SHORT REPORT

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SUCCINOYLATION OF α-SULFONYLCABBANIONS: SIMPLE SYNTHESES OF *SYM*-1,4-DIKETONES

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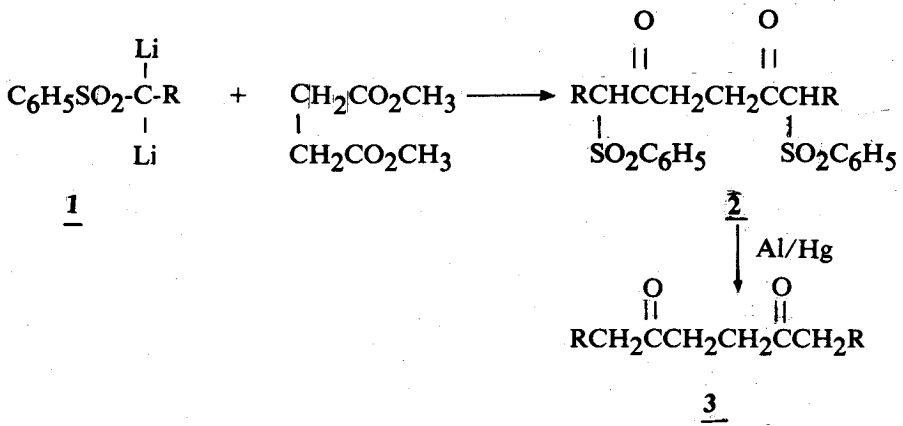
Abstract

Reactions of α α dilithio carbanions derived from (phenylsulfonyl)alkanes with dimethyl succinate followed by reductive cleavage with aluminum amalgam in aqueous tetrahydrofuran provide convenient syntheses of various sym-*1,4-diketones. The analogous reactions with succinic anhydride lead to moderate yields of γ-keto acids.*

Numerous synthetic methods have been developed for the preparation of 1, 4-diketones, because these substances are important intermediates for syntheses of some natural products and related compounds containing the cyclopentenone moiety[1] and the furan ring[2]. One of the representative and attractive routes to 1,4-diketones involves the conjugate addition of acyl carbanion equivalents, which may be nitro-stabilized[3] or sulfur-stabilized[4] to enones. Many other synthetic routes to 1,4-diketones have been reported[5]

Our project concerning the preparation of γ-alkylidene-γ-butyrolactones[6] led us to study the reaction of 1,1-dilithio alkylphenylsulfones with succinic acid derivatives. We found that treatment of the dilithio derivative **1**, which could be easily obtained by the reaction of alkyl phenylsulfone and *n*-butylithium (2 equivalents) in tetrahydrofuran at 0° in the presense of *N,N,N′,N′*-tetramethylethylenediamine (2 equiv)[7], with dimethyl succinate (1.5 equiv.)[8] at 0° yielded the ketosulfone **2** in moderate to good yields (39-90%).



The ketosulfones **2** were subjected to reductive cleavage by treatment with Al/Hg in a mixture of tetrahydrofuran and water (9:1) at room temperature to give *sym*-1,4-diketones **3** in good yields. It should be mentioned that the reductive cleavage of phenylsulfonyl groups in **2** by using an equimolar amount of Al/Hg was, in most cases, incomplete. The effective reduction was performed by portionwise addition of excess Al/Hg to a THF/H_2O solution of the ketosulfone **2** at room temperature, and the reaction was monitored by silica gel thin-layer chromatography. The reduction normally required about 10-25 equivalents of Al/Hg. It should be noted that over-reduction has never been observed.

The results of these experiments are summarized in Table 1.

