(Phenylseleno)acetic acid based precursor for the regiospecific synthesis of 1-phenylseleno-2-alkanones

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ABSTRACT
A new procedure for the regiospecific synthesis of 1-(phenylseleno)alkan-2-ones starting from (phenylseleno)acetic acid has been developed. When (phenylseleno)acetyl chloride, generated from the corresponding acid, was allowed to react with phenylthio(alkyl)cuprate(I) reagents, 1-(phenylseleno)alkan-2-ones were obtained in fair to good yields.

GRAPHICAL ABSTRACT

INTRODUCTION
α-Phenylselenenyl ketones are versatile intermediates in organic synthesis, particularly for the introduction of unsaturated functions via mild syn-elimination of the corresponding selenoxide.[1] On the other hand, only a few studies have been reported on the synthetic use of 1-(phenylseleno)alkan-2-ones 1. These compounds cannot undergo classical syn-elimination, however, they are particular organoseleno intermediates that can be reduced to the corresponding β-hydroxy selenides[2] (path a, Fig. 1) as well as regiospecifically alkylated in the presence of a base[3] or through its silyl enol ether derivative[4] by virtue of the stabilizing effect of the neighboring phenylseleno group (path b, Fig. 1). Lewis acids, such as titanium tetrachloride[5] or BF₃, have been found efficient in promoting stereoselective cross-aldol reactions of 1-(phenylseleno)alkan-2-ones with various aldehydes (path c, Fig. 1).[6] Moreover, γ,δ-unsaturated 1-(phenylseleno)alkan-2-ones were employed as precursors of radical intermediates to promote carbocyclization reactions (path d, Fig. 1).[7] N-Allyl-β-aminoalkyl phenyl selenides could also be prepared by the sodium cyanoborohydride reduction of N-allylimines of 1-(phenylseleno)alkan-2-ones (path e, Fig. 1).[8] Finally, α-arylation of 1 with electron-rich arenes has been recently
achieved under organic photoredox catalysis (path f, Fig. 1). In addition to their synthetic versatility, a specific series of \( \alpha \)-phenylseleno ketones has been shown to possess Glutathione peroxidase-like biological properties.

While a number of procedures are accessible to provide \( \alpha \)-phenylseleno ketones from cyclic and alkyl aryl ketones, efficient control over the regioselectivity remains problematic for unsymmetrical ketones featuring \( \alpha \) and \( \alpha' \) carbons equally susceptible to selenenylation. So far, the available synthetic approaches to the preparation of compounds 1, are based on the formation of a C–Se or C–C bond, and they can be classified in the following main categories: the use of terminal olefins in bromophenylselenenylation-oxidation procedures (path g, Fig. 1); the direct electrophilic phenylselenenylation of methyl alkyl ketones (path h, Fig. 1); the oxidation of \( \beta \)-hydroxy selenides, obtained by addition of Grignard reagents to phenylseleno acetaldehyde (path i, Fig. 1); the homologation of phenylseleno esters with diazomethane (path i, Fig. 1); and the reaction of Weinreb amides (path m, Fig. 1) with lithium substituted \( \alpha \)-phenylseleno carbanion. Furthermore, some other synthesis of 1-(phenylseleno)alkan-2-one have also been reported in the literature, involving the hydroboration-oxidation of alkynylphenylselenide, the electrophilic phenylselenenylation of a regioselectively formed enolsilyl ether intermediate, the formal substitution of \( \alpha \)-halomethyl ketones with tributylstannyl phenylselenide, and the reaction of \( \alpha \)-phenylselenomethylzinc and copper organometallic reagents with acyl chlorides. Although the above methods can represent useful synthetic approaches to compounds 1, some of them suffer from disadvantages and drawbacks, mainly the handling of selenium reagents which are unstable to air and moisture, difficult to obtain starting materials, low regioselectivity, unsatisfying yields, and loss of versatility.

