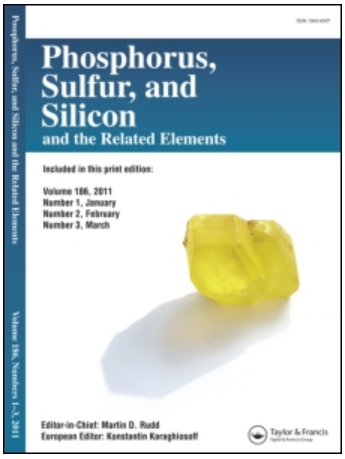

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Novel Stereoselective Phase Transfer Catalytic Synthesis and Some Applications of (E)-2-Chlorovinylthioarenes and Hetarenes

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NOVEL STEREOSELECTIVE PHASE TRANSFER CATALYTIC SYNTHESIS AND SOME APPLICATIONS OF (*E*)-2-CHLOROVINYLTHIOARENES AND HETARENES

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*A novel two-step method for the preparation of (*E*)-2-chlorovinylthioarenes (or hetarenes) from thiols and 1,1,2-trichloroethane in the phase transfer catalytic systems solid K_2CO_3 / solid KI / 18-crown-6 / xylene and solid KOH / 18-crown-6 / toluene has been developed. (*E*)-2-chlorovinylthioarenes were isolated in yields up to 98%. Utilization of (*E*)-2-chlorovinylthioarenes in the Heck and Stille reactions has been shown.*

Keywords: Chlorovinylthioarenes; Heck reaction; phase transfer catalytic system; Stille reaction

INTRODUCTION

Functionalized unsaturated sulfur containing compounds have been investigated as intermediates in organic synthesis.[1–3] Among these compounds 2-halovinyl sulfides have been extensively studied.[4,5] For example, 2-chlorovinyl sulfides are the excellent synthons for the preparation of vinyl selenides[6] or polyenediynes.[7]

The general methods for the synthesis of 2-chorovinyl sulfides are based on the reaction of thiols or sodium thiolates with *cis*- or *trans*-1,2-dichloroethenes[5,8,9] or addition of terminal acetylenes to arylsulfenyl chlorides in AcOH[10,11] or EtOAc.[12] 2-Halovinylthioarenes were obtained by the thermal decomposition of β-arylmercaptoacrylic acids in the presence of chlorine or bromine.[13] Reactions of benzenethiolate anions with several polychloroethanes also were studied.[14] However,

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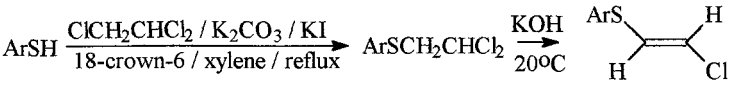
selectivity and yields of such reactions usually were low. The reaction of PhSNa with $CH_2ClCHCl_2$ in DMF afforded the desired product PhSCH=CHCl in yield up to 11%, PhSCH=CHSPh (27–58% yield) being the main product.

The stereoselective synthesis of 2-chlorovinylthioarenes in good preparative yields is solved in this article.

RESULTS AND DISCUSSION

We have developed a novel two-step phase transfer catalytic (PTC) method for the preparation of (*E*)-2-chlorovinylthioarenes (or hetarenes) from thiols and 1,1,2-trichloroethane (Scheme 1). The first step included the synthesis of 2,2-dichloroethyl aryl (or hetaryl) sulfides **7–11** by the interaction of thiols **1–6** with 1,1,2-trichloroethane in the PTC system solid K_2CO_3/solid KI/18-crown-6/xylene. The use of the solid KOH in this process leads to the decomposition of the alkylating agent 1,1,2-trichloroethane. 2,2-Dichloroethyl sulfides **7–11** in the solid KOH/18-crown-6/toluene system stereoselectively afforded *E*-isomers of 2-chlorovinylthioarenes (or hetarenes) in yields up to 98%.



1 -6 **7 - 11** **12 - 16**

Ar = phenyl (**1**, **7**, **12**); 2-pyridyl (**2**, **8**, **13**); 2-pyrimidyl (**3**, **9**); 2-benzimidazolyl (**4**, **14**); 2-benzoxazolyl (**5, 10, 15**); 2-benzothiazolyl (**6, 11, 16**)

