First Synthesis of Functionalized Benzonitriles by Formal [3+3] Cyclocondensations of 1,3-Bis(silyloxy)buta-1,3-dienes

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

Key Words: arenas, benzonitriles, cyclizations, regioselectivity, silyl enol ethers

Functionalized benzonitriles represent important building blocks for the synthesis of natural products, pharmaceuticals, agrochemicals, herbicides, and dyes. Their industrial scale syntheses mostly rely on the ammoxidation of toluenes. In addition, the reaction of aryl halides with copper(I) cyanide (Rosenmund–von Braun reaction) and the reaction of diazonium salts with copper(I) cyanide (Sandmeyer reaction) are frequently used. In 2003, a catalytic variant has been reported.[1] In recent years, nickel- and palladium-catalyzed cyanations of aryl halides have been developed.[2] 5-Cyanosalicylates can be regarded as highly functionalized benzonitrile derivatives containing an additional ester and hydroxyl group. They have been prepared by classic transformation of the corresponding oximes into the nitriles,[3] by application of the Rosenmund–von Braun reaction,[4] by application of palladium(0)-catalyzed reactions using $Zn(CN)_2$ or KCN,[5] and by Grignard reaction of 4-hydroxy-3,5-diiodobenzonitrile with carbon dioxide.[6] Despite the recent progress in this area, cyanation reactions often suffer from low catalyst productivities (compared to other palladium-catalyzed coupling reactions). In addition, reactions of *ortho*-substituted aryl halides are often problematic or not possible at all or require the use of toxic thallium reagents.[7] Last but not the least, the regioselective synthesis of the required starting materials, functionalized or highly substituted aryl halides or triflates, can be a difficult and tedious task.

An alternative strategy for the synthesis of functionalized benzonitriles relies on the use of appropriate cyano-substituted building blocks in cyclization reactions. For example, ethyl 4-amino-5-cyanosalicylate and related compounds have been prepared by base-mediated cyclization of ethoxymethylenemalononitrile with β-keto esters.[8] 4-Amino-5-cyano-2-hydroxyisophthalic acid diethyl ester has been synthesized by KOH-mediated cyclization of diethyl acetone-1,3-dicarboxylate with 3-oxopentanedioic acid diethyl ester.[9] 4-Amino-2-hydroxy-5-cyanoacetophenone is available by cyclization of malodinitrile with 2-acetyl-3-methoxyacrylic acid methyl ester.[10] Benzonitriles have been prepared also based on Diels–Alder reactions of cyano-substituted alkynes or buta-1,3-dienes.[11] Recently, Pulido and Barbero have reported the synthesis of methyl 3-cyano-4-hydroxy-2-methylbenzoate by [4+2] cycloaddition of 3-cyano-2,4-bis(silyloxy)penta-1,3-diene with propynoic acid methyl ester.[12]

Chan and co-workers were the first to report[13] the synthesis of salicylates by formal [3+3] cyclizations of 1,3-bis(silyloxy)buta-1,3-dienes[14] with 3-silyloxy-2-en-1-ones. In recent years, this strategy has been applied to the synthesis of various functionalized arenes.[15] Herein, we report what are, to the best of our knowledge, the first [3+3] cyclocondensations of 1,3-bis(silyloxy)buta-1,3-dienes with cyano-substituted 3-ethoxy- and 3-silyloxy-2-en-1-ones. These reactions provide a convenient and regioselective approach to a variety of functionalized 5-cyanosalicylates, which are not readily available by other methods.

2-Cyano-3-ethoxy-2-en-1-ones **2a–e** were prepared, following a known procedure,[16] by reaction of ketonitriles **1a–e** with ethyl orthoformiate and acetic anhydride. 1,3-Bis(silyloxy)buta-1,3-dienes **3a–l** were prepared from the corresponding β-keto esters in two steps.[13]

The $TiCl_4$-mediated cyclization of **2a** with **3a** afforded the 5-cyanosalicylate **4a** (Scheme 1). The best yield was obtained when the reaction was carried out in a highly concentrated solution.[17] The cyclization proceeded with excellent regioselectivity. The formation of product **4a** might be explained by $TiCl_4$-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** (S_N' 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)buta-1,3-dienes **3a–h** afforded the 5-cyanosalicylates **4a–l** in 40–61% yields (Table 1). The substituents R^1, located next to the carbonyl group of **2a–e**, have no significant influence on the yields. Likewise, the substitution pattern of the diene has no significant influence on the yield.

