Novel and Efficient Procedure for the Regiocontrolled Preparation of α-(Phenylsulfanyl) Carbonyl Compounds

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A new procedure for the regiocontrolled synthesis of α-(phenylsulfanyl) carbonyl compounds has been developed, making use of lithium naphthalenide induced reductive sulfenylation of α-cyano carbonyl compounds as a key operation. Through this protocol, a variety of α-(phenylsulfanyl) carbonyl compounds has been prepared in moderate to high yields. The completely regioselective sulfenylation was observed in most of the cases.

Keywords: Nitriles; Sulfur; Lithium naphthalenide; Reductive sulfenylation.

INTRODUCTION

α-(Phenylsulfanyl) carbonyl compounds are of considerable importance in synthetic chemistry where they can be used to great advantage in a variety of organic transformations.[1,2] In view of their broad synthetic utility, there have been numerous procedures developed for the preparation of these substrates,[3] with most of them highlighting direct sulfenylation of enolates[4] or enol derivatives[5] and S_N2 displacement of α-halogenated carbonyl compounds with the sulfide.[6] However, even with these precedents, the regioselective synthesis of some α-(phenylsulfanyl) ketone compounds is still not easily achieved due to difficult access into the regiodefined precursors, thus making the development of more efficient synthetic strategies necessary. In conjunction with our studies on addition and cyclization reactions involving carbon-centered radicals resulting from C-Se bond cleavage, we have recently developed a highly efficient procedure for the regiocontrolled preparation of α-(phenylselanyl) ketones.[7] Our approach is based on the reductive decyanation of α-cyano ketones using lithium naphthalenide (LN) as the reducing reagent, followed by the rapid one-pot selenenylation of the resulting enolates with phenylselenenyl bromide (PhSeBr); this gives the corresponding α-(phenylselanyl) ketones in the overall replacement of the cyano group with a phenylselanyl group. Through this protocol, a wide range of α-cyano ketones were efficiently converted into the corresponding α-(phenylselanyl) ketones with the complete control over the regiochemistry. Meeting with these promising results, we were interested in extending this strategy into the syntheses of α-(phenylsulfanyl) carbonyl compounds. Herein, we wish to report the first examples of the LN-induced reductive sulfenylation of the α-cyano carbonyl compounds to yield the corresponding α-(phenylsulfanyl) carbonyl compounds.

RESULTS AND DISCUSSION

Our original investigation was conducted on α-cyano ketone **1a** under the reaction conditions developed earlier for the reductive selenenylation reaction,[7] except for replacing PhSeBr with commercially available diphenyl disulfide (PhSSPh) as a sulfenylating reagent.[4] Thus, **1a** was first treated with LN (5 equiv)[8,9] in THF at -40 °C for 20 minutes to give the corresponding ketone enolate. The subsequent addition of 1.2 equivalents of PhSSPh to the reaction mixture followed by further reaction at the same temperature for an additional 30 minutes afforded the desired sulfenylated product **2a** in 56% yield, and 2-benzylcyclohexanone in 30% yield resulted from the decyanation. Compared with the high yield (87%) of the corresponding reductive α-selenenylation reaction of **1a**,[7] the relatively low-yielding formation of **2a** in this case could be possibly attributed to the weaker electrophilicity of PhSSPh than that of PhSeBr to the enolate intermediate. After examining several reaction conditions, we found that 84% yield of **2a** could be obtained when the sulfenylation reaction was performed by using 2 equivalents of PhSSPh and with the reaction mixture being slowly warmed up from -40 to -10 °C within 30 minutes (Scheme I). Following this, the reaction

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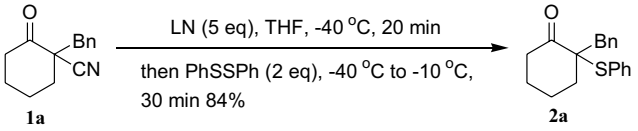
Scheme I

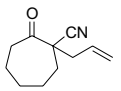
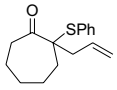
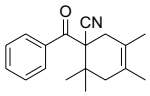
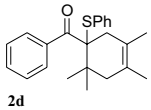
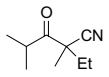
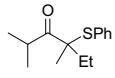
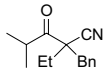
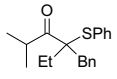
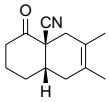
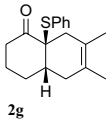
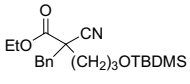
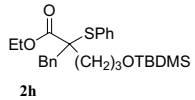
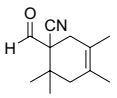
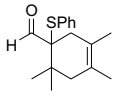


conditions depicted in Scheme I were further applied to a variety α-cyano carbonyl compounds (**1b-i**).[10] The experimental results are compiled in Table 1.

