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Preparation of α-Arylseleno-substituted Zinc and Copper Organometallics and their Application in the Synthesis of α-Arylselenomethyl Ketones†

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α-Arylseleno-substituted zinc and copper organometallics, prepared by zinc insertion into the carbon–chlorine bond of α-chloromethyl aryl selenides and with CuCN–2LiCl transmetallation to the corresponding copper reagents, react with acyl chlorides to give α-arylselenomethyl ketones based on the formation of a new carbon–carbon bond.

Organolithiums bearing a selenium-stabilized carbanion have played an important role in organic synthesis.[1] They easily convert the selenium group into various other functionalities and allow the synthesis of more complex organoselenium compounds with concomitant formation of a new carbon–carbon bond. However, the high reactivity of these reagents prohibits the presence of most functional groups in these organometallics. In addition, the high thermal instability means that their preparations and reactions can be carried out only at low temperature (usually −78 °C). Herein, we report a new approach to α-selenocarbanions of zinc and copper, which complement the known organolithium reagents.

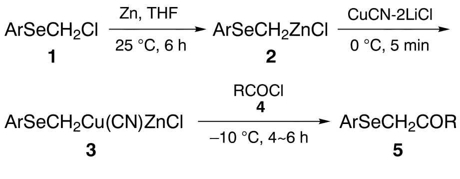
Knochel *et al.*[2] found that, in the zinc organometallics undergoing insertion, oxygen and sulfur functional groups at the α position could not only be tolerated, but also both atoms could considerably facilitate the insertion of zinc into a carbon–halide bond. We have now observed that a selenium atom exerts a similar effect and allows insertion of zinc into an adjacent carbon–chlorine bond. Thus, the treatment of an α-chloromethyl phenyl selenide **1** with zinc dust (activated *in situ* with 1,2-dibromoethane and chlorotrimethylsilane) in THF at 25 °C for 6 h provides the corresponding organozinc chloride **2** in good yield (75%) (Scheme 1). In contrast, it was found that α-chloroalkyl alkyl selenides such as chloromethyl butyl selenide do not insert zinc under the similar conditions. Comasseto *et al.*[3] have reported an α-methylseleno ethenyl zinc organometallic prepared by insertion of zinc (powder) into a sp[2] carbon–iodine bond. However, its low reactivity to organic electrophiles and the poor stereoselectivity of the products limited its application. By the addition of CuCN–2LiCl, organozinc chlorides **2** can easily be converted into the copper organometallics **3**, which can be anticipated to be more useful in the synthesis of selenium-containing compounds.

α-Phenylseleno carbonyl compounds are important synthetic intermediates with a wide range of utilities in organic synthesis.[4] They have been used for regioselective introduction of various functional groups by displacing the phenylseleno group, especially for stereoselective transformation of carbon–carbon double bonds *via* the well established *syn*-elimination process. A selenium functional group is usually introduced into a molecule by the attack of electrophilic organoselenium reagents (such as PhSeBr, PhSeCl) on enols and ketones,[5] olefins[6] or acetylenes,[7] or by the substitution of nucleophilic organoselenium reagents (such as PhSeNa, $PhSeSmI_2$) for α-halogenated ketones.[8] In addition, the direct insertion of diazomethane into selenoesters[9] is also a good synthetic method. However all these methods are founded on the formation of a carbon–selenium bond. In our experiments the copper organometallics **3** can react smoothly with acyl chlorides **4** to afford a series of α-arylseleno methyl ketones **5** based first on the formation of a carbon–carbon bond (Scheme 1). The results are summarized in Table 1.

Table 1 α-Arylselenomethyl ketones

Compound	Ar	R	Reaction time/h	Yield (%)[a]
5a	Ph	Ph	4	75
5b	Ph	Me	6	85
5c	p-MeC_6H_4	Ph	4	80
5d	Ph	p-ClC_6H_4	4	70
5e	Ph	p-BrC_6H_4	4	76
5f	p-MeC_6H_4	Me	6	83
5g	Ph	$Me[CH_2]_3CH_2$	6	82

[a] Isolated yields of pure products.



Scheme 1 Ar = Ph, p-MeC_6H_4; R = Ph, p-ClC_6H_4, p-BrC_6H_4, Me, $Me[CH_2]_3CH_2$

In conclusion, zinc α-selenocarbanions can be conveniently prepared under mild conditions. Besides their high thermal stability (no decomposition at 25 °C under an inert atmosphere for 30 h), they can be efficiently transmetallated to zinc–copper reagents, which display an excellent reactivity toward acyl chlorides affording α-arylselenomethyl ketones depending on the formation of a carbon–carbon bond.

Experimental

^1H NMR spectra were recorded in CCl_4 on a JEOL PMX 60si spectrometer using hexamethyldisiloxane (HMDSO) as internal standard. Chemical shifts are reported as δ in units of parts per million (ppm). IR spectra were obtained on a PE683 spectrometer. THF was distilled from sodium–benzophenone immediately before use. Chloromethyl selenides were prepared according to the literation.[10] Acyl chlorides were redistilled prior to use. The remaining chemicals were obtained from commercial sources. All reactions were performed under a nitrogen atmosphere.

