTAL

Melting points were recorded in open capillaries using a Buchi melting-point B540 apparatus. Column chromatography was performed using silica gel (60- to 120-mesh size), and thin-layer chromatography (TLC) was carried out using aluminum sheets precoated with silica gel 60F254. All solvents and chemicals used were reagent grade procured commercially and used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 200 spectrometer. Infrared spectra were recorded with ATI Matt-son RS-1 FTIR spectrometer. Elemental analysis was performed on Flash EA 1112 Thermo Finnigan instrument.

Procedure A: Ethyl 2-Cyano-3,3-diphenyl Acrylate (2a)

A mixture of benzophenone **1a** (20.0 g, 110 mmol), ethyl cyanoacetate (13.65 g, 121 mmol), and a catalytic amount of β-alanine (0.9 g) was refluxed with separation of water with a Dean–Stark water trap in a mixed solvent of benzene (100 ml) and glacial acetic acid (20 ml). Separation of water was rapid during the first 2 h but became slower afterward. Azeotropic distillation continued for a period of 90 h. Benzene was removed under reduced pressure, and the crude product was dissolved in ethyl acetate and washed with water. The ethyl acetate layer was separated, dried over Na_2SO_4, and concentrated in vacuo to afford the residue, which was chromatographically purified on silica gel using pet. ether/EtOAc (9.8:0.2) as eluent to give **2a** (19.6 g, 64%) as white solid, mp 97–99°C, lit.[25] 97.6–98.9°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.15 (t, $J = 7.2$ Hz, 3H), 4.15 (q, $J = 7.2$ Hz, 2H), 7.13–7.18 (m, 2H), 7.33–7.50 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.4, 61.9, 103.8, 116.6, 127.9, 128.2, 129.0, 129.9, 130.1, 131.1, 138.0, 138.3, 162.4, 168.7; IR (KBr): 3020, 2220, 1958, 1731, 1558, 1445, 1368, 1246, 1111, 757 cm$^{-1;}$. Anal. calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.82; H, 5.62; N, 4.95. Compounds **2b**, **2c**, and **2d** were similarly synthesized by using this procedure.

Procedure B: 3,3-Diphenylacrylonitrile (3a)

A mixture of ethyl 2-cyano-3,3-diphenyl acrylate **2a** (15 g, 54 mmol), sodium chloride (0.949 g, 16.2 mmol), and H_2O (0.584 g, 32.5 mmol) in 35 ml of DMSO was heated up to 160–170°C for 4 h. After completion of the reaction, the reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude residue, which was chromatographically purified on silica gel by using pet.ether/EtOAc, (9.9:0.1) to afford the pure product **3a** (8 g, 72%) as colorless liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.74 (s, 1H), 7.25–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 94.8, 117.8, 128.40, 128.48, 128.5, 129.4, 129.9, 130.3, 136.9, 138.8, 163.0; IR (KBr): 3018, 2239, 1951, 1599, 1496, 1216, 1025, 880 cm^{-1}. Anal. calcd. for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.82. Found: C, 87.89; H, 5.48; N, 6.71. Compounds **3b**, **3c**, and **3d** were similarly synthesized by using this procedure.

Procedure C: 3-Hydroxy-3,3-Diphenylpropanenitrile (2′a)

To a stirred solution of anhydrous THF (20 ml), n-butyl lithium in hexane 1.6 M (13.4 ml, 21.46 mmol) was added at -80 °C under an argon

