Efficient Preparation of α,α-Dialkyl-α-(phenylselanyl)acetates and α,β-Unsaturated Esters from the Corresponding α,α-Dialkyl-α-cyanoacetates by a Lithium Naphthalenide Induced Reductive Selenenylation Process

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Abstract: An array of α,α-dialkyl-α-(phenylselanyl)acetates has been synthesized very efficiently from readily available α,α-dialkyl-α-cyanoacetates, by use of lithium naphthalenide induced reductive α-selenenylation as a key operation. Moreover, the selenyl esters thus generated in situ could be converted further, in a one-pot treatment with hydrogen peroxide and acetic acid, into the corresponding α,β-unsaturated esters in moderate to high yields. The C=C bond formation was highly regio- and/or diastereoselective in some cases.

Key words: nitriles, selenium, reductive selenenylation, lithium naphthalenide, α,β-unsaturated esters

α-(Phenylselanyl) carbonyl compounds are of considerable importance in synthetic chemistry.1 They are commonly used as starting materials for the preparation of α,β-unsaturated carbonyl derivatives1a and some other synthetically useful compounds.1b,c,2–4 Furthermore, their application as elaborated precursors in the promotion of various radical-mediated processes5 has also been described widely. In addition to their synthetic versatility, a specific series of α-(phenylselanyl) ketones and acids have been shown to exhibit antioxidant activity like that of glutathione peroxidase;6 this indicates that these compounds might have the potential to serve as anticancer, antiviral, and anti-inflammatory agents. Because of their synthetic and biological importance, it is not surprising to find that diverse strategies toward the synthesis of α-(phenylselanyl) carbonyl compounds have been reported in the past years. Among them, methodologies based on the selenenylation of enolates or enol derivatives of the corresponding carbonyl compounds appear to be the most frequently documented ones.7

We have been working on devising more powerful and versatile methods for the preparation of α-(phenylselanyl) carbonyl compounds, and have recently reported a highly efficient procedure for the preparation of α-(phenylselanyl) ketones from the corresponding α-cyano ketones.8 Our approach is based on the reductive decyanation of α-cyano ketones; reduction with lithium naphthalenide (LN) is followed by the rapid one-pot selenenylation of the resulting enolates with phenylselenyl bromide (PhSeBr);

this gives the corresponding α-(phenylselanyl) ketones with the overall replacement of the cyano group by a phenylselenyl group. Through this protocol, a great variety of α-cyano ketones have been efficiently converted into the corresponding α-(phenylselanyl) ketones with complete control over the regiochemistry. Meeting with these promising results, we were interested in extending the lithium naphthalenide induced reductive selenenylation process to the synthesis of other types of α-(phenylselenyl) carbonyl compounds. In this paper, we wish to report our findings concerning the efficient preparation of α-(phenylselenyl) esters from the corresponding α-cyano esters.

As a class of highly substituted synthetic intermediates, α,α-dialkyl-α-(phenylselanyl)acetates 1 (Scheme 1) have been shown to have broad utility in synthetic chemistry, particularly in the preparation of α,β-unsaturated esters,9,10 as well as the generation of free radicals to undergo coupling and/or annulation reactions10c–e to establish complex molecules. Several synthetic routes have been reported for generating these compounds. For 1 with two identical alkyl groups (R1 = R2), the direct dialkylation of α-(phenylselanyl)acetates appears to be the most straightforward approach.9 On the other hand, compounds 1 possessing two different alkyl substituents (R1 ≠ R2) are usually synthesized either by the selenenylation of the enolates of α,α-dialkylacetates 2 by use of an appropriate phenylselenenylating reagent PhSeX (X = Cl, Br, SePh) (Scheme 1, Approach A)5d,10 or, alternatively, by the alkylation of the enolates of α-alkyl-α-(phenylselanyl)acetates 3 (Scheme 1, Approach B).9 Selanyl esters 3 can be synthesized by the substitution of α-alkyl-α-haloacetates 4 with the phenylselenide anion generated from the reaction of diphenyl diselenide with sodium borohydride, or by the selenenylation of the enolates of α-alkylacetates 5 (Scheme 1).

These methods suffer from several drawbacks. For instance, the transformation from 5 to 3 and then from 3 to 1 in Approach B is often complicated by side reactions including overselenenylation and competitive alkylation of the selenium atoms.9,12 Additionally, the starting materials are less available, and this coupled with the need for relatively strong basic conditions may also impede the applicability of Approaches A and B.