TABLE 1

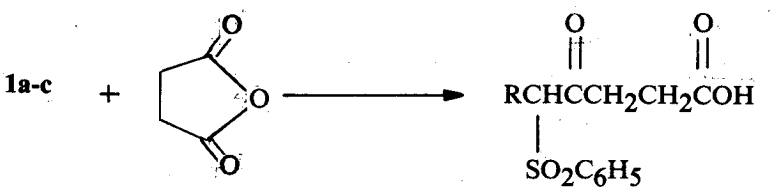
PREPARATION OF BIS(PHENYLSULFONY)ALKANEDIONES **(3 a-i)** AND *SYM*-1, 4-DIKETONES **(2 a-i)**.

R	Bis(phenylsulfonyl)-alkanedione	Yield %[a]	Diketone	Yield %[a]
CH_3	**2a**	73	**3a**	93
C_2H_5	**2b**	51	**3b**	55[b]
n-C_3H_7	**2c**	82	**3c**	54[b]
n-C_4H_9	**2d**	90	**3d**	62[b]
n-C_5H_{11}	**2e**	39	**3e**	93[b]
n-C_6H_{13}	**2f**	41	**3f**	86[b]
n-C_7H_{15}	**2g**	37	**3g**	72[b]
n-C_8H_{17}	**2h**	39	**3h**	73[b]
n-$C_{10}H_{21}$	**2i**	46	**3i**	94[b]

a Products were purified by preparative layer chromatography (Silica gel PF_{254})

b. Ref.12

We have also briefly investigated the reaction of the dianions **1a-c** with succinic anhydride. Treatment of the dianion (1 equiv) with succinic anhydride (1 equiv.) at 0° for 1 h afforded the ketoacids **4a-c** in moderate yields.

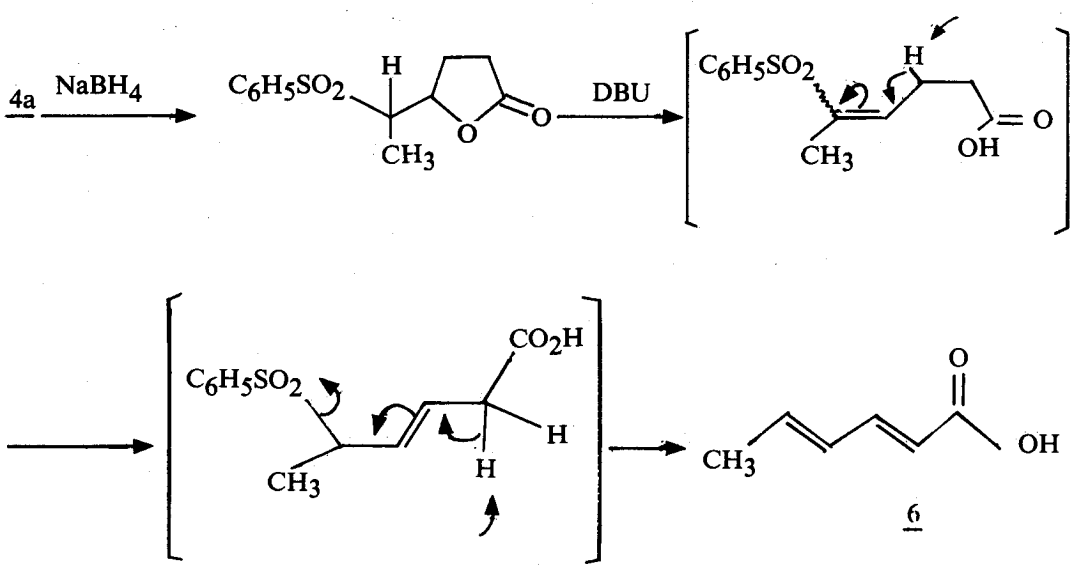


4a :R = CH_3 (73.4%)

4b: R = C_2H_5 (42%)

4c : R = n-C_3H_7 (62 %)

Finally, to demonstate the synthetic utility of the highly functionalized ketoacids **4** for synthesis of α,β,γ,δ -bisunsaturated carboxylic acids, we selectively reduced the keto function of **4a** with an excess of sodium borohydride in aqueous methanol at room temperature whereupon the γ-butyrolactone **5** was obtained as a diastereomeric mixture. Treatment of **5** with an excess of 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) at 90° for 1.5 h yielded sorbic acid **6** in 44% yield. We believe that the reaction leading to **6** proceeded *via* ring opening of the γ-butyrolactone followed by isomerisation of the double bond and finally elimination of phenylsulfinic acid, as shown below.



