Short Access to 4-Alkenylbenzonitriles: Reaction of Anionic Reduced Forms of Terephthalonitrile with Alkenyl Bromides

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Received 17 March 2007

Abstract: Direct one-pot syntheses of 4-(ω-alkenyl)-benzonitriles in high yields have been achieved via the reaction of terephthalonitrile dianion with allyl or ω-alkenyl bromides in liquid ammonia.

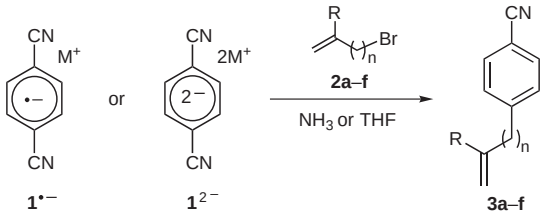
Key words: reductive alkylation, terephthalonitrile dianion and radical anion, *para*-(ω-alkenyl)benzonitriles

Alkenylbenzonitriles might be promising building blocks for functionalized arylcyclopropanes[1] and, sequentially, compounds displaying biological and pharmocological activity.[2] However, the conventional approaches, such as any kind of Friedel–Crafts chemistry, Wurtz–Fittig-type reactions, catalyzed or electrochemical cross-couplings either cannot be applied to prepare them in principle or suffer from restricted availability of starting materials and sophisticated experimental procedures.

Thereupon, we have turned to the Birch-type reductive alkylation[3] of terephthalonitrile (**1**) with the difference that the stable radical anion $\mathbf{1}^{\bullet -}$ and dianion $\mathbf{1}^{2-}$ are active anionic intermediates to be alkylated rather than cyclohexadienyl anion which works in the traditional approach. Both $\mathbf{1}^{\bullet -}$ and $\mathbf{1}^{2-}$ were shown to be not protonated in liquid ammonia and were highly active towards alkyl halides thus providing 4-alkylbenzonitriles and 2-alkyl-1,4-dicyano-benzenes in good yields.[4,5]

The reactions of Na and Li salts of $\mathbf{1}^{\bullet -}$ or $\mathbf{1}^{2-}$ with allyl, methallyl, and 2-fluoroallylbromides (**2a**–**c**, R = H, CH_3, F) in liquid ammonia lead to the formation of 4-allylbenzonitriles (**3a**–**c**) in yields up to 80% (Figure 1, Table 1). Besides, 4-propenylbenzonitriles, 4-(1-vinylbut-3-enyl)benzonitriles, and 1,4-diallylbenzenes arise as byproducts due to the further transformations of **3**. Benzonitrile was also found together with its allylated products.[6,7]

The product distribution depends both on whether $\mathbf{1}^{\bullet -}$ or $\mathbf{1}^{2-}$ is used and on the nature of the allylic reagent (Table 1) whereas the counter ion in the salt of $\mathbf{1}^{\bullet -}$ or $\mathbf{1}^{2-}$ is less important (entries 1, 2, 11, 12). Allylation of the radical anion $\mathbf{1}^{\bullet -}$ salts provides **3a**,**b** in moderate yields



a n = 1, R = H; **b** n = 1, R = Me; **c** n = 1, R = F
d n = 2, R = H; **e** n = 3, R = H; **f** n = 4, R = H

Figure 1

(entries 1 and 4). Keeping in mind that unreacted dinitrile **1** can be separated and recycled quite easily, allylation of $\mathbf{1}^{\bullet -}$ provides reasonable access to nitriles **3a**,**b**.

The addition of allylbromide (**2a**) to the dianion $\mathbf{1}^{2-}$ sodium salt in liquid ammonia at –70 °C ('regular' mixing procedure) slightly increased the yield of **3a** to 60% (entry 2). Even better yield (80%) was obtained when a suspension of the $\mathbf{1}^{2-}$ salt in liquid ammonia was added to allylbromide in THF at –33 °C ('inverted' mixing, entry 3), thus guaranteeing a permanent excess of allylbromide over allylbenzonitrile **3a** and minimizing the concentration of highly basic $\mathbf{1}^{2-}$. The reaction of $\mathbf{1}^{2-}$ with methallylbromide (**2b**) proved to be more selective than with **2a**, providing allylated benzonitrile **3b** in 75% yield at –70 °C (entry 5). In contrast, the reaction of the $\mathbf{1}^{2-}$ salt with 3-bromo-2-fluoropropene (**2c**)[8] at different temperatures (–33 °C to –70 °C) gave only traces of 4-(2-fluoroallyl)benzonitrile (**3c**). A little improvement (16% of **3c**) was observed when changing the solvent from liquid ammonia to THF (entry 6). The dependence of the yields of *ipso*-allylated products **3a**–**c** from the substituent in the reagent **2**, the temperature, and change of solvent from liquid NH_3 to THF might be due to a competition of S_N vs. ET mechanisms.[4,5,9,10]

