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INTRAMOLECULAR ACYLATION OF α -(PHENYLSULFINYL) CARBANIONS: A CONVENIENT SYNTHESIS OF SUBSTITUTED CYCLOHEX-2-ENONES

MANAT POHMAKOTR, PRANEE PHINYOCHEEP and SIRIRAT CHANCHARUNEE
Department of Chemistry, Faculty of Science, Mahidol University, Rama VI Road, Bangkok 10400, Thailand.

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Abstract

A convenient synthesis of substituted cyclohex-2-enones, which involves the intramolecular acylation of an α -(phenylsulfinyl) carbanion followed by pyrolysis, is described.

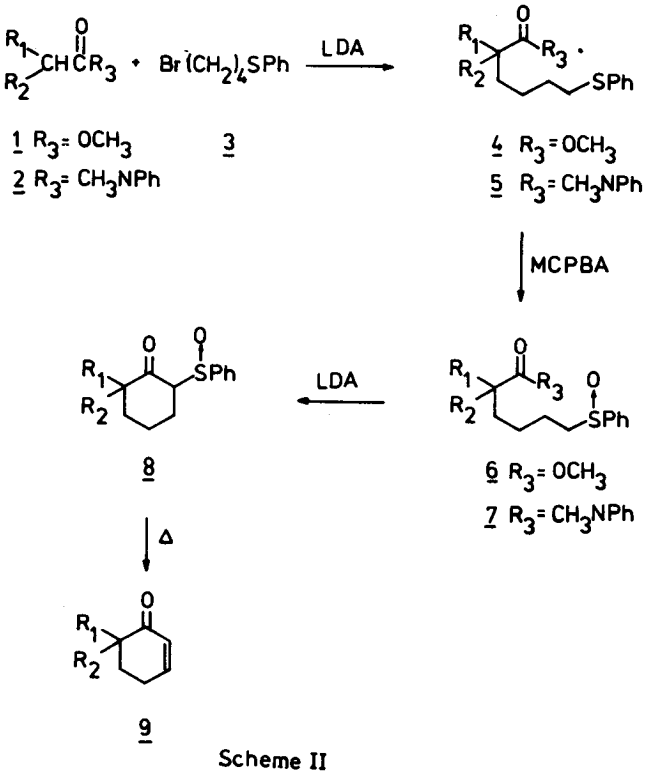
Recently we described convenient syntheses of 5-substituted-cyclopent-2 -enones[1] and 5-methylenecyclopent-2-enones[2] based on the intramolecular acylation of an α-(phenylsulfinyl)carbanion, as the key reaction. We now report an adaptation of this method which can be used for the preparation of 6,6-disubstituted cyclohex-2-enones **(9)** (Scheme 1).

The enolate anion generated from either the ester **(1)** or the amide **(2)** by treatment with lithium diisopropylamide (LDA) was alkylated with 1-bromo-4-(phenylsulfenyl)butane **(3)**. The resulting sulfide [**(4)** or **(5)**, repectively] was not purified but was treated immediately with m-chloroperbenzoic acid (MCPBA) which yielded the corresponding sulfoxide [**(6)** or **(7)**] . When the sulfoxide [**(6)** or **(7)**] was treated with LDA in tetrahydrofuran (THF) at - 78° C, intramolecular acylation occurred and it was converted into the 6,6-disubstituted 2-(phenylsulfinyl)cyclohexanone **(8)** as a mixture of diastereoisomers. Pyrolysis of this compound **(8)** at 120° C under reduced pressure gave a good yield of the 6,6-disubstituted cyclohex-2-enone **(9)**. The results of these experiments are summarized in Table 1.

This sequence was then modified (Scheme II) to provide a simple synthesis of 6,6-disubstituted 5-hydroxycyclohex-2-enones **(14)**.