Our recent studies on some addition and cyclization reactions involving carbon-centered radicals resulting from C–Se bond cleavage required the efficient generation of
highly substituted α-(phenylselanyl)acetates with a broad structural diversity. On the basis of our previous experiences, we envisaged that a process involving the reductive selenenylation of α-cyano esters might lead to an attractive method. Our strategy consisted of first introducing the selected alkyl groups to the α-position of cyanoacetate 6, to provide α,α-dialkyl-α-cyanoacetates 7 (Scheme 2), which would then be subjected to reductive selenenylation, thus giving the desired products 1 by intentional control of the substitutions at the quaternary carbon center (Scheme 2). To our knowledge, the preparation of α-(phenylselanyl) ester compounds by such an approach is unprecedented.

Scheme 2 Proposed synthesis of 1 by a reductive selenenylation approach

Our investigation began with the preparation of substrates 7a–i (Table 1, entries 1–3), starting from commercially available ethyl cyanoacetate. As described below, one of the salient features of the current process lies in the ease of introducing two alkyl substituents, either identical or different, into the acetate unit. Thus, by a modification of the procedure developed by Oediger and Moller, disubstituted cyanoacetates 7a–c were easily prepared by treatment of ethyl cyanoacetate with benzyl bromide (2.2 equiv) or 1,5- or 1,4-dibromobutane (1.1 equiv) in N,N-dimethylformamide and with the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (2.2 equiv) as base at 80 °C for two hours. Yields were typically around 90%. For cyanoacetates 7d–i with two different alkyl groups (Table 1, entries 4–9), a two-step synthetic operation was applied. First, the monoalkylated intermediates were prepared by alkylation of ethyl cyanoacetate with one equivalent iodoethane (7d,h,i), 3-bromopropyl tert-butyl dimethylsilyl ether (7e), or 2-iodopropane (7f,g) in benzene with diazabicyclo[5.4.0]undec-7-ene (1.2 equiv) at room temperature for one day. The monoalkylated intermediates were then treated with 1.2 equivalents of the appropriate alkylation agent (BnBr, Mel, EtI, or PrI) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.3 equiv) in N,N-dimethylformamide at room temperature for 20 hours; this gave the

Table 1 Reductive α-Selenenylation of α,α-Dialkyl-α-cyanoacetates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material 7*</th>
<th>R1</th>
<th>R2</th>
<th>Product 1*#</th>
<th>Yield* (%)</th>
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<td>Bn</td>
<td>Bn</td>
<td>1a</td>
<td>95</td>
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<tr>
<td>2</td>
<td>7b</td>
<td>(CH2)3</td>
<td></td>
<td>1b</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>7c</td>
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<td></td>
<td>1c</td>
<td>83</td>
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<tr>
<td>4</td>
<td>7d</td>
<td>Et</td>
<td>Bn</td>
<td>1d</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>7e</td>
<td>(CH2)3OTBDMS</td>
<td></td>
<td>1e</td>
<td>95</td>
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<tr>
<td>6</td>
<td>7f</td>
<td>i-Pr</td>
<td>Me</td>
<td>If</td>
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<tr>
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<td>7g</td>
<td>i-Pr</td>
<td>Et</td>
<td>Ig</td>
<td>76</td>
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<td>7h</td>
<td>Me</td>
<td>Et</td>
<td>Ih</td>
<td>79</td>
</tr>
<tr>
<td>9</td>
<td>7i</td>
<td>Pr</td>
<td>Et</td>
<td>Il</td>
<td>90</td>
</tr>
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</table>

* R1 = Et in all cases.

# The structures of new selanylacetates 1b,c,e–g,i were established from their spectroscopic data (1H and 13C NMR, IR, and MS).

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unsymmetrically substituted cyanoacetates 7. The yields over two steps ranged from 75% to 95%. Thus, a broad range of α,α-dialkyl-α-cyanoacetates 7 was prepared, with the efficient incorporation of various alkyl groups into the molecules.