atmosphere, followed by a solution of acetonitrile (1.02 ml, 19.51 mmol) in THF (15 ml). After stirring the reaction mixture for 1 h at −80°C, benzophenone (3.55 g, 19.5 mmol) in anhydrous THF (20 ml) was added to the resulting white suspension over a period of 5 min and stirred further for 30 min at −80 °C. The bath was removed after 30 min, and the pale yellow solution was further stirred for 10 min after attaining room temperature and then poured into an ice water–hydrochloric acid mixture. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo to obtain the residual crude product, which was purified by column chromatography using pet. ether/EtOAc (8.5:1.5) as a eluent to obtain **2′a** (3.9 g, 90%); white solid, mp 141–143°C, lit.[26] 142–143°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.80 (s, 1H), 3.28 (s, 2H), 7.31–7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 32.5, 76.4, 117.1, 125.7, 128.1, 128.6, 143.8; IR (KBr): 3390, 2269, 1884, 1683, 1449, 1378, 1189, 1055 cm^{-1}. Anal. calcd. for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.60; H, 5.79; N, 6.38. Compounds **2′b**, **2′c**, and **2′d** were similarly synthesized using this procedure.

Procedure D: 3,3-Diphenylacrylonitrile (3a from 2′a)

A solution of 3-hydroxy-3,3-diphenylpropanenitrile **2′a** (3.5 g, 15.69 mmol) in dry CH_2Cl_2 (30 ml) was stirred under an atmosphere of argon. Dry pyridine (1.50 ml, 18.52 mmol) was added, and the reaction mixture was cooled to 0°C using an ice–salt mixture. After 20 min, $SOCl_2$ (1.27 ml, 17.42 mmol) was added dropwise at 0°C over a period of 10 min and stirred at room temperature for 3 h. After completion of reaction, ice–cold water (10 ml) and CH_2Cl_2 (30 ml) was added to the reaction mixture. The CH_2Cl_2 layer was then washed with dilute HCl, water, and $NaHCO_3$ (5%, 15 ml). The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo to afford the residue, which was chromatographically purified on silica gel using pet.ether/EtOAc (9.9:0.1) as a eluent to afford the product **3a** as colorless liquid (2.79 g, 87%).

Procedure E: 2,2-Diphenylcyclopropanecarbonitrile (4a)

Sodium hydride (2.48 g, as 60% dispersion in mineral oil, 62.43 mmol) was washed with dry hexane and suspended in anhydrous DMSO (40 ml) under a nitrogen atmosphere. Trimethylsulfoxonium iodide (13.73 g, 62.43 mmol) was added in portions to the heterogeneous reaction mixture, which was stirred until the foaming subsided. The reaction was cooled to 0°C, and 3,3-diphenylacrylonitrile **3a** (8 g, 39.02 mmol) dissolved in anhydrous

DMSO (20 ml) was added to the reaction mixture over a period of 20 min. The reaction mixture was allowed to warm to room temperature with stirring overnight. The crude reaction mixture was slowly poured into saturated aqueous ammonium chloride, and the resulting mixture was further diluted with ethyl acetate. The phases were separated, and the aqueous layer was extracted several times with ethyl acetate. The combined organic fractions were dried over Na_2SO_4 and concentrated in vacuo to obtain a crude product, which was chromatographically purified on silica gel using pet. ether/EtOAc (9.5:0.5) to afford **4a** (4.68 g, 55%) as a white solid, mp 108–110 °C, lit.[27] 107–108°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.78 (dd, $J = 5.5$ Hz, $J = 9.2$ Hz, 1H), 2.01 (t, $J = 5.5$ Hz, 1H), 2.20 (dd, $J = 5.5$ Hz, $J = 9.2$ Hz, 1H), 7.20–7.46 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 12.0, 20.8, 38.0, 119.3, 127.2, 127.6, 127.7, 128.60, 128.66, 129.2, 138.3, 142.1; IR (KBr): 3058, 2213, 1662, 1592, 1494, 1445, 1355, 1251, 1078, 827 cm^{-1}. Anal. calcd. for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39; found: C, 87.48; H, 5.75; N, 6.45. Compounds **4b**, **4c**, and **4d** were synthesized similarly using this procedure.