General Procedure for Preparation of α-Phenylselenomethylzinc Chlorides **2**.—A dry three-necked flask equipped with a magnetic stirring bar and a thermometer under nitrogen was charged with zinc dust (0.19 g, 3 mmol) and flushed three times with nitrogen. 1,2-Dibromoethane (0.02 g, 0.1 mmol) in THF (2 ml) was then added. The resulting zinc suspension was gently heated to boiling and then cooled again to room temperature. The same activation process was repeated twice and chlorotrimethylsilane (0.02 g,

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Table 2 Spectral data for compounds **5a**–**5g** (all oils)

Compound	^{1}H NMR	IR
5a α-Phenylselenoacetophenone[5c]	3.98 (s, 2 H), 7.07–7.52 (m, 8 H), 7.67–7.93 (m, 2 H)	3085, 2940, 2865, 1685, 1605, 1590, 1485, 1450, 1275, 1010, 715, 700, 685
5b α-Phenylselenoacetone[5c]	2.13 (s, 3 H), 3.41 (s, 2 H), 7.13–7.63 (m, 5 H)	3080, 2940, 1715, 1585, 1485, 1360, 1230, 1020, 690, 675
5c α-(*p*-Methylphenyl)selenoacetophenone[8b]	2.24 (s, 3 H), 3.92 (s, 2 H), 6.94, 7.03 (d, 2 H), 7.32–7.46 (m, 5 H), 7.72–7.90 (m, 2 H)	3040, 2940, 2860, 1685, 1605, 1590, 1475, 1450, 1275, 1010, 740, 700, 680
5d *p*-Chloro-α-phenylselenoacetophenone[8b]	3.93 (s, 2 H), 7.10–7.43 (m, 7 H), 7.63–7.85 (m, 2 H)	3080, 2970, 2940, 2870, 1685, 1600, 1580, 1490, 1275, 1090, 1010, 735, 685
5e *p*-Bromo-α-phenylselenoacetophenone[8b]	3.93 (s, 2 H), 7.06–7.65 (m, 9 H)	3080, 2940, 2860, 1685, 1595, 1485, 1270, 1070, 1000, 750, 680
5f α-(*p*-Methylphenyl)selenoacetone[9]	2.08 (s, 3 H), 2.24 (s, 3 H), 3.35 (s, 2 H), 6.93 (d, 2 H), 7.28 (d, 2 H)	3080, 2940, 2870, 1715, 1475, 1360, 1230, 1035, 740
5g 1-Phenylselenoheptan-2-one[5e]	0.83 (t, 3 H), 1.06–1.77 (m, 6 H), 2.46 (t, 2 H), 3.40 (s, 2 H), 7.06–7.46 (m, 5 H)	2970, 2940, 2880, 1710, 1590, 1485, 1020, 730, 685

0.1 mmol) added. After 10 min of stirring at room temperature, α-chloromethyl phenyl selenide (0.21 g, 1 mmol) in THF (2 ml) was added dropwise over 10 min. The mixture was stirred for 6 h at 25 °C. The reaction was monitored and the yield estimated by ^{1}H NMR analysis of hydrolysed aliquots. After 6 h the peak at δ 4.77 (s, $\mathrm{PhSeC}H_2\mathrm{Cl}$) disappeared and that at δ 2.23 (s, $\mathrm{PhSeC}H_3$) reached a maximum, approximately 75% yield. The excess of zinc was allowed to settle and the resulting clear solution was ready to use for further transformation.

Conversion of Seleno-substituted Organozinc Chlorides **2** *into the Corresponding Copper Reagents* **3**.—A dry flask equipped with a magnetic stirring bar under nitrogen was charged with lithium chloride (0.085 g, 2.0 mmol; previously dried under vacuum at 130 °C for 2 h) and copper cyanide (0.087 g, 1.0 mmol) and flushed three times with nitrogen. The mixture was dissolved in dry THF (2 ml). The resulting yellowish solution was cooled to −78 °C and the zinc reagent **2**, prepared as described above, was slowly added *via* cannula. The reaction mixture was allowed to warm to 0 °C for 5 min and then cooled again to −78 °C. Acyl chloride (0.6 mmol) was added and the mixture allowed to warm to −10 °C and maintained at this temperature for 4 h in the case of the aryl-substituted acyl chlorides, for 6 h in the case of alkyl-substituted acyl chlorides. Then the mixture was treated with a saturated solution of NH_4Cl (10 ml) and NH_4OH (10 ml), extracted with diethyl ether (20 ml × 2) and the organic layer washed with brine and dried with $MgSO_4$. The solvents were evaporated and the product separated from the residue through preparative TLC (silica gel) with cyclohexane–ethyl acetate (20:1) as eluent. Yields are indicated in Table 1. For physical and spectral data see Table 2.

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