Lithium Naphthalenide Induced Reductive Selenenylation of α-Cyano Ketones: A Regiocontrolled Process for α-Phenylseleno Ketones and One-Pot Conversion into Enone System

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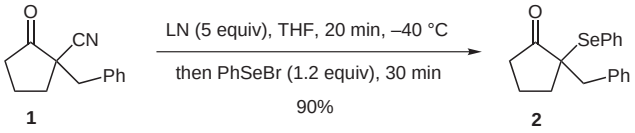
Abstract: An efficient procedure for the regiocontrolled synthesis of α-phenylseleno ketones has been developed, making use of the lithium naphthalenide induced reductive selenenylation of the α-cyano ketone system as a key operation. Moreover, seleno ketones thus generated in situ, upon subsequent treatment with hydrogen peroxide and acetic acid, could be further converted into the corresponding enones with a high degree of regioselectivity, presumably due to the lithium salt mediated selenoxide *syn*-elimination process.

Key words: lithium naphthalenide, α-phenylseleno ketones, regioselectivity, α-cyano ketones, reductive selenenylation

α-Phenylseleno ketones are of great importance in synthetic chemistry where they are commonly used as the substrates for preparation of α,β-unsaturated ketones[1] or the intermediates for synthesizing polycyclic compounds via a free-radical cyclization process.[2] In addition to their synthetic versatility, a specific series of α-phenylseleno ketones as reported by Cotgreave et al.[3] has been shown to possess glutathione peroxidase-like biological properties, indicating that α-phenylseleno ketones might have potential to serve as anticancer, antiviral and anti-inflammatory agents,[4] and/or as the selenium source of selenoproteins, which are essential for human immune system and known to play a critical role in reducing the incidence of a wide variety of cancers, particularly that of the prostate.[5,6]

While a number of procedures are accessible to provide α-phenylseleno ketones, an efficient control over the regioselectivity remains problematic for unsymmetrical ketones with the α and α′ carbons to a ketone carbonyl equally susceptible to selenenylation.[7–11] Herein, we wish to report that a convenient synthetic method, making use of the lithium naphthalenide (LN)[12] induced reductive selenenylation of α-cyano ketones as a key operation, has been developed to facilitate the formation of the corresponding α-phenylseleno ketones with complete regioselectivity. It was found that α-cyano ketones could be readily reduced with LN under mild conditions (–40 °C) to give the corresponding ketone enolates.[13] When the reduction was followed by the addition of a phenylselenenylating agent, α-selenenylation was effected, resulting in the specific replacement of the cyano group with a phenylseleno group. A typical experiment is depicted in Scheme 1.[14] However, it is noteworthy that among several phenylselenenylating agents investigated, phenylselenyl bromide is superior to its counterparts such as phenylselenyl chloride (65% yield) and diphenyl diselenide (52% yield) in offering compound **2**.



Scheme 1

This reductive selenenylation process proved to be general as outlined in Table 1. In all cases examined, the reactions proceeded smoothly and the desired products were obtained in synthetically useful yields (75–92%). Substrates **1** and **3**–**9** are prepared by alkylation of the corresponding α-cyano ketones using an appropriate alkylating agent and lithium hydride (LiH) in THF at room temperature for 24 hours, which are readily accessible via the Thorpe–Ziegler reaction,[15] the base-induced rearrangement of isoxazoles[16] or the α-cyanation of ketones.[17] On the other hand, substrates **10** and **11** were constructed from Diels–Alder reaction of 2,2-dimethyl-1-cyanobenzoylethene with isoprene and 2,3-dimethyl-1,3-butadiene, respectively, in the presence of $ZnCl_2$ as catalyst,[18] and substrate **12** was prepared according to the procedure reported in the literature.[13]

In addition to providing a direct access to a variety of α-phenylseleno ketones which are otherwise difficult to synthesize, the aforementioned reductive selenenylation process also found a synthetic application in converting α-cyano ketones into enones by modification of the phenylseleno group. It was found that the keto selenides thus obtained via reductive selenenylation, without isolation, could be directly oxidized to give the corresponding enones with high regiocontrol of the double–bond formation, presumably due to the intermediacy of rich lithium salts derived from the preceding reaction (vide infra). This one-pot selenenylation–oxidative-elimination process was found to be general as illustrated in Table 2. In terms