Procedure F: 4,5-Dihydro-2-(2,2-Diphenylcyclopropyl)-1*H*-imidazole (5a)

A mixture of 2,2-diphenylcyclopropanecarbonitrile **4a** (0.790 g, 3.60 mmol) and sulfur (0.029 g, 0.90 mmol) in ethylenediamine (5 ml) was refluxed with stirring for 4 h. After completion of the reaction, ethylenediamine was removed under reduced pressure to obtain a yellow solid, which was dissolved in $CHCl_3$, and the organic layer was washed with water and dried over anhydrous Na_2SO_4. A thick oily residue was obtained after evaporation of solvent, which was chromatographically purified on silica gel using CH_3OH/Et_3N (9.8:0.2) to afford a sticky product, which was recrystallized from pet. ether **5a** (0.830 g, 88%) as a white solid; mp 100–102°C, lit.[10]103–104°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.70 (dd, $J = 5.8$ Hz, $J = 8.8$ Hz, 1H), 2.10 (t, $J = 5.8$ Hz, 1H), 2.66 (dd, $J = 5.8$ Hz, $J = 8.8$ Hz, 1H), 3.17–3.28 (m, 2H), 3.40–3.51 (m, 2H), 4.09 (s, 1H), 7.20–7.48 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.7, 25.5, 37.6, 49.5, 126.3, 127.0, 127.4, 128.3, 128.4, 129.6, 140.3, 144.9, 166.1; IR (KBr): 3140, 2970, 2400, 2219, 1617, 1495, 1446, 930 cm^{-1}. Anal. calcd. for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.59; H, 6.74; N, 10.49. Compounds **5b**, **5c**, and **5d** were synthesized similarly using this procedure.

Procedure G: 2-(2,2-diphenylcyclopropyl)-1*H*-imidazole (6a)

To a mixture of 4,5-dihydro-2-(2,2-diphenylcyclopropyl)-1*H*-imidazole **5a** (0.5 g, 1.90 mmol) and K_2CO_3 (0.290 g, 2.10 mmol) in DMSO

(15 ml), diacetoxyiodo(benzene) (DIB) (0.614 g, 2.10 mmol) was added. Then the mixture was stirred for 48 h at room temperature under an argon atmosphere. After completion of the reaction, the reaction mixture was diluted with sat. aq $NaHCO_3$ and EtOAc and was stirred for 5 min. The mixture was extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo to obtain the residual crude product, which was purified by column chromatography using EtOAc/MeOH (9.9:0.1) as a eluent to afford (±)-2-(2,2-diphenylcyclopropyl)-1*H*-imidazole **6a** (0.357 g, 72%) as an off-white solid; mp 218–220 °C. ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz): δ 1.76 (dd, $J = 5.5$ Hz, $J = 9.2$ Hz, 1H), 2.31 (t, $J = 5.5$ Hz, 1H), 2.85 (dd, $J = 5.5$ Hz, $J = 9.2$ Hz, 1H), 6.71 (s, 2H), 7.05–7.36 (m, 10H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$/DMSO-*d6*, 50 MHz): δ 18.2, 25.1, 37.8, 125.9, 126.1, 127.5, 127.7, 128.2, 130.1, 140.9, 144.7, 146.1; IR (KBr): 3365, 3140, 1581, 1496, 1462, 1377, 1077, 862 cm^{-1}. Anal. calcd. for $C_{18}H_{16}N_2$: C, 83.05; H, 6.19; N, 10.76. Found: C, 82.87; H, 6.24; N, 10.59. Compounds **6b**, **6c**, and **6d** were synthesized similarly using this procedure.

Other Compounds

Ethyl 3,3-*bis*(4-Chlorophenyl)-2-cyanoacrylate (**2b**)

Compound **1b** (20 g, 80 mmol) was reacted as described in procedure A to give **2b** as a white solid (18 g, 65%); mp 90–92°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.21 (t, $J = 7.1$ Hz, 3H), 4.19 (q, $J = 7.1$ Hz, 2H), 7.05–7.12 (m, 2H), 7.31–7.44 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.7, 62.4, 104.6, 116.3, 128.6, 129.0, 130.6, 131.5, 136.2, 136.3, 136.9, 138.0, 162.0, 166.4; IR (cm^{-1}): 3020, 2219, 1911, 1732, 1590, 1490, 1247, 1215, 1093, 833 cm^{-1}. Anal. calcd. for $C_{18}H_{13}Cl_2NO_2$: C, 62.45; H, 3.78; Cl, 20.48; N, 4.05. Found: C, 62.52; H, 3.84; Cl, 20.56; N, 4.22.