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Experimental Section

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.

General Procedure for Synthesis of the Bis(phenylsulfony)alkanediones **2a-i**

A solution of 1-(phenylsulfonyl)alkane[9] (2.5 mmol) and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA, 0.66 ml, 5 mmol) in THF (10 ml) was treated with *n*-BuLi (1.87 *M* solution in hexane, 2.66 ml, 5 mmol) under argon at 0°. The resulting solution or suspension was stirred at 0° for 1 h, and then dimethyl succinate (0.25 ml, 1.9 mmol) was added dropwise. The stirred reaction mixture was then allowed to warm up to room temperature overnight. After being acidified with dil.aq. HCl, the mixture was extracted with ethyl acetate. The combined extracts were washed with water and brine then dried over anhydrous $MgSO_4$. Evaporation gave a crude product which was purified by preparative thin-layer chromatography (silica gel PF_{254}) using 70 % ethyl acetate in hexane as eluting solvent.

2,7-Bis(phenylsulfonyl)octane-3,6-dione (**2a**): mp 154.5-156°; NMR(DMSO-d_6)δ 1.26 (d, J = 7Hz, 2xCH_3), 2.94(s, 2xCH_2CO), 4.75(q, J = 7Hz, 2x$CHSO_2$), 7.45-7.99 (m, 2xPh); IR(Nujol) 1715, 1370, 1150, 730, 690 cm^{-1}; MS, m/e (%) = 286(47), 168(80), 137(71), 136(100), 121(38), 81(41), 77(16).

3,8-Bis(phenylsulfony) decane-4,7-dione (**2b**): mp 123-124°; NMR($CDCl_3$) δ 0.87 (t, J = 7Hz, 2xCH_3), 1.90(m, 2xCH_2), 3.02(m, 2xCH_2CO), 4.05(2xt, J = 7Hz, 2x$CHSO_2$), 7.33--7.93(m, 2xPh); IR (Nujol) 1715, 1585, 1310, 755, 720, 685 cm^{-1}; MS, m/e(%) = 450(9), 141(43), 125(52), 77(100), 56(77), 43(66).

4,9-Bis(phenylsulfony) dodecane-5,8-dione (2c) : mp 159-160°; NMR(CDC_3) δ 0.86-2.10 (m, 2x$CH_3CH_2CH_2$), 3.05(m, 2xCH_2CO), 4.17(2xt, J = 8Hz, 2x$CHSO_2$), 7.49-8.03(m, 2xPh); IR (Nujol) 1715, 1585, 1305, 1148, 728, 690 cm^{-1}; MS, m/e (%) = 478 (3), 281(83) 139(93), 125(88),77(100).

5,10-Bis(phenylsulfony)tetradecane-6,9-dione(**2d**) : mp 184.5-186° ; NMR($CDCl_3$)δ 0.84-2.13-(m, 2x$CH_3(CH_2)_3$, 3.02(m, 2xCH_2C0), 4.13(2xt, J = 8Hz, 2x$CHSO_2$), 7.48-7.94(m, 2xPh); IR(Nujol) 1713, 1585, 1310, 1145, 725, 685 cm^{-1}; MS, m/e(%) = 506(1), 295(72), 223(56), 153(100), 151(52), 143(53), 125(85), 77(67).

