First Synthesis of 5-Cyanosalicylates by Formal [3+3] Cyclocondensations of 1,3-Bis(silyloxy)-1,3-butadienes

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Abstract: A variety of functionalized benzonitriles were regioselectively prepared by formal [3+3] cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes with 3-ethoxy- and 3-silyloxy-2-cyano-2-en-1-ones.

Key words: arenes, benzonitriles, cyclizations, regioselectivity, silyl enol ethers

Functionalized benzonitriles represent important building blocks for fine chemical synthesis. In addition, they are important substrates of various dyes, pharmaceuticals, agrochemicals, herbicides, and pesticides.1 The present paper is focussed on the synthesis of functionalized 5-cyanosalicylates, which can be regarded as functionalized 4-cyanophenols. This substructure is present in a great variety of pharmacologically active compounds; in fact, a Beilstein database search reveals more than 900 4-cyanophenols which show a broad spectrum of pharmacological activities. 5-Cyanosalicylates and 2-acyl-4-cyanophenols are the specific derivatives studied in the present report. Their pharmacological properties include, for example, antiallergic activity,2 inhibition of HIV-1,3 anti-dopaminergic activity,4 vasorelaxing activity,5 inhibition of LTD4-induced contraction of lung membranes,6 leukotriene D4 inhibitory activity,7 antibacterial activity,8 binding to CHO cell membranes,9 antagonistic activity against βT3 cells,10 inhibition of recombinant human aldehyde reductase,11 or inhibition of catechol O-methyltransferase.12

Simple benzonitriles are prepared on industrial scales by ammoxidation of toluenes. In addition, ‘classical’ reactions of copper(I) cyanide with aryl halides or aryl diazonium salts using, for example, the Rosenmund-von-Braun or the Sandmeyer reaction, are often used. In recent years, various catalytic variants have been developed.13,14 Substituted 5-cyanosalicylates represent highly functionalized arenes containing a nitrile, ester and hydroxy group. Due to their polyfunctional nature, they represent versatile synthetic building blocks. 5-Cyanosalicylates have been previously prepared by transformation of oximes into nitriles,15 by cyonation of aryl halides,16 by palladium(0)-catalyzed reaction of aryl halides with zinc or potassium cyanide,17 and by Grignard reaction of 4-hydroxy-3,5-diiodobenzonitrile with carbon dioxide.18 Despite their great synthetic utility, catalytic cyimations can suffer from several drawbacks, such as low turnover numbers. In addition, reactions of ortho-substituted aryl halides are often problematic or not possible at all or require the use of toxic thallium reagents.19 It is important to note that the synthesis of the required starting materials – functionalized or highly substituted aryl halides or triflates – can be a difficult and tedious task due to the low ortholpara regioselectivity of electrophilic substitutions, harsh reaction conditions, and several other drawbacks.

An interesting alternative approach to the synthesis of benzonitriles is based on the application of a ‘building-block strategy’. Examples include the base-mediated cyclocondensation of ethoxymethylene-malononitrile with β-keto esters,20 the cyclization of diethyl acetone-1,3-dicarboxylate with 3-oxopentanedioic acid diethyl ester,21 and the reaction of malonodinitrile with methyl 2-acetyl-3-methoxyacrylate.22 Another building-block approach to the synthesis of benzonitriles relies on [4+2] cycloaddition reactions of cyano-substituted dienes or dienophiles.23 This includes, for example, the [4+2] cycloaddition of 3-cyano-2,4-bis(silyloxy)penta-1,3-diene with methyl propynoate.24 Recently, we have reported25 the synthesis of functionalized 5-cyanosalicylates by formal [3+3] cyclocondensations26,27 of 1,3-bis(silyloxy)-1,3-butadienes28 with cyano-substituted 3-ethoxy- and 3-silyloxy-2-en-1-ones. These reactions provide a convenient and regioselective approach to a variety of 5-cyanosalicylates which are not readily available by other methods. Herein, we report a comprehensive study on the preparative scope of this approach.

2-Cyano-3-ethoxy-2-en-1-ones 2a–e were prepared, following a known procedure,29 by reaction of ketonitriles 1a–e with ethyl orthoformate and acetic anhydride (Table 1). 1,3-Bis(silyloxy)-1,3-butadienes 3a–k were prepared from the corresponding β-keto esters in two steps.16 The titanium tetrachloride mediated cyclization of 2a with 3a afforded the 5-cyanosalicylate 4a (Scheme 1). The cyclization proceeded with excellent regioselectivity. The formation of product 4a might be explained by titanium tetrachloride mediated conjugate addition of the terminal carbon atom of 3a to 2a, to give intermediate A,
cyclization via the central carbon of 3a to give intermediate B (SN\textsuperscript{+} reaction), and subsequent aromatization. The formal [3+3] cyclization of 2-cyano-3-ethoxy-2-en-1-ones 2a–e with 1,3-bis(silyloxy)-1,3-butadienes 3a–k afforded the 5-cyanoacilicates 4a–ac in 33–64% yields (Table 2). The substituent R\textsuperscript{1}, located next to the carbonyl group of 2a–e, has some influence on the yields. Better yields were generally obtained for the products 4h–ac derived from 2b–e, containing an aryl group, compared to products 4a–g, derived from 2a, which contains a methyl group. The best yields were observed for the products derived from chloro- or bromo-substituted enones 2c and 2d. This might be explained by the fact that the electron-withdrawing halogen atoms increase the reactivity of the enone. The substitution pattern of the diene had no significant influence on the yield.

