Synthesis of 2-Substituted 1,3,4-Thiadiazol-5-ylacetic, Propionic, and Glutaric Acids

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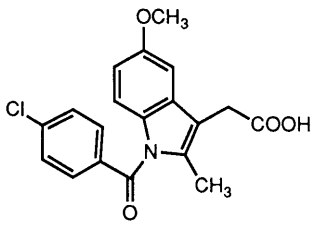
1,3,4-Thiadiazol-5-ylacetic, propionic, and glutaric acids (3—5) were synthesized *via* ethyl 2-substituted 1,3,4-thiadiazol-5-ylacetates (11 and 17) as key intermediates.

Keywords 2,3-dihydro-1,3,4-thiadiazole; 2-substituted 1,3,4-thiadiazol-5-ylacetate; 2-benzoyl-1,3,4-thiadiazol-5-ylacetic acid; ethyl bromoacetate; alkylation; hydrolysis; 1,3,4-thiadiazol-5-ylpropionic acid; 1,3,4-thiadiazol-5-ylglutaric acid

Previously, we have reported the synthesis of 5-substituted 3-acetyl-2-phenyl-2,3-dihydro-1,3,4-thiadiazoles by nucleophilic substitution of the methylsulfinyl group of 3-acetyl-5-methylsulfinyl-2-phenyl-2,3-dihydro-1,3,4-thiadiazole and the synthesis of 2-methylsulfinyl-5-phenyl-1,3,4-thiadiazole by the reaction of 3-acetyl-5-methylsulfinyl-2-phenyl-2,3-dihydro-1,3,4-thiadiazole 1-oxides with base.[1] We have also reported that a sulfonyl group at the 2 position of 1,3,4-thiadiazoles can be substituted with nucleophiles.[2]

We now report the application of these methods to the synthesis of novel 1,3,4-thiadiazole derivatives, which are expected to have antiinflammatory activity, based on the structures of indomethacin (**1**) and oxaprozin (**2**) (Chart 1). This paper describes the synthesis of 2-benzoyl-1,3,4-thiadiazol-5-ylacetic acid (**3a**), 3-(2-substituted 1,3,4-thiadiazol-5-yl)propionic acid derivatives (**4**) and 3-(2-substituted 1,3,4-thiadiazol-5-yl)glutaric acid derivatives (**5**) (Chart 2).

The synthetic route to the acetic acid derivative **3a** is shown in Chart 3. Benzoylation of phenylacetaldehyde



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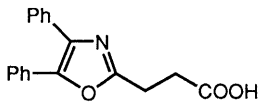

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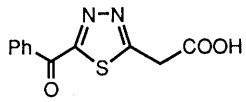
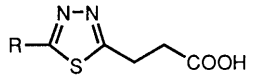
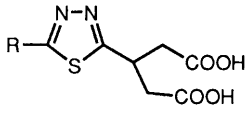
Chart 1



