A Novel Route to the Synthesis of α-Arylselenosubstituted Carbonyl Compounds and Nitriles

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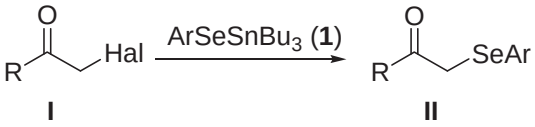
(Received June 27, 2005; CL-050820)

Activated alkyl halides such as α-halocarbonyl compounds and α-halonitriles easily react with tributyltin arylselenides both in fluoride-mediated reaction and without any additives. The former protocol gives corresponding selenides under the mild conditions in near quantitative yields.

Trialkyltin arylselenides $ArSeSnAlk_3$[1] **1** proved to be excellent sources of ArSe-group in cross-coupling reactions catalyzed by transition metal complexes,[2] non-catalytic reactions with arene diazonium salts,[2b,2d] fluoride-mediated nucleophilic substitution in activated aryl fluorides[3] and alkyl halides,[2d] in reactions with acyl halides,[4] epoxides,[5] and acetals.[6] It followed from the literature data that tin selenides **1** are species of high reactivity. Thus it was rather unexpected that the reaction of activated halides **I** required Pd catalysis (Scheme 1).[4b]

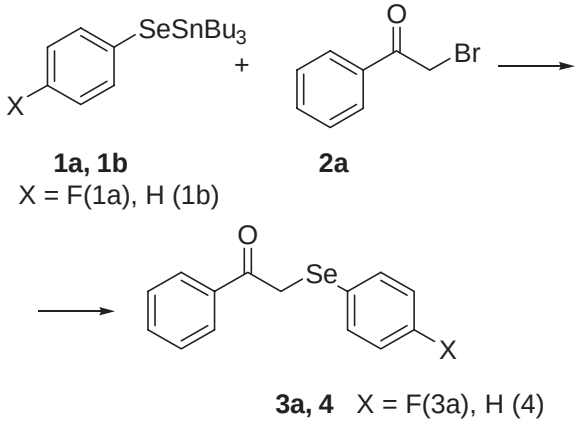


I **II**

Scheme 1.

Because of a significant synthetic value of selenides **II**[7] we undertook a study of this reaction under non-catalytic conditions. The reaction of α-bromoacetophenone **2a** with **1a** (Scheme 2) gives selenide **3a** in almost quantitative yield after 3 h of heating in acetonitrile (Table 1, No. 1).

Earlier we showed that addition of fluoride ions significantly accelerated the reaction of alkyl halides with tin selenides **1**.[2d] Here, we have found that the use of KF in the presence of TEBACl allows the reaction to proceed under the significantly milder conditions. In this case, the substitution was complete



Scheme 2.

Table 1. Reaction of α-bromoacetophenone (**2a**) with tin selenides under different conditions (Scheme 2)

No.	[SnSe]	Solv.	Additives	Time /h	T /°C	Yield /%
1	**1a**	MeCN	—	3	81	98[a]
2	**1a**	MeCN	2 equiv. KF, 10 mol % TEBACl[b]	1.5	20	99[a]
3	**1a**	CH_2Cl_2	2 equiv. KF, 10 mol % TEBACl	1	20	99[a]
4	**1b**[4b]	Toluene	5 mol % $Pd(PPh_3)_4$	6	80	90[c]
5	**1a**	Toluene	—	18	80	92[a]

[a]According to ^{19}F NMR. [b]TEBACl: triethylbenzylammonium chloride. [c]According to GLC.

