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Stereoselective Synthesis of 3-Alkylcinnamonitriles

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Abstract Stereoselective synthesis of (2Z)-3-arylselenocinnamonitriles and coupling them with Grignard reagents catalysized by CuI, giving the trisubstituted alkenes with main retention products.

The synthesis of trisubstituted alkenes has attracted more and more attention of chemists in recent years because many biologically active compounds have the skeletion of trisubstituted alkenes[1-3]. Vinyl selenides are important precursors of various alkenes because their seleno groups are easily to be substituted by varied reagents[4]. For example, vinyl selenides couple with Grignard reagents catalysized by $Ni(PPh_3)_2Cl_2$, forming substituted alkenes[5]. Vinyl selenides react with lithium n-butyl, the seleno groups being substituted by lithium, then react with electrophilic reagents, also forming substituted alkenes[6]. But all of these methods are not suitable for synthesis of alkenes containing ester, cyano etc. groups because of the utilization of active organometallic reagents. So we developed a method of coupling reaction of Grignard reagents with vinyl selenides linking cyano group catalysized by CuI, in which the cyano groups were not affected, probably because the Grignard reagents and CuI formed less active organic copper reagents.

For studying this methodology, we prepared several (2Z)-3-phenylselenocinnamonitriles **3** from addition of phenylpropiolonitrile **1** with selenoesters **2**.

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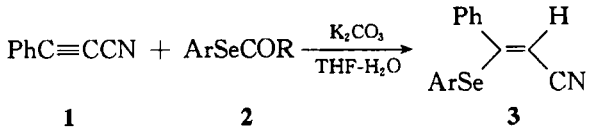
Equal molar amount of phenylpropiolonitrile **1**, selenoesters **2** and potassium carbonate were refluxed for 4h in THF containing water, giving the (2Z)-3-arylselenocinnamonitriles **3** with stereoselectivity and high yields (Table 1).



1 **2** **3**

The selenoesters were affected by potassium carbonte, hydrolysized to form potassium arylselenides, which added nucleophilly to phenylpropiolonitrile, forming the products **3**. Because of the space hinderation, the bulky phenyl was in *anti*-position with cyano.

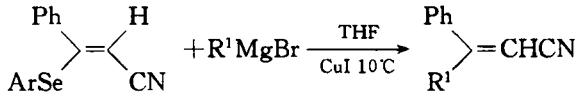
Table 1 Stereoselective synthesis of (2Z)-3-arylselenocinnamonitriles

Entry	Ar	R	M. P. (℃)[a]	Yield (%)[b]
3a	Ph	CH_3	32—34	89
3b	p-$CH_3OC_6H_4$	CH_3	93—95	93
3c	p-ClC_6H_4	Ph	67—69	96

a. Melting points are uncorrected.

b. Isolated yields.

The coupling reaction of (2Z)-3-arylselenocinnamonitriles **3** with Grignard reagents **4** was catalysized by equal amount CuI in anhydrous THF at 10℃. Because equal amount of catalyst was present, the Grignard reagents have more possibility to react with CuI and less possibility to react with cyano than using cat. amount of catalyst. The Grignard reagents were added slowly in drops to the mixture of **3** and CuI in THF at 10℃, the cyano not being affected, forming the products **5** with main retention configuration (Table 2)[7][8].



3 **4** **5**

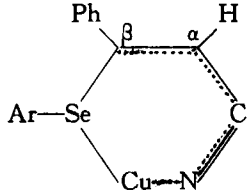
Table 2 Coupling reaction of (2Z)-3-arylselenocinnamonitriles with Grignard reagents

Entry	Ar	R[1] [a]	Yield (%)	Ritio[b] E/Z
5a	p-Cl-C_6H_4	CH_3	81	80 : 20
5b	Ph	C_2H_5	96	95 : 5
5c	Ph	n-C_4H_9	89	88 : 12
5d	Ph	i-C_4H_9	87	70 : 30
5e	p-$MeOC_2H_4$	Ph	92	—

a. 2 Eg. amount of Grignard reagents were used.

b. Determined by ^{1}H-NMR.

The mechanism of the coupling reaction involved Grignard reagents react with CuI to form organic copper reagents. Then the copper reagents and **3** formed procucts from the intermediates complex **6**. The alkyl or phenyl attacked at β-carbon perpendicularly. In *anti* products, the bulky phenyl and cyano have far distance so have small space interreaction. So the *anti* products were main.



6

This method provided a newly, effective way for synthesis of trisubstituted alkenes containing cyano, overcame the affection of Grignard reagents to the sensitive cyano, and expanded the utilization of vinyl selenides in synthesis of alkenes.

