α,β-Unsaturated Nitriles: An Efficient Conjugate Addition with Potassium Benzeneselenolate and Potassium Benzenesulfenylate

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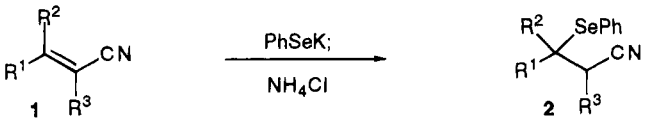
The Michael addition of benzeneselenide anions to activated alkenes is an excellent method for preparing functionalized selenides.[1] The resultant selenides are ideal precursors for radical cyclizations[2] or can be regioselectively eliminated to the parent alkene, providing a useful method for temporarily protecting olefins.[3] However, α,β-unsaturated nitriles are conspicuously absent from reports of activated alkenes that undergo this type of conjugate addition reaction.[1]

Surprisingly, sodium benzeneselenolate in ethanol adds to the nitrile function of benzylidene malononitrile rather than adding conjugately.[4] This reactivity is typical of several selenium nucleophiles, such as aluminum selenide[5] and hydrogen selenide,[6] that add to nitrile groups to afford selenocarboxamides. In this context we report a *conjugate* addition of the benzeneselenolate anion to α,β-unsaturated nitriles as a convenient method for preparing β-phenylseleno nitriles.

On the basis of the known reactivity of the benzeneselenolate anion,[7] we anticipated that in polar aprotic solvents PhSeK would react conjugately with α,β-unsaturated nitriles. As expected, PhSeK was found to add smoothly to citronitrile (**1a**) in various aprotic solvents to afford the corresponding β-phenylseleno nitrile **2a** (Table 1). This reaction showed a marked dependence on the solvent, affording good yields in HMPA alone (entry 1) but becoming increasingly sluggish in THF–HMPA solvent mixtures (entries 2–4). At THF–HMPA ratios greater than 4:1 no measurable reaction is observed, even after 14 days (entry 4). DMF and DMSO are effective solvents (entries 5 and 6), affording the conjugate adduct in yields comparable to that with HMPA alone, but the reaction is considerably slower in DMF and DMSO (compare entries 5 and 6 with entry 1). We speculate that the nucleophilicity of PhSeK varies in the solvents examined since less polar solvent mixtures give virtually the same yield of **2a**, but at extended reaction times.[8] A similar solvent effect has been observed in the selenolate-induced cleavage of cyclopropanecarbonitrile that occurs smoothly in DMF but not in benzene.[9]

Table 1. Addition of KSePh to Various α,β-Unsaturated Nitriles

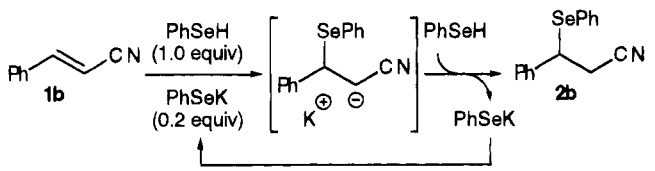


entry no.	series	R^1	R^2	R^3	solvent[a]	time	yield (%)
1	**a**	$PhCH_2CH_2$	Me	H	A	1 h	85
2	**a**	$PhCH_2CH_2$	Me	H	B	8 days	95
3	**a**	$PhCH_2CH_2$	Me	H	C	15 days	97
4	**a**	$PhCH_2CH_2$	Me	H	D	14 days	~0
5	**a**	$PhCH_2CH_2$	Me	H	E	8 days	88
6	**a**	$PhCH_2CH_2$	Me	H	F	25 days	92
7	**b**	Ph	H	H	A	3 h	93
8	**c**	MeO	H	H	A	23 h	74
9	**d**	H	Et	H	A	23 h	85
10	**e**	H	H	Me	A	3 h	85
11	**f**	H	H	CH_2CH_2CN	A	10 h	94

[a] A = HMPA, B = THF–HMPA, 1:1 (v/v), C = THF–HMPA, 2:1 (v/v), D = THF–HMPA, 4:1 (v/v), E = DMSO, and F = DMF.