6,11-Bis(phenylsulfonyl) hexadecane-7,10-dione (**2e**): mp 145-147°; NMR ($CDCi_3$) δ 0.85-2.10(m, 2x$CH_3(CH_2)_4$), 3.02(m, 2xCH_2CO), 4.10(2xt, J = 7Hz, 2x$CHSO_2$), 7.34-7.93-(m, 2xPh); IR(Nujol) 1715, 1590, 1310, 1150, 735, 690 cm^{-1}; MS. m/e (%) = 534(7), 81(100), 77(68), 55(42).

7,12-Bis(phenylsulfony)octadecane-8,11-dione (**2f**);mp 140-142°: NMR ($CDCl_3$) δ 0.85--2.14 (m, 2x$CH_3(CH_2)_5$), 3.02(m, 2xCH_2CO), 4,10(2xt, J = 7Hz, 2x$CHSO_2$), 7.34-8.0 (m, 2xPh); IR(Nujol) 1720, 1318, 1150, 735, 690 cm^{-1}; MS, m/e (%) = 562(2), 420(39), 402(45), 181(34), 125(54), 77(100), 55(58).

8,13-Bis(phenylsulfonyl)icosane-9,12-dione (**2g**) :mp 97-99°; NMR($CDCl_3$) δ 0.88-2.15-(m, 2x$CH_3(CH_2)_6$), 3.05(m, 2xCH_2CO), 4.10(t, J = 7Hz, 2x$CHSO_2$), 7.40-7.93(m, 2xPh); IR (Nujol) 1712, 1590, 1320, 1160, 722, 680 cm^{-1}; MS; m/e (%) = 590(0.5), 195(67), 141(61), 125(69), 77(100), 55(95).

9,14-Bis(phenylsulfony)docosane-10,13-dione (**2h**) :mp 103-105°; NMR($CDCl_3$) δ 0.87-2.13-(m, 2x$CH_3(CH_2)_7$),3.03(m, 2xCH_2CO), 4.11(t, J = 7Hz, 2x$CHSO_2$), 7.37-7.49(m, 2xPh); IR(Nujol) 1712, 1590, 1311, 1163, 725, 685, cm^{-1}; MS, m/e (%) = 618(0), 125(78), 77(100), 43(44).

11,16-Bis(phenylsulfony)hexacosane-12,15-dione (**2i**) : mp 109-111°; NMR($CDCl_3$) δ 0.89-2.10-(m, 2x$CH_3(CH_2)_9$), 3.0(m, 2xCH_2CO), 4.07 (t, J = 7Hz, 2x$CHSO_2$, 7.45-7.92(m, 2xPh); IR(Nujol) 1717, 1590, 1330, 1160, 725, 685 cm^{-1}; MS. m/e (%) = 676(0.5), 209(56), 143(65), 97(42), 83(39), 77(100), 57(38), 43(48).

General Procedure for Preparation of 1,4-Diketones **3a-i** *from Compounds* **2a-i**

Al/Hg has been prepare[10] by dipping strips of Aluminum foil into 2% aqueous $HgCl_2$ for 15 sec and then washing them quickly with absolute ethnol and anhydrous ether. The strips are immediately cut into small pieces and used at once. Al/Hg (10-25 mmol) was added portionwise to a THF/H_20 (9:1, 15 ml) solution of the ketosulfones **2a-i** (1 mmol) at room temperature. The resulting mixture was stirred until the Al/Hg had been consumed, filtered through a sintered glass funnel. The filtrate was taken into ether, washed with H_2O and brine then dried over anhydrous $MgSO_4$. The crude product obtained was purified by preparative thin-layer chromatography (25 % ethyl acetate in hexane).

Octane-3,6-dione (**3a**) : liquid ; NMR(CCl_4) δ 1.02 (t, J = 7Hz, 2x3H), 2.40(q, J=7Hz, 2x2H), 2.53(s,2x2H); IR($CHCl_3$) 1715 cm^{-1}; Ms, m/e (%) = 142(23), 123(92), 113(77), 77(92), 57(100).