As shown in Table 1, when subjected to the reductive sulfenylation conditions, both monocyclic and acyclic α-cyano ketones **1b-f** were smoothly converted into the corresponding sulfenylated products **2b-f** in good to high yields (50-95%) (entries 1-5). Also, the reactions of **1b-c** and **1e-f** proceeded in a completely regiocontrolled fashion to afford **2b-c** and **2e-f** as the only detectable regioisomers (entries 1, 2 and 4, 5). As for the bicyclic cyano ketone **1g**, the desired product **2g** was produced in a moderate yield under the conditions (entry 6), along with a complex byproduct mixture presumably resulting from polysulfenylation. The attempts of using reduced amounts of LN and/or PhSSPh only resulted in incompletion of the reactions instead of the improvement on the yield of **2g**. In addition to the ketone precursors, the reductive sulfenylation process was also applied to α-cyano ester **1h** and α-cyano aldehyde **1i**. Following a reported procedure,[11] compound **1h** was prepared by the alkylation of ethyl cyanoacetate with 3-bromopropyl *tert*-butyldimethylsilyl[12] ether and 1,8-dizaobicylo[5.4.0]undec-7-ene (DBU) in benzene, followed by the reaction of the resulting monoalkylated intermediate with benzyl bromide and DBU in DMF. On the other hand, compound **1i** was constructed from the Diels-Alder reaction of isopropylidenemalononitrile[13] with 2,3-dimethyl-1,3-butadiene (20 equiv) in the presence of $ZnCl_2$ (2 equiv) as catalyst (benzene, 80 °C, 2 days), and the subsequent reduction of the resulting adduct with DIBAL-H.[14] As illustrated in entries 7 and 8, **1h** underwent the reaction efficiently to furnish **2h** in 85% yield, while the reaction of **1i** afforded α-(phenylsulfanyl) aldehyde **2i** only in 29% yield, together with a significant amount of unidentified byproducts.

In summary, we have demonstrated that the LN-induced reductive α-sulfenylation of α-cyano carbonyl substrates can serve as an efficient method for the synthesis of a number of structurally diverse α-(phenylsulfanyl) carbonyl compounds. In most cases, the complete regioselectivity as well as good to high yields were observed for the reactions.

Table 1. LN-Induced reductive α-sulfenylation of α-cyano compounds

Entry	Substrate	Product	Yield (%)[a]
1	 **1b**	 **2b**	90
2	 **1c**	 **2c**	83
3	 **1d**	 **2d**	95
4	 **1e**	 **2e**	65
5	 **1f**	 **2f**	50
6	 **1g**	 **2g**	32[b]
7	 **1h**	 **2h**	85
8	 **1i**	 **2i**	29

[a] Yield refers to isolated product.
[b] *cis*-Addition product is temporarily assigned based on previous similar examples.[7]

EXPERIMENTAL

Unless otherwise stated, all of the starting materials were obtained from commercial suppliers and used without further purification. Reactions were performed under an atmosphere of nitrogen. Tetrahydrofuran (THF) was distilled from sodium-benzophenone, and benzene and dimethyl formamide (DMF) were distilled from calcium hydride before use. TLC analysis was carried out on Merck 25 DC-Alufolien Kieselgel $60F_{254}$ aluminum-backed plates visualised by using UV light, or by means of an ethanolic solution of vanillin (5%) with sulphuric acid (5%). All of the prod-

ucts were purified by flash chromatography using Merck Art.9385 Kiesegel 60 silica gel (230-400 mesh). NMR spectra (^{1}H, ^{13}C) were recorded on a Brücker 400 spectrometer using deuteriochloroform ($CDCl_3$) as solvent. Chemical shifts measurements are reported in delta (δ) units. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Coupling constants (J) are reported in Hertz (Hz). Infrared (IR) spectra were recorded on an IR-FT JASCO 410 spectrophotometer (neat) and resonances are reported in wave numbers (cm^{-1}). High resolution mass spectra (HRMS) were determined by using a A. E. I. model MS-50 mass spectrometer in fast atom bombardment (FAB) mode. GC-MS spectra were recorded on a Thermo Finnigan TRACE Gas Chromatography mass spectrometer in electron ionization mode.