The configuration of all products was established by spectroscopic methods (2D NMR). The structure of **4a** was in-

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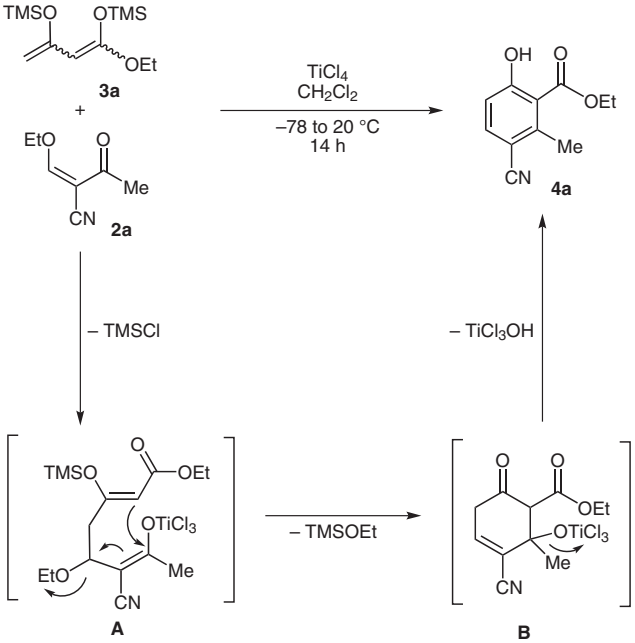
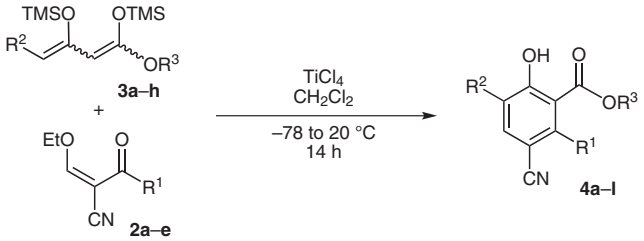


Scheme 1 Possible mechanism of the formation of **4a**

Table 1 Synthesis of **4a–l**



2	3	4	R^1	R^2	R^3	Yield (%)[a]
2a	**3a**	**4a**	Me	H	Et	33
2a	**3b**	**4b**	Me	Me	Me	41
2a	**3c**	**4c**	Me	Et	Et	40
2a	**3d**	**4d**	Me	*n*-Hex	Me	42
2a	**3e**	**4e**	Me	*n*-Hept	Me	40
2b	**3b**	**4f**	Ph	Me	Me	43
2b	**3c**	**4g**	Ph	Et	Et	42
2b	**3f**	**4h**	Ph	*n*-Bu	Me	41
2b	**3g**	**4i**	Ph	*n*-Oct	Me	40
2c	**3b**	**4j**	4-ClC_6H_4	Me	Me	61
2d	**3h**	**4k**	4-BrC_6H_4	*n*-Non	Me	57
2e	**3g**	**4l**	4-$MeOC_6H_4$	*n*-Oct	Me	50

[a] Yields of isolated products.

dependently confirmed by X-ray crystal structure analysis (Figure 1).[18]

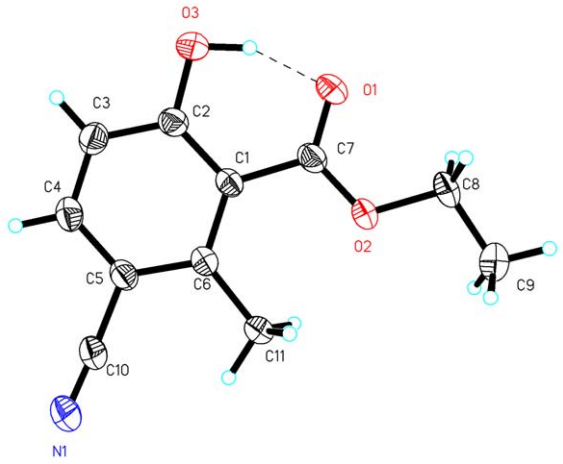
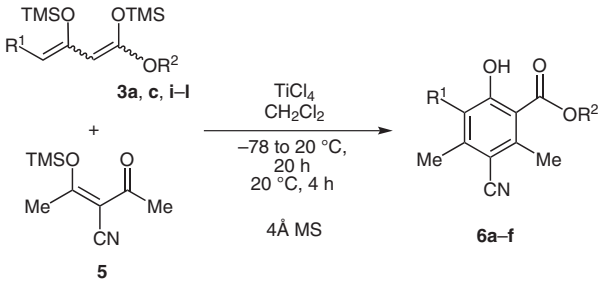


Figure 1 ORTEP plot of **4a** (hydrogen at O3 found in the difference map and refined freely)

Table 2 Synthesis of **6a–f**: Products and Yields



3	6	R^1	R^2	Yield of **6** (%)[a]
3i	**6a**	H	Me	34
3a	**6b**	H	Et	41
3j	**6c**	H	*i*-Bu	40
3k	**6d**	H	*t*-Bu	8
3l	**6e**	Et	Me	44
3c	**6f**	Et	Et	58

[a] Yields of isolated products.