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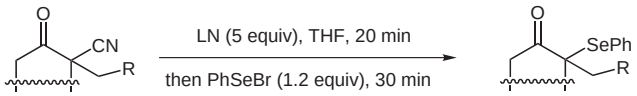
of cyclic α-cyano ketones examined (entries 1–6 and 11), with the exception of a six-membered-ring substrate (entry 3) which gave a mixture of endo- and exocyclic enones in 2:1 ratio, the procedure was found to proceed with regioselectivity to provide the exocyclic products exclusively in good to excellent yields (72–95%).

Table 1 Reductive Selenenylation of α-Cyano Ketones with Lithium Naphthalenide



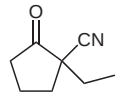
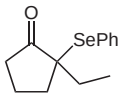
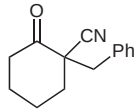
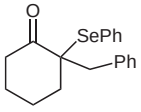
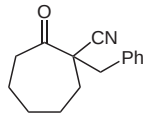
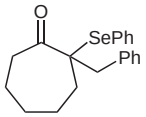
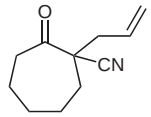
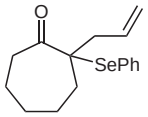
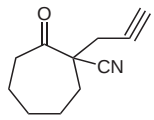
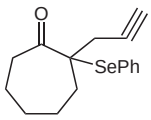
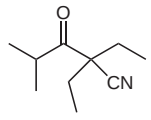
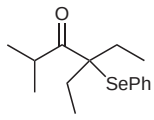
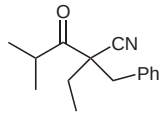
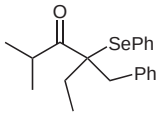
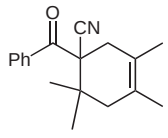
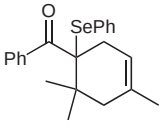
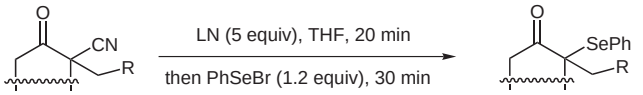
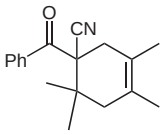
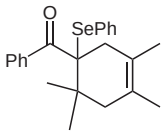
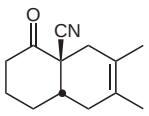
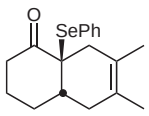
Entry	α-Cyano ketone	Product	Temp (°C)	Yield (%)[a]
1	 **3**		–40	85
2	 **4**		–40	87
3	 **5**		–40	87
4	 **6**		–40	88
5	 **7**		–40	75[b]
6	 **8**		–40	85
7	 **9**		–40	92
8	 **10**		–40	86

Table 1 Reductive Selenenylation of α-Cyano Ketones with Lithium Naphthalenide (continued)



Entry	α-Cyano ketone	Product	Temp (°C)	Yield (%)[a]
9	 **11**		–40	91
10	 **12**		–40	89[c]

[a] Yields are for isolated, chromatographically pure products.
[b] 7.0 equiv of LN and 2.2 equiv of PhSeBr were required to complete the reaction.
[c] *cis*-Addition product is temporarily assigned based on previously closely resembled examples.[13]