3a



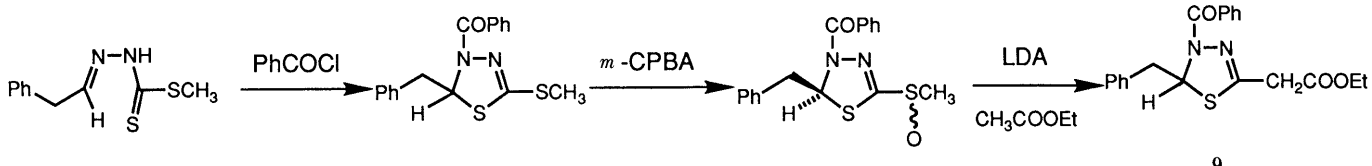
4a—e



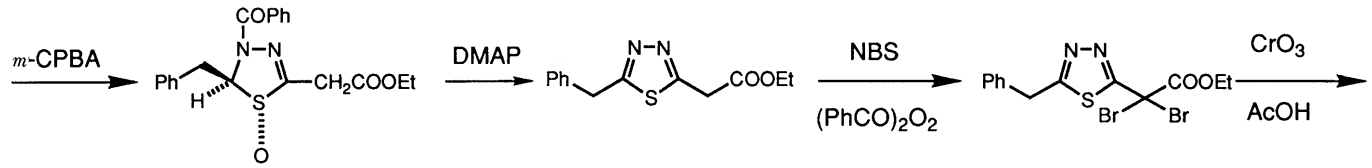
5a—e

a : R=PhCO
b : R=Ph
c : R=4-ClPh
d : R=4-BrPh
e : R=$PhCH_2$

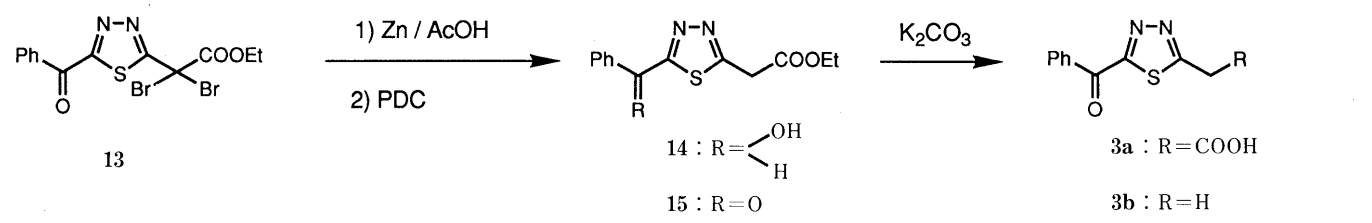
Chart 2



6 7 8 9



10 11 12



13

14 : R=

15 : R=O

3a : R=COOH

3b : R=H

Chart 3

methylthio(thiocarbonyl)hydrazone (**6**) prepared by the condensation of methylthio(thiocarbonyl)hydrazide with phenylacetaldehyde gave 3-benzoyl-2-benzyl-5-methylthio-2,3-dihydro-1,3,4-thiadiazole (**7**) in 98% yield. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of compound **7** showed a 2-H absorption at δ 6.55 with an upfield shift of 0.91 ppm from that of the methine proton of **6**, in good agreement with reported chemical shifts of other 2-protons of 2,3-dihydro-1,3,4-thiadiazole derivatives.[3] Oxidation of **7** with *m*-chloroperbenzoic acid (*m*-