3,3-*bis*(4-Chlorophenyl)-3-hydroxypropanenitrile (**2′b**)

Compound **1b** (4 g, 16 mmol) was reacted as described in procedure C to give **2′b** as a white solid (3.95 g, 85%); mp 115–117°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.87 (s, 1H), 3.23 (s, 2H), 7.29–7.39 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 32.3, 75.6, 116.7, 127.1, 128.7, 134.2, 141.9; IR (KBr) 3385, 2262, 1890, 1650, 1485, 1462, 1367, 1254, 1168, 1094 cm^{-1}. Anal. calcd. for $C_{15}H_{11}Cl_2NO$: C, 61.67; H, 3.79; Cl, 24.27; N, 4.79. Found: C, 61.80; H, 3.67; Cl, 24.39; N, 4.90.

3,3-*bis*(4-Chlorophenyl)acrylonitrile (**3b**)

Compound **2b** (10 g, 28.90 mmol) was reacted as described in procedure B to give **3b** as a white solid (5.65 g, 71%). Compound **3b** from 2′**b**): Compound **2′b** (3 g, 10.27 mmol) was reacted as described in procedure D to give **3b** as a white solid (2.54 g, 90%); mp 100–102 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.73 (s, 1H), 7.19–7.25 (m, 2H), 7.34–7.47 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 95.6, 117.3, 128.9, 129.0, 129.6, 130.8, 134.8, 136.3, 136.80, 136.87, 160.5; IR (KBr) 3019, 2216, 1909, 1590, 1494, 1403, 1253, 1093, 834 cm^{-1}. Anal. calcd. for $C_{15}H_9Cl_2N$: C, 65.72; H, 3.31; Cl, 25.86; N, 5.11. Found: C, 65.80; H, 3.17; Cl, 25.75; N, 5.24.

2,2-*bis*(4-Chlorophenyl) cyclopropanecarbonitrile (**4b**)

Compound **3b** (8.5 g, 31.02 mmol) was reacted as described in procedure E to give **4b** as a white solid (4.65 g, 52%); mp 139–140°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.82 (dd, $J = 5.5$ Hz, $J = 9.2$ Hz, 1H), 2.05 (t, $J = 5.5$ Hz, 1H), 2.25 (dd, $J = 5.5$ Hz, $J = 9.2$ Hz, 1H), 7.18–7.39 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 12.3, 20.9, 36.9, 118.8, 128.9, 129.0, 129.1, 130.5, 133.4, 134.0, 136.9, 140.1; IR (KBr) 3019, 2241, 1596, 1492, 1401, 1215, 758 cm^{-1}. Anal. calcd. for $C_{16}H_{11}Cl_2N$: C, 66.69; H, 3.85; Cl, 24.61; N, 4.86. Found: C, 66.80; H, 3.62; Cl, 24.44; N, 4.98.

