New Synthetic Applications of (Bromozinco)-acetonitrile ($BrZnCH_2CN$)

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The use of α-bromonitriles in modified Reformatsky syntheses, that is addition of organozinc intermediates derived from α-bromonitriles to carbonyl compounds, has been well documented[1]. Recently, we reported a new application of the *C*-metallated Reformatsky intermediate **1a** as a nucleophilic reagent towards halogen-containing electrophiles[2].

A priori, (bromozinco)-acetonitrile (**1b**, cyanomethylzinc bromide, prepared from zinc and α-bromoacetonitrile) should be a more versatile nucleophilic reagent than **1a** as the cyano group can undergo several transformations[3].

$BrZn-CH_2-COOC_4H_9\text{-}t$ **1a**

$BrZn-CH_2-CN$ **1b**

Other authors have already proposed for **1b** a *C*-metallated structure on the basis of ^{1}H-N.M.R. and I.R. spectra. The ^{13}C-N.M.R. data reported in Table 1 confirm the presence of a Zn—C bond: otherwise than observed for **1a**, the C-2 is significantly shifted downfield (with respect to acetonitrile) indicating a more polarized Zn—C bond, in agreement with the reactivity towards halogen containing electrophiles.

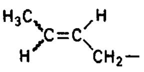
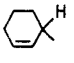
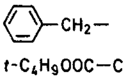
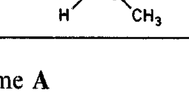
Table 1. ^{13}C-N.M.R. Data for (Bromozinco)-acetonitrile (**1b**)

Solvent	Chemical shift[a] δ [ppm] C-1	C-2	Coupling Constant J_{C-H} [Hz]
dimethyl sulfoxide	128.1 (+10.7)	− 8.5 (− 9.5)	132
tetrahydrofuran	131.8 (+13.9)	−10.1 (−11.5)	132
pyridine	130.3 (+ 6.7)	−11.5 (− 8.0)	130

[a] The values in brackets are the differences in ppm of the chemical shifts for **1b** as compared to those of acetonitrile.

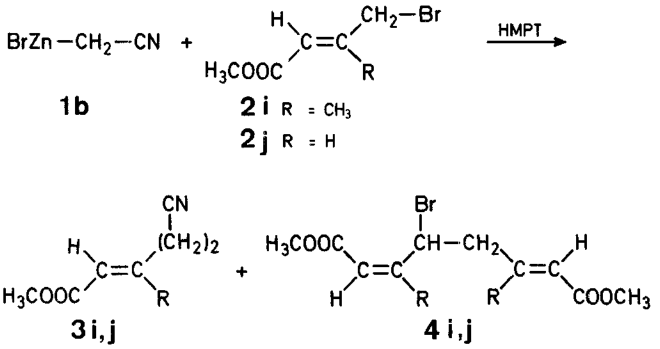
While alkyl bromides are unaffected and heating is required for activated bromides, the tested propargyl and allyl iodides react at room temperature. γ,δ-Unsaturated nitriles are obtained with the advantage, in some cases, of mild experimental conditions[6], brevity[7], or avoidance of dialkylation products[8] in comparison to the reported methods. The tested 4-bromo-α,β-unsaturated esters show a different behaviour depending on the substitution and on the configuration of the double bond (Scheme A).

$$\underset{\mathbf{1b}}{BrZn-CH_2-CN} + \underset{\mathbf{2a\text{-}i}}{R-X} \xrightarrow{HMPT} \underset{\mathbf{3a\text{-}i}}{R-CH_2-CN} + ZnBrX \cdot HMPT$$

2,3	R in **2,3**	X in **2**
a	C_2H_5	J
b	$H_2C=CH-CH_2-$	J or Br
c		Br
d	$(H_3C)_3Si-C\equiv C-CH_2-$	J
e		J
f		J
g	$t\text{-}C_4H_9OOC-CH_2-$	Br
h		Br

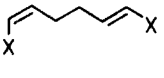
Scheme A

Methyl (*Z*)-4-bromo-3-methyl-2-butenoate[9] (**2h**, Scheme A) reacts to gives the expected product **3h** in better yields than those reported using cyanomethylcopper[10]. In contrast, the corresponding (*E*)-isomer[9] (**2i**) affords a mixture of the expected **3i** and of the dimer **4i** (Scheme **B**). Analogously, reaction of methyl (*E*)-4-bromo-2-butenoate affords **4j** as main product in about 20% yield (40% conversion of the starting methyl 4-bromo-2-butenoate).