3-Cyano-4-(trimethylsilyloxy)pent-3-en-2-one (**5**) was prepared by silylation of known[19] 3-cyano-acetylacetone. The $TiCl_4$-mediated [3+3] cyclocondensation of **5** with **3a**,**c**,**i–l** afforded the 5-cyanosalicylates **6a–f** in moderate yields (except for **6d**, Table 2).[20] 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 $TiCl_4$-mediated cleavage of the *tert*-butyl ester.

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)buta-1,3-dienes with cyano-substituted enones. The products are not readily available by other methods. The reactions are easy to be carried out,

and the starting materials are readily available. We currently study the preparative scope of the methodology and applications to the synthesis of pharmacologically active products.

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(17) **Typical Experimental Procedure for the Synthesis of 4a–l**
To a stirred solution of CH_2Cl_2 (3 mL per 1.0 mmol of **2a**–**e**) of **2a**–**e** was added **3a**–**h** (1.1 mmol) and, subsequently, $TiCl_4$ (1.1 mmol) at –78 °C under argon atmosphere. The temperature of the reaction mixture was allowed to rise to 20 °C over 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 CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (SiO_2, heptanes–EtOAc) to give **4a**–**l**. Starting with **2a** (0.209 g, 1.5 mmol) and **3a** (0.446 g, 1.65 mmol), **4a** was isolated as a colorless solid (101 mg, 33%), mp 86–87 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 2.72 (s, 3 H, CH_3), 4.42 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH_3), 6.84 (d, ^3J = 8.8 Hz, 1 H, Ar), 7.53 (d, ^3J = 8.8 Hz, 1 H, Ar), 11.78 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1 (CH_3), 20.8 (OCH_2CH_3), 61.7 (OCH_2), 104.8 (*C*CN), 112.6 (*C*CO_2Et), 116.0 (CH), 117.4 (CN), 136.7 (CH), 145.5 (*C*CH_3), 164.8 (COH), 169.6 (C=O). IR (neat): ν = 3072 (w), 2991 (w), 2923 (w), 2851 (w), 2777 (w), 2692 (w), 2589 (w), 2224 (w), 1660 (s), 1588 (m), 1570 (w), 1476 (m), 1450 (w), 1398 (m), 1375 (s), 1348 (m), 1318 (m), 1302 (m), 1231 (s), 1182 (w), 1146 (m), 1108 (w), 1057 (w), 1021 (m), 996 (w), 909 (w), 856 (m), 831 (m), 723 (w), 632 (w), 609 (w), 558 (w) cm^{-1}. MS (GC-MS, 70 eV): *m/z* (%) = 205 (26) [M^+], 159 (100), 130 (22), 103 (8), 77 (12), 51 (6). HRMS (EI): *m/z* calcd for $C_{11}H_{11}NO_3$: 205.07334; found: 205.073572.

(18) CCDC-703181 contains 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.

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(20) **Typical Experimental Procedure for the Synthesis of 6a–f**
To a CH_2Cl_2 solution of **5** was added $TiCl_4$ at –78 °C in the presence of MS (4 Å). The appropriate bis(silyl enol ether) **3** was subsequently added. The reaction mixture was allowed to warm to 20 °C during 20 h and was stirred for further 4 h. To the solution was added CH_2Cl_2, the MS were removed, and a sat. aq soln of $NaHCO_3$ was added. The organic layer was separated, and the aqueous layer was repeatedly

extracted with CH_2Cl_2. All organic extracts were combined, dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (SiO_2) to give salicylates **6**. Starting with **5** (188 mg, 0.95 mmol), CH_2Cl_2 (3.0 mL), MS (4 Å, 0.4 g), $TiCl_4$ (0.11 mL, 1.0 mmol), and **3i** (356 mg, 1.4 mmol), compound **6a** was isolated by column chromatography (SiO_2; *n*-heptane–EtOAc, 10:1) as a colorless solid (67 mg, 34%), mp 109–110 °C; R_f = 0.21 (*n*-heptane–EtOAc, 10:1); reaction time 21 h. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.48 (d, ^4J = 0.9 Hz, 3 H, $ArCH_3$), 2.75 (s, 3 H, $ArCH_3$), 3.98 (s, 3 H, OCH_3), 6.76 (s, 1 H, CH_{Ar}), 11.72 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 21.8 ($ArCH_3$), 52.7 (OCH_3), 107.0, 111.0, 117.3 (2 × C_{Ar}, CN), 117.4 (CH_{Ar}), 146.6, 148.4 (C_{Ar}), 165.1, 171.0 ($C_{Ar}OH$, CO). IR (KBr): ν = 3431 (br, m), 2957 (m), 2217 (s), 1668 (s), 1601 (s), 1581 (s), 1442 (s), 1368 (s), 1358 (s), 1319 (s), 1241 (s), 810 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 205 (83) [M^+], 174 (76), 173 (100), 145 (66), 144 (37), 116 (20), 91 (14). Anal. Calcd for $C_{11}H_{11}NO_3$ (205.21): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.64; H, 5.52; N, 6.65.