2-(2,2-*bis*(4-Chlorophenyl)cyclopropyl)-4,5-dihydro-1*H*-imidazole (**5b**)

Compound **4b** (0.7 g, 2.43 mmol) was reacted as described in procedure F to give **5b** as a white solid (0.684 g, 85%); mp 155–158°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.62 (dd, $J = 5.5$ Hz, $J = 9.0$ Hz, 1H), 2.00 (t, $J = 5.5$ Hz, 1H), 2.46 (dd, $J = 5.5$ Hz, $J = 9.0$ Hz, 1H), 2.71 (brs, 1H), 3.15–3.27 (m, 2H), 3.38–3.50 (m, 2H), 7.13–7.29 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.5, 25.6, 36.4, 49.6, 128.5, 128.7, 130.9, 132.3, 132.9, 138.5, 143.1, 164.8; IR (KBr): 3153, 2974, 2400, 1621, 1493, 1215, 846 cm^{-1}. Anal. calcd. for $C_{18}H_{16}Cl_2N_2$: C, 65.27; H, 4.87; Cl, 21.41; N, 8.46. Found: C, 65.42; H, 4.71; Cl, 21.24; N, 8.54.

2-(2,2-*bis*(4-chlorophenyl)cyclopropyl)-1*H*-imidazole (**6b**)

Compound **5b** (0.290 g, 0.87 mmol) was reacted as described in procedure G to give **6b** as a white solid (0.196 g, 68%); mp 224–226°C. ^{1}H NMR

($CDCl_3$/DMSO-*d*6, 200 MHz): δ 1.75 (dd, $J = 5.5$ Hz, $J = 9.2$ Hz, 1H), 2.31 (t, $J = 5.5$ Hz, 1H), 2.87 (dd, $J = 5.5$ Hz, $J = 9.2$ Hz, 1H), 6.76 (s, 2H), 7.09 (s, 4H), 7.23 (s, 4H), 7.42 (s, 1H); ^{13}C NMR ($CDCl_3$/DMSO-*d6*, 50 MHz): δ 18.4, 25.1, 36.5, 127.8, 128.2, 129.4, 130.8, 130.9, 131.8, 139.4, 144.2, 144.4; IR (KBr): 3497, 3356, 1668, 1583, 1462, 1220, 1377, 861 cm^{-1}. Anal. calcd. for $C_{18}H_{14}Cl_2N_2$: C, 65.67; H, 4.29; Cl, 21.54; N, 8.51; Found: C, 65.79; H, 4.42; Cl, 21.34; N, 8.49.

Ethyl 2-Cyano-3,3-*bis*(4-fluorophenyl)acrylate (**2c**)

Compound **1c** (20 g, 91.74 mmol) was reacted as described in procedure A to give **2c** as a white solid (16.7 g, 58%); mp 114–116°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.20 (t, $J = 7.2$ Hz, 3H), 4.18 (q, $J = 7.2$ Hz, 2H), 7.04–7.19 (m, 6H), 7.38–7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.7, 62.2, 103.8, 115.5 (d, $J = 22.0$ Hz), 115.8 (d, $J = 22.0$ Hz), 116.7, 131.5 (d, $J = 9.00$ Hz), 132.6 (d, $J = 9.00$ Hz), 134.1, 134.1, 134.2, 164.0 (d, $J = 252.4$ Hz), 164.5 (d, $J = 252.4$ Hz), 166.8; IR (KBr): 3010, 2225, 1931, 1605, 1513, 1250, 844 cm^{-1}. Anal. calcd. for $C_{18}H_{13}F_2NO_2$: C, 69.01; H, 4.18; N, 4.47. Found: C, 68.90; H, 4.25; N, 4.62.

3,3-*bis*(4-Fluorophenyl)-3-hydroxypropanenitrile (**2′c**)

Compound **1c** (4 g, 18.34 mmol) was reacted as described in procedure C to give **2′c** as a white solid (4.1 g, 86%); mp 98–100 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.82 (s, 1H), 3.24 (s, 2H), 7.00–7.12 (m, 4H), 7.31–7.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 32.71, 75.68, 115.4 (d, $J = 21.6$ Hz), 116.9, 127.6 (d, $J = 8.4$ Hz), 139.5 (d, $J = 3.3$ Hz), 162.2 (d, $J = 248.1$ Hz); IR (KBr): 3384, 2267, 1898, 1603, 1508, 1461, 1387, 1231, 1164, 1065 cm^{-1}. Anal. calcd. for $C_{15}H_{11}F_2NO$: C, 69.49; H, 4.28; F, 14.66; N, 5.40. Found: C, 69.58; H, 4.12; N, 5.26.

