A convenient synthesis of (*E*)- α-halo-α, β-unsaturated nitriles

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Dedicated to Professor Chengye Yuan on the occasion of his 80th birthday
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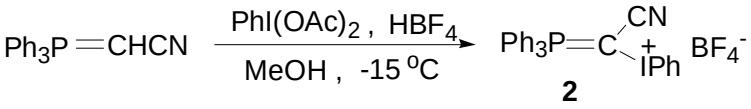
Abstract
(*E*)-α-Halo-α, β-unsaturated nitriles were synthesized through the tandem nucleophilic substitution-Wittig reaction of α-cyano-α-hypervalent iodine phosphonium ylide that was used as umpolung ylide.

Keywords: Wittig reaction, hypervalent iodine phosphonium ylide, α-halo-α,β-unsaturated nitrile

It is well known that α-halo-α, β-unsaturated nitriles are useful intermediates in organic synthesis and capable of undergoing many useful organic transformations.[1]

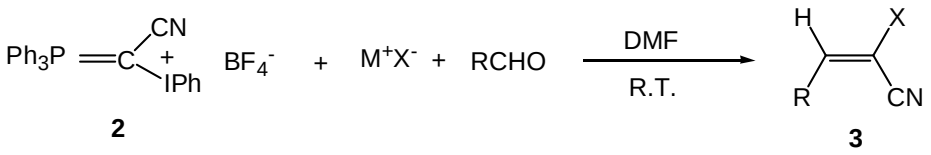
Recently, we have reported a new synthetic method of the synthesis of α-halo-α, β-unsaturated esters and ketones by the tandem nucleophilic substitution-Wittig reaction of α-hypervalent iodine functionalized ylides which were used as umpolung ylides because of introducing hypervalent iodine at α-carbon in ylides.[2]

In our continuing study on this new type of reaction, we synthesized α-cyano-α-hypervalent iodine phosphonium ylide **2** by applying the similar protocol[3] (Scheme 1) and studied their application in detail.



Scheme 1

We found that α-cyano-α-hypervalent iodine phosphonium ylide **2** could also undergo the tandem nucleophilic substitution-Wittig reaction to afford α-halo-α, β-unsaturated nitriles. The reaction sequence is shown in Scheme 2 and the results are summarized in Table 1.



2 **3**

Scheme 2

Table 1. Preparation of (*E*)-α-halo-α, β-unsaturated nitriles

Entry	M^+X^-	R	Product	Time (h)	Yield[a]	Ratio(*E*:*Z*)[b]
1	Me_4NCl	*p*-NO_2-C_6H_4	**3a**	18	84	94/6
2	n-Bu_4NCl	*p*-Cl-C_6H_4	**3b**	24	80	92/8
3	n-Bu_4NBr	*p*-NO_2-C_6H_4	**3c**	18	89	95/5
4	n-Bu_4NBr	*p*-Cl-C_6H_4	**3d**	24	81	91/9
5	Et_4NI	*p*-NO_2-C_6H_4	**3e**	18	92	95/5
6	n-Bu_4NBr	*p*-CH_3O-C_6H_4	**3f**	48	70	93/7
7	n-Bu_4NBr	PhCH=CH	**3g**	28	74	93/7

[a] Isolated yield of purified (*E*)-**3** based on aldehyde.
[b] The ratios of *E*-isomer to *Z*-isomer were determined by ^{1}H NMR spectra (400 MHz in $CDCl_3$)

The configuration of 2-chloro-3-(*p*-nitrophenyl)- propenenitrile (**3a**) was determined as *E* type by X-ray single-crystal diffraction analysis (Figure 1).

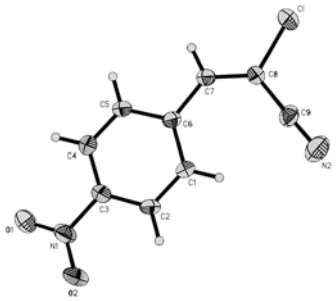


Figure 1. X-ray structure of 2-chloro-3-(*p*-nitrophenyl)- propenenitrile (**3a**).

In conclusion, we have developed a stereoselective method for the synthesis of (*E)*- α-halo-α, β-unsaturated nitriles by three-component reaction of α-cyano-α-hypervalent iodine phosphonium ylide with aldehydes and halides. The present procedure has the advantages of readily available starting materials, simple procedures, mild reaction conditions and good stereoselectivity.

Experimental Section

General Procedures. All reactions were carried out in Schlenk tubes under nitrogen atmosphere. ^{1}H NMR spectra were measured at 400 MHz in $CDCl_3$ with TMS as internal standard. Mass spectra were obtained by EI method. IR spectra were obtained by use of neat capillary cells (liquid samples) or KBr disks (solid samples). Melting points were uncorrected.