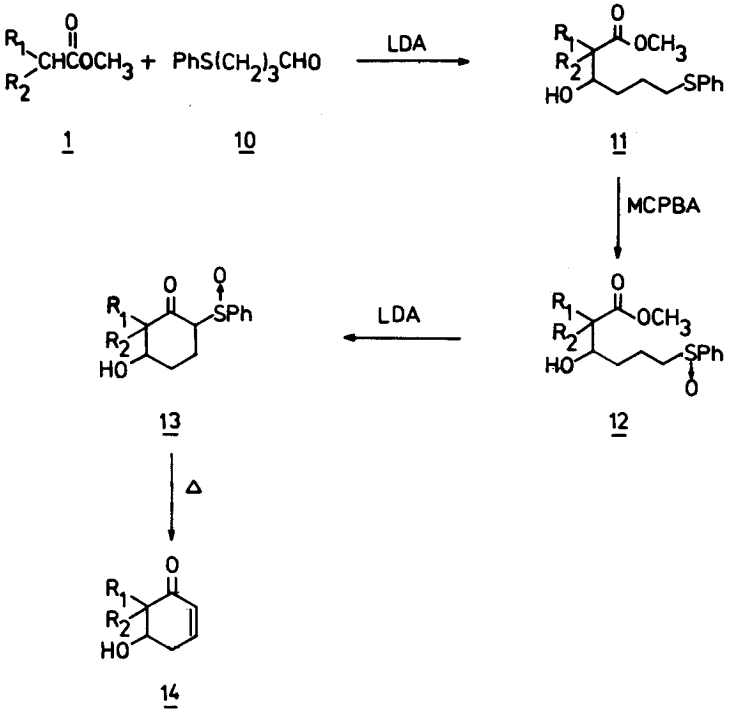
In this case, treatment of the enolate anion derived from the ester **(1)** with 4-(phenylsulfenyl)butanal **(10)** gave the hydroxy sulfide **(11)**. Oxidation of this substance **(11)** with MCPBA yielded the sulfoxide **(12)** which was obtained as a mixture of diastereoisomers. When the sulfoxide **(12)** was treated with LDA in THF at -78°C cyclization occurred and the product **(13)**, which again consisted of a mixture of diastereoisomers, was formed in good yield. Pyrolysis of this product, as before, then

Scheme I



1 R_3= OCH_3
2 R_3= CH_3NPh
3
4 R_3= OCH_3
5 R_3= CH_3NPh
6 R_3= OCH_3
7 R_3= CH_3NPh
8
9

Scheme II



1
10
11
12
13
14

gave the 6,6-disubstituted 5-hydroxycyclohex-2-enone **(14).** The results of these experiments are also included in Table 1.

Melting points were determined on an Electrothermal melting point apparatus. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM 360L instrument operating at 60 MHz. The mass spectra (MS) were measured with a Dupont 490F GC - MS instrument.

The general procedures outlined in Scheme 1 and Scheme 2 are illustrated by the conversion of methyl 2-methylpropanoate into 6,6-dimethylcyclohex-2-enone **(9a)** and 5-hydroxy-6,6-dimethylcyclohex-2-enone **(14a),** respectively. Details of preparations of the related compounds **(9b)** to **(9h)** and **(14b)** to **(14e),** and the spectra of these substances and the intermediates involved in these syntheses, have been deposited.*

Table 1. Percentage Yields of Sulfoxides, Ketosulfoxides and Substituted Cyclohex-2-enones, Prepared According to Schemes I and II