With the required cyanoacetates 7 in hand, we turned our attention to subjecting them to the key reductive selenenylation reaction (Table 1). To our delight, we found that the protocol previously developed for α-cyano ketones proved equally successful for α-cyano esters, as shown by the results in Table 1. In all cases examined, starting materials 7a–i were readily reduced (over ca. 25 min) with lithium naphthalenide under mild conditions (–45 °C) to give the corresponding ester enolates. Subsequent addition of phenylselenenyl bromide effected the selenenylation, providing the desired α-(phenylselenyl) esters 1a–i in synthetically useful yields (76–95%; Table 1). As a typical example, treatment of ethyl 2-benzyl-2-cyano-3-phenylpropanoate (7a) with five equivalents of lithium naphthalenide in tetrahydrofuran at –45 °C for 25 minutes followed by the addition of 1.2 equivalents of phenylselenenyl bromide and further reaction at the same temperature for an additional 15 minutes afforded ethyl 2-benzyl-3-phenyl-2-(phenylselenyl)propanoate (1a) in 95% yield after the usual workup and chromatographic purification (Table 1, entry 1). It is noteworthy that among several phenylselenenylating agents investigated, phenylselenenyl bromide was found to be superior to its counterparts, such as phenylselenenyl chloride and diphenyl diselenide, in offering the products in relatively higher yields. As described above, in conjunction with the efficient means for alkylation of ethyl cyanoacetate, the lithium naphthalenide induced reductive selenenylation of cyanoacetates provides a useful tool for the preparation of highly substituted α-(phenylselenyl)acetates. In addition to broad substrate diversity, this procedure also has the advantages of operational simplicity, relatively mild reaction conditions, and high-yielding formation of products.

To further demonstrate the synthetic utility of the reductive selenenylation process, we also attempted to convert the in situ generated selenylacetates 1 without isolation into the corresponding α,β-unsaturated esters by a one-pot treatment with an oxidizing reagent. To date, few cases have been reported for the transformation of unsymmetrically substituted α,α-dialkyl-α-(phenylselenyl)acetates 1 (R1 R2) into the corresponding α,β-unsaturated esters. This is presumably due to the lack of efficient preparative methods for the starting materials. In the light of the efficiency of the above-mentioned protocol, we envisaged that a one-pot combination of reductive selenenylation with oxidative elimination would permit the convenient generation of a series of synthetically useful α,β-unsaturated esters, which are otherwise difficult to synthesize.

This one-pot operation was first attempted with cyanoacetate 7a (Scheme 3). We were pleased to find that with the completion of the reductive selenenylation of 7a, as indicated by TLC analysis, the subsequent addition of water, acetic acid (4 equiv), and hydrogen peroxide (8 equiv) to the reaction mixture at –45 °C, followed by reaction for an additional 30 minutes with the temperature increasing from –45 °C to –10 °C led to the exclusive formation of (E)-α,β-unsaturated ester 8a in 85% isolated yield (Scheme 3), with the spectral data (1H and 13C NMR) in good agreement with those reported in the literature. It deserves to be noted that the methods previously described for the preparation of 8a and its analogues often involve much more drastic reaction conditions than those described here. The one-pot selenenylation–oxidative elimination process was subsequently also applied to other α-cyano acetates 7b–j, and the results are compiled in Table 2.

As shown in Table 2, under these conditions, the two cyclic α-cyano acetates 7b and 7c were both smoothly converted into the corresponding α,β-unsaturated esters 8b and 8c in 82% and 81% yield, respectively (Table 2, entries 1 and 2). At the same time, application of these conditions to substrates 7 substituted with two different alkyl groups allowed us to inspect the regio- and stereoselectivity regarding the introduction of unsaturation more closely (Table 2, entries 3–9). For substrates 7d and 7e bearing a benzyl group, the procedure was found to proceed with complete regio- and stereoselectivity, giving products 8d and 8e, respectively, in high yields exclusively as the E-isomers (Table 2, entries 3 and 4). Furthermore, the completely regioselective formation of the C=C double bond was also observed for substrates 7f and 7g, in which the in situ oxidative elimination reaction took place exclusively on the less substituted β-carbons instead of the more substituted ones, affording 8f (Table 2, entry 5) or an E,Z-isomeric mixture of 8g and 8g′ in favor of the E-form (E/Z = 62:38) (Table 2, entry 6). With cyanoacetate 7h, the reaction displayed a moderate degree of regioselectivity in giving a mixture of two constitutional isomers 8h and 8h′ in 73% yield, with the less substituted 8h as the major product (8h/8h′ = 59:41) (Table 2, entry 7). In these cases (Table 2, entries 5–7), the preferential generation of the less substituted α,β-unsaturated esters can, presumably, be attributed to the carbanion character of the β-carbon undergoing the elimination. Therefore, during the transition state of the oxidative elimination, the less substituted β-carbon would be more prone to hydrogen abstraction by the selenoxide oxygen than the more substituted one, for stability reasons. This rationalization can be further supported by the result shown for the reaction of 7i (Table 2, entry 8): an equal amount of the two constitutional isomers 8i and 8i′, both E-isomers, was ob-
Table 2  Conversion of α-Cyanoacetates into α,β-Unsaturated Esters by the One-Pot Selenenylation–Oxidative Elimination Process