4-(ω-Alkenyl)benzonitriles (**3d**–**f**, up to 83%) were formed by alkylation of $\mathbf{1}^{\bullet -}$ or $\mathbf{1}^{2-}$ with 4-bromobut-1-ene (**2d**), 5-bromopent-1-ene (**2e**), and 6-bromohex-1-ene (**2f**), respectively, (entries 7–12) besides minor amounts of 2-(ω-alkenyl)-1,4-dicyanobenzenes (<10%). Here, unlike to the reactions with allylic bromides, no isomerization and no subsequent alkylation of primary products occurred. Also, the amount of byproducts arising from benzonitrile was low.

SYNLETT 2007, No. 10, pp 1616–1618
Advanced online publication: 07.06.2007
DOI: 10.1055/s-2007-982549; Art ID: G08207ST

Table Reactions of $\mathbf{1}^{-}$ or $\mathbf{1}^{2-}$ with Alkenyl Bromides **2**

Entry	Anionic reagent	Alkenyl bromide	Temp (°C)	Main products (yield, %)[b]
1	$\mathbf{1}^{\bullet-}$ Li^+/Na^+	**2a**	–33	**3a** (50/53)
2	$\mathbf{1}^{2-}$ 2 (Li^+/Na^+)	**2a**	–70	**3a** (57/60)
3[c]	$\mathbf{1}^{2-}$ 2 Na^+	**2a**	–33	**3a** (80)
4	$\mathbf{1}^{\bullet-}$ Na^+	**2b**	–33	**3b** (65)
5	$\mathbf{1}^{2-}$ 2 Na^+	**2b**	–70	**3b** (75)
6[d]	$\mathbf{1}^{2-}$ 2 Na^+	**2c**	–78	**3c** (16)
7	$\mathbf{1}^{\bullet-}$ Na^+	**2d**	–33	**3d** (50)
8	$\mathbf{1}^{2-}$ 2 Na^+	**2d**	–33	**3d** (73)
9[c]	$\mathbf{1}^{\bullet-}$ Na^+	**2e**	–33	**3e** (24)
10	$\mathbf{1}^{2-}$ 2 Na^+	**2e**	–33	**3e** (73)
11	$\mathbf{1}^{\bullet-}$ Na^+/K^+	**2f**	–33	**3f** (48/56)
12	$\mathbf{1}^{2-}$ 2 (Na^+/K^+)	**2f**	–33	**3f** (79/83[4c])

[a] Unless otherwise stated, reactions were performed in liquid NH_3, concentration of $\mathbf{1}^{\bullet-}$ or $\mathbf{1}^{2-}$ salt was 0.1–0.2 M, molar ratio of $\mathbf{1}^{\bullet-}$ to alkenyl bromide 2:1, of $\mathbf{1}^{2-}$ to alkenyl bromide 1:1.15, reaction time of 30–50 min.
[b] Isolated yield. For $\mathbf{1}^{\bullet-}$ reactions, yield is given taking into account that two equiv of $\mathbf{1}^{\bullet-}$ are required to form one equiv of alkylated product.
[c] 'Inverted' mixing experiment.
[d] The reaction was performed in THF.

In summary, reactions of $\mathbf{1}^{\bullet-}$ or $\mathbf{1}^{2-}$ with alkenyl bromides **2** provide a new convenient one-pot synthesis of 4-allyl- and 4-(ω-alkenyl)benzonitriles **3** in good yields. The protocol of $\mathbf{1}^{2-}$ alkylation is comparable or superior to those described in literature[11–15] both in product yields, availability of starting materials, and experimental simplicity.

The 'Regular' Procedure of $\mathbf{1}^{\bullet-}$ or $\mathbf{1}^{2-}$ Alkylation

The alkylating reagent **2** was added dropwise to a stirred solution of the $\mathbf{1}^{\bullet-}$ salt or suspension of the $\mathbf{1}^{2-}$ salt generated by the addition of alkali metal (for $\mathbf{1}^{\bullet-}$ ca. 0.95 equiv, for $\mathbf{1}^{2-}$ ca. 2.1 equiv)[4a–c] to a suspension of **1** in liquid NH_3 (50–100 mL). The mixture was stirred under an atmosphere of evaporating NH_3 at desired temperature for 30–50 min. Then, Et_2O (50 mL) was added and the mixture was stirred until NH_3 has evaporated completely and r.t. has been reached. Afterwards, H_2O (50 mL) was added to the residue. The solid dinitrile **1** was filtered off, washed sequentially with Et_2O and H_2O and air-dried. The combined liquid phases were separated and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined ethereal layer was washed with H_2O (3 × 25 mL), dried ($MgSO_4$), and the solvent was evaporated. The individual products were isolated by TLC (fixed layer of silica gel) or by column chromatography.