R^1	R^2	Sulfoxide	Ketosulfoxide	Cyclohex-2-enone	Reference
CH_3	CH_3	**6a** (88)	**8a** (89)*	**9a** (75)	3
CH_3	Ph	**6b** (72)*	**8b** (78)*	**9b** (91)	
$-(CH_2)_5-$		**6c** (73)	**8c** (95)*	**9c** (80)	
Ph	Ph	**6d** (81)	**8d** (63)*	**9d** (64)	4
CH_3	H	**7a** (74)*	**8e** (74)*	**9e** (70)	5
CH_3CH_2	H	**7b** (75)*	**8f** (70)*	**9f** (91)	6
n-C_3H_7	H	**7c** (64)*	**8g** (89)*	**9g** (84)	6
n-C_4H_9	H	**7d** (72)*	**8h** (82)*	**9h** (96)	
CH_3	CH_3	**12a** (52)*	**13a** (70)*	**14a** (84)	
CH_3	Ph	**12b** (61)*	**13b** (60)*	**14b** (79)	
$-(CH_2)_5-$		**12c** (62)*	**13c** (80)*	**14c** (71)	
CH_3	n-C_3H_7	**12d** (69)*	**13d** (71)*	**14d** (75)	
n-C_3H_7	n-C_3H_7	**12e** (74)*	**13e** (75)*	**14e** (72)	

**Obtained as a mixture of diastereoisomers.*

* Copies of this material are available on application to the Editor.

6,6-Dimethylcyclohex-2-enone **(9a)**

(i) Methyl 2-methylpropanoate **(1)**, $R^1 = R^2 = CH_3$ (0.70 ml, 6 mmol) was added to a cooled (-78°C) solution of LDA (6 mmol) in THF (20 ml) then the mixture was stirred at 0°C for 1 h. Hexamethylphosphoramide (HMPA) (1 ml, 6 mmol) was then added at -78° C followed by the dropwise addition of a solution of 1-bromo-4-(phenylsulfenyl)butane **(3)** (1.25 g, 5 mmol). After allowing the stirred mixture to reach room temperature overnight, sat. aq. NH_4Cl was added, followed by water. The mixture was extracted with ethyl acetate then the organic layer was washed with water and brine; after drying ($MgSO_4$) the extract was evaporated to afford methyl 2,2-dimethyl-6-(phenylsulfenyl)hexanoate **(4)**, $R_1 = R_2 = CH_3$ as a yellow oil (1.47 g). NMR (CCl_4)δ: 1.13 (s, 6H, 2 $\times CH_3$); 1.26-2.00 (m, 6H, 3 $\times CH_2$); 2.66-3.00 (m, 2H, $PhCH_2$); 3.60 (s, 3H, OCH_3); 6.93-7.40 (m, 5H, ArH).

(ii) A cooled (-78° C) solution of this product (1.47 g, 5.50 mmol) in methylene chloride (50 ml) was treated slowly with a solution of 90% m-chloroperbenzoic acid (0.96 g, 5 mmol) in the same solvent (50 ml). The reaction was monitored by thin layer chromatography and when complete was poured into a mixture of sat. aq. $NaHCO_3$ (100 ml) and ethyl acetate (100 ml). The organic layer was washed with sat. aq. $NaHCO_3$ water and brine then dried ($MgSO_4$) and evaporated. After purification by preparative layar chromatography (PLC) on silica gel with 40% ethyl acetate in hexane methyl 2,2-dimethyl -6-(phenylsulfinyl)hexanoate **(6a)** was obtained as a yellow oil (1.24 g, 88%). IR (neat): 1725, 1470, 1440, 1160, 1050, 750, 690 cm^{-1}. NMR (CCl_4) δ : 1.13 (s, 6H, 2xCH_3); 1.23 - 2.13 (m, 6H, 3xCH_2): 2.70 (m, 2H, CH_2SOPh); 3.61 (s, 3H, OCH_3); 7.30 - 7.80 (m, 5H, ArH). MS (m/e): 282 (M^+,8%), 265 (6), 222 (7), 181 (33), 157 (29), 97 (66), 73 (48), 55 (100).