The conjugate addition is effective with both β-substituted (Table 1, entries 7–9) and α-substituted acrylonitriles (Table 1, entries 10 and 11). In the case of cinnamonitrile, the crystalline adduct **2b** proved suitable for X-ray analysis and further verified the structural assignment.[10] Interestingly, with methyleneglutaronitrile (Table 1, entry 11) no reaction occurs at the aliphatic nitrile group[11] and the β-phenylseleno nitrile **2f** is the sole product detected. The ease of this reaction is demonstrated by the chemoselective addition of benzeneselenide to an enol ether (Table 1, entry 8) without causing any observable demethylation. In a related case, sodium benzenethiolate caused demethylation of α-methoxycinnamonitrile rather than adding to the unsaturated nitrile in a Michael sense.[12]

The reaction can also be performed in a "buffered-solution mode" employing potassium benzeneselenolate in the presence of excess benzeneselenol. In the case of cinnamonitrile the yield obtained under these conditions is 94%, but the reaction time increases from 3 to 18 h.



The buffered solution method has been used for the Michael addition of lithium benzenethiolate to 4-*tert*-butyl-1-cyanocyclohexene.[13] Similar sulfenylate additions have been performed using aqueous conditions,[14]

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(9) Smith, A. B., III; Scarborough, R. M., Jr. *Tetrahedron Lett.* **1978**, 1649.
(10) The authors have deposited atomic coordinates for **2b** with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.
(11) No intermediates were detected (TLC and GCMS) that would correspond to the addition of benzeneselenolate to the nitrile group.
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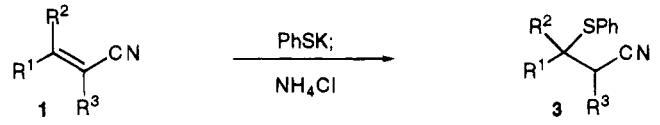
0022-3263/95/1960-4299$09.00/0

Table 2. Addition of KSPh to Various α,β-Unsaturated Nitriles



entry no.	series	R^1	R^2	R^3	solvent[a]	time	yield (%)
1	**a**	$PhCH_2CH_2$	Me	H	A	4 h	97
2	**a**	$PhCH_2CH_2$	Me	H	B	5 days	~100
3	**a**	$PhCH_2CH_2$	Me	H	C	10 days	97
4	**a**	$PhCH_2CH_2$	Me	H	D	14 days	~0
5	**a**	$PhCH_2CH_2$	Me	H	E	2 days	94
6	**a**	$PhCH_2CH_2$	Me	H	F	7 days	92
7	**b**	Ph	H	H	A	4	95
8	**c**	MeO	H	H	A	23	92
9	**f**	H	H	CH_2CH_2CN	A	10	95

[a] A = HMPA, B =THF–HMPA, 1:1 (v/v), C = THF–HMPA, 2:1 (v/v), D = THF–HMPA, 4:1 (v/v), E = DMSO, and F = DMF.

but some conjugate adducts have eluded preparation with this procedure.[15] We therefore examined the addition of potassium benzenethiolate to representative acrylonitriles, using the anhydrous procedure developed with PhSeK (Table 2). The addition reaction proceeds readily with nitriles of different substitution patterns and is comparable to the corresponding selenide reactions in both yield and reaction time. The addition of PhSK exhibits a similar solvent effect, proceeding readily in HMPA, but at diminished rates in DMF, DMSO, and THF–HMPA solvent mixtures (compare entry 1 with entries 2–6).

In summary, a route to β-phenylseleno nitriles and β-phenylsulfenyl nitriles has been developed that employs anhydrous conditions. The addition of potassium benzeneselenolate and potassium benzenethiolate to various α,β-unsaturated nitriles occurs in a conjugate manner with no competitive addition to the nitrile group. The method is efficient and convenient, and provides access to β-phenylsulfenyl nitriles that may otherwise be difficult to obtain.

Experimental Section

NMR spectra were recorded in $CDCl_3$ (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR) and are reported in ppm (δ) relative to TMS using $CHCl_3$ as an internal reference. All reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere. Anhydrous solvents were distilled from sodium benzophenone ketyl or CaH_2. Bulk solvents for chromatography and workup of reactions were distilled through glass. Radial chromatography was performed on a Chromatotron using individually prepared 2-mm rotors and a stepped solvent gradient (hexanes, EtOAc–hexanes 1:19, 1:9, 3:17, 1:4).