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were run on PMR-60MHz instrument (TMS/CCl_4). IR spectra were racorded on a Perkin-Elmer-683 spectrophotometer. Mass spectra were recorded on an HP-5989A instrument. Selenoesters were prepared according reference[9]. Phenylpropiolonitriles were prepared from aminolysis of phenylpropiolonate then dehydration with P_2O_5.

Preparation of (2Z)-3-arylselenocinnamonitriles

Phenylpropiolonitrile (0.63g, 5mmole), selenoester (5mmole)and potassium carbonate (0.69g, 5mmole) were refluxed for 4h in 20ml THF containing 1% water under N_2. Most of the solvent was evaporated *in vacuo* and 20ml water was added to the residue. Extracted with Et_2O (3×25ml) and the combined organic phase was washed with NH_4Cl soln., dried over Na_2SO_4. Removed most of the Et_2O, the residue was recrystallized from Et_2O, obtained the yellow solid product.

(2Z)-3-*phenylselenocinnamonitrile*. **3a**

^{1}H-NMR δ(ppm) 5.73(s,1H), 6.86-7.33(m,10H). IR(KBr,cm^{-1}) 2220, 1580,1450,1230,1022,1005,820,760. MS (m/e) 285(M^+),258,204,169, 128,77.

(2Z)-3-(*p-methoxylphenylseleno*)*cinnamonitrile*. **3b**

^{1}H-NMR δ(ppm) 3.56(s,3H), 5.60(s,1H), 6.30-6.53(m,2H), 6.90-7.26(m,7H). IR(KBr,cm^{-1}) 2220,1600,1570,1500,1300,1250,1175, 1035,825,760. MS (m/e) 315(M^+),284,235,187,169,128,77.

(2Z)-3-(*p-chlorophenylseleno*)*cinnamonitrile*. **3c**

^{1}H-NMR δ(ppm) 5.78(s,1H), 6.30-6.53(m,2H), 6.82-7.45(m,9H). IR (KBr,cm^{-1}) 2220,1570,1482,1092,1010,815,760. MS (m/e) 319(M^+), 284,239,169,128,77.

Coupling reaction of **3** *and Grignard reagents catalysized by CuI.*

Under N_2, CuI (0.19g,1mmole) was stirred in 10ml anhy. THF and several drops of Grignard reagent were added. (2Z)-3-Arylselenocinnamonitrile (1mmole) were added and then stirred for 5min. The Grignard reagent (2mmole) were added slowly in drops at 10℃. The mixture was stired for 2h at the same temperature. Then filtered away the solid residue and washed it with Et_2O (20ml). The filtrat was added to the soln. of NH_4Cl in water, the water phase was extracted with Et_2O (2×20ml). Washed the combined organic phase with water (2×40ml), dried over Na_2SO_4. The solvent was evaporated in reduced pressure and the residue was purificated with prepared TLC on silica gel (CH_2Cl_2/n-Hexane=1∶4).

3-*Phenylbutenitrile*. **5a** E/Z=80∶20

^{1}H-NMR δ(ppm) 2.16(s,0.6H,Z-CH_3), 2.33(s,2.4H,E-CH_3), 5.20(s, 0.2H,Z-H),5.43(s,0.8H,E-H),7.23-7.38(m,5H). IR(neat, cm^{-1}) 2221, 1620,1460,825,755.

3-*Phenylpentenitrile* **5b** E/Z=95 : 5

^{1}H-NMR δ(ppm) 1.06(t,3H),2.43(q,0.1H,Z-CH_2),2.80(q,1.9H,E-CH_2),5.16(s,0.05H,Z-H),5.27(s,0.95H,E-H),7.20-7.45(m,5H). IR (neat, cm^{-1}) 2221,1618,1505,1460,830,760.

3-*Phenylheptenitrile* **5c** E/Z=88 : 12

^{1}H-NMR δ(ppm) 0.80-1.53(m,7H),2.46(m,0.24H,Z-CH_2),2.76(m,1.76H,E-CH_2),5.20(s,0.12H,Z-H),5.33(s,0.88H,E-H), 7.06-7.43(m,5H). IR(neat, cm^{-1}) 2222,1620,1455,830,760.

5-*Methyl*-3-*phenylhexenitrile* **5d** E/Z=70 : 30

^{1}H-NMR δ(ppm) 0.70-1.50(m,7H), 2.32(d,0.6H,Z-CH_2),2.65(d,1.4H,E-CH_2),5.16(s,0.3H,Z-H),5.33(s,0.7H,E-H),7.10-7.36(m,5H). IR(neat, cm^{-1}) 2222,1620,1475,825,760.

MS (m/e) 186(M^+),170,143,115.

3,3-*Diphenylpropenitrile* **5e**

^{1}H-NMR δ(ppm) 5.56(s,1H), 7.16-7.43(m,10H). IR(neat, cm^{-1}) 2221, 1630,1602,1505,1455,1362,1250,1080,970,825,775.

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