Dianion of Sulfinylacetone as a Synthetic Equivalent of β-Enolate of Propionic Acid: A Novel Synthesis of Carboxylic Acids from Alkyl Halides with Three-Carbon Elongation

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The reaction of the dianion of phenylsulfinylacetone with alkyl halides afforded β-keto sulfoxides, which were first chlorinated with hexachloroethane and then treated successively with KH and *t*-BuLi to give carboxylic acids in three-steps in moderate overall yields from the alkyl halides. This procedure affords a good method for a synthesis of carboxylic acids from alkyl halides with three-carbon elongation.

Key words carboxylic acid; sulfoxide; sulfoxide-lithium exchange; alkylidene carbenoid; three-carbon elongation

Carboxylic acids and their derivatives are obviously among the most important and fundamental compounds in organic and synthetic organic chemistry. Innumerable studies on the preparation and chemistry of carboxylic acids and their derivatives have already been reported.[1—5] Oxidation of primary alcohols and aldehydes is the elemental way for the synthesis of carboxylic acids.[6—9] Other interesting methods are the use of umpoled synthons[10] such as hydroxycarbonyl anion ($^-$COOH) and α-carbanion of acetic acid ($^-CH_2COOH$) with several electrophiles. Synthetic equivalents of the carboxylic acid β-enolates ($^-CH_2CH_2COOH$) are also known,[11—15] albeit in limited number.

We recently reported a versatile procedure for one-carbon elongation of methyl esters,[16] aldehydes, and carboxylic acid chlorides[17] to carboxylic acids and their derivatives *via* α-chloro-β-keto sulfoxides (Chart 1). In continuation of our interest in the synthesis of carboxylic acids and their derivatives, herein we report a new synthesis of carboxylic acids **5** from phenylsulfinylacetone **1** and alkyl halides through 1-chloro-1-(phenylsulfinyl)-2-alkanone **4** as shown in Chart 2. It is interesting to note that in this procedure the dianion of phenylsulfinylacetone **2** is a synthetic equivalent of the carboxylic acid β-enolate **6**.

Phenylsulfinylacetone **1** was easily prepared in large quantity from chloroacetone and sodium benzenethiolate in ethanol ((phenylthio)acetone; 89%) followed by oxidation with 3-chloroperoxybenzoic acid in CH_2Cl_2 at −15 °C (96%).

Representative example of this procedure is reported for the synthesis of undecanoic acid **5a** (Chart 2 and Table 1, entry 1). Generation of the dianion **2** and alkylation with alkyl halides were first investigated using sodium hydride and *n*-butyllithium, and 1-iodooctane[18,19]; however, the desired alkylated product **3a** was obtained in only up to 50% yield. After some investigation, use of 2.2 eq of lithium diisopropylamide (LDA)[20] in tetrahydrofuran-hexamethylphosphoramide (THF-HMPA) at 0 °C to room temperature was found to be the conditions of choice and the desired **3a** was obtained in 82% yield.

Mono chlorination of the β-keto sulfoxide **3** was investigated by using **3a** as an representative example, and again we found that the mono chlorination was not an easy task. The results for the chlorination are summarized in Table 2.

First, **3a** was treated with *N*-chlorosuccinimide (NCS) in chloroform at room temperature.[21] Dichlorination was found to be the main reaction with this reagent to give **7** in good yield (entry 1). Next, we investigated the reaction of a carbanion with an electrophilic chlorinating agent. The β-keto sulfoxide **3a** was first treated with LDA followed by sulfuryl chloride. This reaction was found to be effective for this purpose; however, significant amount of the dichlorinated product **7** was still obtained (entry 2). We finally found that hexachloroethane was the reagent of choice for this mono chlorination (entry 3). The amounts of the base and hexachloroethane were investigated (entries 4—6) and the conditions shown in entry 6 were finally found to give the best result to afford the desired **4a** in 85% yield.