(iii) A solution of the sulfoxide **(6a)** (0.096 g, 3.40 mmol) in THF (5 ml) was added dropwise to a cooled (-78° C) solution of LDA (10.20 mmol) in THF (30 ml). After stirring for 1 h. The mixture was warmed to 0°C, stirred for a further 1 h then quenched with sat. aq. NH_4Cl and extracted with ethyl acetate. The extract was washed with sat. aq. NH_4Cl, water and brine then dried ($MgSO_4$) and evaporated to yield 6,6-dimethyl-2-(phenylsulfinyl) cyclohexanone **(8a)** which formed pale yellow crystals (0.60g, 71%) m.p. 130 - 131° C from ether. IR (Nujol): 1695, 1580, 1040, 750, 690 cm^{-1}. NMR ($CDCl_3$) δ : 1.10 (s, 6H, 2xCH_3); 1.56-2.23 (m, 6H, 3xCH_2); 3.60 (m, 1H, CHSOPh); 7.33 - 7.80 (m, 5H, ArH). MS (m/e): 250 (M^+, 87%), 202 (7), 126 (53), 125 (64), 109 (15), 97 (100), 86 (23), 78 (47), 77 (38), 69 (36), 68 (49).

(iv) The neat sulfoxide **(8a)** was subjected to pyrolysis at 120°C/0.1-0.2 Torr for 2-3 h and the product was purified by PLC. 6,6-Dimethylcyclohex-2-enone **(9a)** was then obtained as a colourless liquid, the spectra of which agreed with those recorded in the literature[3].

5-Hydroxy-6,6-dimethylcyclohex-2-enone **(14a)**

(i) Oxalyl chloride (1.70 ml, 20 mmol) was added to a stirred solution of dimethyl sulfoxide (1.4 ml, 20 mmol) in methylene chloride (40 ml) under argon at -78°C. After 25 min a solution of 4-(phenylsulfenyl)butan-1-ol (1.83 g, 10 mmol) in methylene chloride (40 ml) was added; stirring was continued at -78°C for 10 min, then triethylamine (5.6 ml, 50 mmol) was added. The solution was allowed to warm to room temperature, quenched with 10% aq. H_2SO_4 and extracted with methylene chloride. The extract was washed in turn with 10% aq. H_2SO_4, sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to yield 4-(phenylsulfenyl)butanal **(10)** as a viscous oil (1.91 g). NMR (CCl_4) δ: 1.57-2.33 (m, 2H, CH_2); 2.37-2.70 (m, 2H, CH_2CO); 2.90 (t, J= 7Hz, 2H, CH_2S): 7.00 - 7.47 (m, 5H, ArH); 9.70 - 9.87 (br. s, 1H, CHO).

(ii) Methyl 2-methylpropanoate (1.00 ml, 8 mmol) was added dropwise to a cold (-78°C) stirred solution of LDA prepared from N, N-diisopropylamine (1.13 ml, 8 mmol) in THF (10 ml) by treatment with n-BuLi (8 mmol) under argon, in the usual way. A solution of 4-(phenylsulfenyl)butanal **(10)** (1.09 g, 6 mmol) was then added dropwise and stirring was continued at -78°C for 2.5 h, then the solution was quenched with sat. aq. NH_4Cl and extracted with methylene chloride. After washing with sat. aq. NH_4Cl, water and brine, the dried ($MgSO_4$) extract was evaporated and the remaining yellow liquid was purified by PLC on silica gel with 30% methylene chloride in hexane to yield methyl 2,2-dimethyl-3-hydroxy-6-(phenylsulfenyl)hexanoate **(11a)** as a viscous oil (1.32 g, 77%). NMR (CCl_4) δ: 1.10 (s, 6H, 2×CH_3); 0.91 - 2.10 (m, 4H, 2×CH_2); 2.57 - 3.10 (m, 3H, 0H and CH_2SPh); 3.30 - 3.70 (m, 1H, C*H*OH); 3.50 (s, 3H, OCH_3); 6.93 - 7.73 (m, 5H, ArH).