General procedure for the stereoselective synthesis of (*E*)-α-halo-α, β-unsaturated nitriles 3 by the tandem reaction of umpolung ylides 2

A mixture of α-hypervalent iodine functionalized phosphonium ylides **2** (2 mmol), tetrakisalkylammonium halide (2 mmol), and aldehyde (2 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 18-48 h. After the reaction was complete, the organic phase was washed with water (10 mL× 2) and dried over magnesium sulfate. After evaporation of the solvent, the crude product was purified by preparative TLC (silica gel, hexane-ethyl acetate as eluent) to give α-halo-α, β-unsaturated nitriles **3**.

(*E*)-2-Chloro-3-(*p*-nitrophenyl)-propenenitrile (3a). mp 82-84 °C(lit.[4] mp 85-86 °C). ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.45 (s, 1H), 7.86 (d, J = 8.6 Hz, 2H), 8.32 (d, J = 8.8 Hz, 2H). IR ν (cm^{-1}): 3110, 2224, 1593, 1518, 1347, 1012, 903, 817. MS (m/z):210 (M+2, 33.3), 208 (M, 99.1), 178 (53.4), 150 (81.9), 127 (96.2), 126 (100.0), 100 (58.2), 99 (52.0), 75 (58.7), 50 (77.9).

(*E*)-2-Chloro-3-(*p*-chlorophenyl)-propenenitrile (3b). mp 48-50 °C (lit.[4] mp 51-52 °C). ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.31 (s, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H). IR ν (cm^{-1}): 2926, 2219, 1637, 1591, 1492, 1122, 1014, 830. MS (m/z): 199 (M+2, 55.8), 197 (87.2), 164 (31.4), 162 (100.0), 127 (38.6), 126 (32.5), 75 (36.0), 50 (33.4).

(*E*)-2-Bromo-3-(*p*-nitrophenyl)-propenenitrile (3c). mp 96-98 °C(lit.[4] mp 98-100 °C). ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.67 (s, 1H), 7.87 (d, J = 8.8 Hz, 2H), 8.31 (d, J = 8.8 Hz, 2H). IR ν (cm^{-1}): 3111, 2213, 1585, 1515, 1346, 1110, 999, 917, 862, 799. MS (m/z): 254 (M+2, 41.0), 252 (M, 41.0), 224 (24.0), 222 (25.1), 127 (100.0), 115 (36.0), 100 (40.5), 75 (25.6), 50 (47.8).

(*E*)-2-Bromo-3-(*p*-chlorophenyl)-propenenitrile (3d). mp 46-48 °C (lit.[4] mp 48-50 °C). ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.42 (d, J =8.5 Hz, 2H), 7.52 (s, 1H), 7.65 (d, J = 8.4 Hz). IR ν (cm^{-1}): 3028, 2209, 1589, 1485, 1098, 997, 894, 806. MS (m/z): 243 (M+2, 100.0), 241 (75.4), 208 (30.8), 206 (33.1), 162 (56.9), 127 (82.4), 126 (66.2), 99 (37.7), 75 (63.1), 50 (56.2).

(*E*)-2-Iodo-3-(*p*-nitrophenyl)-propenenitrile (3e). mp 108-110 °C(lit.[5] mp 108-110 °C) . ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.86 (d, J = 8.8 Hz, 2H), 7.89 (s, 1H), 8.28 (d, J = 8.8 Hz, 2H). IR ν (cm^{-1}): 3041, 2212, 1582, 1514, 1348, 1110, 912, 849. MS (m/z): 300 (M, 100.0), 270 (31.0), 127 (96.3), 115(68.1), 100 (46.8), 76(39.6), 50 (69.9).

(*E*)-2-Bromo-3-(*p*-methoxyphenyl)-propenenitrile (3f). mp 64-66 °C(lit.[4] mp 66-67 °C). ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 6.97 (d, J = 9.2 Hz, 2H), 7.49 (s, 1H), 7.71 (d, J = 8.8 Hz, 2H). IR ν (cm^{-1}): 3034, 2207, 1608, 1589, 1515, 1303, 1264, 1183, 1022, 826. MS (m/z): 139 (M+2, 94.9), 237 (M, 100.0), 224 (20.8), 222 (21.8), 158 (28.7), 115 (38.1), 114 (38.1), 88 (31.8), 77 (20.4), 63 (36.0), 50 (23.7)

(*E*)-2-bromo-5-phenyl-2,4-pentadienenitrile (3g). mp 58-56 °C(lit.[6] mp 58-60 °C) . ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 6.97 (d, J = 16 Hz, 1H), 7.05 (q, 1H), 7.36 (d, J = 9.1 Hz, 1H), 7.42 (m, 3H), 7.54 (m, 2H). IR ν (cm^{-1}): 3027, 2206, 1613, 1574, 1449, 1296, 1151, 971, 754, 691. MS (m/z): 235 (M+2, 30.7), 233 (M, 32.2), 154 (100.0), 153 (36.8), 127 (93.5), 77(24.9), 63 (21.8), 51(30.7).

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