Scheme **B**

Recently, other authors[11] proposed a new one-step synthesis (with yields from 30 to 87%) of differently substituted (*E*),(*Z*)-1,5-dienes of general formula **6** starting from the 3,3-dioxide of 3-thiabicyclo[3.2.0]heptane-6,7-dicarboxylic anhydride.

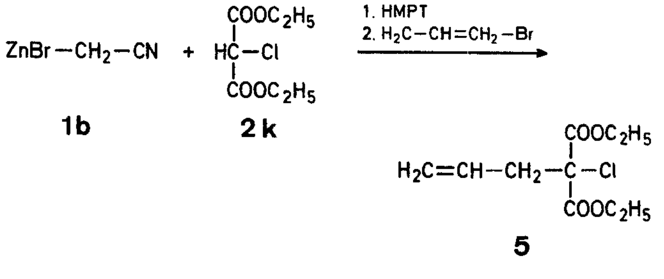


6 a X = $-CH_2-OH$
b X = $-COOH$
c X = $-CH_2-OAc$
d X = $-COOCH_3$

Other existing methods for preparing (*E*),(*Z*)-divinylethane systems[12] consist of multi-step procedures and give variable yields. Compounds **4i, j** could be useful unsymmetrically substituted (*Z*),(*E*)-1,5-dienes. However, we were not able to raise the yields or to avoid formation of tarry materials during distillation.

Action of **1b** as a base explains the formation of **4i** and **4j**. The different acidity of the γ-hydrogens in the (*E*)- and (*Z*)-4-bromo-3-methyl-2-butenoates could be explained in terms of steric inhibition of resonance, that is, decrease in delocalization due to increasing deviation from coplanarity[13]. Stabilization of the (*Z*)-configuration in the Reformatsky-type intermediate (obtained by γ-deprotonation of methyl 4-bromo-2-butenoate) via a six-membered ring involving coordination of the zinc atom with the γ-position and the ester group could possibly account for the stereoselection of the dimerization to **4i,j**.

Another example of **1b** acting as a base is the reaction with diethyl 2-chloropropanedioate (**2k**). Quenching with allyl bromide (Scheme C) affords **5** in a more convenient procedure than the reported treatment of the sodium salt of diethyl 2-(2-propenyl)-propanedioate with 5-chloro-5-nitro-2-phenyl-1,3-dioxan[14].