The final step was conducted under the similar conditions as described before.[16] Treatment of the α-chloro-β-keto sulfoxide **4a** with 2-eq of KH in THF at 0 °C affords a potassium enolate, which was then reacted with 4 eq of *t*-butyllithium to afford a lithium alkylidene carbenoid. This gave a

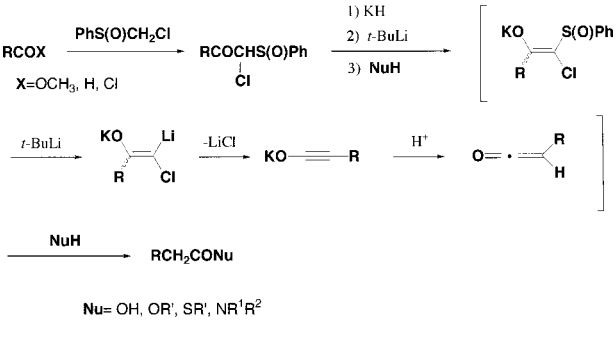

Chart 1

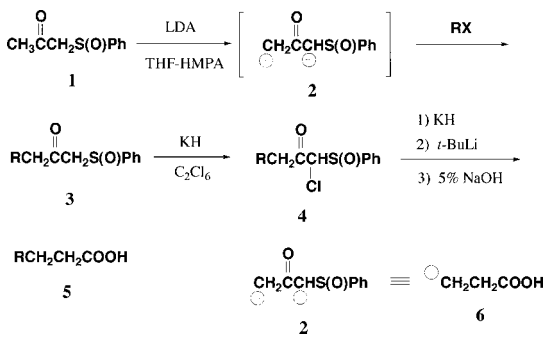

Chart 2

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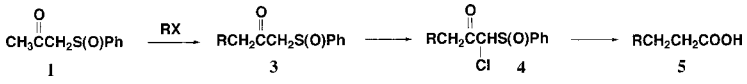
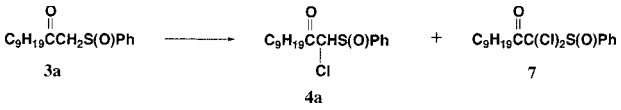
Table 1. The Synthesis of Carboxylic Acids from Alkylhalides with Three-Carbon Elongation



Entry	RX	3		4		5
		Conditions	(Yield/%)	Conditions[a)]	(Yield/%)	(Yield/%)
1	$C_8H_{17}I$	r.t. 1 h	**3a** (82)	1) 40 min 2) 2 h	**4a** (85)	**5a** (77)
2	$PhCH_2Br$	0 °C 30 min	**3b** (78)	1) 40 min 2) 3 h	**4b** (77)	**5b** (74)
3	$CH_3CH_2CHCH_3$ | I	r.t. 1.5 h	**3c** (79)	1) 40 min 2) 1 h	**4c** (72)	**5c** (82)
4	$C_5H_{11}C{\equiv}CCH_2Cl$	r.t. 1.5 h	**3d** (70)	1) 40 min 2) 2 h	**4d** (88)	**5d** (69)

a) 1): The conditions for the treatment of **3** with KH. 2): The conditions for the treatment of the enolate with C_2Cl_6.

Table 2. Mono Chlorination of 1-(Phenylsulfinyl)-2-undecanone **3a**



Entry	Conditions and chlorinating agent	4a	7
		Yield/%	Yield/%
1	NCS (1.8 eq), $CHCl_3$, room temp. for 8 h	6	85
2	LDA (1.0 eq), THF, −78 °C, 10 min then SO_2Cl_2 (1.5 eq), −78 °C, 10 min	40	25
3	NaH (1.0 eq), THF, 0 °C, 10 min then C_2Cl_6 (1.0 eq), 0 °C, 17 h[a)]	49	4
4	KH (1.0 eq), THF, room temp., 30 min then C_2Cl_6 (1.0 eq), room temp. for 4 h	66	trace
5	KH (2.0 eq), THF, room temp., 40 min then C_2Cl_6 (1.5 eq), room temp. for 3 h	70	trace
6	KH (2.5 eq), THF, room temp., 40 min then C_2Cl_6 (1.5 eq), room temp. for 2 h	85	trace

a) Other conditions using NaH gave worse results.

ketene with rearrangement of the alkyl group. Finally, the reaction of this ketene with 5% NaOH gave the desired carboxylic acid **5a** in 77% yield. The other examples are shown in Table 1.

Here we have developed a new method for the synthesis of carboxylic acid from an alkyl halide with three-carbon elongation.