As for acyclic substrates (entries 7 and 8), in each case only a single regioisomer (*E*-form) was formed in quantitative yield (90–95%). All enones obtained were characterized by spectroscopic methods and where applicable, NOE experiments were extensively performed to determine the stereochemistry assigned. As well, the spectral data of compounds **13**–**17** are in good agreement with those reported in the literature.[9b,19–22] As a typical example, α-phenylseleno ketone **2** thus generated in situ following the protocol in Scheme 1 was further treated with acetic acid (4 equiv) and H_2O_2 (8 equiv) at –40 °C to give the corresponding enone product **13** in 85% yield over two steps.[14] Mechanistically, the regioselectivity observed in compound **13** might be tentatively explained by invoking the intermediacy of the lithium ion to stabilize the preferred conformation of the selenoxide intermediate required for introducing the *exo* double bond via *syn*-elimination (Figure 1). This proposal is supported by the following preliminary findings. When isolated compound **2** was treated with 5 equivalents of LiBr followed by addition of acetic acid (4 equiv) and H_2O_2 (8 equiv) in CH_2Cl_2 at 0 °C, a mixture of exo- and endocyclic products were

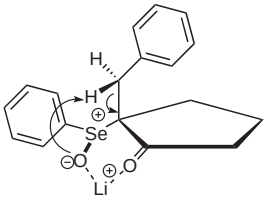
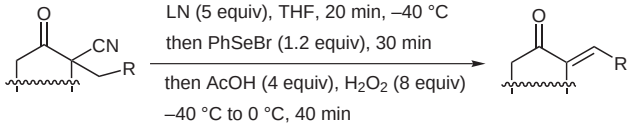


Figure 1

formed in 7:1 ratio (86% yield); however, for comparison, when the same reaction was carried out in the absence of LiBr, the desired exo- and endocyclic **13** were obtained in 1:1.5 ratio (81% yield).

Table 2 One-Pot Conversion of α-Cyano Ketones into α,β-Unsaturated Ketones



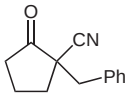
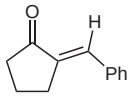
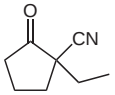
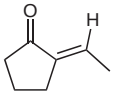
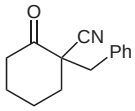
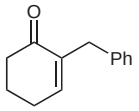
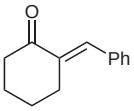
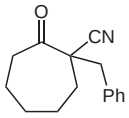
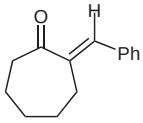
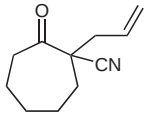
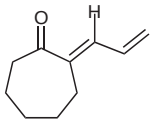
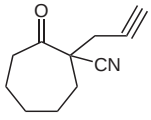
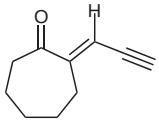
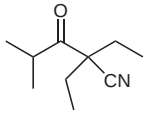
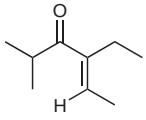
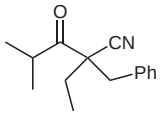
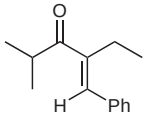
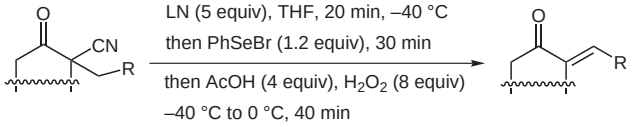
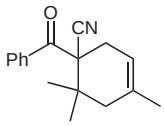
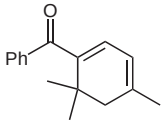
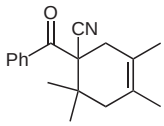
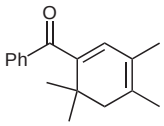
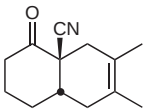
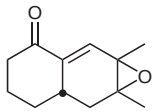
Entry	α-Cyano ketone	Product	Yield (%)[a]
1		 **13**	85
2		 **14**	75
3		 **15**  **16** *endo*/*exo* (*E*) 67:33	97
4		 **17**	95
5		 **18**	91
6		 **19**	72
7		 **20**	90
8		 **21**	95

Table 2 One-Pot Conversion of α-Cyano Ketones into α,β-Unsaturated Ketones (continued)



Entry	α-Cyano ketone	Product	Yield (%)[a]
9		 **22**	98
10		 **23**	95
11		 **24**	77[b]

[a] Yields are for isolated, chromatographically pure products.
[b] Only a single diastereomer was formed; its stereochemistry remains to be determined.