Table 1  Synthesis of 2a–e

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<th>Yield (%)\textsuperscript{a}</th>
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<td>a</td>
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<tr>
<td>b</td>
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<tr>
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<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
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<td>e</td>
<td>4-(MeO)C\textsubscript{6}H\textsubscript{4}</td>
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\textsuperscript{a} Reaction conditions: 1a–e (1.0 equiv), HC(OEt)\textsubscript{3} (3.0 equiv), Ac\textsubscript{2}O, reflux, 2 h.

\textsuperscript{b} Yield of isolated products.

Scheme 1  Possible mechanism for formation of 4a

Table 2  Synthesis of 4a–ac

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</table>

\textsuperscript{a} Yield of isolated products.
An optimization study was carried out for the synthesis of 4e (Table 3). The best yields were obtained when the reaction was carried out in a highly concentrated solution, however, the stoichiometry (2a–3e–TiCl₄ = 1:1:1:1.1), the temperature (slow warming from –78 to 20 °C), and the reaction time also played important roles. The use of TMSOTf, BF₃·OEt₂, and SnCl₄ resulted in the formation of complex mixtures. The moderate yields might be explained by TiCl₄-mediated oxidative dimerization of the diene; this type of reaction has been previously reported. In addition, some hydrolysis of the enone was observed.

Table 3  Optimization of the Synthesis of 4e

<table>
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<tr>
<th>Entry</th>
<th>2a:3e:TiCl₄</th>
<th>Conc of 2a (mol/L)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>4e (%)</th>
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<td>–78 → 20</td>
<td>14</td>
<td>20</td>
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<td>0.5</td>
<td>–78 → 20</td>
<td>14</td>
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<td>–78 → 20</td>
<td>14</td>
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<td>14</td>
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<td>0.5</td>
<td>–78 → 20</td>
<td>5</td>
<td>15</td>
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</table>

* All experiments were carried out on a 1.0 mmol scale.

The configuration of all products was established by spectroscopic methods (2D NMR). The structures of benzonitriles 4b–d,i.o.t were independently confirmed by X-ray crystal structure analyses – one of which is exemplarily depicted in Figure 1.31

Figure 1  Ortep plot of 4c (hydrogen at O3 found in the difference map and refined freely)

3-Cyano-4-(trimethylsilyloxy)pent-3-en-2-one (5) was prepared by silylation of known 3-cyano-acetylacetone. The TiCl₄-mediated [3+3] cyclocondensation of 5 with 3a,b,d,l–n afforded the 5-cyanosalicylates 6a–f in moderate yields (except for 6d) (Table 4). The best yields were again obtained when the reactions were carried out in a highly concentrated solution. The low yield of 6d can be explained by TiCl₄-mediated cleavage of the tert-butyl ester.

Table 4  Synthesis of 6a–f

<table>
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<th>R²</th>
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<td>d</td>
<td>f</td>
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</table>

* Yields of isolated products.

In conclusion, we have reported a convenient and regioselective synthesis of functionalized benzonitriles by what are, to the best of our knowledge, the first formal [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes with cyano-substituted enones. The products are not readily available by other methods. The reactions are easy to perform and the starting materials are readily available. We are currently studying the preparative scope of the methodology and applications to the synthesis of pharmacologically active products.

All solvents were dried by standard methods and all reactions were carried out under an Argon atmosphere. For ¹H and ¹³C NMR spectra, the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, i-Bu) or electrospray ionization (ESI). For preparative scale chromatography, silica gel 60 (0.063–0.200 mm, 70–230 mesh) was used.

2-Cyano-3-ethoxy-2-en-1-ones 2a–e; General Procedure

To a flask containing Ac₂O (2.5 mL/10.0 mmol of 1a) was added ketonitrile 1a–e (1.0 equiv) and CH(OEt)₃ (3.0 equiv). The mixture was stirred under reflux for 2 h, then Ac₂O was removed in vacuo and the solid residue was purified by crystallization from EtOH to give 2a–e.

2-(Ethoxymethylene)-3-oxobutane-nitrile (2a)

Starting with 1a (2.00 g, 24.4 mmol) and CH(OEt)₃ (12.17 mL, 73.1 mmol), 2a was isolated after recrystallization from EtOH.

Yield: 3.387 g (100%); brown crystals; mp 70–71 °C.

3-Cyano-4-(trimethylsilyloxy)pent-3-en-2-one (5) was prepared by silylation of known 3-cyano-acetylacetone. The TiCl₄-mediated [3+3] cyclocondensation of 5 with
IR (KBr): 3060 (w), 2929 (w), 2850 (w), 1738 (m), 1721 (m), 1604 (m), 1532 (m), 1462 (m), 1460 (m), 1423 (m), 1377 (m), 1308 (m), 1288 (m), 1231 (m), 1182 (m), 1158 (m), 1104 (m), 1010 (m), 980 (m), 906 (m), 872 (s), 749 (s), 689 (m), 626 (m), 564 (m), 576 (m), 559 (m), 533 (m) cm⁻¹.