3,3-*bis*(4-Fluorophenyl)acrylonitrile (**3c**)

Compound **2c** (9 g, 28.75 mmol) was reacted as described in procedure B to give **3c** as a white solid (5.2 g, 75%). Compound **3c** from **2′c**): Compound **2′c** (3.8 g, 14.67 mmol) was reacted as described in procedure D to give **3c** as a white solid (3.0 g, 85%); mp 80–82°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.61 (s, 1H), 7.01–7.37 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 94.7, 115.7 (d, $J = 21.8$ Hz), 115.7 (d, $J = 21.8$ Hz), 117.5, 130.3 (d, $J = 8.6$ Hz), 131.5 (d, $J = 8.6$ Hz), 133.7 (d, $J = 100.5$ Hz), 133.7 (d, $J = 100.5$ Hz), 160.7, 163.5 (d, $J = 252.3$ Hz), 164.0 (d, $J = 252.3$ Hz);

IR (KBr) 3027, 2215, 1943, 1602, 1495, 1237, 1160, 843 cm^{-1}. Anal. calcd. for $C_{15}H_9F_2N$: C, 74.68; H, 3.76; F, 15.75; N, 5.81. Found: C, 74.51; H, 3.89; N, 5.75.

2,2-*bis*(4-Fluorophenyl)cyclopropanecarbonitrile (**4c**)

Compound **3c** (8 g, 31.19 mmol) was reacted as described in procedure E to give **4c** as a white solid (4.24 g, 50%); mp 97–99 °C, lit[15] 95°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.77 (dd, $J = 5.5$ Hz, $J = 9.2$ Hz, 1H), 1.99 (t, $J = 5.5$ Hz, 1H), 2.19 (dd, $J = 5.5$ Hz, $J = 9.2$ Hz, 1H), 6.94–7.10 (m, 4H), 7.18–7.25 (m, 2H), 7.36–7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 12.3, 21.0, 36.8, 115.6 (d, $J = 21.6$ Hz), 115.9 (d, $J = 21.6$ Hz), Hz), 119.1, 129.3 (d, $J = 8.3$ Hz), 130.9 (d, $J = 8.3$ Hz), 136.2 (d, $J = 158.9$ Hz), 136.2 (d, $J = 158.9$ Hz), 161.8 (d, $J = 247.3$ Hz), 162.1 (d, $J = 247.3$ Hz); IR (KBr): 3019, 2240, 1889, 1661, 1602, 1512, 1219, 1159, 837, 758 cm^{-1}. Anal. calcd. for $C_{16}H_{11}F_2N$: C, 75.28; H, 4.34; F, 14.88; N, 5.49. Found: C, 75.36; H, 4.20; N, 5.35.

2-(2,2-*bis*(4-Fluorophenyl)cyclopropyl)-4,5-dihydro-1*H*-imidazole (**5c**)

Compound **4c** (0.8 g, 3.12 mmol) was reacted as described in procedure F to give **5c** as a white solid (0.841 g, 90%); mp 112–115°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.61 (dd, $J = 5.8$ Hz, $J = 9.0$ Hz, 1H), 1.96 (t, $J = 5.8$ Hz, 1H), 2.46 (dd, $J = 5.8$ Hz, $J = 9.0$ Hz, 1H), 3.14–3.24 (m, 2H), 3.37–3.49 (m, 2H), 6.89–7.03 (m, 4H), 7.18–7.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.6, 25.5, 36.2, 49.9, 115.1 (d, $J = 21.4$ Hz), Hz), 115.2 (d, $J = 21.4$ Hz), 128.9 (d, $J = 8.0$ Hz), 131.0 (d, $J = 8.0$ Hz), 138.3 (d, $J = 227.7$ Hz), 138.4 (d, $J = 227.7$ Hz), 161.2 (d, $J = 246.3$), 161.6 (d, $J = 246.3$ Hz), 165.1; IR (KBr): 3150, 2924, 1594, 1510, 1461, 1377, 1223, 1158, 830 cm^{-1}. Anal. calcd. for $C_{18}H_{16}F_2N_2$: C, 72.47; H, 5.41; F, 12.74; N, 9.39. Found: C, 72.52; H, 5.60; N, 9.22.