General Procedure for Conjugate Addition Reactions. To dry THF-washed (3 × 0.5 mL) potassium hydride (0.45 mmol) at rt was added neat HMPA (1.44 mmol). To the resultant heterogeneous solution was sequentially added neat benzeneselenol (0.54 mmol) and neat unsaturated nitrile (0.45 mmol). The reaction was monitored by TLC, and upon completion saturated aqueous NH_4Cl was added. The aqueous portion was extracted with EtOAc. The combined extracts were washed three times with water and concentrated under reduced pressure, and the resultant crude material was purified by radial chromatography.

3-Methyl-5-phenyl-3-(phenylselenyl)pentanenitrile (2a). The general procedure was employed with 81 μL, 0.46 mmol, of citronitrile (**1a**) for 1 h. Purification afforded 128.5 mg (85%) of nitrile **2a** as a yellow oil: IR (film) 3027, 2247, 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (s, 3H), 1.88–1.94 (m, 2H), 2.57 (ABq, J = 16.9, $\Delta\nu$ = 18.3 Hz, 2H), 2.72–2.83 (m, 1H), 2.87–2.98 (m, 1H), 7.13–7.41 (m, 8H), 7.64–7.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.4, 31.6 (two coincident signals), 42.1, 45.4, 117.5, 125.7, 128.3, 129.1, 129.3, 138.2, 141.2; MS m/z 329 (M^+).

3-Phenyl-3-(phenylselenyl)propanenitrile (2b). The general procedure was employed with 59 μL, 0.47 mmol, of cinnamonitrile (**1b**) for 3 h. The residue was purified by crystallization from hexanes to afford 125.0 mg (93%) of nitrile **2b** as a white solid (mp 42–43 °C): IR (KBr) 2937, 2230, 1472 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59–2.76 (m, 2H), 4.16 (dd, J = 8.8, 6.2 Hz, 1H), 6.93–7.21 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 24.9, 41.5, 117.6, 127.1, 127.6, 128.0, 128.7, 128.8, 129.2, 135.9 138.7; MS m/z 287 (M^+).

Buffered-Solution Mode. To a THF-washed (3 × 0.5 mL) suspension of potassium hydride (4.0 mg, 0.1 mmol) in THF (0.2 mL) at rt was added neat benzeneselenol (63 μL, 0.59 mmol). To the resultant heterogeneous solution was sequentially added HMPA (257 μL, 1.5 mmol) and neat cinnamonitrile (**1b**, 87 μL, 0.50 mmol). After 18 h, saturated aqueous NH_4Cl was added and the mixture was extracted with EtOAc. The extracts were washed three times with water, and the resultant solution was concentrated under reduced pressure. The residue was purified by crystallization from hexanes to afford 187.1 mg (94%) of nitrile **2b**.

3-Methoxy-3-(phenylselenyl)propanenitrile (2c). The general procedure was employed with 40 μL, 0.47 mmol, of 3-methoxyacrylonitrile (**1c**) for 23 h. Purification afforded 85.0 mg (74%) of nitrile **2c** as a yellow oil: IR (film) 3056, 2251, 1534, 1067 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (d, J = 6.6 Hz, 2H), 3.22 (s, 3H), 4.66 (t, J = 6.6 Hz, 1H), 6.95–7.08 (m, 3H), 7.25–7.28 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.8, 57.7, 81.2, 116.8, 125.2, 128.7, 129.2, 136.4; MS m/z 241 (M^+).

3-(Phenylselenyl)pentanenitrile (2d). The general procedure was employed with 65 μL, 0.66 mmol, of a 70% w/w solution of *cis*-pentenenitrile (**1d**) for 23 h. Purification afforded 133.1 mg (85%) of nitrile **2d** as a yellow oil: IR (film) 3058, 2248, 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (t, J = 7.30 Hz, 3H), 1.38–1.54 (m, 2H), 2.28 (dd, J = 17, 7.1 Hz, 1H), 2.38 (dd, J = 17, 5.7 Hz, 1H), 2.89 (br quintet, 1H), 6.95–7.05 (m, 3H), 7.26–7.29 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 12.1, 24.4, 27.3, 40.9, 117.7, 126.8, 128.4, 129.2, 135.7; MS m/z 239 (M^+).