1H NMR (250 MHz, CDCl₃): δ = 1.41 (t, J = 7.2 Hz, 3 H, OCH₂CH₃), 4.36 (q, J = 7.2 Hz, 2 H, OCH₂CH₃), 7.40–7.52 (m, 3 H, CH₃), 7.77–7.82 (m, 2 H, CHAr), 8.05 (s, 1 H, CH).

13C NMR (75 MHz, CDCl₃): δ = 15.4 (CH₃), 74.3 (OCH₂), 94.1 (CCN), 114.7 (CCN), 128.5 (2 × CH₂), 128.7 (2 × CH₂), 133.1 (CH₂), 136.9 (C₆H₅), 174.4 (CH), 187.9 (CO).

GC–MS (EI, 70 eV): m/z (%) = 231 (23) [M⁺], 216 (2), 202 (6), 188 (4), 174 (3), 160 (2), 139 (5), 131 (10), 127 (29), 155 (29), 143 (8), 115 (5), 96 (4), 76 (21), 68 (6), 50 (12), 29 (12).


2-Chlorobenzyl-3-ethoxyacrylonitrile (2c) Starting with 2-(4-Chlorobenzoyl)-3-ethoxyacrylonitrile (2d) was isolated after recrystallization from EtOH.

Yield: 0.097 g (34%); yellow solid; mp 84–85 °C.

IR (KBr): 3060 (w), 2929 (w), 2844 (w), 2215 (m), 1911 (w), 1738 (m), 1602 (m), 1597 (m), 1574 (m), 1556 (m), 1504 (m), 1462 (m), 1450 (m), 1423 (m), 1377 (m), 1308 (m), 1255 (s), 1167 (s), 1125 (m), 1022 (s), 974 (m), 960 (m), 838 (s), 812 (m), 800 (m), 751 (m), 700 (m), 632 (m), 605 (m), 541 (m), 531 (m) cm⁻¹.

1H NMR (250 MHz, CDCl₃): δ = 1.41 (t, J = 7.1 Hz, 3 H, OCH₂CH₃), 3.80 (s, 3 H, OCH₃), 4.33 (q, J = 7.1 Hz, 2 H, OCH₂CH₃), 3.80 (s, 3 H, OCH₃), 4.33 (q, J = 7.0 Hz, 2 H, OCH₂CH₃), 6.87–6.90 (m, 2 H, CH₂), 7.86–7.89 (m, 2 H, CH₂), 8.02 (s, 1 H, CH).

13C NMR (75 MHz, CDCl₃): δ = 15.3 (CH₃), 55.6 (OCH₃), 74.0 (OCH₂), 93.6 (CCN), 113.8 (2 × CH₂), 115.1 (CN), 131.3 (2 × CH₂), 161.2, 163.7 (CAr), 174.0 (CH), 185.8 (CO).

GC–MS (EI, 70 eV): m/z (%) = 216 (21), 202 (6), 188 (4), 174 (3), 160 (2), 139 (5), 131 (10), 107 (6), 92 (11), 77 (13), 64 (5), 50 (2).


Methyl 3-Cyano-6-hydroxy-2-methylbenzoate (4a) Starting with 2a (0.209 g, 1.5 mmol) and CH(OEt)₃ (3 × 20 mL) was isolated after crystallization from EtOH.

Yield: 0.606 g (96%); orange crystals; mp 187–190 °C.

IR (KBr): 3066 (w), 2929 (w), 2841 (w), 1738 (m), 1602 (m), 1597 (m), 1574 (m), 1556 (m), 1504 (m), 1462 (m), 1450 (m), 1423 (m), 1377 (m), 1308 (m), 1255 (s), 1167 (s), 1125 (m), 1022 (s), 974 (m), 960 (m), 838 (s), 812 (m), 800 (m), 751 (m), 700 (m), 632 (m), 605 (m), 541 (m), 531 (m) cm⁻¹.

1H NMR (250 MHz, CDCl₃): δ = 1.41 (t, J = 7.1 Hz, 3 H, OCH₂CH₃), 3.80 (s, 3 H, OCH₃), 4.33 (q, J = 7.0 Hz, 2 H, OCH₂CH₃), 6.87–6.90 (m, 2 H, CH₂), 7.86–7.89 (m, 2 H, CH₂), 8.02 (s, 1 H, CH).

13C NMR (75 MHz, CDCl₃): δ = 15.3 (CH₃), 55.6 (OCH₃), 74.0 (OCH₂), 93.6 (CCN), 113.8 (2 × CH₂), 115.1 (CN), 131.3 (2 × CH₂), 161.2, 163.7 (CAr), 174.0 (CH), 185.8 (CO).