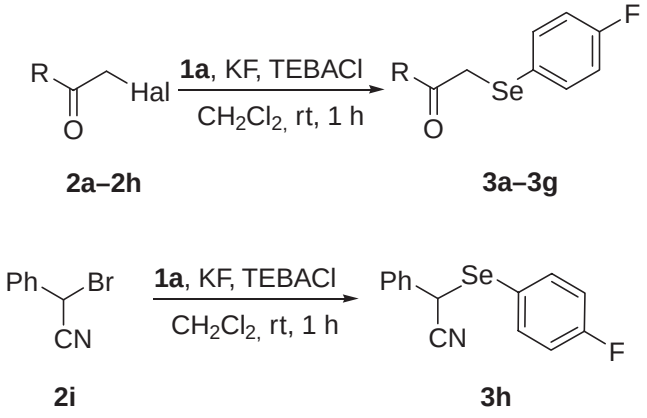
after 1–1.5 h at room temperature in polar solvents such as MeCN (Table 1, No. 2) and CH_2Cl_2 (Table 1, No. 3) to afford **3a** in almost quantitative yield. For comparison, the Pd-catalyzed reaction in toluene[4b] gives the same result as the reaction in acetonitrile (Table 1, Nos. 1 and 4). Without catalyst in toluene reaction proceeds very slow (Table 1, No. 5). For further investigations we preferred dichloromethane due to a higher solubility of tin selenide **1a** in it.

Under the optimized conditions a number of halogenides **2a**–**2i** containing both α-carbonyl- and α-CN-group were introduced into the reaction (Scheme 3), the latter being monitored by ^{19}F NMR spectroscopy.

In all cases (Table 2), the corresponding selenides **3a**–**3i** were obtained in excellent yields. Contrary to results published earlier[4b] we have shown that under our conditions, yields of **3** are almost independent on the nature of halide **2**. Whereas the Pd-catalyzed coupling of 4-methoxyphenacyl bromide **2c** with $PhSeSnBu_3$ requires 6 h at 110 °C for completion and furnished the corresponding selenide in moderate yield (43%),[4b] the fluoride-assisted reaction with $4\text{-}FC_6H_4SeSnBu_3$ gives **3c** in 96% yield after 1 h at room temperature (Table 2, No. 3). Similarly, when ethyl chloroacetate **2f** used instead of ethyl bromoacetate **2e** the yield of ethyl 4-fluorophenylselenoacetate **3e** remained almost the same (Table 2, Nos. 5 and 6) in contrast to Pd-catalyzed reaction[4b] where the application of α-chloroacetophenone instead of α-bromoacetophenone drastically decreased the yield.

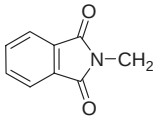
The authors of publication[4b] reported that they failed to reproduce the results described by us for the reaction of Bu_3Sn-SeAr with acyl chlorides RCOCl.[4a] According to their data, the yield in non-catalytic version of this reaction did not exceed 24%. We have repeated our experiments and confirm that under the stated conditions (chloroform, room temperature) the reaction produces the corresponding selenoester in 92–98% yield.

In conclusion, we have developed a new efficient method



Scheme 3.

Table 2. Synthesis of α-arylselenosubstituted carbonyl compounds and nitriles (Scheme 3)[a]

No.	R	Hal		Product	Yield/%
1	Ph	Br	**2a**	**3a**	97
2	4-FC_6H_4	Br	**2b**	**3b**	96
3	4-$MeOC_6H_4$	Br	**2c**	**3c**	96
4	4-$NO_2C_6H_4$	Br	**2d**	**3d**	97
5	EtO	Br	**2e**	**3e**	99
6	EtO	Cl	**2f**	**3e**	97
7	Me	Cl	**2g**	**3f**	97
8		Cl	**2h**	**3g**	96
9	Ph(CN)CH-	Br	**2i**	**3h**	97

[a]Reaction conditions: KF (2 mmol), **1a** (1.05 mmol), **2** (1.0 mmol), and 10 mol % (0.1 mmol) TEBACl in 2 mL of CH_2Cl_2 under Ar.

for the synthesis of α-selenocarbonyl and α-selenonitrile compounds based on the fluoride-mediated reaction of tributyltin arylselenides with the corresponding halides. This reaction proceeds under mild conditions with excellent yields of the products.

This work was supported by Russian Foundation for Basic Research (No. 05-03-32941).