A similar observation on the product distribution (*exo*/*endo* = 1:1.3) has also been made previously by Reich et al., where the oxidation reaction was conducted under treatment with H_2O_2 without the presence of lithium salts.[23] The results disclosed above appear to be of great significance in the enone-synthesis chemistry, thus prompting us to undergo a systematical investigation on the phenylselenoxide *syn*-elimination process mediated with different lithium salts as well as other relevant metal salts. A detailed account of the mechanistic study will be published elsewhere in due course.

As described above, we have developed a highly efficient and completely regiocontrolled procedure for the preparation of α-phenylseleno ketones starting from readily available α-cyano ketones. Moreover, α-phenylseleno ketones thus formed, without isolation, could be further oxidized to afford the corresponding α,β-unsaturated ketones with high regioselectivity, presumably due to the intermediacy of the lithium salts provided by the preceding reductive selenenylation. This newly developed one-pot process for direct conversion of α-cyano ketones into enone system is expected to have broad synthetic utility in light of the high degree of regiocontrol and operational simplicity.

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(14) Satisfactory spectral and LC-MS or HRMS analytical data were obtained for all new compounds. A typical experiment is outlined as follows: To a solution of α-cyano ketone **1** (110 mg, 0.55 mmol) in THF (10 mL) at –40 °C was added LN (7.5 mL, 0.365 M, 2.75 mmol) dropwise. The resulting dark green solution was stirred at the same temperature for 20 min followed by addition of phenylselenyl bromide (156 mg, 0.66 mmol) in one portion. The resulting mixture was continued to stir for additional 30 min at –40 °C and then quenched with sat. aq NH_4Cl and extracted with EtOAc (2 × 10 mL). The combined extracts were washed with brine, dried with Na_2SO_4, and concentrated to give the crude residue, which was subjected to flash chromatography on silica gel (EtOAc–*n*-hexane, 1:50) to afford the corresponding α-phenylseleno ketone **2** as a colorless oil (165 mg, 90%). IR (neat): 1729, 1604, 1577 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.72–2.13 (m, 5 H), 2.59 (ddd, *J* = 18.1, 8.1, 2.0 Hz, 1 H), 3.08 (d, *J* = 13.7 Hz, 1 H), 3.27 (d, *J* = 13.7 Hz, 1 H), 7.08–7.11 (m, 2 H), 7.19–7.25 (m, 3 H), 7.30–7.35 (m, 2 H), 7.39–7.45 (m, 1 H), 7.52–7.61 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 33.0, 36.1, 41.0, 59.5, 126.5, 126.6, 128.3, 129.0, 129.6, 130.5, 137.6, 138.0, 211.6. MS (EI): *m/z* = 331.2 [M + 1]. Instead of quenching with sat. aq NH_4Cl, after ketone **2** was generated in situ following the aforementioned protocol, AcOH (0.13 mL, 2.21 mmol) and H_2O_2 (0.43 mL of 35% H_2O_2, 4.41 mmol) were sequentially added to the above reaction mixture at –40 °C. The resulting solution was then warmed to 0 °C in 40 min and quenched with sat. aq $NaHCO_3$ followed by extraction with EtOAc (2 × 10 mL). The combined organic layers were washed with H_2O, brine, dried with Na_2SO_4, and concentrated to give the crude product, which was purified by flash chromatography on silica gel (EtOAc–*n*-hexane, 1:25) to give *exo*-(*E*)-**13**[9a,b] (81 mg) in 85% yield over two steps.
(*E*)-2-Benzylidenecyclopentanone (13): IR (neat): 1706, 1622, 1487 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.04 (m, 2 H), 2.42 (t, *J* = 7.9 Hz, 2 H), 2.98 (dt, *J* = 7.2, 2.7 Hz, 2 H), 7.36–7.44 (m, 4 H), 7.54 (dd *J* = 7.4, 1.1 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 29.4, 37.8, 128.7, 129.3, 130.5, 132.3, 135.6, 136.1, 208.0. HRMS (EI): *m/z* calcd for $C_{12}H_{12}O$: 172.0889; found: 172.0877.
2-Allyl-2-phenylselenocycloheptanone (6a): IR (KBr): 3072, 2926, 2855, 1686, 740, 691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.14–1.27 (m, 1 H), 1.33–1.46 (m, 2 H), 1.61 (dd, *J* = 14.7, 10.7 Hz, 1 H), 1.73–1.94 (m, 3 H), 2.21–2.30 (m, 2 H), 2.40–2.48, (m, 2 H), 3.17 (td, *J* = 11.2, 2.4 Hz, 1 H), 5.06 (br d, *J* = 17.1 Hz, 1 H), 5.14 (br d, *J* = 10.5 Hz, 1 H), 5.92–6.05 (ddm, *J* = 17.1, 10.5 Hz, 1 H), 7.26–7.31 (tm, *J* = 7.2 Hz, 2 H), 7.34–7.41 (m, 1 H), 7.41–7.46 (dm, *J* = 7.2 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 26.3, 30.4, 32.1, 36.9, 39.6, 60.7, 118.2, 127.2, 129.0, 129.4, 135.1, 137.5, 207.3. LC-MS (ES): *m/z* = 331 $[M + 23]^+$.
(*E*)-2-Allylidenecycloheptanone (18): IR (neat): 1699, 1613, 1579 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.62–1.80 (m, 6 H), 2.47–2.57 (m, 2 H), 2.62–2.68 (m, 2 H), 5.49 (dd, *J* = 9.9, 1.7 Hz, 1 H), 5.63 (dd, *J* = 16.7, 1.7 Hz, 1 H), 6.63 (ddd, *J* = 16.7, 11.5, 9.9 Hz, 1 H), 7.00 (d, *J* = 11.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.3, 27.5, 29.8, 31.3, 43.4, 125.4, 131.6, 135.2, 140.3, 204.8. LC-MS (ES): *m/z* = 151 $[M + 1]^+$.