Synthesis of 2-benzyl-2-phenylsulfanyl-cyclohexanone (2a); General procedure of reductive α-sulfenylation

A 0.365 M solution of LN in THF (9.6 mL, 3.52 mmol)[8] precooled to -40 °C was quickly added by syringe to a solution of **1a** (150 mg, 0.70 mmol) in anhydrous THF (10 mL) at -40 °C under a N_2 atmosphere. The resulting dark-green mixture was stirred at -40 °C for 20 min, and then solid diphenyl disulfide (307 mg, 1.41 mmol) was added in one portion. The stirring mixture was slowly warmed to -10 °C within 30 min and quenched with H_2O (10 mL) and extracted with ethyl acetate (2 × 15 mL). The combined extracts were washed with saturated aqueous NaCl (10 mL), dried with Na_2SO_4 and concentrated. Purification by chromatography on silica gel (hexane-ethyl acetate 30:1) afforded **2a** as a viscous oil (175 mg, 84%).

IR (neat): 3060, 2937, 1699, 1581, 750, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43-1.53 (m, 1H), 1.64 (broad, d, *J* = 13.4 Hz, 1H), 1.81-1.97 (m, 2H), 1.97-2.18 (m, 2H), 2.33 (broad, d, *J* = 15 Hz, 1H), 2.82 (d, *J* = 13.9 Hz, 1H), 3.29 (d, *J* = 13.9 Hz, 1H), 3.31-3.36 (m, 1H), 7.15-7.25 (m, 5H), 7.31-7.40 (m, 3H), 7.43 (broad, d, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 26.3, 36.0, 37.9, 41.6, 61.5, 126.4, 127.9, 129.0, 129.3, 130.8, 131.2, 135.9, 137.3, 206.3; HRMS-FAB: *m/z* $[M]^+$ calcd. for $C_{19}H_{20}OS$: 296.1235; found: 296.1235.

2-Ethyl-2-phenylsulfanyl-cyclopentanone (2b)

The typical procedure for the preparation of **2a** was followed; **1b** (110 mg, 0.80 mmol) was used as starting material. Flash chromatography (hexane-ethyl acetate 30:1) afforded **2b** as a colorless oil. Yield: 159 mg (90%).

IR (neat): 3057, 2966, 1730, 1587, 752, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.4 Hz, 3H), 1.49 (dq, J_1 = 14.5 Hz, J_2 = 7.4 Hz, 1H), 1.69 (dq, J_1 = 14.5 Hz, J_2 = 7.4 Hz, 1H), 1.86-1.98 (m, 1H), 1.98-2.08 (m, 2H), 2.09-2.25 (m, 2H), 2.62-2.72 (m, 1H), 7.28-7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.8, 18.0, 25.8, 33.9, 36.0, 61.4, 128.7, 129.4, 130.2, 137.0, 211.9; HRMS-FAB: *m/z* $[M+H]^+$ calcd. for $C_{13}H_{17}OS$: 221.1000; found: 221.1002.

2-Allyl-2-phenylsulfanyl-cycloheptanone (2c)

The typical procedure for the preparation of **2a** was followed; **1c** (150 mg, 0.85 mmol) was used as starting material. Flash chromatography (hexane-ethyl acetate 20:1) afforded **2c** as a colorless oil. Yield: 183 mg (83%).

IR (neat): 3074, 2927, 2856, 1697, 1637, 1439, 750, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12-1.28 (m, 1H), 1.34-1.49 (m, 2H), 1.55-1.63 (m, 1H), 1.76-1.88 (m, 2H), 1.88-2.00 (m, 1H), 2.15-2.28 (m, 2H), 2.36-2.49 (m, 2H), 3.21 (broad, t, *J* = 11.9 Hz, 1H), 5.06 (broad, d, *J* = 17.0 Hz, 1H), 5.14 (broad, d, *J* = 10.1 Hz, 1H), 6.01 (dm, *J* = 17.0 Hz, 1H), 7.27-7.32 (m, 2H), 7.32-7.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 26.5, 30.4, 32.3, 36.3, 39.6, 62.4, 118.2, 128.8, 129.4, 130.6, 134.4, 136.6, 207.9; HRMS-FAB: *m/z* $[M+H]^+$ calcd. for $C_{16}H_{21}OS$: 261.1313; found: 261.1309.