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8 Typical procedure: KF (2 mmol) was added to a mixture of **1a** (1.05 mmol), **2** (1.0 mmol), and 10 mol % (0.1 mmol) TEBACl in 2 mL of CH_2Cl_2 under Ar. The reaction mixture was stirred 1 h at room temperature, precipitated Bu_3SnF filtered off and the solvent was removed in vacuo. The resulting crude product was purified by column chromatography (SiO_2, hexane or hexane/EtOAc–9:1) to give **3**. **3a**: ^{1}H NMR (400 MHz, $CDCl_3$), δ 4.44 (s, 2H, CH_2), 7.14 (m, 2H), 7.53 (m, 4H), 7.64 (m, 1H), 7.96 (m, 2H); ^{19}F NMR ($CDCl_3$), δ −1.94; ^{77}Se NMR ($CDCl_3$), δ −139.5. **3b**: ^{1}H NMR (400 MHz, $CDCl_3$), δ 4.43 (s, 2H, CH_2), 7.14 (m, 2H), 7.33 (m, 2H), 7.53 (m, 2H), 8.05 (m, 2H); ^{19}F NMR ($CDCl_3$), δ −1.67, 6.32; ^{77}Se NMR ($CDCl_3$), δ −134.8. **3c**: ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.82 (s, 3H, CH_3O), 4.06 (s, 2H, CH_2), 6.90 (m, 4H), 7.47 (m, 2H), 7.81 (m, 2H); ^{19}F NMR ($CDCl_3$), δ −2.29; ^{77}Se NMR ($CDCl_3$), δ −138.3. **3d**: ^{1}H NMR (400 MHz, $CDCl_3$), δ 4.85 (s, 2H, CH_2), 7.14 (m, 2H), 7.53 (m, 2H), 8.08 (d, 2H, J = 8.72 Hz), 8.34 (d, 2H, J = 8.72 Hz); ^{19}F NMR ($CDCl_3$), δ −1.42; ^{77}Se NMR ($CDCl_3$), δ −133.1. **3e**: ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.09 (t, 3H, $\mathbf{C}H_3CH_2O$, J = 7.16 Hz), 3.35 (s, 2H, $^2J_{H-Se}$ = 14.3 Hz); 4.01 (q, 2H, $CH_3C\mathbf{H}_2O$, J = 7.17 Hz), 6.89 (m, 2H), 7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 9.93 ($\mathbf{C}H_3CH_2O$), 24.04 ($CH_3\mathbf{C}H_2O$), 57.13 (CH_2Se, $^1J_{C-Se}$ = 124.9 Hz), 110.5 (d, C, $^4J_{C-F}$ = 2.5 Hz), 112.2 (d, CH, J_{C-F} = 21.9 Hz), 132.2 (d, CH, J_{C-F} = 7.6 Hz), 158.2 (d, C, $^1J_{C-F}$ = 248.0 Hz), 166.60 (CO); ^{19}F NMR ($CDCl_3$), δ −2.52; ^{77}Se NMR ($CDCl_3$), δ −130.6. **3f**: ^{1}H NMR (400 MHz, $CDCl_3$), δ 2.22 (s, 3H, CH_3), 3.50 (s, 2H, CH_2), 6.93 (m, 2H), 7.46 (m, 2H); ^{19}F NMR ($CDCl_3$), δ −2.22; ^{77}Se NMR ($CDCl_3$), δ −149.1. **3g**: ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.54 (s, 2H, CH_2), 4.67 (s, 2H, CH_2), 6.88 (m, 2H), 7.52 (m, 2H), 7.60 (s, 2H), 7,71 (s, 2H); ^{19}F NMR ($CDCl_3$), δ −1.28; ^{77}Se NMR ($CDCl_3$), δ −134.6. **3h**: ^{1}H NMR (400 MHz, $CDCl_3$), δ 4.87 (s, 1H, CH), 6.88 (m, 2H), 7.42 (m, 1H), 7.49 (m, 2H), 7.55 (m, 2H), 7.62 (m, 2H); ^{19}F NMR ($CDCl_3$), δ −1.34; ^{77}Se NMR ($CDCl_3$), δ −138.2.

Published on the web (Advance View) September 10, 2005; DOI 10.1246/cl.2005.1348