Reports from our laboratory have demonstrated the usefulness of organoselenium intermediates in organic synthesis as well as their use in the synthesis of heterocyclic compounds and derivatives of natural products. We have recently disclosed the stereoselective synthesis of substituted tetrahydrofurans, and tetrahydropyrans starting from 4-(phenylseleno)butanoic, and 5-(phenylseleno)pentanoic acids, respectively. Based on these results, we hypothesized that (phenylseleno)acetic acid could be a valuable precursor for the synthesis of 1-(phenylseleno)alkan-2-ones (Scheme 1) by the use of organometallic reagents.
Herein, we report a new connective strategy for the preparation of 1-(phenylseleno)alkan-2-ones 1 in which the (phenylseleno)acetyl chloride 3, easily obtained from the corresponding (phenylseleno)acetic acid 2, was employed as a valuable acylating agent of organometallic reagents. To the best of our knowledge, there is only one report in the literature dealing with the employment of (phenylseleno)acetyl chloride as the reagent for the preparation of 4-phenylchalcogeno allenic esters.[26] To test the feasibility of the proposed synthetic approach, we initially attempted the addition of a tetrahydrofuran solution of acyl chloride 3 to an excess of commercial methyl magnesium bromide tetrahydrofuran solution (2 equiv.), at 0°C (NaCl-ice mixture). The reaction was monitored by TLC, and the complete consumption of the starting material was observed after one hour. However, the desired ketone 1a was obtained in very low yields, together with methyl phenyl selenide as the major by-product (Table 1, entry 1). Methyl phenyl selenide was formed through the interaction between the Grignard reagent and the selenium atom. In fact, it is known that the α-phenylseleno carbonyl compounds are deselenated by nucleophiles and bases, as already reported.[27] Further efforts to increase yields in product 1a, by lowering the reaction temperature or using a slight excess (1.2 equiv.) of the Grignard reagent, were unfruitful.

Negative results were also obtained in the presence of a slight excess (1.3 equiv.) of lithiumdimethylcuprate (the Gilman’s reagent), and when a simple cuprate, obtained by treating a 1:1(mol/mol) mixture of methylmagnesium bromide with copper(I) iodide, was employed at −18°C (Table 1, entries 2 and 3). Unlikely, the use of a mixed magnesium cuprate, namely thienyl-methyl-copper(I) magnesium bromide, at −40°C, did not allow us to obtain 1a in appreciable yields (Table 1, entry 4). In that case, any possible

Table 1. Preliminary experiments and optimization of the reaction conditions.a

| Entry | Organometallic reagent (RM) | T (°C) | Time (h)b | 1a isolated yield (%) |
|-------|-----------------------------|-------|-----------|----------------------|
| 1     | MeMgBr                      | −18   | 1         | 10%d                 |
| 2     | Me₂CuLi                     | −40   | 2         | Tracesd               |
| 3     | MeMgBr + CuIi               | −18   | 2         | –                    |
| 4     | Me(2-Th)CuMgBrLi            | −40   | 4         | 17%d                 |
| 5     | Me(PhS)CuMgBrLi            | −40   | 2         | 37                   |
| 6     | Me(PhS)CuMgBrLi            | −70   | 1         | 64                   |

aAll reactions were carried out in tetrahydrofuran with 1 mmol of 3.
bTime elapsed between addition of 3 and the reaction quenching.
c2 equiv. of organometallic reagent were used.
dMethylselenobenzene was detected by GC-MS analysis.
e1.3 equiv. of organometallic reagent were used.
f1 equiv. of organometallic reagent was used.