GC–MS (EI, 70 eV): m/z (%) = 231 (23) [M⁺], 216 (21), 202 (6), 188 (4), 174 (3), 160 (2), 139 (5), 107 (6), 92 (11), 77 (13), 64 (5), 50 (2).

HRMS (EI): m/z [M⁺] calcd for C₁₂H₁₀O₂N: 231.08899; found: 231.08938.

Cyanosilacylates 4a–ac; General Procedure

To a stirred solution of 2a–e in CH₂Cl₂ (2.0 mL/1.0 mmol of 2) was added 3a–k (1.1 mmol) and, subsequently, TiCl₄ (1.1 mmol) at –78 °C under an argon atmosphere. The temperature of the reaction mixture was allowed to rise to 20 °C during 14 h with stirring. To the solution was added HCl (10%, 20 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH₂Cl₂ (3 × 20 mL) and the combined organic layers were dried (Na₂SO₄), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel; heptanes–EtOAc) to give 4a–ac.

Methyl 3-Cyano-6-hydroxy-2-methylbenzoate (4a) Starting with 2a (0.209 g, 1.5 mmol) and 3a (0.430 g, 1.7 mmol), 4a was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.606 g (96%); orange crystals; mp 187–190 °C.
Starting with Methyl 3-Cyano-6-hydroxy-2,5-dimethylbenzoate (4c)

HRMS (EI): [M +] calcd for C_{10}H_{9}O_{3}N: 191.05769; found: 191 (76) [M+], 160 (68), 159 (100), 131 (55), 130 (48), 103 (21), 77 (21), 76 (15), 63 (4), 51 (11).

HRMS (EI): [M+CH_{3}] calcd for C_{12}H_{12}O_{4}N: 239.09204; found: 239.09225 (M+1, 35).
IR (KBr): 2955 (m), 2894 (m), 1594 (m), 1426 (m), 1444 (m), 1000 (m), 756 (m), 699 (m), 668 (m), 658 (w), 549 (m) cm⁻¹.

1H NMR (250 MHz, CDCl3): δ = 0.64 (t, J = 8.3 Hz, 3 H, OCH3CH2), 3.89 (q, J = 7.0 Hz, 2 H, OCH2CH3), 7.14–7.19 (m, 2 H, CH2), 7.34–7.37 (m, 3 H, CH3), 6.64 (d, J = 8.6 Hz, 1 H, CH), 11.47 (s, 1 H, OH).

13C NMR (75 MHz, CDCl3): δ = 128.8 (CH2), 116.9 (OCH3), 118.4 (CH2), 128.3 (2 × CH3N), 157.5 (CONH), 165.1 (CO).


GC–MS (EI, 70 eV): m/z (%) = 267 (32) [M⁺], 236 (19), 235 (100), 234 (15), 207 (12), 206 (16), 179 (10), 178 (14), 151 (10), 76 (7).


Methyl 6-Cyano-6-ethyl-3-hydroxybiphenyl-2-carboxylate (4k)
Starting with 2b (0.302 g, 1.5 mmol) and 3e (0.522 g, 1.7 mmol), 4k was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.190 g (41%); slightly yellow viscous oil.

IR (KBr): 2954 (w), 2920 (w), 2223 (w), 1742 (w), 1663 (m), 1593 (w), 1465 (w), 1395 (s), 1333 (m), 1314 (m), 1261 (m), 1205 (s), 1170 (m), 1074 (w), 1029 (w), 985 (w), 856 (w), 815 (m), 759 (s), 699 (s), 658 (m), 549 (m) cm⁻¹.

1H NMR (250 MHz, CDCl3): δ = 0.86 (t, J = 7.0 Hz, 3 H, CH3), 1.26–1.35 (m, 2 H, CH2), 1.46–1.55 (m, 2 H, CH2), 2.59 (t, J = 7.9 Hz, 2 H, CH2), 3.33 (s, 3 H, OCH3), 7.08–7.13 (m, 2 H, CH2), 7.27–7.31 (m, 3 H, CH3), 8.46 (s, 1 H, CH), 11.45 (s, 1 H, OH).

13C NMR (75 MHz, CDCl3): δ = 139.8 (CH2), 22.5, 29.2, 31.2 (CH2), 52.2 (OCH3), 105.2 (CCN), 112.7 (COCOOCH3), 118.1 (CN), 127.9 (2 × CH3N), 131.2 (C16H17O3N), 137.0 (CH3), 139.1, 146.6 (CH2), 163.0 (COH), 170.9 (CO).

GC–MS (EI, 70 eV): m/z (%) = 309 (40) [M⁺], 277 (25), 259 (18), 244 (10), 236 (17), 235 (100), 234 (35), 221 (8), 206 (10), 178 (11), 177 (15), 151 (18).


Methyl 6-Cyano-4-ethyl-3-hydroxybiphenyl-2-carboxylate (4l)
Starting with 2b (0.302 g, 1.5 mmol) and 3g (0.591 g, 1.7 mmol), 4l was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.221 g (42%); light yellowish oil.