Scheme C

Table 2. Reactions of **1b** with Electrophiles **2a–k**

Product	Yield [%]	b.p. [°C]/torr	Molecular Formula[a] or Lit. b.p. [°C]/torr	M.S. *m/e*	I.R. (film) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$) δ[ppm]
3a	43[b]	114–118°/760	115–117°/760[17]	69 (M$^+$)	2250 (CN)	1.1 (t, 3H, J = 7 Hz); 1.7 (dq, 2H, J = 7 Hz); 2.35 (t, 2H, J = 7 Hz)
3b	65 (X = J)[c] 57 (X = Br)[d]	50–55°/25	60–61°/40[6]	81 (M$^+$)	2240 (CN); 1640 (C=C)	2.35 (m, 4H); 5.07 (d, 1H, J = 11 Hz); 5.10 (d, 1H, J = 16 Hz); 5.75 (m, 1H)
3c	58	80–82°/40	78–80°/35[7]	95 (M$^+$)	2220 (CN); 1630 (C=C)	1.6 (d, 3H, J = 6 Hz); 2.3 (m, A$_2$B$_2$-system, 4H); 5.45 (m, 2H)
3d	78	55–57°/0.3	$C_8H_{13}NSi$ (151.3)	136 (M$^+$–CH$_3$)	2190 (CN)	1.15 (s, 9H); 2.55 (m, 4H)
3e	44[e]	75°/0.3	97°/15[8]	121 (M$^+$)	2220 (CN); 1630 (C=C)	1.4–2.5 (m, 9H); 5.58 (br. d, 1H, J = 11 Hz); 5.7 (br. d, 1H, J = 11 Hz)
3f	56[f]	76–80°/0.15	113°/9[18]	131 (M$^+$)	2220 (CN)	2.65, 2.9 (A$_2$B$_2$-system, 4H); 7.3 (m, 5H)
3g	58[g]	120–125°/13	$C_8H_{13}NO_2$ (155.3)	155 (M$^+$)	2260 (CN); 1730 (C=O)	1.39 (s, 9H); 2.42 (m, 4H)
3h	67	65–70°/0.3	–[h]	153 (M$^+$)	2240 (CN); 1715 (C=O); 1650 (C=C)	1.90 (d, 3H, J = 1.4 Hz); 2.5 (m, 2H); 2.78 (m, 2H); 3.6 (s, 3H); 5.7 (m, 1H)
3i	35	65–70°/0.4	–[i]	153 (M$^+$)	2240 (CN); 1715 (C=O); 1650 (C=C)	2.20 (d, 3H, J = 1.2 Hz); 2.52 (m, 4H); 3.70 (s, 3H); 5.75 (m, 1H)
4i[j]	15	110–115°/0.2	$C_{12}H_{17}BrO_4$ (305.1)	275, 273 (M$^+$–OCH$_3$)	1720 (C=O); 1660 (C=C)	1.7 (d, 3H, J = 1.4 Hz); 2.12 (d, 3H, J = 1.2 Hz); 2.2–2.6 (m, 2H); 3.62 (s, 3H); 3.64 (s, 3H); 4.10 (dd, 1H, J = 7.5 Hz, 7 Hz); 5.65 (m, 1H); 6.05 (m, 1H)
3j	8	60–65°/0.15	$C_7H_9NO_2$ (139.2)	124 (M$^+$–CH$_3$)	2240 (CN); 1715 (C=O); 1655 (C=C)	2.48 (m, 4H); 3.7 (s, 3H); 5.92 (d, 1H, J = 17 Hz); 6.9 (dt, 1H, J = 17 Hz, 7 Hz);
4j	16–22	80–85°/0.2	$C_{10}H_{13}BrO_4$ (297.1)	278, 276 (M$^+$)	1720 (C=O); 1660 (C=C)	2.60 (m, 2H); 3.7 (s, 3H); 3.72 (m, 1H); 5.85 (d, 1H, J = 16 Hz); 6.20 (dd, 1H, J = 9 Hz, 7 Hz); 6.38 (d, 1H, J = 9 Hz); 6.88 (dt, 1H, J = 16 Hz, 7 Hz)
5	71	62–65°/0.15	96–97°/1.3[14]	199 (M$^+$–Cl)	1745 (C=O); 1640 (C=C)	1.3 (t, 6H, J = 7 Hz); 2.95 (d, 2H, J = 7 Hz); 4.3 (q, 4H, J = 7 Hz); 5.20 (d, 1H, J = 11 Hz); 5.25 (d, 1H, J = 16 Hz); 5.85 (m, 1H)

[a] The microanalyses showed the following deviations from the calculated values: C ±0.47, H ±0.43, N ±0.44; exception: **4i**, C −0.54.

[b] Reaction for 4 h at 40–45°C.

[c] Reaction in DMSO-d_6, product detected by C.L.C. (3% OV1 CWS 80/100, 2 m column, column temperature: 60°C) and ^{1}H-N.M.R. spectrometry.

[d] Reaction for 3 h at 45–50°C and overnight at room temperature.

[e] Reaction for 8 h at room temperature; about 80% conversion of 3-bromocyclohexene to 3-iodocyclohexene; 3-bromocyclohexene does not react with **1b**.

[f] Reaction for 8 h at room temperature; about 80% conversion of α-bromotoluene to α-iodotoluene; 13% of iodide recovered; α-bromotoluene does not react with **1b**.

[g] Starting material (15%) recovered.

[h] Ref.[10], δ = 1.94 ppm (β-methyl substituent).

[i] Ref.[10], δ = 2.07 ppm (β-methyl substituent).

[j] (E),(Z)-configuration assumed from analogy with **4j**.

All reactions were carried out under a nitrogen atmosphere and monitored by G.L.C. (performed on a C. Erba fractovap 2350 using a 3% OV1 CWS 80/100 2m column). Purification of the products was made by bulb-to-bulb distillation. Separation of the mixture **3i/4i** and **3j/4j** was achieved by distillation through a Vigreux column under reduced pressure. I.R. spectra were determined on a Perkin-Elmer 681 spetrometer. Mass spectra were recorded on a Varian Matt 112 spectrometer. ^{1}H-N.M.R. spectra were recorded at 80 MHZ on a Brucker WP 80, with the exception for compound **4j** which was analyzed at 200 MHZ on a Varian FT 200 spectrometer. The microanalyses for new compounds were determined on a Perkin Elmer 240 Elemental analyzer and are in agreement with the proposed compositions.