Decane-4,7-dione (**3b**) : mp 30-31°; NMR($CDCl_3$) δ 0.9(t, J = 7Hz, 2x3H), 1.64(sext, J = 7Hz, 2x2H), 2.43(t, J = 7Hz, 2x2H), 2.67(s, 2x2H); IR(Nujol) 1700 cm^{-1}; MS, m/e (%) = 170(5), 127(100), 71(97), 43(93).

Dodecane-5, 8-doine (**3c**) : mp 47-49°; NMR($CDCl_3$) δ 0.9 -1.48(m, 2x7H), 2.48(t, J = 7Hz, 2x2H), 2.70(s, 2x2H); IR(Nujol) 1705 cm^{-1}; MS, m/e(%) = 198(3), 141(81), 85(93), 57(100), 41(42).

Tetradecane-6,9-dione (**3d**): mp 57-58.5°; NMR($CDCl_3$)δ 0.87-1.87(m, 2x9H), 2.43 (t, J = 7Hz, 2x2H), 2.65(s, 2x2H; IR(Nujol) 1700 cm^{-1}; MS, m/e (%) = 226(15), 170(93), 155(100), 127(80), 99(90), 71(67).

Hexadecane-7,10-dione (**3e**): mp 66.5-68°; NMR ($CDCl_3$) δ 0.87-1.87(m), 2.45(t, J = 7Hz, 2x2H), 2.66(s, 2x2H); IR(Nujol) 1700 cm^{-1}; MS, m/e (%) = 254(24), 184(95), 169(62), 141(57), 113(67), 85(33), 43(100).

Octadecane-8,11-dione (**3f**): mp 71-73°; NMR($CDCl_3$) δ 0.9-1.86(m), 2.46(t, J = 7Hz, 2x2H), 2.70(s, 2x2H); IR(Nujol) 1700 cm^{-1}; MS. m/e (%) = 282(100), 198(75), 155(67), 127(49), 99(64), 43(75).

Isocane-9, 12-dione (**3g**) : mp 80-81°; NMR($CDCl_3$) δ 0.90-1.7(m), 2,45(t, J = 7Hz, 2x2H), 2.67(s, 2x2H); IR(Nujol) 1700 cm^{-1}; MS, m/e (%) = 310(42), 212(100), 197(46), 169(77), 141(67), 71(54), 57(65), 43(61).

Docosane-10,13-dione (**3h**): mp84.5-85°; NMR($CDCL_3$) δ 0.9-1.9(m), 2.47(t, J = 7Hz, 2x2H), 2.67 (s, 2x2H); IR (NUjol) 1700 cm^{-1}; MS, m/e (%) = 338(10), 226(74), 183(64), 155(54), 115(82), 71(62), 57(59), 43(100).

Hexacosane-12,15-dione(**3i**) : mp 92-92.5°; NMR($CDCl_3$) δ 0.9-1.8(m), 2.46(t, J = 7Hz, 2x2H), 2.67(s,2x2H); IR(Nujol)1700 cm^{-1}; MS,m/e (%) = 394(12), 254(65), 114(100), 57(65), 43(71).

General Methods for Preparation of 5-phenylsulfonyl-4-oxocalkanoic Acids **4a-c.**

A solution of 1-(phenylsulfonyl) ethane (0.85 g, 5 mmol) in THF (20 ml) and TMEDA (1.29 ml, 10 mmol) under argon at 0° was treated with *n*-Buli (1.65 M solution in hexane, 6.4 ml, 10 mmol). The resulting mixture was stirred for 1 h at 0°, and then succinic anhydride (0.6 g, 6 mmol) in THF (10 ml) was added dropwise. The reaction mixture was stirred and allowed to warm to room temperature overnight. Water was then added, and the reaction mixture was extracted with ethyl acetate in order to remove unreacted starting materials. The aqueous layer was acidified with 2*N* aq. HCl and then extracted with ethyl acetate. The combined extracts were washed with water and brine then dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product obtained was purified by preparative chromatographed on a layer of silica gel to give 5-phenylsulfonyl-4-oxo-hexanoic acid (**4a**) as semi-solid (0.99 g, 73.4 %). NMR ($CDCl_3$): δ 1.13 (d, J = 7.5 Hz, 3H), 2.36-3.36(m, 4H), 4.26(q, J = 7.5Hz, 1H). 7.24 (br.s, 1H, CO_2H), 7.4-8.0 (m, 5H); IR (film) 3500-2500, 1725, 1713, 1303, 1145, 720, 690 cm^{-1}.