(iii) A solution of 90% m-chloroperbenzoic acid (1.18 g, 6.20 mmol) in methylene chloride (30 ml) was added dropwise to a cold (-78°C) solution of methyl 2,2-dimethyl-3-hydroxy-6-(phenylsulfenyl)hexanoate **(11a)** (1.76 g, 6.20 mmol) in the same solvent. The reaction was monitored by TLC, then worked up in the usual way to afford a yellow oil (1.69 g) which was purified by PLC on silica gel with 70% ethyl acetate in hexane. Methyl 2,2-dimethyl-3-hydroxy-6-(phenylsulfinyl)hexanoate **(12a)** was then obtained as a colourless solid (1.25 g, 68%) m.p. 77 - 78°C. IR (Nujol): 3320, 1745, 1255, 1130, 1025, 995 cm^{-1}. NMR ($CDCl_3$) δ: 1.13 (s, 6H, 2×CH_3); 1.27-2.23 (m, 4H, 2×CH_2); 2.85 (br.t, J =7Hz, 2H, C*H*OH and OH); 3.63 (s, 3H, OCH_3); 7.20 - 7.70 (m, 5H, ArH). MS (m / e): 300 (M^+ + 2, 26%), 280 (5), 197 (13), 173 (14, 141 (31), 126 (17), 113 (100), 102 (34), 95 (60), 87 (16), 85 (16), 78 (42), 77 (34), 69 (33), 59 (21), 55 (21).

(iv) A solution of methyl 2,2-dimethyl-3-hydroxy-6-(phenylsulfinyl)hexanoate **(12a)** (0.52 g, 1.74 mmol) was added dropwise to a cold (-78°C) stirred solution of LDA prepared from N,N-diisopropylamine (1.11 ml, 7.83 mmol) and nBuLi (7.83 mmol) in THF (14 ml) under argon. After stirring at -78°C for 1 h and at 0°C for 1.5 h the yellow solution was quenched with sat. aq. NH_4Cl and extracted with ethyl acetate. The extract

was washed and dried as usual then evaporated and the resulting yellow foam was purified by PLC on silica gel with 60% ethyl acetate in hexane. .6,6-Dimethyl-5-hydroxy-2-(phenylsulfinyl) cyclohexanone **(13a)** was then obtained as a colourless foam (0.32 g, 69.8%). IR ($CHCl_3$): 3400, 1730, 1410, 1100, 1040, 1020 cm^{-1}. NMR ($CDCl_3$) δ : 0.90 - 1.43 (m, 6H, 2×CH_3); 1.43-2.23 (m, 4H, 2×CH_2); 3.2-4.3 (m, 3H, C*H*SOPh, C*H*OH, and OH); 7.30 - 7.80 (m, 5H, ArH). MS (m/e): 250 (M^+, 10%) 234 (3), 218 (9), 186 (15), 154 (2), 141 (16), 125 (100), 110 (28), 109 (61), 97 (33), 78 (14), 77 (60), 65 (23).

(v) 6,6-Dimethyl-5-hydroxy-2-(phenylsulfinyl) cyclohexanone **(13a)** (0.19 g) was heated at 100 - 120°C/0.2 Torr for 1 h, then the brown liquid was purified by PLC on silica gel with chloroform, whereupon 6,6-dimethyl-5-hydroxycyclohex-2-enone **(14a)** was obtained as an oil (0.09 g, 84%). IR (neat) : 3400, 1670, 1400, 1060, 820 cm^{-1}. NMR (CCl_4) :1.00 and 1.07 (2×s, 2×3H, 2×CH_3); 2.23 - 2.63 (m, 2H, CH_2CHO); 3.00 - 3.33 (br.s, 1H, OH); 3.47-3.93 (m, 1H, C*H*OH); 5.83 (dt, J =10, 2Hz, 1H, CH =C*H*CO); 6.71 (dt, J =10, 4Hz, 1H, *CH* =CHCO). MS (m/e): 140 (M^+, 25%), 123 (7), 122 (7), 97 (54), 79 (23), 72 (100), 69 (41), 68 (50), 57 (77).

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บทคัดย่อ

ได้บรรยายถึงวิธีการเตรียมสารประกอบ substituted cyclohexenones โดยผ่านปฏิกริยา intramolecular acylation ของα-sulfinyl carbanion และปฏิกริยา pyrolysis