Experimental

1-(Phenylsulfinyl)undecan-2-one (3a) To a solution of LDA (1.32 mmol) in 1 ml of THF at 0 °C was added HMPA (0.3 ml) followed by a solution of **1** (109 mg; 0.6 mmol) in THF. After being stirred for 30 min, 1-iodooctane (120 mg; 0.5 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by adding sat. aq. NH_4Cl. The product was purified by silica-gel column chromatography to afford **3a** (120 mg; 82%) as colorless crystals; mp 83.5—84 °C (AcOEt–hexane). IR (KBr) 1706 (CO), 1089, 1032 (SO), 734 cm^{-1}. ^{1}H-NMR δ 0.87 (3H, t, J=6.8 Hz), 1.23 (12H, m), 1.45—1.55 (2H, m), 2.38—2.54 (2H, m), 3.75, 3.88 (each 1H, d, J=13.6 Hz), 7.51—7.55 (3H, m), 7.64—7.67 (2H, m). MS *m/z* (%) 294 (M^+, 1), 277 (22), 169 (18), 155 (21), 125 (100). *Anal.* Calcd for $C_{17}H_{26}O_2S$: C, 69.34; H, 8.90; S, 10.89. Found: C, 69.20, H, 8.75, S, 10.81. Other β-keto sulfoxides (**3b**—**d**) were synthesized in a similar manner and are summarized in Table 1.

3b: Colorless crystals; mp 69—70 °C (AcOEt–hexane). IR (KBr) 1715 (CO), 1442, 1355, 1087, 1035 (SO), 1010 cm^{-1}. ^{1}H-NMR δ 2.79—2.86 (4H, m), 3.74, 3.84 (each 1H, d, J=13.4 Hz), 7.12—7.27 (5H, m), 7.51—7.59 (5H, m). MS *m/z* (%) 272 (M^+, 3), 256 (23), 147 (83), 125 (48), 105 (79). *Anal.* Calcd for $C_{16}H_{16}O_2S$: C, 70.55; H, 5.92; S, 11.77. Found: C, 70.33; H, 5.83; S, 12.03.

3c: Colorless oil; IR (neat) 1716 (CO), 1443, 1372, 1089, 1039 (SO), 998, 748 cm^{-1}. ^{1}H-NMR δ 0.81—0.87 (6H, m), 1.13—1.30 (2H, m), 1.84—1.93 (1H, m), 2.25, 2.32 (each 0.5H, dd, J=7.9, 16.9 Hz), 2.43, 2.49 (each 0.5H, dd, J=5.6, 17.0 Hz), 3.73, 3.76 (each 0.5H, d, J=5.8 Hz), 3.87, 3.90 (each 0.5H, d, J=7.3 Hz), 7.52—7.54 (3H, m), 7.65—7.67 (2H, m). MS *m/z* (%) 238 (M^+, 2), 221 (20), 182 (15), 125 (100). Calcd for $C_{13}H_{18}O_2S$: M, 238.1027. Found: *m/z* 238.1032.

3d: Colorless crystals; mp 59—60 °C (AcOEt–hexane). IR (KBr) 1706 (CO), 1037 (SO), 730, 686 cm^{-1}. ^{1}H-NMR δ 0.88 (3H, t, J=7.0 Hz), 1.28—1.33 (4H, m), 1.42—1.45 (2H, m), 2.06—2.10 (2H, m), 2.36—2.40 (2H, m), 2.62—2.76 (2H, m), 3.81, 3.89 (each 1H, d, J=13.7 Hz), 7.52—7.66 (5H, m). MS *m/z* (%) 290 (M^+, 3), 273 (8), 165 (50), 123 (100). *Anal.* Calcd for $C_{17}H_{22}O_2S$: C, 70.30; H, 7.63; S, 11.04. Found: C, 70.31, H, 7.47, S, 10.33.