5-Phenylsulfonyl-4-oxo-heptanoic acid (**4b**): mp 104-105.5°; NMR($CDCl_3$) δ 0.88 (t, J = 7Hz, 3H), 1.9 (quint, J = 7Hz, 2H), 2.46-3.27(m, 4H), 4.05(dd, J = 8,6Hz, 1H), 7.33-7.9 (m,5H), 8.23-8.9(br.s, 1H, CO_2H); IR(Hujol) 3500-2500, 1720, 1710, 1305, 1145, 720, 690 cm^{-1}.

5-Phenylsulfonyl-4-oxo-octanoic acid(**4c**):semi-solid; NMR($CDCl_3$) δ 0.58-1.98 (m, 7H), 2.36-3.25(m, 4H), 4.08(m, 1H), 7.15-8.03(m, 5H), 8.99(br.s, 1H); IR(film) 3500-2500, 1720, 1710, 1305, 1143, 720, 690 cm^{-1}.

Preparation of 5-(1-Phenylsulfonylethyl)-2,3,4,5-tetrahydrofuran-2-one(**5**)

A solution of $NaBH_4$ (1.78 g) in water (7 ml) was added dropwise to a solution of **4a** (0.99 g,

3.65 mmol) in methanol(15ml) at room temperature. The resulting mixtrue was stirred at this temperature overnight, then acidified with 2*N* aq. HCl and extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated to give a crude product which was purified by preparative thin-layer chromatography (silica gel, 35% ethyl acetate in hexane); the diastereomeric mixture **5** was then obtained as a semi-solid (0.44 g, 47%). NMR($CDCl_3$)δ1.35(d, J = 7Hz, 3H), 2.00-2.87(m, 4H), 3.34--3.82 (quint, J = 7Hz, 1H), 4.72-5.12(m,1H), 7.53 and 7.90 (m, 5H); IR(film) 1780, 1595, 1315, 1150, 725, 690 cm^{-1}; MS, m/e (%) = 254(M^+,0.1).

Preparation of (E), (E)-2,4-hexadienoic acid(6)

A mixture of 5 (0.15 g, 0.58 mmol) and DBU (0.13 ml, 0.89 mmol) was heated at 90 °C for 1.5 h. The mixture was then taken into $CHCl_3$, filtered and evaporated to give a crude white solid product. Purification by preparative thin-layer chromatography (silica gel, 40% ethyl actate in hexane) gave 0.03 g (44%) of pure sorbic acid (**6**) (mp 135-137°, Lit.[11] 134.5°).

References and Notes

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8. The reaction of the dianion **1** (R = CH_3, 2 equivalents) with 1 equivalent of dimethyl succinate afforded the ketosulfone **2a** in 59% yield. A yield of 33% of **2a** was obtained with 2 equivalents of dimethyl succinate. The best yield (73%) of **2a** was achieved by using 1.5 equivalent of dimethyl succinate as indicated in the text.
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บทคัดย่อ

ได้สังเคราะห์ sym-1, 4-diketones จากปฏิกิริยา succinoylation ของ 1,1-dilithio-(phenylsulfonyl)alkanes และนอกจากนี้ยังได้บรรยายถึงการเตรียม 5-phenylsolfonyl-4-oxoalkanoic acids