SCHEME 1

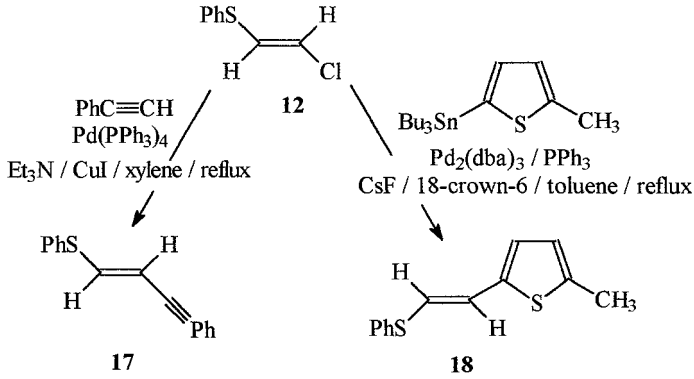
Thiophenol (**1**) smoothly reacted with 1,1,2-trichloroethane in K_2CO_3/KI/18-crown-6/xylene system giving 2,2-dichloroethylthiobenzene (**7**) in excellent yield (92%). Similar reaction of 2-mercaptopyridine, 2-mercaptopyrimidine, and 2-mercaptobenzothiazole led to the desired products in 54–58% yields. However, under described conditions 2-mercaptopyrimidine formed the sulfide **9** as the hydrochloride salt. After water addition the system has pH ~ 6. The hydrolysis of the salt by saturated aqueous solution of $NaHCO_3$ (pH ~ 9) was necessary for isolation of free base **9**. 2-(2,2-Dichloroethylthio)benzoxazole (**10**) was obtained only in 11% yield. Thus, the reactivity of thiols **5**, **6** is correlated with the electron-donating properties of the heteroatom in the ring. The benzimidazole thiol undergoes direct chlorovinylation in the system $ClCH_2CHCl_2/K_2CO_3$/KI/18-crown-6/xylene giving 2-(2-cholorovinylthio)benzimidazole (**14**) in 1% yield.

The dehydrochlorination of 2,2-dichloroethyl derivatives **7**, **8**, **10**, **11** occurred in the presence of KOH at the room temperature. The 2-chlorovinylthiohetarenes **12**, **13**, **15**, **16** were isolated in 53–98% yields. According to ^{1}H NMR spectroscopic data the dehydrochlorination step of reaction proceeded stereoselectively. The characteristic doublet of the SCH= group proton with J = 12.8–13.6 Hz indicates that all the obtained products have *E*-configuration. 2-(2,2-Dichloroethylthio)pyrimidine **9** underwent the full decomposition in the system solid KOH/18-crown-6/toluene.

The further dehydrochlorination of 2-chlorovinylthiohetarenes **12**, **13**, **15**, **16** did not occur under above described conditions and the attempts to prepare the acetylenes of the type HetSC≡CH were unsuccessful.

The synthesis of the 2-chlorovinylthiohetarenes can be realized also as one-pot process. For example, the chlorovinylation of thiophenol (**1**) readily proceeded in the system $ClCH_2CHCl_2/K_2CO_3/KI$/18-crown-6 (molar ratio $ClCH_2CHCl_2 : K_2CO_3 : KI$: 18-crown-6 = 1 : 2.2 : 3 : 2 : 0.1) in xylene with the subsequent treatment of reaction mixture with 4 equivalents of solid KOH. *E*-2-Chlorovinylthiobenzene **12** was obtained in 88% yield.

The synthesized 2-chlorovinylthioarenes can be used in the stereoselective synthesis of different *E*-2-substituted vinyl sulfides (Scheme 2).



SCHEME 2

The utilization of *E*-2-chlorovinylthiobenzene (**12**) in the system PhC≡CH/$Pd(PPh_3)_4$/CuI/Et_3N/xylene afforded Heck type reaction[15] product **17** in 43% yield. The Stille reaction[16] of 2-chlorovinylthiobenzene **12** with 2-methyl-5-tributylstannylthiophene in the $Pd_2(dba)_3$/PPh_3/CsF/18-crown-6/toluene system gave stereoselectively *E*-isomer of 1-phenylthio-2-(5-methyl-2-thienyl)ethene in 42% yield. High

efficiency of above system was recently demonstrated in the synthesis of unsymmetric diynes.[17]

EXPERIMENAL

^{1}H and ^{13}C NMR spectra were recorded on a Varian 200 Mercury spectrometer (200 MHz) using $CDCl_3$ as a solvent and HMDSO as the internal standard. Mass spectra were registered on a GC-MS HP 6890 (70 eV) apparatus. GC analysis was performed on a Chrom-5 instrument equipped with a flame-ionization detector using a glass column packed with 5% OV-101/Chromosorb W-HP (80–100 mesh, 1.2 m × 3 mm). Thiols **1–6**, 1,1,2-trichloroethane, 18-crown-6 and palladium catalysts (Acros) were used without purification.