4-(2-Methylallyl-benzonitrile (3b, Entry 5)[15,16]

Starting with $\mathbf{1}^{2-}$ sodium salt (10.0 mmol) and **2b** (11.4 mmol), **3b** (1.17 g, 75%) was isolated by column chromatography (R_f = 0.20; cyclohexane–EtOAc, 10:1) as a pale yellow oil.

4-(But-3-enyl)benzonitrile (3d, Entry 8)[4a,13a,b]

Starting with $\mathbf{1}^{2-}$ sodium salt (6.1 mmol) and **2d** (6.7 mmol), **3d** (0.70 g, 73%) was isolated by TLC (R_f = 0.5; hexane–Et_2O, 9:1) as a pale yellow oil.

4-(Pent-4-enyl)benzonitrile (3e, Entry 10)[14a,c]

Starting with $\mathbf{1}^{2-}$ sodium salt (6.0 mmol) and **2e** (6.6 mmol), **3e** (0.75 g, 73%) was isolated by TLC (R_f = 0.4; hexane–Et_2O, 9:1) as a pale yellow oil.

4-(Hex-5-enyl)benzonitrile (3f, Entry 12)[4c]

Starting with $\mathbf{1}^{2-}$ sodium salt (3.0 mmol) and **2f** (3.5 mmol), **3f** (0.44 g, 79%) was isolated by TLC (R_f = 0.6; hexane–Et_2O, 9:1) as a pale yellow oil.

The 'Inverted' Mixing Procedure (Entry 3)

The NH_3 (50 mL) was condensed to dinitrile **1** (0.64 g 5.0 mmol) in a cooled (–70 °C) dropping funnel equipped with a pressure-equalization arm, a stirrer and a gas vent, and Na (0.24 g, 10.3 mmol) was added. Then, the suspension of the $\mathbf{1}^{2-}$ salt was added dropwise to stirred precooled (–30 °C) allylbromide (**2a**, 0.9 mL, 10.4 mmol) in THF (4 mL) during 15 min. After 10 min the reaction mixture was worked up as described above and separated by column chromatography (cyclohexane–EtOAc, 20:1) to provide 4-allylbenzonitrile (**3a**)[11b] (0.57 g, 80%, R_f = 0.24) as a pale yellow oil.

4-(2-Fluoroallyl)benzonitrile (3c, Entry 6)

THF (30 mL) was added under argon to nitrile **1** (0.38 g, 3.0 mmol). Then, at –70 °C and continuous stirring NH_3 (30 mL) was condensed into the mixture, Na (0.14 g, 6.1 mmol) was added, and NH_3 was evaporated. The suspension of $\mathbf{1}^{2-}$ salt in THF was cooled to –78 °C in an argon flow and fluoroallylbromide (**2c**)[8] (0.37 mL, 3.2 mmol) was added. The reaction mixture was stirred for 45 min and worked up as described above. The product mixture was separated by column chromatography (cyclohexane–EtOAc, 20:1) and HPLC (cyclohexane–EtOAc, 30:1) providing **3c** (0.08 g, 16%) as a colorless oil. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.42 (2 H, d, *J* = 16.4 Hz), 4.00 (1 H, dd, *J* = 48.7, 3.0 Hz), 4.54 (1 H, dd, *J* = 17.0, 3.0 Hz), 7.36 (2 H, d, *J* = 8.4 Hz), 7.59 (2 H, d, *J* = 8.4 Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 26.9, 35.8, 92.4, 111.0, 118.7, 129.7, 132.4, 141.5. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –94.75 (1 F, ddt, *J* = 48.7, 17.0, 16.4 Hz). MS (EI): *m/z* (%) = 161 (100) [M^+], 141 (55), 133 (43), 116 (6), 114 (10), 89 (6), 63 (5).

Acknowledgment

This work was supported by the Deutsche Forschungsgemeinschaft (DFG), grant no. 436 RUS 17/107/05, and the Russian Foundation for Basic Research (RFBR), grant no. 05-03-32309a.

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