1-Chloro-1-(phenylsulfinyl)undecan-2-one (4a) To a flame-dried flask was added KH (50 mg; 1.25 mmol) and 2 ml of THF. To the suspension was added a solution of **3a** (147 mg; 0.5 mmol) in 1 ml of THF and the reaction mixture was stirred for 40 min. After the evolution of H_2 ceased, a solution of C_2Cl_6 (142 m; 0.6 mmol) in 1 ml of THF was added and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by sat. aq. NH_4Cl and the product was purified by silica-gel column chromatography to afford 141 mg (85%) of **4a** (a mixture of two diastereomers) as a colorless oil. IR (neat) 1702 (CO), 1468, 1443, 1398, 1088, 1055 (SO), 743, 688 cm^{-1}. ^{1}H-NMR δ 0.88 (3H, t, J=7.0 Hz), 1.25 (12H, m), 1.49—1.57 (2H, m), 2.33—2.40 (0.5H, m), 2.49—2.55 (0.5H, m), 2.67—2.77 (1H, m), 4.99 (0.5H, s), 5.00 (0.5H, s), 7.47—7.70 (5H, m). MS *m/z* (%) 328 (M^+, 7), 155 (33), 125 (100). Calcd for $C_{17}H_{25}ClO_2S$: M, 328.1262. Found: *m/z* 328.1252. Other α-chloro-β-keto sulfoxides (**4b**—**d**) were synthesized in a similar manner and are summarized in Table 1.

4b: Colorless oil; IR (neat) 1714 (CO), 1444, 1089, 1056 (SO), 746, 699 cm^{-1}. ^{1}H-NMR δ 2.62—2.91 (3H, m), 3.01—3.12 (1H, m), 4.99 (0.57H, s), 5.03 (0.43H, s), 7.12—7.63 (10H, m). MS *m/z* (%) 306 (M^+, 9), 181 (22), 145 (17), 125 (100). Calcd for $C_{13}H_{18}O_2S$: M, 306.0479. Found: *m/z*

306.0475.

4c: Colorless oil; IR (neat) 1716 (CO), 1462, 1444, 1087, 1057 (SO), 747, 688 cm^{-1}. ^{1}H-NMR δ 0.84—0.90 (6H, m), 1.14—1.35 (2H, m), 1.85—1.97 (1H, m), 2.22—2.79 (2H, m), 4.95, 4.96, 4.97, 4.99 (each 0.25H, s), 7.54—7.72 (5H, m). MS *m*/*z* (%) 272 (M^+, 10), 157 (7), 125 (100), 99 (34). Calcd for $C_{13}H_{17}ClO_2S$: M, 272.0637. Found: *m*/*z* 272.0645.

4d: Colorless oil; IR (neat) 1732, 1716 (CO), 1444, 1089, 1056 (SO), 747, 688 cm^{-1}. ^{1}H-NMR δ 0.89 (3H, t, J=7.0 Hz), 1.29—1.33 (4H, m), 1.44—1.47 (2H, m), 2.08—2.12 (2H, m), 2.37—2.40 (2H, m), 2.54—2.62 (0.5H, m), 2.71—2.80 (0.5H, m), 2.92—3.03 (1H, m), 5.06 (0.45H, s), 5.07 (0.55H, s), 7.54—7.70 (5H, m). MS *m*/*z* (%) 324 (M^+, 0.4), 307 (19), 151 (7), 143 (8), 125 (100). Calcd for $C_{17}H_{21}ClO_2S$: M, 324.0950. Found: *m*/*z* 324.0965.

Undecanoic Acid (5a) To a flame-dried flask KH (24 mg; 0.6 mmol) and 2 ml of THF were added. To this suspension was added dropwise a solution of **4a** (100 mg; 0.3 mmol) in 1 ml of THF and the reaction mixture was stirred at 0 °C for 30 min. After the evolution of H_2 ceased, the reaction mixture was cooled to −78 °C and *t*-BuLi (1.2 mmol) was added and the reaction mixture was stirred for 20 min. The reaction was quenched by adding 5% NaOH (0.5 ml) and the reaction mixture was stirred for 10 min, and at 0 °C for 10 min. To the reaction mixture was added $CHCl_3$ and the whole was extracted three times with 5 ml of 5% NaOH. The water layers were combined and acidified with HCl and extracted with $CHCl_3$. The product was purified with short silica-gel column to give 44 mg (78%) of **5a** as a colorless oil. **5a** and **5b** are known compounds.

5c: Colorless oil; IR (neat) 2961, 2875, 1712 (CO), 1463, 1102 cm^{-1}. ^{1}H-NMR δ 0.86—0.89 (6H, m), 1.15—1.51 (4H, m), 1.65—1.72 (1H, m), 2.27—2.42 (2H, m), 10.07 (1H, s). MS *m*/*z* (%) 113 (7), 57 (100), 41 (38).