Result and discussion

Scheme 1. Our proposed connective strategy for the synthesis of 1 (RM indicates organometallic reagents).
fragmentation of 1a and/or 3, due to the attack of the organometallic reagent onto selenium atom, and the consequent expulsion of the stabilized enolate, cannot be excluded. Furthermore, when the acyl chloride 3 reacted with phenylthio-methyl-copper(I) magnesium bromide (1 equiv.), an arylhetero(alkyl)cuprate(I) reagent, the expected phenylseleno ketone 1a was obtained in a 37% yield (Table 1, entry 5). Because of the thermal instability of the phenylthio-methyl-copper(I) magnesium bromide above $-40^\circ$C, an excess (1.3 equiv.) of the mixed cuprate reagent was then reacted with acyl chloride 3 (1 equiv.) at $-70^\circ$C in THF (Table 1, entry 6). Gratifyingly, $\alpha$-(phenylseleno)acetone 1a was isolated in good yields (63%). Various authors have been reported different methods for the synthesis of 1a, which can be obtained in 48–91% yields. Encouraged by these preliminary results, and in order to test the scope of the reaction, we explored the preparation of other 1-(phenylseleno)alkan-2-ones, starting from different phenylthio-alkyl-copper(I) reagents (Table 2).

Thus, ketone 1b was obtained in a good yield (68%), using an n-butyl lithium solution to prepare the corresponding phenylthio(butyl)copper reagent. Only three other synthetic procedures have already been reported to prepare 1b, in 64–74% yields. The use of commercially available octylmagnesium bromide, let us to obtain the phenyl-selenomethyl ketone 1c in a 59% yield. The Kuwajima oxidation of 1-decene with diphenylselenide, in the presence of $t$-butyl hydroperoxide, afforded an inseparable 9:1 mixture of 1c and $\alpha$-phenylselenodecanale, in a total 70% yield. When benzylmagnesium chloride was employed, the corresponding phenyl substituted ketone 1d was formed in a good yield (60%). This result was comparable to that reported by Back, for the reaction of a selenoester with diazomethane, in the presence of copper phenylselenide as the catalyst. It is worth noting that phenylthio group transfer from arylhetero(alkyl)copper reagents to the (phenylseleno)acetyl chloride 3, has been observed in some cases, based on the GC-MS detection of S-phenyl-(phenylseleno)thioacetate as the by-product, in the crude reaction mixture. We further observed that the reaction crude products were often contaminated by variable amounts of the corresponding esters (GC-MS detection), formed by the reaction of 3 with the lithium or magnesium alkoxide, initially present in the organometallic reagent solution. It is known, that these reagents often contain not negligible amounts of the corresponding alkoxides, resulting from the contact with oxygen. Accordingly, 1-(phenylseleno)alkan-2-one 1e was firstly obtained together with the corresponding ester, which was produced by the reaction of 3 with the magnesium alkoxide present in the Grignard reagent. In this case, chromatographic separation of the mixture was not possible. Thus, the crude product was treated with DIBAL-H, in tetrahydrofuran at $-15^\circ$C, to give the corresponding pure $\beta$-hydroxyselenenide 4 (55% yield), after column chromatography. Interestingly, the silyloxy functionalized 1-phenylseleno-2-alkanone 1f was easily obtained in an appreciable 58% yield. Our procedure was also tested using secondary alkyl Grignard reagents, e.g., the commercially available sec-butylmagnesium chloride. In that case, the reaction afforded the expected (phenylseleno)ketone 1g in good yields (72%).

It is known that organozinc reagents react with acyl chlorides, and readily form a new carbon-carbon bond in the presence of an appropriate catalyst, such as Pd(0)-complex species (Negishi cross-coupling). This evidence, prompted us to carry out a test, by reacting the acyl chloride 3 and a butylzinc chloride solution, in the presence of
Table 2. Substrate scope<sup>a</sup>.

| Entry | RM          | Ketone       | Yield (%)<sup>b</sup> |
|-------|-------------|--------------|------------------------|
| 1     | MeMgBr      | O=C=SePh     | 63                     |
| 2     | nBuLi       | O=C=SePh     | 68                     |
| 3     | nOctylMgBr  | O=C=SePh     | 59                     |
| 4     | BnMgCl      | O=Ph=C=SePh  | 60                     |
| 5     | PhCH<sub>2</sub>MgBr | OH  | 55<sup>c</sup> |
| 6     | TBDPSO<sub>3</sub>MgBr | O=C=SePh | 58                     |
| 7     | secBuMgCl   | O=C=SePh     | 72                     |

<sup>a</sup>Reaction conditions: RM (1.3 mmol), 3 (1 mmol) in tetrahydrofuran at −70 °C and quenching after 40 min.