General Method of Synthesis of 2,2-Dichloroethylthioarenes(or Hetarenes) 7–11

2,2-Dichloroethylthiobenzene (7)

1,1,2-Trichloroethane (4.1 ml, 44 mM) was added under stirring to the mixture of thiophenol (2.20 g, 20 mM), K_2CO_3(8.28 g, 60 mM), KI (6.64 g, 40 mM), and 18-crown-6 (528 mg, 2 mM) in 25 ml of xylene. The reaction mixture was refluxed 2 h (GC-MS control), cooled, and filtered. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography using hexane: ethyl acetate (5 : 1) as eluent. Yield of **7** was 3.8 g (98%). Compounds **8–10** (see Table I) were similarly prepared.

General Method of Synthesis of *E*-2-Chlorovinylthioarenes (or Hetarenes) 12, 13, 15, 16

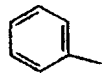
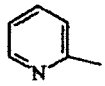
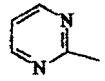
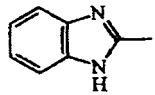
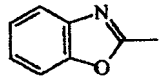
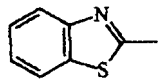
2-Chlorovinylthiobenzene (12)

Finely powdered KOH (1.12 g, 10 mM) was added to the solution of **7** (2.07 g, 10 mM) and 18-crown-6 (264 mg, 1 mM) in 25 ml of toluene. Reaction mixture was stirred 45 min (GC-MS control) at room temperature, filtered, and evaporated. The residue was purified by column chromatography using hexane: toluene (2 : 1) as eluent. The yield of **12** was 1.67 g (98%). Compounds **13–16** (see Table I) were similarly prepared.

One-Pot Synthesis of *E*-2-Chlorovinylthiobenzene (12) from Thiophenol (1)

1,1,2-Trichloroethane (4.1 ml, 44 mM) was added under stirring to a mixture of thiophenol (2.20 g, 20 mM), K_2CO_3 (8.28 g, 60 mM), KI

TABLE I Synthesis of Dichloroethyl **7–11** (ArSH: $ClCH_2CHl_2$: K_2CO_3 : KI : 18-crown-6 = 1 : 2.2 : 3 : 2 : 0.1) and Chlorovinyl **12–16** ($ArSCH_2CHCl_2$: KOH : 18-crown-6 = 1 : 3 : 0.1) Derivatives

No.	Ar	Alkylation, h	No.	Yield of $ArSCH_2CHCl_2$, %	Dehydrochlorination, h	No.	Yield of, $ArSCH{=}CHCl$, %
1		2.0	**7**[a]	92	2.0	**12**[a]	98
2		2.0	**8**	58	5.0	**13**	69
3		6.0	**9**	55	2.5	—	0
4		4.0	—	—	—	**14**	1[b]
5		11.0	**10**	11	2.0	**15**	53
6		5.0	**11**	54	0.7	**16**	95

[a] **7** and **12** were prepared previously.[14]

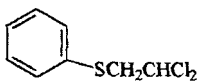
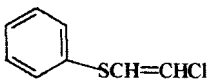
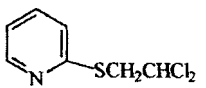
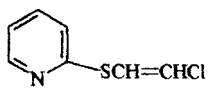
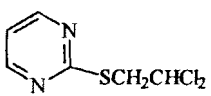
[b] The benzimidazole thiol undergoes direct chlorovinylation in the system $ClCH_2CHCl_2$/K_2CO_3/KI/18-crown-6/xylene.

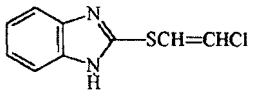
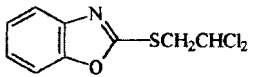
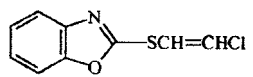
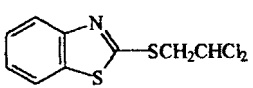
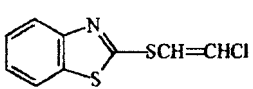
(6.64 g, 40 mM), and 18-crown-6 (528 mg, 2 mM) in 25 ml of xylene. The reaction mixture was refluxed 2 h (GC-MS control) and cooled. Finely powdered KOH (4.48 g, 80 mM) was added to the reaction mixture under vigorous stirring. The reaction mixture was stirred 7 h (GC-MS control) at room temperature, filtered, and evaporated. The residue was purified by column chromatography using hexane : toluene (2 : 1) as eluent. The yield of **12** was 3.0 g (88%).