2-Methyl-3-(phenylselenyl)propanenitrile (2e). The general procedure was employed with 31 μL, 0.37 mmol, of methacrylonitrile (**1e**) for 3 h. Purification afforded 70.3 mg (85%) of nitrile **2e** as a yellow oil: IR (film) 3056, 2240, 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (d, J = 7.0 Hz, 3H), 2.46 (br sextet, 1H), 2.63 (dd, J = 12.8, 7.0 Hz, 1H), 2.77 (dd, J = 12.8, 7.5 Hz, 1H), 6.96–7.00 (m, 3H), 7.22–7.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 18.0, 26.5, 30.4, 121.5, 127.6, 128.2, 129.1, 133.4; MS m/z 225 (M^+).

4-Cyano-5-(phenylselenyl)pentanenitrile (2f). The general procedure was employed with 43 μL, 0.40 mmol, of 2-methyleneglutaronitrile (**1f**) for 10 h. Purification afforded 98.0 mg (94%) of nitrile **2f** as a yellow oil: IR (film) 3056, 2247, 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92–2.16 (m, 2H), 2.44–2.59 (m, 2H), 2.83–3.14 (m, 3H), 7.26–7.40 (m, 3H), 7.52–7.62 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.9, 27.8, 28.2, 31.7, 117.7, 119.2, 127.6, 128.2, 129.4, 133.9; MS m/z 264 (M^+).

3-Methyl-5-phenyl-3-(phenylthio)pentanenitrile (3a). The general procedure was employed with 76 μL, 0.43 mmol, of citronitrile (**1a**) for 4 h. Purification afforded 117.0 mg (97%) of **3a** as a yellow oil: IR (film) 3027, 2247, 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (s, 3H), 1.82–1.92 (m, 2H), 2.45 (ABq, J = 16.7, $\Delta\nu$ = 19.1 Hz, 2H), 2.74–2.84 (m, 1H), 2.91–3.01 (m, 1H), 7.13–7.41 (m, 8H), 7.64–7.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.6, 30.7 (two coincident signals), 41.4, 49.0, 117.4, 126.2, 128.3, 128.6, 129.1, 129.8, 137.6, 141.0; MS m/z 281 (M^+).

3-Phenyl-3-(phenylthio)propanenitrile (3b). The general procedure was employed with 43 μL, 0.34 mmol, of cinnamonitrile (**1b**) for 4 h. Purification afforded 77.8 (95%) of nitrile **3b** as a white solid (mp 40.5–41.5 °C): IR (KBr) 2927, 2229 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.89 (br d, J = 7 Hz, 2H), 4.41 (br t, J = 7 Hz, 1H), 7.26–7.41 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 25.0, 49.2, 117.1, 127.4, 128.4, 128.6, 128.9, 129.2, 132.5, 133.7, 138.2; MS m/z 239 (M^+).

3-Methoxy-3-(phenylthio)propanenitrile (3c). The general procedure was employed with 33 μL, 0.40 mmol, of 3-methoxyacrylonitrile (**1c**) for 23 h. Purification afforded 70 mg (92%)

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of nitrile **3c** as a yellow oil: IR (film) 3056, 2251, 1534, 1156 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.68 (br d, J = 7 Hz, 2H), 3.56 (s, 3H), 4.76 (br t, J = 7 Hz, 1H), 7.32–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.3 , 56.5, 84.5 116.4, 128.9, 129.1, 129.5, 135.0; MS *m/z* 193 (M^+).

4-Cyano-5-(phenylthio)pentanenitrile (3f). The general procedure was employed with 42 μL, 0.39 mmol, of 2-methyleneglutaronitrile (**1f**) for 10 h. Purification afforded 79 mg (95%) of nitrile **3f** as a yellow oil: IR (film) 3056, 2247, 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92–2.08 (m, 1H), 2.16–2.27 (m, 1H), 2.46–2.69 (m, 2H), 2.82–2.94 (m, 1H), 3.02–3.13 (m, 1H), 3.20–3.29 (m, 1H), 7.32–7.40 (m, 3H), 7.45–7.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.1, 27.0, 31.2, 36.4, 117.6, 118.9, 128.1, 129.5, 131.6, 133.0; MS *m/z* 216 (M^+).

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Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra of all new compounds and an ORTEP drawing of **2b** (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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