IR (neat): 2952 (w), 2924 (m), 2854 (w), 2223 (w), 1745 (w), 1664 (m), 1599 (w), 1566 (w), 1439 (m), 1335 (m), 1234 (m), 1146 (m), 1074 (w), 990 (w), 897 (w), 815 (m), 760 (s), 724 (w), 699 (s), 549 (w) cm⁻¹.

1H NMR (250 MHz, CDCl3): δ = 0.82 (t, J = 7.6 Hz, 3 H, CH3), 1.26–1.35 (m, 8 H, 4 × CH2), 1.51–1.61 (m, 2 H, CH2), 2.62 (t, J = 7.6 Hz, 2 H, CH2), 3.37 (s, 3 H, OCH3), 7.12–7.17 (m, 2 H, CH2), 7.30–7.36 (m, 3 H, CH3), 7.49 (s, 1 H, OH).

Methyl 6-Cyanosalicylate 3\(\text{-}\)hydroxy-6\(\text{-}\)octylphenyl-2\(\text{-}\)carboxylate (4m)

Starting with 2b (0.302 g, 1.5 mmol) and 3h (0.614 g, 1.7 mmol), 4m was isolated after chromatography (silica gel; heptanes–EtOAc). Yield: 0.219 g (40%); yellowish oil.

IR (neat): 2952 (w), 2923 (m), 2853 (m), 2224 (w), 1749 (w), 1665 (m), 1600 (w), 1567 (w), 1436 (m), 1335 (m), 1234 (m), 1205 (s), 1146 (m), 1074 (w), 999 (w), 907 (m), 816 (m), 760 (s), 727 (w), 700 (s), 549 (w) cm\(^{-1}\).

\[^{1}C\,\text{NMR}\, (75\,\text{MHz, CDCl}_{3})\]: \(\delta = 14.0\, (\text{CH}_{3}), 22.6, 28.9, 29.1, 29.4, 29.5, 31.8\, (\text{CH}_{3}), 52.2\, (\text{OCH}_{3}), 104.9\, (\text{CCN}), 112.7\, (\text{CCOOCH}_{3}), 118.1\, (\text{CN}), 127.9\, (2\times\text{CH}_{2}), 128.1\, (3\times\text{CH}_{2}), 128.2\, (2\times\text{CH}_{2}), 129.2\, (2\times\text{CH}_{3}), 130.7\, (\text{Ca})_{\text{ar}}, 130.8\, (2\times\text{CH}_{2}), 134.4, 135.3\, (\text{CH}_{3}), 138.7\, (\text{CH}_{2}), 139.4, 149.5\, (\text{Ca})_{\text{ar}}, 162.7\, (\text{COH}), 171.7\, (\text{CO})\).

MS (ESI): \([M^{+}]\) calcd for C\(_{27}\)H\(_{24}\)ClNO\(_{3}\): 436.0962; found: 436.0961.

Methyl 6-Cyanosalicylate 3\(\text{-}\)hydroxy-4\(\text{-}\)methylphenyl-2\(\text{-}\)carboxylate (4o)

Starting with 2e (0.353 g, 1.5 mmol) and 3e (0.457 g, 1.7 mmol), 4o was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.275 g (61%); white solid; mp 167–169 °C.

IR (KBr): 3034 (w), 2938 (w), 2848 (w), 2227 (w), 1932 (w), 1837 (w), 1667 (m), 1597 (m), 1557 (w), 1500 (w), 1435 (m), 1353 (m), 1332 (s), 1268 (m), 1203 (m), 1169 (m), 1147 (m), 1042 (w), 1017 (m), 981 (m), 902 (w), 868 (w), 809 (s), 771 (m), 659 (w), 613 (m), 548 (m) cm\(^{-1}\).

\[^{1}H\,\text{NMR}\, (250\,\text{MHz, CDCl}_{3})\]: \(\delta = 2.24\, (3\,\times\text{CH}_{3}), 3.42\, (3\,\times\text{CH}_{3}), 7.06–7.10\, (2\times\text{H}, \text{CH}_{2}\text{C}_{\text{ar}}), 7.31–7.35\, (2\times\text{H}, \text{CH}_{2}\text{C}_{\text{ar}}), 7.51\, (1\times\text{H}, \text{CH}_{3}), 11.61\, (1\times\text{H}, \text{OH})\).

\[^{13}C\,\text{NMR}\, (75\,\text{MHz, CDCl}_{3})\]: \(\delta = 14.7\, (\text{CH}_{3}), 51.4\, (\text{OCH}_{3}), 103.9\, (\text{CCN}), 111.3\, (\text{CCOOCH}_{3}), 116.8\, (\text{CH}), 127.2\, (2\times\text{CH}_{2}), 128.5\, (2\times\text{CH}_{2}), 133.2, 136.3\, (\text{Ca})_{\text{ar}}, 136.6\, (\text{CH}_{2}), 144.7\, (\text{Ca})_{\text{ar}}, 162.4\, (\text{COH}), 169.4\, (\text{CO})\).

GC–MS (EI, 70 eV): \([M^{+}]\) calcd for C\(_{20}\)H\(_{16}\)ClNO\(_{3}\): 364.0647; found: 364.0647.