2-(2,2-*bis*(4-Fluorophenyl)cyclopropyl)-1*H*-imidazole (**6c**)

Compound **5c** (0.180 g, 0.60 mmol) was reacted as described in procedure G to give **6c** as a white solid (0.126 g, 71%); mp 224–226°C. ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz): δ 1.66 (dd, $J = 5.8$ Hz, $J = 9.2$ Hz, 1H), 2.15 (t, $J = 5.8$ Hz, 1H), 2.79 (dd, $J = 5.8$ Hz, $J = 9.2$ Hz, 1H), 6.67 (s, 2H), 6.75 (d, $J = 8.8$ Hz, 2H), 6.86 (t, $J = 8.8$ Hz, 2H), 7.01–7.08 (m, 2H), 7.17–7.24 (m, 2H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 50 MHz): δ 17.4, 24.0, 35.4, 113.6 (d, $J = 24.1$ Hz), 114.0 (d, $J = 24.1$ Hz), 128.5 (d,

$J = 8.0$ Hz), 130.8 (d, $J = 8.0$ Hz), 138.60 (d, $J = 253.5$ Hz), 138.65 (d, $J = 253.5$ Hz), 143.5, 159.6 (d, $J = 242.8$); IR (KBr): 3356, 3152, 1595, 1583, 1511, 1462, 1377, 1233, 1106, 832 cm^{-1}. Anal. calcd. for $C_{18}H_{14}F_2N_2$: C, 72.96; H, 4.76; F, 12.82; N, 9.45. Found: C, 73.12; H, 4.55; N, 9.28.

Ethyl 2-Cyano-2-(*9H*-fluoren-9-ylidene)acetate (**2d**)

Compound **1d** (20 g, 111.1 mmol) was reacted as described in procedure A to give **2d** as a orange solid (17.7 g, 58%); mp 97–99°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.45 (t, $J = 7.2$ Hz, 3H), 4.48 (q, $J = 7.2$ Hz, 2H), 7.17–7.58 (m, 6H), 8.00 (d, $J = 8.0$ Hz, 1H), 8.55 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.9, 62.9, 99.6, 116.3, 119.9, 126.2, 127.8, 128.1, 128.5, 132.7, 134.3, 135.3, 141.9, 142.1, 154.7, 162.4; IR (KBr): 3020, 2211, 1960, 1732, 1584, 1450, 1248, 1155, 857 cm^{-1}. Anal. calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.45; H, 4.58; N, 4.95.

2-(9-Hydroxy-*9H*-fluoren-9-yl)acetonitrile (**2′d**)

Compound **1d** (4 g, 22.2 mmol) was reacted as described in procedure C to give **2′d** as a white solid (4.3 g, 87%); mp 98–100°C, lit.[28] 97.5–98.5°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.37 (s, 1H), 2.96 (s, 2H), 7.32–7.48 (m, 4H), 7.65–7.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 29.2, 78.1, 116.7, 120.3, 123.5, 128.4, 130.0, 138.8, 145.7; IR (KBr): 3370, 2257, 1608, 1451, 1063, 942, 862 cm^{-1}. Anal. calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.62; H, 5.14; N, 6.28.

