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REGIODEFINED SYNTHESIS OF α-BROMO, α-PHENYLTHIO, AND α-PHENYLSELENO KETONES BY MEANS OF SPECIFIC SUBSTITUTION OF THE TRIMETHYSILYL GROUP IN α-TRIMETHYLSILYL KETONES

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Summary

Regiodefined α-monobromo ketones are readily obtained by the interaction of bromine with an equivalent of α-trimethylsilyl ketones, in an excellent yield. Analogous selective substitution of the trimethylsilyl group on phenylthio and phenylseleno groups can be attained by the reaction of phenylsulfenyl chloride or phenylselenenyl bromide with α-trimethylsilyl ketones in the presence of zinc bromide in dichloromethane.

Introduction

In spite of the synthetic utility of aliphatic ketones, there is no direct methodology to differentiate between two α-positions of unsymmetrically substituted ketones except where an appreciable energy difference is present between two enolate forms [1–3]. Tedious and lengthy procedures are therefore required in order to introduce any functional group into the specific α-site of the ketone. These problems would be circumvented if α-substituted ketones which include a proton-equivalent functional group as an auxiliary are synthesized specifically. Thus, α-trimethylsilyl ketones (**1**) were designed as the key intermediate to satisfy the requirements and the regiocontrolled procedures for their synthesis [4–6].

Recently we reported the regio- and stereocontrolled synthesis of trimethylsilyl enol ethers (**2**) by means of the isomerization of **1** under thermal or catalytic conditions [7]. Since it is well known that silyl enol ethers react regiospecifically with various types of electrophile through addition-elimination or direct substitution [8,9], the regiospecific substitution of trimethylsilyl group in **1** is realized by relayed reactions (Route 1 in Scheme 1). However, the direct conversion of **1** is interesting from the synthetic point of view. Previously few examples were reported with regard to the reaction of **1** [10,11] because of the lack of a convenient synthetic method

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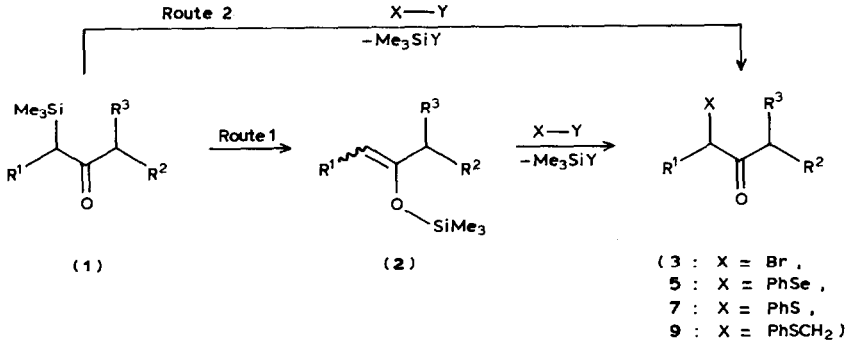


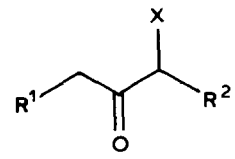
SCHEME 1

[12–19]. Here we describe successful reactions of **1** with bromine, phenylselenenyl bromide, and phenylsulfenyl chloride to give respectively **3**, **5**, and **7** in good yields.

Results and discussion

When an equimolar amount of bromine was added dropwise to a dichloromethane solution of **1a** at −78°C, bromine was consumed immediately to give **3a** as a sole product. The structure of **3a** was deduced from the ^{1}H NMR spectrum which showed the absence of regioisomer **4a** (less than 3%). The regiochemical purity did not change during bulb-to-bulb distillation. Analogous bromine substitution of **1b–1l** was carried out successfully. The structures were confirmed by comparison of ^{1}H NMR spectra with those in the literature for **3b** [22], **3c** [25], and **3d** [21] and by the fact that the diagnostic signals of the methine-proton bonded to bromine (a sharp quartet for **3e**, **3f**, and **3h** and a sharp triplet for **3i**, **3j**, **3k**, and **3l**) did not

	R^1	R^2	R^3
a	H	CH_3	H
b	H	n-C_4H_9	H
c	H	CH_3	CH_3
d	H	C_2H_5	C_2H_5
e	CH_3	n-C_4H_9	H
f	CH_3	n-C_5H_{11}	H
g	CH_3	n-C_4H_9	C_2H_5
h	CH_3		$-(CH_2)_5-$
i	n-C_5H_{11}	CH_3	H
j	n-C_5H_{11}	C_2H_5	H
k	n-C_5H_{11}	n-C_4H_9	H
l	n-C_5H_{11}	CH_3	CH_3



(**4** : X = Br ,
6 : X = PhSe ,
8 : X = PhS)