GC–MS (EI, 70 eV): \([M^{+}]\) calcd for C\(_{20}\)H\(_{18}\)ClNO\(_{3}\): 386.0553; found: 386.0553.

Synthesis of 5\(\text{-}\)Cyanosalicylates 1629
Starting with 2c (0.353 g, 1.5 mmol) and 3h (0.614 g, 1.7 mmol), 4r was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.354 g (59%); pale-yellow solid; mp 68–71 °C.

IR (KBr): 2953 (w), 2925 (m), 2854 (w), 2224 (w), 1666 (m), 1600 (w), 1576 (w), 1496 (w), 1438 (m), 1397 (m), 1342 (m), 1341 (m), 1259 (w), 1206 (m), 1172 (m), 1091 (m), 1016 (w), 990 (w), 906 (m), 816 (w), 730 (s), 649 (w) cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.81 [t, 3J = 7.4 Hz, 3 H, (CH₃)₂CH₂], 1.17–1.34 (m, 10 H, 5 × CH₃), 1.49–1.58 (m, 2 H, CH₂), 2.61 (t, 3J = 7.4 Hz, 2 H, CH₂), 3.42 (s, 3 H, OCH₃), 7.06–7.12 (m, 2 H, 2 × CH₉Ph), 7.31–7.35 (m, 2 H, 2 × CH₉Ph), 7.51 (s, 1 H, CHAr), 11.59 (s, 1 H, OH).

13C NMR (75 MHz, CDCl₃): δC = 14.1 (CH₂), 22.6, 28.8, 29.2, 29.3, 29.4, 36.9 (CH₃), 52.5 (OCH₃), 104.9 (CCN), 112.5 (CCOOCO), 117.9 (CN), 128.3 (CH₂), 129.5 (2 × CH₉Ph), 132.7, 134.1 (C₆H₅), 139.0 (CH₉Ph), 145.5 (C₆H₅), 163.2 (COH), 170.0 (CO).

GC–MS (EI, 70 eV); m/z (%) = 399 (22) [M⁺], 332 (38), 270 (10), 268 (21), 235 (18), 234 (100), 177 (15).

HRMS (EI); m/z [M⁺] calcd for C₃₂H₂₂O₅NCl: 399.15957; found: 399.15957.

Methyl 4¢-Chloro-6-cyano-3-hydroxy-4-octylphenyl-2-carboxylate (4s)

Starting with 2e (0.353 g, 1.5 mmol) and 3j (0.522 g, 1.7 mmol), 4s was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.319 g (62%); light-yellow solid; mp 74–76 °C.

IR (KBr): 2955 (m), 2928 (m), 2868 (w), 2224 (w), 1741 (w), 1665 (s), 1599 (m), 1575 (w), 1496 (m), 1436 (s), 1397 (m), 1385 (w), 1345 (m), 1325 (m), 1314 (m), 1263 (m), 1204 (s), 1169 (m), 1148 (m), 1089 (s), 1016 (m), 1000 (m), 981 (m), 945 (w), 904 (w), 888 (w), 861 (w), 820 (m), 771 (m), 738 (m), 660 (m), 634 (m), 545 (m) cm⁻¹.

1H NMR (250 MHz, CDCl₃): δ = 0.89 (d, 3J = 6.7 Hz, 6 H, 2 × CH₃), 2.0–2.19 (m, 1 H, CH₂CH₃), 2.51 (d, 3J = 7.2 Hz, 2 H, CH₂), 3.43 (s, 3 H, OCH₃), 7.08–7.13 (m, 2 H, CH₂CH₃), 7.32–7.36 (m, 2 H, CH₂CH₃), 7.47 (s, 1 H, CHAr), 11.57 (s, 1 H, OH).

13C NMR (75 MHz, CDCl₃): δC = 21.4 (2 × CH₂), 27.0 (CH₂CH₃), 37.8 (CH₃), 51.5 (OCH₃), 103.8 (CCN), 111.6 (CCOOCO), 116.9 (CN), 127.3 (2 × CH₂), 128.6 (2 × CH₂CH₃), 130.5, 133.3, 136.4 (C₆H₅), 137.0 (CH₉Ph), 144.6 (C₆H₅), 162.2 (COH), 169.6 (CO).

GC–MS (EI, 70 eV); m/z (%) = 343 (29) [M⁺], 277 (20), 276 (100), 270 (16), 268 (44), 234 (39), 177 (24), 151 (5), 130 (2), 88 (2), 43 (5).

HRMS (EI); m/z [M⁺] calcd for C₁₉H₁₉O₄NCl: 343.09697; found: 343.096981.
1H NMR (300 MHz, CDCl3): δ = 0.73 [t, J = 7.5 Hz, 3 H, (CH3)2CH], 1.07–1.20 (m, 6 H, 3 × CH3), 1.42–1.50 (m, 2 H, CH2), 2.51 (t, J = 7.5 Hz, 2 H, CH2), 3.42 (s, 3 H, OCH3), 6.90–6.95 (m, 2 H, 2 × CHPh), 7.36–7.39 (m, 3 H, 3 × CHAr), 11.49 (s, 1 H, OH).