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(18) **1-Benzoyl-4,6,6-trimethylcyclohex-3-enecarbonitrile (10):** IR (KBr): 2232, 1692, 1596, 1578 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (s, 3 H), 1.21 (s, 3 H), 1.72 (br s, 3 H), 1.96 (d, *J* = 17.9 Hz, 1 H), 2.31 (d, *J* = 17.9 Hz, 1 H), 2.58 (br d, *J* = 17.8 Hz, 1 H), 2.90 (br d, *J* = 17.8 Hz, 1 H), 5.32 (br s, 1 H), 7.42–7.48 (tm, *J* = 7.3 Hz, 2 H) 7.52–7.58 (tm, *J* = 7.3 Hz, 1 H), 8.04–8.08 (dm, *J* = 7.3 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7, 23.8, 27.7, 33.1, 36.7, 44.0, 53.2, 115.2, 121.7,128.4, 129.1, 132.9, 133.9, 137.5, 195.3. LC-MS (ES): *m/z* = 253 $[M]^+$.
1-Benzoyl-3,4,6,6-tetramethylcyclohex-3-enecarbonitrile (11): IR (KBr): 2232, 1692, 1595, 1578 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.08 (s, 3 H), 1.20 (s, 3 H), 1.66 (br s, 6 H), 1.90 (d, *J* = 17.8 Hz, 1 H), 2.38 (br d, *J* = 18.0 Hz, 1 H), 2.44 (d, *J* = 17.8 Hz, 1 H), 2.88 (br d, *J* = 18.0 Hz, 1 H), 7.43–7.48 (tm, *J* = 7.8 Hz, 2 H), 7.53–7.59 (tm, *J* = 7.8 Hz, 1 H), 8.04–8.08 (dm, *J* = 7.8 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 19.0, 22.5, 27.7, 36.6, 38.6, 45.7, 51.4, 120.3, 121.8, 125.2, 128.4, 129.1, 132.8, 137.8, 195.4. LC-MS (ES): *m/z* = 267 $[M]^+$.

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