Palladium Catalyzed Synthesis of *E*-1-henylthio-4-phenylbut-1-en-3-yne (17)

Tetrakis(triphenylphosphine) palladium (58 mg, 0.05 mM) was added at room temperature under an argon atmosphere to a solution of **12** (170 mg, 1 mM) in xylene (1 ml). The mixture was stirred for an additional 45 min. A solution of phenylacetylene (102 mg, 1 mM) in triethylamine (303 mg, 3 mM) was added followed by copper iodide (20 mg, 0.1 mM). The reaction mixture was refluxed 10 h, phenyl acetylene

TABLE II MS, ^{1}H, and ^{13}C NMR Spectroscopic Data of 2,2-Dichloroethyl and 2-Chlorovinyl Sulfides **7–16**

No.	Compound	MS, m/z (I, %)	^{1}H NMR, δ ppm	^{13}C NMR, δ ppm
7		206 (M^+, 27), 123 (M^+-$CHCl_2$, 100), 109 (PhS, 27), 65 (12), 45 (12)	3.56 (d, 2H, J = 6.4 Hz, SCH_2); 5.60 (t, 1H, J = 6.4 Hz, $CHCl_2$); 7.20–7.49 (m, 5H, Ph)	47.2 (SCH_2); 71.0 ($CHCl_2$); 127.8; 129.0; 129.3; 131.4; 133.3
12		170(M^+, 50), 135(M^+-Cl, 100), 134(56), 109(18), 91(41), 69(12), 51(18)	6.27 (d, 1H, J = 12.8 Hz, SCH); 6.56 (d, 1H, J = 12.8 Hz, CHCl); 7.23–7.34 (m, 5H, Ph)	120.3; 125.5; 126.0; 126.8; 127.2; 129.2; 129.5; 134.0
8		207 (M^+, 10), 174 (32), 172 (M^+-Cl, 85), 136 (61), 124 (17), 111 (100), 78 (44), 67 (16), 51 (15)	3.90 (d, 2H, J = 6.4 Hz, SCH_2); 5.99 (t, 1H, J = 6.4 Hz, $CHCl_2$); 6.00–7.26 (m, 2H, H-3, H-5); 7.40–7.60(m, 1H, H-4); 8.38–8.48 (m, 1H, H-6)	42.1(SCH_2); 71.7 ($CHCl_2$); 120.1; 122.3; 136.3; 149.6; 156.4
13		171 (M^+, <1), 136 (M^+-Cl, 100), 111 (2), 92 (5), 78 (18), 67 (4), 57 (5), 51 (8)	6.45 (d, 1H, J = 13.6 Hz, SCH); 7.06 (d, 1H, J = 13.6 Hz, CHCl); 7.0–7.10 (m, 1H, H-5); 7.14–7.25 (m, 1H, H-3); 7.50–7.59 (m, 1H, H-4); 8.43–8.47 (m, 1H, H-6)	120.5; 120.7; 121.7; 122.5; 136.6; 149.8; 157.0
9		208 (M^+, 7), 175 (18), 173 (M^+-Cl, 52), 137 (63), 125 (32), 112 (100), 98 (21), 85 (13), 79 (23), 61 (15), 58 (27), 57 (30), 53 (31)	3.86 (d, 2H, J = 6.4 Hz, SCH_2); 5.99 (t, 1H, J = 6.4 Hz, $CHCl_2$); 7.03 (t, 1H, J = 5Hz, H-5); 8.54 (d, 2H, J = 5Hz, H-4, H-6)	43.2 (SCH_2); 71.1 ($CHCl_2$); 117.2; 157.6