Hexamethylphosphoric triamide (HMPT; Fluka), distilled from calcium hydride (under nitrogen at 110°C/18 torr) was kept over conditioned 13X molecular sieves (4 h; 0.03 torr; 250°C). Tetrahydrofuran and diethyl ether (C. Erba) were distilled from lithium aluminium hydride before use. Zinc wool was activated as described[15]. 3-Iodocyclohexene (**2e**), α-iodotoluene (**2f**), and 3-iodo-1-trimethylsilyl-1-propyne (**2d**) were prepared from the corresponding bromides as described below. Methyl (Z)- and methyl (E)-4-bromo-3-methyl-2-butenoate were prepared and separated by H.P.L.C. as described[9]. The other starting materials, as well as α-bromotoluene and 3-bromopropyne, were supplied by Aldrich. 3-Bromo-1-cyclohexene was obtained from Ventron GmbH.

3-Bromo-1-trimethylsilyl-1-propyne:

A solution of *n*-butyllithium in hexane (1.6 molar from Aldrich; 10 mmol) is added dropwise to a stirred solution of anhydrous diisopropylamine (1 g, 9.9 mmol) in anhydrous diethyl ether (12 ml). After about 15 min, a solution of freshly distilled 3-bromo-1-propyne (1 g, 8.4 mmol) in anhydrous ether (15 ml) is added dropwise at −70 °C. Chlorotrimethylsilane (1 g, 9 mmol) is added and the mixture is allowed to warm to room temperature. It is worked up with a saturated solution of ammonium chloride (25 ml) and extracted with ether (3 × 20 ml). The organic phase is dried with sodium sulfate and the solvent removed at atmospheric pressure. Distillation of the residue under reduced pressure affords 3-bromo-1-trimethylsilyl-1-propyne; yield: 1.33 g (70%); b.p. 73–75 °C/28 torr (Lit.[16], b.p. 71–73 °C/26 torr).

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 0.2$ (s, 9H); 3.8 ppm (s, 2H).

M.S.: $m/e = 222$ (M^+).

(Bromozinco)-acetonitrile (1b):

A few drops of pure bromoacetonitrile are added with vigorous stirring to zinc wool (1.4 g, 21.5 mmol). As soon as the reaction starts the remaining bromoacetonitrile (total amount 2.57 g, 21.5 mmol) in anhydrous tetrahydrofuran (5 ml) is added dropwise at −5 °C. Higher temperatures, due to the exothermic reaction and resulting in the formation of brown solutions, are to be avoided. Solvent removal in vacuo affords a colorless foamy compound, which is directly used for structural elucidation and nucleophilic reactions, and is identified as a 1:1 molar complex of **1b** with tetrahydrofuran; yield: 5.4 g (98%).

^{1}H-N.M.R. ($DMSO{-}d_6/TMS_{int}$); $\delta = 0.6$ (s, 2H, $ZnCH_2$); 1.8 (m, 4H); 3.6 ppm (m, 4H).

Reaction of 1b with Methyl (*Z*)-4-Bromo-3-methyl-2-butenoate (2h); Typical Procedure for Bromides 2:

Methyl (*Z*)-4-bromo-3-methyl-2-butenoate (**2h**; 1.35 g, 7 mmol) is added to **1b** (1:1 complex with tetrahydrofuran; 2.6 g, 10 mmol) in anydrous hexamethylphosphoric triamide (5 ml). The mixture is stirred for 10 h, diluted with ether (10 ml) and filtered. The filtrate is worked up with dilute hydrochloric acid (1:4; 10 ml) and extracted with ether (3 × 10 ml). The organic phase is dried with sodium sulfate and the solvent removed at atmospheric pressure. Bulb-to-bulb distillation of the residue under reduced pressure affords **3h**; yield: 0.65 g (67%); see Table 2.

Reaction of 1b with 1-Trimethylsilyl-3-bromo-1-propyne (2d); Typical Procedure for Iodides 2:

1-Trimethylsilyl-3-bromo-1-propyne (2.7 g, 15 mmol) is added to a stirred suspension of potassium iodide (2.6 g, 16 mmol) in anhydrous hexamethylphosphoric triamide (10 ml). After 15 min at 40 °C, this mixture is added to **1b** (complexed with tetrahydrofuran; 6.4 g, 25 mmol) and the mixture is treated as described above to afford **3d**; yield: 1.6 g (78%); see Table 2.

Diethyl-2-Chloro-2-(2-propenyl)-propanedioate (5):

Diethyl-2-chloropropanedioate (**2k**; 1.27 g, 8 mmol) is added to **1b** (complexed with tetrahydrofuran; 3.1 g, 12 mmol) in anhydrous hexamethylphosphoric triamide (10 ml). The mixture is stirred for 1 h, then 3-bromo-1-propene (1.1 g, 9 mmol) is added and the stirring is continued overnight. Work up as described above affords **5**; yield: 1.28 g (71%); see Table 2.

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