TABLE 1

α-BROMO KETONE 3 DERIVED FROM α-SILYL KETONE 1

Entry	α-Bromo ketone 3	Yield [a] (%)	B.p. [b] (°C/Torr)	IR ν(C=O) (cm^{-1})	^{1}H NMR (ppm) δ(Br–C–OH) [c]	δ((O=C)–C–H) [d]
1	**3a**	95	60/2	1710	3.75 (s)	2.65 (q, *J* 7.4 Hz)
2	**3b**	85	72/1.5	1712	3.76 (s)	2.62 (t, *J* 6.5 Hz)
3	**3c**	81	68/2	1713	3.91 (s)	3.10 (sept., *J* 6.8 Hz)
4	**3d**	98	66/2	1713	3.68 (s)	2.63 (quint., *J* 6.8 Hz)
5	**3e**	86	99/4	1713	4.28 (q, *J* 7.5 Hz)	2.61 (d.t, *J* 6.9 Hz)
6	**3f**	98	103/1.5	1712	4.30 (q, *J* 6.9 Hz)	2.65 (d.t, *J* 6.5 Hz)
7	**3g**	100	85/0.5	1713	4.34 (q, *J* 6.5 Hz)	2.5–3.1 (m)
8	**3h**	100	93/1	1712	4.38 (q, *J* 6.3 Hz)	2.3–3.1 (m)
9	**3i**	93	102/1.5	1715	4.14 (t, *J* 6.9 Hz)	2.5–3.0 (m)
10	**3j**	95	88/1	1714	4.20 (t, *J* 6.8 Hz)	2.64 (d.t, *J* 6.3 Hz)
11	**3k**	89	95/0.7	1714	4.24 (t, *J* 6.8 Hz)	2.5–2.8 (m)
12	**3l**	88	93/0.7	1715	4.25 (t, *J* 6.8 Hz)	3.00 (sept., *J* 7.0 Hz)

[a] Isolated yield. [b] Bulb-to-bulb distillation. [c] Methine or methylene protons. [d] Methine or methylene protons.

collapse in the ^{1}H NMR spectra. The corollary was also supported by comparison of **3f** with **3i** and by comparison of **3j** with the authentic mixed sample from 4-decanone. The results summarized in Table 1 reveal that the trimethylsilyl group of **1** is specifically replaced by the bromine atom. The reported method for the regiodefined synthesis of **3** includes the homologation of aldehydes or carboxylic esters using α-bromo carbanions under strictly controlled conditions [20–24]. Since starting ketones **1** are prepared readily and with complete selectivity by rhodium catalyzed methods [4–6] and are more stable than trimethylsilyl enol ethers, the accomplishment of regiocontrol in the presence of unstable **3** demonstrated the utility of **1**.

On the other hand, when phenylselenenyl bromide or phenylsulfenyl chloride was used to react with **1a**, the expected product **5a** or **7a** was obtained in a poor yield and accompanied with the regioisomer **6a** (**5a**/**6a** = 80/20) or **8a** (**7a**/**8a** = 90/10) at room temperature. The addition of a catalytic amount of zinc bromide, however, drastically improved the yield and the regioselectivity of **5a** or **7a**. The analogous phenylselenenylation of **1** proceeded to give **5b**, **5h**, **5i**, **5j**, and **5l** with retention of regiochemistry. The structures of these products were determined by IR and ^{1}H NMR spectra and elemental analyses. The regiochemical purity was determined by GLC analyses. Regiochemical control in the synthesis of α-phenylseleno ketones **5** has been reported from a different point of view [26–28]; however, it requires the specific manipulation which is not applicable to the synthesis of **3**. Therefore, our new approach is very convenient for the synthesis of **3**, **5**, and **7** because these compounds are readily derived from the common intermediate **1**.

Although the precise role of zinc bromide is not clear at present, the isomerization of **1a** to **2a** at the first stage can be excluded under the reaction conditions. In fact, in the reaction of **1a** with benzoyl chloride, phenacyl bromide, and diethyl chlorophosphate, all starting compounds were recovered intact even in the presence of zinc bromide. It suggests that the trimethylsilyl group of **1** is directly substituted

by incoming electrophiles. Similarly, chloromethylphenyl thioether reacts with **1a**; with the aid of zinc bromide, to give **9a**

Experimental

All reactions were carried out in an atmosphere of argon or nitrogen. The IR spectra in carbon tetrachloride were recorded on a Jasco IRA-2. A Jeol C-60HL or a Hitachi R-600 was used to record the ^{1}H NMR spectra in carbon tetrachloride using tetramethylsilane as the internal standard. GLC analyses were performed on a Shimazu GC-4BPT with TCD and a 2m × 3mm i.d. column of 10% PEG-2M on Uniport B. α-Trimethylsilyl ketones **1** were prepared by the reported method [4–6].

Synthesis of α-bromo ketones (3).