14		175 (M^+-Cl, 100), 150 (10), 149 (10), 133 (10), 131 (13), 122 (11), 91 (10), 64 (12), 63 (11), 39 (10)	6.54 (d, 1H, J = 13.2 Hz, SCH); 6.87 (d, 1H, J = 13.2 Hz, CHCl); 7.22–7.26 (m, 2H, H-5, H-6); 7.53–7.58 (m, 2H, H-4, H-7); 8.50 (bs, 1H, NH)	114.6; 120.2; 123.0; 124.6; 139.2; 146.8
10		247 (M^+, 14), 212 (M^+-Cl, 12), 151 (100), 150 (20), 122 (47), 63 (15)	3.95 (d, 2H, J = 6.4 Hz, SCH_2); 6.16 (t, 1H, J = 6.4 Hz, $CHCl_2$); 7.22–7.33 (m, 2H, H-5, H-6); 7.40–7.45 (m, 1H, H-7), 7.56–7.60 (m, 1H, H-4)	43.8 (SCH_2); 70.2 ($CHCl_2$); 110.1; 118.7; 124.3; 124.6; 128.3; 152.1; 162.7
15		211 ((M^+, 5), 177 (10), 176 (M^+-Cl, 100), 122 (20), 63 (17)	6.64 (d, 1H, J = 13.2 Hz, SCH); 6.97 (d, 1H, J = 13.2 Hz, CHCl); 7.24–7.32 (m, 2H, H-5, H-6); 7.43–7.49 (m, 1H, H-7); 7.60–7.67 (m, 1H, H-4)	110.1; 118.5; 118.9; 124.5; 124.6; 124.8; 141.6; 151.9; 161.3
11		263 (M^+, 8), 228 (15), 168 (11), 167 (M^+-Cl, 100), 166 (27), 122 (9), 108 (17), 69 (8)	4.04 (d, 2H, J = 6.4 Hz, SCH_2); 6.17 (t, 1H, J = 6.4 Hz, $CHCl_2$); 7.22–7.46 (m, 2H, H-5, H-6); 7.72–7.76 (m, 1H, H-7), 7.84–7.88 (m, 1H, H-4)	44.6 (SCH_2); 70.7 ($CHCl_2$); 121.1; 127.8; 124.7; 126.2; 135.4; 152.7; 164.13
16		227 (M^+, 2), 193 (13), 192 (M^+-Cl, 100), 148 (8), 108 (7)	6.69 (d, 1H, J = 13.2 Hz, SCH); 6.96 (d, 1H, J = 13.2 Hz, CHCl); 7.28–7.49 (m, 2H, H-5, H-6); 7.74–7.82 (m, 1H, H-7); 7.87–7.94 (m, 1H, H-4)	120.6; 121.0; 122.1; 124.7; 126.4; 128.3; 135.4; 153.4; 164.4

(102 mg, 1 mM) was once more added, and then refluxed for an additional 10 h (GC-MS control), cooled to the room temperature, filtered, and isolated by column chromatography, using hexane as eluent. Product **17** was isolated in 42% yield (100 mg). M.p. 80–81°C.

MS (I_{rel}, %) m/z: 236 (M^+, 100), 235 (57), 234 (42), 221 (18), 203 (21), 202 934), 191 (21), 1134 (11), 126 (17), 121 (26), 115 (33), 89 (12), 77 (27), 63 (13), 51 (35), 39 (13).

^{1}H NMR ($CDCl_3$/HMDSO) δ ppm: 6.28 and 6.57 (both d, 2H, J = 12.8 Hz, CH=CH); 7.34 (m, 3H, Ph); 7.52 (m, 2H, Ph).

^{13}C NMR ($CDCl_3$) δ ppm: 73.9 and 81.5 (C≡C); 121.8 (SC); 127.2 (PhCH); 128.2; 128.3; 128.4; 129.2; 129.5; 131.6; 132.5.

Palladium Catalyzed Synthesis of *E*-1-phenylthio-2-(5-methyl-2-thienyl)ethene (18)

The mixture of **12** (170 mg, 1 mmol), tris(dibenzylideneacetone)dipalladium (0) (13.7 mg, 0.015 mM), and triphenylphosphine (15.7 mg, 0.06 mM) in toluene (1.5 ml) were stirred for 5 min in an atmosphere of argon at room temperature. 18-Crown-6 (26 mg, 0.1 mM), dry cesium fluoride (334 mg, 2.2 mM), and 2-methyl-5-tributylstannylthiophene (273 mg, 1 mmol) were added to the reaction mixture under stirring under argon. The reaction was carried out under vigorous stirring at reflux temperature for 20 h with GC-MS control, cooled, filtered, and isolated by column chromatography using hexane:ethyl acetate (1 : 1) as eluent in 43% yield (106 mg).

MS (I_{rel}, %) m/z: 232 (M^+, 100), 217 (M^+-Me, 14), 199 (17), 187 (33), 185 (31), 173 (13), 153 (15), 140 (12), 121 (54), 111 (32), 97 (10), 77 (30), 51 (30), 39 (18).

^{1}H NMR ($CDCl_3$/HMDSO) δ ppm: 2.44 (s, 3H, Me); 6.54 (d, 1H, J = 15.3 Hz, thienyl-CH); 6.60 (d, 1H, J = 2.4 Hz, H-4); 6.71 (d, 1H, J = 2.4 Hz, H-3); 6.80 (d, 1H, J = 15.3 Hz, SCH); 7.31–7.4 (m, 5H, Ph).

^{13}C NMR ($CDCl_3$) δ ppm: 15.5 (Me); 120.3 (SC); 125.3 (C-thienyl); 125.5; 126.7; 126.9; 129.1; 134.9; 135.5; 139.2; 139.4.

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