<sup>b</sup>Isolated yield after column chromatography.

<sup>c</sup>Isolated after reduction of the crude mixture of ketone 1e and ester with DIBAL-H.

Scheme 2. Negishi type reaction to 1b.
tetrakis(triphenylphosphine)-palladium(0) (Scheme 2). Unfortunately, ketone 1b was obtained only in a poor yield (38%).

**Conclusion**

We have developed a new and regiospecific strategy for the synthesis of 1-(phenylseleno)alkan-2-ones based on the formation of a carbon-carbon bond. The easily accessible (phenylseleno)acetic acid served as a valuable precursor for the formation of carbon–carbon bonds, through the addition of different phenylthio-alkyl-copper(I) reagents to (phenylseleno)acetyl chloride. Our procedure complements the existing methodologies for the construction of $\alpha$-phenylselenenyl ketones. Further studies on this chemistry are in progress.

**Experimental**

**General procedure for the synthesis of 1a–g**

According to the protocol of Posner and Whitten,[28] a dry, 50 mL, three-neck round-bottom flask was charged with 2.5 M n-butyllithium solution (1.3 mmol), and the flask was cooled with an ice bath under argon atmosphere. A solution of thiophenol (0.14 mL, 1.3 mmol) in 4 mL of dry tetrahydrofuran was added to the cooled, stirred solution. After 15 min, copper(I) iodide (0.26 g, 1.4 mmol) was added. The resulting clear yellow solution was stirred for 10 min and then cooled to $-65/-70^\circ\text{C}$ with an acetone/dry-ice cooling bath. To the yellow suspension (some copper thiophenoxide separates from the solution), a solution of the organomagnesium or organolithium reagent (1.3 mmol) was added with a syringe. The resulting cloudy yellow-orange solution of the cuprate reagent is stirred at $-70/-60^\circ\text{C}$ for ten minutes. With a syringe, a solution of acyl chloride 3 (1 mmol) in 1 mL of anhydrous tetrahydrofuran was added dropwise, with stirring, to the cold reaction. The resulting cloudy reagent mixture was stirred for 30–40 min and then quenched by the addition of saturated ammonium chloride aqueous solution (2 mL) allowing it to reach room temperature. The copious precipitate of copper(I) thiophenoxide was separated by suction filtration and washed thoroughly with several portions of diethyl ether ($4 \times 4$ mL). After separation, the aqueous phase was extracted with three portions of diethyl ether (10 mL) and the ethereal phase was then washed with brine and dried with sodium sulfate. The solvent was removed *in vacuo* and the residue chromatographed on a silica gel column to afford the corresponding ketone 1.

**1-(Phenylseleno)decan-2-one (1c)**

According to the general procedure, the ketone 1c was obtained as a pale-yellow oil after chromatography;[31] Eluant Et$_2$O/Hex 4:96; Yield: 0.18 g (59%). $^1$H NMR (CDCl$_3$) $\delta =$ (ppm) 7.58–7.45 (m, 2H), 7.33–7.21 (m, 3H), 3.60 (s, 2H), 2.56 (t, $J = 7.4$ Hz, 2H), 1.62–1.51 (m, 2H), 1.34–1.19 (m, 10H), 0.89 (t, $J = 6.7$ Hz, 3H); $^{13}$C NMR (CDCl$_3$) $\delta =$ (ppm) 205.9, 133.2 (2 C), 129.2 (2 C), 128.9, 127.8, 40.7, 36.0, 31.8, 29.3, 29.1 (2 C), 24.0, 22.6, 14.0.
Full experimental detail, $^1$H and $^{13}$C NMR spectra. This material can be found via the “Supplementary Content” section of this article’s webpage.

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