5d: Colorless oil; IR (neat) 2932, 2859, 1712 (CO), 1435, 1243 cm^{-1}. ^{1}H-NMR δ 0.89 (3H, t, J=7.1 Hz), 1.20—1.56 (6H, m), 1.81 (2H, quintet, J=7.1 Hz), 2.11—2.15 (2H, m), 2.22—2.25 (2H, m), 2.49 (2H, t, J=7.4 Hz), 9.79 (1H, bs). MS *m*/*z* (%) 181 (8), 154 (17), 126 (67), 81 (100).

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References and Notes

1) Some monographs for the chemistry of carboxylic acids and their derivatives, see: Patai S., "The Chemistry of Carboxylic Acids and Esters," John Wiley and Sons, London, 1969.
2) Some monographs for the chemistry of carboxylic acids and their derivatives, see: Zabicky J., "The Chemistry of Amides," John Wiley and Sons, London, 1970.
3) Some monographs for the chemistry of carboxylic acids and their derivatives, see: Patai S., "The Chemistry of Acid Derivatives," Part 1 and 2, John Wiley and Sons, Chichester, 1979.
4) Some monographs for the chemistry of carboxylic acids and their derivatives, see: Sutherland I. O. (ed.), "Comprehensive Organic Chemistry," Vol. 2, Part 9, Pergamon Press, Oxford, 1979.
5) Some monographs for the chemistry of carboxylic acids and their derivatives, see: Patai S., "The Chemistry of Acid Derivatives," Part 1 and 2, John Wiley and Sons, Chichester, 1992.
6) Some recent methods for the oxidation of primary alcohols and aldehydes to carboxylic acids and their derivatives, see: McDonald C. E., Nice L. E., Shaw A. W., Nestor N. B., *Tetrahedron Lett.*, **34**, 2741—2744 (1993).
7) Some recent methods for the oxidation of primary alcohols and aldehydes to carboxylic acids and their derivatives, see: Rhee H., Kim J. Y., *Tetrahedron Lett.*, **39**, 1365—1368 (1998).
8) Some recent methods for the oxidation of primary alcohols and aldehydes to carboxylic acids and their derivatives, see: Zhao M., Song J. L. Z., Desmond R., Tschaen D. M., Grabowski E. J. J., Reider P. J., *Tetrahedron Lett.*, **39**, 5323—5326 (1998).
9) Some recent methods for the oxidation of primary alcohols and aldehydes to carboxylic acids and their derivatives, see: Zhao M., Mano J. L. E., Song Z., Tschaen D. M., Grabowski E. J. J., Reider P. J., *J. Org. Chem.*, **64**, 2564—2566 (1999).
10) Hase T. A., "Umpoled Synthons," John Wiley and Sons, New York, 1987.
11) Nakamura E., Kuwajima I., *J. Am. Chem. Soc.*, **99**, 7360—7362 (1977), and the references cited therein.
12) Ehlinger E., Magnus P., *J. Am. Chem. Soc.*, **102**, 5004—5011 (1980), and the references cited therein.
13) Nakamura E., Kuwajima I., *J. Am. Chem. Soc.*, **105**, 651—652 (1983), and the references cited therein.
14) Werstiuk N. H., *Tetrahedron*, **39**, 205—268 (1983), and the references cited therein.
15) Pastor I. M., Yus M., *Tetrahedron Lett.*, **41**, 5335—5339 (2000), and the references cited therein.
16) Satoh T., Unno H., Mizu Y., Hayashi Y., *Tetrahedron*, **53**, 7843—7854 (1997).
17) Satoh T., Nakamura A., Iriuchijima A., Hayashi Y., Kubota K., *Tetrahedron*, **57**, 9689—9696 (2001).
18) Grieco P. A., Pogonowski C. S., *J. Org. Chem.*, **39**, 732—734 (1974).
19) Kuwajima I., Iwasawa H., *Tetrahedron Lett.*, **1974**, 107—110 (1974).
20) Solladie G., Colobert F., Denni D., *Tetrahedron: Asymmetry*, **9**, 3081—3094 (1998).
21) Tsuchihashi G., Ogura K., *Bull. Chem. Soc. Jpn.*, **44**, 1726 (1971).