13C NMR (75 MHz, CDCl3): δ = 13.1 (CH3), 21.7, 27.8, 28.3, 28.4, 28.5, 28.6, 29.9, 30.9 (CH3), 51.5 (OCH3), 103.8 (CCN), 111.4 (COCOOCH), 116.9 (CN), 121.4 (C6H5), 128.8 (2 × CHAr), 130.2 (2 × CHAr), 131.7 (C6H5), 136.0 (CHAr), 136.9, 144.5 (C6H5), 162.1 (COH), 169.5 (CO).

GC–MS (EI, 70 eV): m/z (%) = 459 (41) [47Br; M⁺], 457 (41) [47Br; M⁺], 427 (9), 390 (5), 368 (4), 346 (90), 330 (7), 314 (22), 288 (14), 235 (73), 224 (11), 205 (22), 177 (22), 158 (13), 129 (42), 116 (100), 97 (21), 85 (34), 71 (48), 57 (74).


Etyl 4-Methoxy-6-cyano-3-hydroxy-biphenyl-2-carboxylate (4y)
Starting with 2e (0.347 g, 1.5 mmol) and 3b (0.453 g, 1.7 mmol), 4y was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.223 g (50%); yellowish solid; mp 116–117 °C.

IR (KBr): 3306 (w), 2978 (w), 2959 (w), 2838 (w), 2537 (w), 2351 (w), 2225 (m), 2175 (w), 2050 (w), 1931 (w), 1682 (m), 1651 (w), 1509 (m), 1517 (m), 1464 (m), 1455 (m), 1395 (m), 1372 (m), 1311 (m), 1294 (m), 1251 (m), 1174 (s), 1138 (m), 1116 (m), 1028 (m), 1016 (m), 948 (m), 929 (w), 808 (w), 827 (w), 848 (m), 835 (s), 806 (m), 795 (m), 778 (m), 742 (m), 723 (m), 706 (m), 646 (m), 621 (m), 579 (m), 558 (m), 532 (m) cm⁻¹.

HRMS: m/z [M⁺] calcd for C17H13O4NBr: 297.09956; found: 297.099391.

Methyl 6-Cyano-3-hydroxy-4-methoxy-4-methylbiphenyl-2-carboxylate (4z)
Starting with 2e (0.346 g, 1.5 mmol) and 3c (0.457 g, 1.7 mmol), 4z was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.266 g (51%); yellowish solid; mp 85–87 °C.

IR (KBr): 2958 (w), 2843 (w), 2219 (w), 1659 (m), 1608 (w), 1555 (w), 1427 (m), 1331 (m), 1308 (s), 1260 (m), 1202 (m), 1176 (m), 1145 (m), 1033 (m), 1019 (m), 983 (m), 902 (m), 862 (w), 808 (s), 767 (m), 661 (w), 648 (m), 535 (m) cm⁻¹.


Methyl 3-O-Methoxy-6-cyano-4-methylbiphenyl-2-carboxylate (4x)
Starting with 2d (0.420 g, 1.5 mmol) and 3c (0.638 g, 1.7 mmol), 4x was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.392 g (57%); yellow solid; mp 65–70 °C.

IR (KBr): 3333 (w), 2949 (m), 2921 (m), 2871 (m), 2847 (m), 2226 (w), 1911 (w), 1736 (m), 1714 (m), 1639 (w), 1599 (m), 1568 (m), 1493 (w), 1458 (m), 1428 (m), 1403 (m), 1392 (w), 1374 (w), 1356 (w), 1334 (w), 1301 (m), 1257 (m), 1237 (m), 1207 (m), 1187 (m), 1176 (m), 1148 (s), 1125 (m), 1072 (m), 1055 (w), 1038 (w), 1028 (w), 1012 (m) cm⁻¹.

1H NMR (250 MHz, CDCl3): δ = 0.82 [t, J = 6.8 Hz, 3 H, (CH3)2CH], 1.18–1.24 (m, 12 H, 6 × CH3), 1.51–1.59 (m, 2 H, CH2), 2.62 (t, J = 7.4 Hz, 2 H, CH2), 3.43 (s, 3 H, OCH3), 7.01–7.05 (m, 2 H, CHAr), 7.48 (s, 1 H, CHAr), 7.49–7.51 (m, 2 H, CHAr), 11.60 (s, 1 H, OH).

13C NMR (75 MHz, CDCl3): δ = 16.5 (CH3), 25.4, 55.3 (OCH3), 105.2 (CCN), 112.8 (COCOOCH), 113.5 (2 × CHAr), 118.3 (CN), 127.4 (C6H5), 129.2 (2 × CHAr), 131.1 (C6H5), 137.7 (CHAr), 146.9, 159.5 (C6H5), 162.9 (COH), 170.9 (CO).

GC–MS (EI, 70 eV): m/z (%) = 297 (45) [M⁺], 266 (19), 265 (100), 264 (12), 250 (11), 222 (9), 166 (9), 140 (8), 39 (8).