The case of 1-bromobutan-2-one (**3a**) is described below as a typical example.

1-Bromobutan-2-one (3a). A dichloromethane solution (10 ml) of bromine (0.43 g, 2.7 mmol) was added dropwise to a stirred dichloromethane solution (20 ml) of **1a** (0.62 g, 2.7 mmol) at −78°C. The brown color disappeared as soon as the bromine was added. The clear pale-yellow solution resulted after addition of bromine was completed; at the same temperature. The solvent was evaporated off under reduced pressure and the residue was purified by bulb-to-bulb distillation to give **3a** (0.39 g, 95%) as a pale-yellow oil.

Synthesis of α-phenylseleno ketones (5)

1-Phenylselenobutan-2-one (5a). Dry zinc bromide (0.088 g, 0.39 mmol) was suspended in 10 ml of dichloromethane. Ketone **1a** (0.21 g, 1.5 mmol) and a dichloromethane solution (15 ml) of phenylselenenyl bromide, prepared in situ from diphenyldiselenide (0.23 g, 0.74 mmol) and bromine (0.12 g, 0.74 mmol), were added successively to the above suspension at −78°C. The mixture was stirred for 15 min at the same temperature. During that time, the mixture changed to a clear orange-yellow solution. Saturated aqueous sodium bicarbonate (10 ml) was added to this solution and the phases were separated. The aqueous phase was extracted with diethyl ether (15 ml × 3), the combined organic portions were washed with water (20 ml), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by column chromatography on silica gel using a mixed solvent (hexane/ethyl acetate = 99/1) as eluent and then by bulb-to-bulb distillation (160°C/0.4 Torr) to give **5a** (0.21 g, 67%) as a yellow oil. IR, ν(C=O): 1700 cm^{-1}. ^{1}H NMR: δ (ppm) 1.08 (CH_3, 3H, t, J 6.8 Hz), 2.50 (CH_2, 2H, q, J 6.8 Hz), 3.43 (CH_2SePh, 2H, s), and 7.0–7.6 (Ph, 5H, m).

GLC analysis of this sample revealed that the product was contaminated by 3% of regioisomer **6a**.

1-Phenylselenoheptan-2-one (5b). Analogous treatment of $ZnBr_2$ (0.042 g, 0.19 mmol), **1b** (0.201 g, 1.08 mmol), and PhSeBr (0.52 mmol) in dichloromethane (16 ml) gave **5b** (0.227 g, 78%) as a yellow oil. B.p.: 165°C/Torr. (Found: C, 57.87; H, 6.58. $C_{13}H_{18}OSe$ calcd.: C, 57.99; H, 6.74%). IR, ν(C=O): 1710 cm^{-1}. ^{1}H NMR: δ (ppm) 0.96 (CH_3, 3H, t, J 6.0 Hz), 1.2–1.8 [$(CH_2)_3$, 6H, m], 2.62 [CH_2C(=O), 2H, t, J 6.9 Hz], 3.60 (CH_2SePh, 2H, s), and 7.3–7.75 (Ph, 5H, m).

1-Cyclohexyl-2-phenylselenenopropan-1-one (5h). Analogous treatment of $ZnBr_2$ (0.035 g, 0.16 mmol), **1h** (0.229 g, 1.08 mmol), and PhSeBr (0.83 mmol) in

dichloromethane (15 ml) gave **5h** (0.187 g, 76%) as an orange-yellow oil. B.p.: 165°C/0.3 Torr. (Found: C, 61.21; H, 6.76. $C_{15}H_{20}OSe$ calcd.: C, 61.01; H, 6.83%). IR, ν(C=O): 1700 cm^{-1}. ^1H NMR: δ (ppm) 1.42 (CH_3, 3H, d, J 7.2 Hz), 1.3–2.0 (Cyclohexyl, 10H, m), 2.6–3.0 [CH–C(=O), 1H, m], 3.91 (CH–SePh, 1H, q, J 7.2 Hz), and 7.3–7.8 (Phenyl, 5H, m).

4-Phenylselenononan-3-one (5i). Analogous treatment of $ZnBr_2$ (0.014 g, 0.60 mmol), **1i** (0.42 g, 2.0 mmol), and PhSeBr (2.0 mmol) in dichloromethane (25 ml) gave **5i** (0.52 g, 88%) as an orange-yellow oil. B.p.: 123°C/0.2 Torr. (Found: C, 60.52; H, 7.63. $C_{15}H_{22}OSe$ calcd.: C, 60.60; H, 7.46%). IR, ν(C=O): 1705 cm^{-1}. ^1H NMR: δ (ppm) 0.87 (CH_3, 3H, broad t., J 6.5 Hz), 1.03 (CH_3, 3H, t, J 6.9 Hz), 2.2–2.9 (CH_2, 2H, m), 3.51 (CH–SePh, 1H, t, J 6.8 Hz), and 7.0–7.7 (Phenyl, 5H, m).