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material 7</th>
<th>Product(s) 8</th>
<th>Yield (%)</th>
</tr>
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<td>77b</td>
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</table>

* Isolated yield.

b Yield of isomeric mixture; $8g/8g' = 62:38$; $8h/8h' = 59:41$; $8i/8i' = 50:50$; $8j/8j' = 51:49$. The ratios were deduced from the integrations of the olefinic proton signals in the $^1$H NMR spectra of the mixtures.

c Compound 7j was synthesized from tert-butyl cyanoacetate by the same procedure used for the synthesis of 7g.

of regioselective reaction to afford a diastereomeric mixture and reasons still unclear to us, the products were confirmed by comparison of their spectral data (\( ^{1}H \) and \( ^{13}C \) NMR) with those reported in the literature. 20 For 8a, NOE experiments were carried out to assign its \( E \)-configuration (Figure 1).

In summary, the reductive selenenylation protocol that we previously described for the preparation of \( \alpha \)-(phenylselan- nyl) ketones has been successfully extended to the generation of a variety of highly substituted \( \alpha \)-(phenylselan- nyl)acetates from readily available \( \alpha \)-cyanocacetates. Additionally, the synthetic utility of the procedure has been further extended by the in situ treatment of the \( \alpha \)-(phenylselan- nyl) esters thus formed with an oxidizing reagent, thus conveniently converting them into trisubstituted or disubstituted \( \alpha \),\( \beta \)-unsaturated esters, many of which are not easily accessible by existing methods.

All reagents were obtained from commercial suppliers and were used without further purification. THF was distilled from sodium– benzophenone, and benzene and DMP were distilled from CaH₂ before use. TLC analysis was carried out on Merck 25 DC-Alufolien (5%). All products were purified by flash chromatography on silica gel, and satisfactory spectral data (\( ^{1}H \), \( ^{13}C \) NMR, IR, and MS) were obtained for them. For the known compounds (8b–d, 8f–8j), the structures were confirmed by comparison of their spectral data (\( ^{1}H \) and \( ^{13}C \) NMR) with those reported in the literature. 20 For 8e, NOE experiments were carried out to assign its \( E \)-configuration (Figure 1).

Figure 1 Results of NOE experiments of compound 8e.
Ethyl 2,3-Dimethyl-2-(phenylselanyl)butyrate (1f)
The typical procedure for the preparation of 1a was followed; 7f (100 mg, 0.59 mmol) was used as starting material. Flash chromatography (hexane–EtOAc, 30:1) provided 1f as a yellow viscous oil. Yield: 150 mg (85%).

IR (KBr): 1719, 1577, 1474, 1438, 741, 692 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 2.74 (t, J = 7.2 Hz, 2 H), 2.15 (m, 4 H), 1.70–1.84 (m, 8 H), 1.29 (s, 3 H), 0.90 (t, J = 7.2 Hz, 2 H), 0.87 (s, 6 H), 0.90 (s, 9 H), 1.35 (t, J = 7.2 Hz, 3 H), 1.29–1.39 (m, 8 H), 1.39–1.51 (m, 1 H), 1.64–1.84 (m, 4 H), 4.08 (q, J = 7.2 Hz, 2 H), 7.29 (br t, J = 7.4 Hz, 2 H), 7.37 (br t, J = 7.4 Hz, 1 H), 7.55 (br d, J = 7.4 Hz, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 13.9, 14.2, 33.2, 35.8, 56.9, 60.9, 103.5, 128.0, 137.6, 140.6, 168.2, 168.3.


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References
Preparation of $\alpha,\alpha$-Dialkyl-$\alpha$-(phenylselanyl)acetates and $\alpha,\beta$-Unsaturated Esters


(17) In theory, the reductive decyanation of $\alpha$-cyano esters requires only two equivalents of lithium naphthalenide. In practice, however, we found that the use of less than five equivalents of lithium naphthalenide (e.g., 4 equiv) often resulted in incompletion of the reaction under the specified conditions (–45 °C, 25 min).