2-(*9H*-Fluoren-9-ylidene)acetonitrile (**3d**)

Compound **2d** (9 g, 32.72 mmol) was reacted as described in procedure B to give **3d** as a yellow solid (4.78 g, 72%). Compound **3d** from **2′d**): Compound **2′d** (4 g, 18.09 mmol) was reacted as described in procedure D to give **3d** as a yellow solid (3.38 g, 92%); mp 110–112°C; lit.[28] 109–111°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.07 (s, 1H), 7.23–7.64 (m, 7H), 8.39 (d, $J =$ 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 88.3, 117.3, 120.06, 120.12, 121.4, 125.1, 127.7, 128.2, 131.60, 131.67, 134.7, 136.2, 140.4, 141.7, 153.2; IR (KBr): 3017, 2213, 1715, 1601, 1451, 1078, 820. Anal. calcd. for $C_{15}H_9N$: C, 88.64; H, 4.46; N, 6.89. Found: C, 88.60; H, 4.58; N, 6.95.

Spiro(cyclopropane-1,9′-fluorene)-2-carbonitrile (4d)

Compound **3d** (9 g, 44.33 mmol) was reacted as described in procedure E to give **4d** as a white solid (5.19 g, 54%); mp 107–109°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.79 (dd, $J = 5.5$ Hz, $J =$ 9.2 Hz, 1H), 2.02 (t, $J = 5.5$ Hz, 1H), 2.22 (dd, $J = 5.5$ Hz, $J = 9.2$ Hz, 1H), 7.28–7.46 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 12.1, 20.9, 38.1, 119.3, 127.2, 127.6, 127.8, 129.2, 138.8, 142.2; IR (KBr): 3024, 2232, 1655, 1461, 1377, 759 cm^{-1}. Anal. calcd. for $C_{16}H_{11}N$: C, 88.45; H, 5.10; N, 6.45. Found: C, 88.27; H, 5.38; N, 6.61.

2-(Spiro(cyclopropane-1,9′-flurene)-2-yl)-4,5-dihydro-1*H*-imidazole (**5d**)

Compound **4d** (1 g, 4.60 mmol) was reacted as described in procedure F to give **5d** as a white solid (1.07 g, 90%); mp 97–99°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.65 (dd, $J = 5.4$ Hz, $J = 9.0$ Hz, 1H), 1.98 (t, $J = 5.4$ Hz, 1H), 2.57 (dd, $J = 5.4$ Hz, $J = 9.0$ Hz, 1H), 3.09–3.25 (m, 2H), 3.34–3.46 (m, 2H), 7.15–7.43 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.6, 25.5, 37.5, 49.6, 126.2, 126.9, 127.4, 128.2, 128.3, 129.6, 140.4, 144.9, 166.0; IR (KBr): 3135, 2925, 1954, 1617, 1463, 1377, 1283, 899 cm^{-1}. Anal. calcd. for $C_{18}H_{16}N_2$: C, 83.05; H, 6.19; N, 10.76. Found: C, 83.21; H, 6.04; N, 10.62.

2-(Spiro(cyclopropane-1,9′-flurene)-2-yl)-1*H*-imidazole (**6d**)

Compound **5d** (0.165 g, 0.63 mmol) was reacted as described in procedure G to give **6d** as a white solid (0.114 g, 70%); mp 219–221 °C. ^{1}H NMR ($CDCl_3$/DMSO-d_6, 200 MHz): δ 1.80 (dd, $J = 5.5$ Hz, $J = 9.2$ Hz, 1H), 2.26 (t, $J = 5.5$ Hz, 1H), 2.92 (dd, $J = 5.5$ Hz, $J = 9.2$ Hz, 1H), 6.74 (s, 2H), 7.10–7.22 (m, 5H), 7.29–7.37 (m, 3H); ^{13}C NMR ($CDCl_3$/DMSO-d_6, 50 MHz): δ 18.1, 25.1, 37.7, 125.9, 126.1, 127.5, 127.7, 128.2, 130.0, 140.9, 144.7, 146.1; IR (KBr): 3460, 3356, 1668, 1582, 1496, 1461, 1377, 861 cm^{-1}. Anal. calcd. for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.54; H, 5.67; N, 10.76.

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