5-Phenylselenodecan-4-one (5j). Analogous treatment of $ZnBr_2$ (0.025 g, 0.11 mmol), **1j** (0.316 g, 1.38 mmol), and PhSeBr (1.25 mmol) in dichloromethane (17 ml) gave **5j** (0.319 g, 82%) as an orange-yellow oil. B.p.: 162°C/0.3 Torr. (Found: C, 61.86; H, 7.52. $C_{16}H_{24}OSe$ calcd.: C, 61.73, H, 7.77%). IR, ν(C=O): 1705 cm^{-1}. ^1H NMR: δ (ppm) 0.92 (CH_3, 3H, t, J 6.0 Hz), 0.93 (CH_3, 3H, t, J 6.5 Hz), 1.1–1.9 ($CH_2 \times 5$, 10H, m), 2.3–2.8 (CH_2, 2H, m), 3.59 (CH–SePh, 1H, t, J 7.5 Hz), and 7.3–7.7 (Phenyl 5H, m).

2-Methyl-4-phenylselenononan-3-one (5l). Analogous treatment of $ZnBr_2$ (0.041 g, 0.18 mmol), **1l** (0.268 g, 1.17 mmol), and PhSeBr (1.17 mmol) in dichloromethane (15 ml) gave **5l** (0.317 g, 87%) as an orange-yellow oil. B.p.: 163°C/0.3 Torr. (Found: C, 61.85; H, 7.51. $C_{16}H_{24}OSe$ calcd.: C, 61.73; H, 7.7%). IR, ν(C=O): 1705 cm^{-1}. ^1H NMR: δ (ppm) 0.91 (CH_3, 3H, broad t, J 6 Hz), 1.08 (CH_3, 3H, d, J 6.8 Hz), 1.15 (CH_3, d, J 6.8 Hz), 1.3–1.9 ($CH_2 \times 4$, 8H, m), 2.95 (Me_2CH, 1H, sept, J 6.6 Hz), 3.68 (CH–SePh, 1H, t, J 7.0 Hz), and 7.3–7.7 (Phenyl, 5H, m).

Synthesis of α-thioketones 7a and 9a

Synthesis of 1-phenylthiobutan-2-one (7a). To a suspension of dry zinc bromide (0.12 g, 0.55 mmol) in 30 ml of dichloromethane, ketone **1a** (0.74 g, 5.1 mmol) was added with stirring and the mixture was cooled to −78°C. A dichloromethane (10 ml) solution of phenylsulfenyl chloride (0.80 g, 5.5 mmol) was added dropwise to the above suspension at the same temperature. The reddish-orange color of phenylsulphenyl chloride faded rapidly after addition, to give a clear, yellow solution. After the addition of phenylsulfenyl chloride the solution was stirred for 30 min at −78°C and diluted with 50 ml of diethyl ether at room temperature. The resulting solution was washed with brine (30 ml × 3), dried over anhydrous $MgSO_4$, and the solvent was evaporated off under reduced pressure. The residue was purified by bulb-to-bulb distillation (155°C/1 Torr) to give **7a** (0.70 g, 77%) as a pale-yellow oil. IR, ν(C=O): 1703 cm^{-1}. ^1H NMR: δ (ppm) 1.03 (CH_3, 3H, t, J 6.8 Hz), 2.56 (CH_2, 2H, q, J 6.8 Hz), 3.51 (CH_2SPh, 2H, s), and 7.15 (Phenyl, 5H, broad s).

Synthesis of 1-phenylthiopentan-3-one (9a). Ketone **1a** (0.26 g, 1.8 mmol) was added to a suspension of zinc bromide (0.025 g, 0.11 mmol) in 10 ml of dichloromethane, with stirring and the mixture was cooled to −78°C. A dichloromethane (2 ml) solution of chloromethyl phenylthio ether (0.29 g, 1.8 mmol) was added dropwise to the above suspension at the same temperature. The resulting solution was stirred for 3 h at room temperature and diluted with 30 ml of diethyl ether. The solution was washed with brine (30 ml × 3), dried over anhydrous $MgSO_4$, and the

solvent was evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel using a mixed solvent (hexane/ethyl acetate = 95/5) as eluent to give **9a** (0.21 g, 61%) as a pale-yellow oil. B.p.: 150°C/0.6 Torr. IR, ν(C=O): 1713 cm^{-1}. ^1H NMR: δ (ppm) 1.00 (CH_3, 3H, t, J 6.8 Hz), 2.28 (CH_2, 2H, q, J 6.8 Hz), 2.4–3.1 ($CH_2 \times 2$, 4H, m), and 6.9–7.1 (Phenyl, 5H, m).

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