1-Benzoyl-1-phenylsulfanyl-3,4,6,6-tetramethyl-3-cyclohexene (2d)

The typical procedure for the preparation of **2a** was followed; **1d** (116 mg, 0.43 mmol) was used as starting material. Flash chromatography (hexane-ethyl acetate 70:1) afforded **2d** as a yellow oil. Yield: 144 mg (95%).

IR (neat): 3055, 2962, 1674, 1653, 1265, 741, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (s, 3H), 1.01 (s, 3H), 1.41 (s, 3H), 1.61 (s, 3H), 1.77 (d, *J* = 18.2 Hz, 1H), 1.92 (d, *J* = 18.2 Hz, 1H), 2.37 (d, *J* = 21.0 Hz, 1H), 2.43 (d, *J* = 21.0 Hz, 1H), 7.21-7.25 (m, 2H), 7.29-7.39 (m, 5H), 7.39-7.46 (m, 1H), 7.89 (broad, d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 18.5, 25.6, 27.2, 37.0, 37.4, 46.6, 67.2, 122.0, 124.6, 127.7, 128.7, 128.9, 129.1, 130.0, 131.1, 136.8, 143.2, 203.4; HRMS-FAB: *m/z* $[M+H]^+$ calcd. for $C_{23}H_{27}OS$: 351.1783; found: 351.1781.

2,4-Dimethyl-4-phenylsulfanyl-3-hexanone (2e)

The typical procedure for the preparation of **2a** was followed; **1e** (136 mg, 0.89 mmol) was used as starting material. Flash chromatography (hexane-ethyl acetate 50:1) afforded **2e** as a colorless oil. Yield: 136 mg (65%).

IR (neat): 2972, 1699, 748, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.4 Hz, 3H), 1.16 (d, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 7.1 Hz, 3H), 1.37 (s, 3H), 1.70 (dq, J_1

= 14.2 Hz, J_2 = 7.2 Hz, 1H), 1.83 (dq, J_1 = 14.2 Hz, J_2 = 7.2 Hz, 1H), 3.38, (septet, J = 6.7 Hz, 1H), 7.27-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.1, 20.3, 20.7, 21.2, 29.2, 34.2, 60.6, 128.3, 128.7, 131.4, 135.5, 211.8; HRMS-FAB: *m/z* $[M+H]^+$ calcd. for $C_{14}H_{21}OS$: 237.1313; found: 237.1311.

4-Benzyl-2-methyl-4-phenylsulfanyl-3-hexanone (2f)

The typical procedure for the preparation of **2a** was followed; **1f** (128 mg, 0.56 mmol) was used as starting material. Flash chromatography (hexane-ethyl acetate 60:1) afforded **2f** as a viscous oil. Yield: 87 mg (50%).

IR (neat): 3060, 2974, 1693, 1603, 746, 692, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, J = 7.3 Hz, 3H), 1.08 (d, J = 6.7 Hz, 3H), 1.18 (d, J = 6.7 Hz, 3H), 1.75 (q, J = 7.3 Hz, 2H), 3.02 (d, J = 14.6 Hz, 1H), 3.25 (d, J = 14.6 Hz, 1H), 3.37 (septet, J = 6.7 Hz, 1H), 7.16-7.25 (m, 5H), 7.28-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.1, 20.5, 21.2, 25.0, 34.6, 36.9, 65.3, 126.5, 128.0, 128.6, 128.8, 130.5, 131.5, 135.0, 137.0, 210.9; HRMS-FAB: *m/z* $[M+H]^+$ calcd. for $C_{20}H_{25}OS$: 313.1626; found: 313.1620.

(1*R,6*S**)-1-Phenylsulfanyl-8,9-diemthylbicyclo[4.4.0]-dec-8-en-2-one (2g)**

The typical procedure for the preparation of **2a** was followed; **1g** (100 mg, 0.49 mmol) was used as starting material. Flash chromatography (hexane-ethyl acetate 40:1) afforded **2g** as a waxy solid. Yield: 45 mg (32%).

IR (neat): 2918, 2850, 1734, 1705, 1265, 739, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 3H), 1.55 (s, 3H), 1.56-1.58 (m, 3H), 1.58-1.66 (m, 1H), 1.75-2.03 (m, 2H), 2.07-2.23 (m, 1H), 2.24-2.53 (m, 3H), 3.40-3.52 (m, 1H), 7.27-7.40 (m, 5H). HRMS-FAB: *m/z* $[M+H]^+$ calcd. for $C_{18}H_{23}OS$: 287.1470; found: 287.1463.