Ethyl 6-Cyano-4-ethyl-3-hydroxy-4'-methoxybiphenyl-2-carboxylate (4aa)

Starting with 2e (0.346 g, 1.5 mmol) and 3d (0.499 g, 1.7 mmol), 4aa was isolated after chromatography (silica gel; heptanes–EtOAc).

Yield: 0.237 g (49%); yellowish solid; mp 54–56 °C.

IR (neat): 2968 (w), 2875 (w), 2223 (w), 1658 (m), 1566 (w), 1515 (s), 1434 (m), 1399 (m), 1373 (m), 1256 (m), 1239 (s), 1189 (s), 1145 (s), 1069 (m), 1065 (w), 1030 (m), 906 (w), 808 (s), 770 (m), 534 (m).

1H NMR (250 MHz, CDCl3): δ = 0.71 (t, J = 7.2 Hz, 2 H, CH2), 1.19 (t, J = 7.2 Hz, 3 H, CH2CH3), 1.17–1.32 (m, 10 H, 5 × CH3), 1.50–1.59 (m, 2 H, CH2), 2.61 (t, J = 7.5 Hz, 2 H, CH2), 3.42 (s, 3 H, OCH3), 3.78 (s, 3 H, OCH3), 6.84–6.90 (m, 2 H, 2 × CH2), 7.05–7.11 (m, 2 H, 2 × CH2), 7.48 (s, 1 H, CHAr), 11.49 (s, 1 H, OH).

13C NMR (75 MHz, CDCl3): δ = 13.1 (CH3), 21.6, 27.9, 28.2, 28.3, 28.4, 28.6, 30.9 (CH3), 51.3, 54.3 (OCH3), 104.1 (CCOOCH3), 111.9 (CAr), 112.4 (2 × CHAr), 117.4 (CN), 128.4 (2 × CHAr), 130.1, 130.8 (CAr), 136.1 (CHAr), 145.5, 158.4 (CAr), 161.7 (COH), 170.0 (CO).

GC–MS (EI, 70 eV): m/z (%) = 396 (21), 395 (97) [M+], 364 (14), 363 (56), 266 (17), 264 (50), 234 (21).

HRMS (EI): m/z [M+]+ calcd for C13H10NO2: 345.09112; found: 345.09126.

Benzonitriles 6a–f; General Procedure

To a solution of 5 in CH2Cl2, was added TiCl4 at –78 °C in the presence of molecular sieves (4 Å). The reaction mixture was allowed to warm to 20 °C during 20 h then stirred for a further 4 h. To this solution was added CH2Cl2, the molecular sieves were removed by filtration and sat. aq NaHCO3 was added. The organic layer was separated and the aqueous layer was then extracted with CH2Cl2 (3 × 100 mL). The combined organic layers were dried (Na2SO4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel; heptanes–EtOAc) to give salicylates 6a–f.
Isobutyl 3-Cyano-6-hydroxy-2,4-dimethylbenzoate (6c)
Starting with \( S \) (188 mg, 1.0 mmol), CHCl\(_3\) (3.0 mL), molecular sieves (4 Å, 0.4 g), TiCl\(_4\) (0.11 mL, 1.0 mmol), and 3 (394 mg, 1.3 mmol), 6c was obtained after 22 h and isolated by column chromatography (silica gel; heptanes–EtOAc, 10:1).

Yield: 91 mg (39%); colourless solid; mp 51–52 °C; \( R_f = 0.29 \) (heptanes–EtOAc, 10:1).

IR (KBr): 3427 (br, w), 2960 (s), 2930 (m), 2875 (m), 2216 (m), 1656 (s), 1318 (s), 1242 (s), 1080 (s), 814 (m) cm\(^{-1}\).

\(^1\)H NMR (250 MHz, CDCl\(_3\)): \( \delta = 1.04 \) [d, \( J = 6.9 \) Hz, 6 H, CH(CH\(_3\))\(_3\)], 2.12 (m, 1 H, OCH\(_2\)CH), 2.48 (s, 3 H, ArCH\(_3\)), 2.79 (s, 3 H, ArCH\(_3\)), 4.19 (d, \( J = 6.4 \) Hz, 2 H, OCH\(_2\)CH), 6.77 (s, 1 H, Ar), 11.88 (s, 1 H, OH).

\(^13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 20.0 \) (CH\(_2\)), 21.4, 22.1 (ArCH\(_3\)), 27.6 (OCH\(_2\)CH), 72.7 (OCH\(_2\)CH), 106.9, 111.2, 117.3 (2 \( \times \) C\(_6\)H\(_5\)), 117.5 (CH\(_2\)), 146.5, 148.3 (C\(_6\)H\(_5\)), 165.3, 170.8 (C\(_6\)OH, CO).

MS (EL, 70 eV): \( m/z \% = 247 \) (64) \( [M^+] \), 191 (55), 174 (81), 173 (100), 145 (26), 91 (14), 57 (23).


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(28) For a review of 1,3-bis(silyloxy)-1,3-butadienes in general, see: Langer, P. Synthesis 2002, 441.


(31) CCDC-716950 contain all crystallographic details of this publication and is available free of charge at: www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44(1223)336033, or deposit@ccdc.cam.ac.uk.