2-Benzyl-5-(*tert*-butyl-dimethyl-silanyloxy)-2-cyano-pentanoic acid ethyl ester (1h)

IR (neat): 2243, 1741, 1471, 1388, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6H), 0.89 (s, 9H), 1.17 (t, J = 7.2 Hz, 3H), 1.52-1.61 (m, 1H), 1.75-1.86 (m, 1H), 1.87-1.95 (m, 1H), 2.04-2.13 (m, 1H), 3.07 (d, J = 13.5 Hz, 1H), 3.20 (d, J = 13.5 Hz, 1H), 3.64 (t, J = 6 Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H), 7.29-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = -5.4, 13.9, 18.3, 25.9, 28.7, 34.1, 43.2, 51.3, 62.1, 62.6, 119.0, 127.8, 128.5, 130.0, 134.2, 168.6; MS (EI, 70 eV): *m/z* 318.1 $[M - t\text{-Bu}]^+$.

1-Formyl-3,4,6,6-tetramethyl-3-cyclohexenecarbonitrile (1i)

IR (neat): 2968, 2733, 2663, 2241, 1728, 1454, 1373, 816, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, 3H), 1.19 (s, 3H), 1.65 (s, 3H), 1.67 (s, 3H), 1.86 (d, J = 18.4 Hz, 1H), 2.17 (d, J = 18.4 Hz, 1H), 2.35 (d, J = 17.8 Hz, 1H), 2.53 (d, J = 17.8 Hz, 1H), 9.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 19.0, 23.3, 25.9, 33.7, 35.3, 43.9, 56.0, 118.5, 119.8, 125.3, 195.1; MS (EI, 70 eV): *m/z* 191.2 $[M]^+$.

2-Benzyl-2-phenylsulfanyl-5-(*tert*-butyl-dimethylsilanyl-oxy)-pentanoic acid ethyl ester (2h)

The typical procedure for the preparation of **2a** was followed; **1h** (138 mg, 0.37 mmol) was used as starting material. Flash chromatography (hexane-ethyl acetate 40:1) afforded **2h** as a yellow oil. Yield: 143 mg (85%).

IR (neat): 3062, 2954, 1724, 1471, 1095, 835, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H), 0.88 (s, 9H), 1.17 (t, J = 7.1 Hz, 3H), 1.60-1.79 (m, 3H), 1.87-2.01 (m, 1H), 3.05 (d, J = 14.1 Hz, 1H), 3.33 (d, J = 14.1 Hz, 1H), 3.50-3.62 (m, 2H), 4.00-4.16 (m, 2H), 7.19-7.25 (m, 5H), 7.28-7.40 (m, 3H), 7.49 (broad, d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = -5.3, 14.0, 18.4, 26.0, 27.8, 29.4, 40.2, 60.0, 61.1, 63.1, 126.8, 128.1, 128.7, 129.2, 130.3, 131.2, 136.5, 136.7, 172.6; HRMS-FAB: *m/z* $[M+H]^+$ calcd. for $C_{26}H_{39}O_3SiS$: 459.2389; found: 459.2386.

3,4,6,6-Tetramethyl-1-phenylsulfanyl-cyclohex-3-ene-carbaldehyde (2i)

The typical procedure for the preparation of **2a** was followed; **1i** (120 mg, 0.63 mmol) was used as starting material. Flash chromatography (hexane-ethyl acetate 40:1) afforded **2i** as a colorless oil. Yield: 50 mg (29%).

IR (neat): 3128, 3059, 2721, 1718, 1660, 1593, 1514, 1410 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (s, 3H), 1.10 (s, 3H), 1.56 (d, J = 19.6 Hz, 1H), 1.61 (s, 3H), 1.66 (s, 3H), 1.67 (d, J = 19.6 Hz, 1H), 1.74 (d, J = 17.6 Hz, 1H), 1.94 (d, J = 17.6 Hz, 1H), 6.96-7.53 (m, 5H), 9.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5, 19.1, 23.3, 28.7, 29.3, 32.0, 46.6, 55.7, 122.2, 124.5, 125.4, 129.1, 130.1, 137.6, 206.0; MS (EI, 70 eV): *m/z* 274.1 $[M]^+$.

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