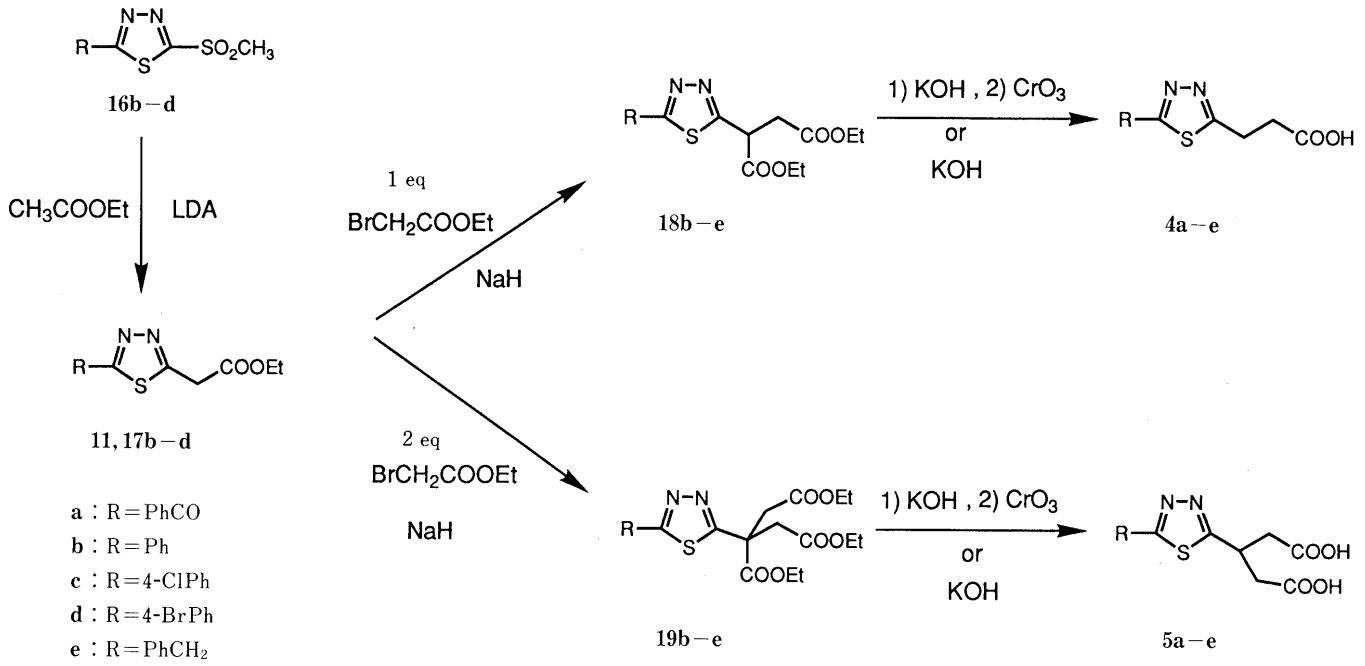


Chart 4

TABLE I. Spectral Data for Diethyl 2-(4-Substituted phenyl)-1,3,4-thiadiazol-5-ylsuccinates (**18b—d**) and Diethyl 3-[2-(4-Substituted phenyl)-1,3,4-thiadiazol-5-yl]-3-ethoxycarbonylglutarates (**19b—d**)

Compd. No.	Yield (%)	mp (°C) (Recrystn. solvent)	IR (KBr) cm^{-1} CO	^{1}H-NMR ($CDCl_3$) δ (J=Hz)	Formula	Analysis Calcd (Found) C	H	N	MS *m/z* (M^+)
18b	47		1745[a] 1730	1.25 (3H, t, J=7, $CH_2C\underline{H}_3$), 1.27 (3H, t, J=7, $CH_2C\underline{H}_3$), 3.29 (2H, d, J=7, CH_2), 4.17 (2H, q, J=7, $C\underline{H}_2CH_3$), 4.30 (2H, q, J=7, $C\underline{H}_2CH_3$), 4.70 (1H, t, J=7, CH), 7.40—7.65 (3H, m, ArH), 7.75—8.10 (2H, m, ArH)	$C_{16}H_{18}N_2O_4S$	334.0987[b] (334.0985)			334
18c	43	76—77 (*n*-Hexane)	1745 1720	1.24 (3H, t, J=7, $CH_2C\underline{H}_3$), 1.27 (3H, t, J=7, $CH_2C\underline{H}_3$), 3.47 (2H, d, J=7, CH_2), 4.14 (2H, q, J=7, $C\underline{H}_2CH_3$), 4.24 (2H, q, J=7, $C\underline{H}_2CH_3$), 4.61 (1H, t, J=7, CH), 7.45 (2H, dd, J=2, 9, ArH), 7.90 (2H, dd, J=2, 9, ArH)	$C_{16}H_{17}ClN_2O_4S$	52.10 (52.01	4.65 4.56	7.60 7.50)	368 370
18d	37	77—78 (*n*-Hexane–benzene)	1745 1720	1.23 (3H, t, J=7, $CH_2C\underline{H}_3$), 1.27 (3H, t, J=7, $CH_2C\underline{H}_3$), 3.27 (2H, d, J=7, CH_2), 4.14 (2H, q, J=7, $C\underline{H}_2CH_3$), 4.24 (2H, q, J=7, $C\underline{H}_2CH_3$), 4.61 (1H, t, J=7, CH), 7.60 (2H, dd, J=2, 9, ArH), 7.83 (2H, dd, J=2, 9, ArH)	$C_{16}H_{17}BrN_2O_4S$	46.50 (46.52	4.15 4.05	6.78 6.59)	412 414
19b	94		1740[a] 1735	1.21 (6H, t, J=7, $CH_2C\underline{H}_3$), 1.32 (3H, t, J=7, $CH_2C\underline{H}_3$), 3.46 (4H, s, CH_2), 4.09 (4H, q, J=7, $C\underline{H}_2CH_3$), 4.32 (2H, q, J=7, $C\underline{H}_2CH_3$), 7.30—7.60 (3H, m, ArH), 7.80—8.15 (2H, m, ArH)	$C_{20}H_{24}N_2O_6S$	420.1354[b] (420.1389)			420
19c	95		1745[a] 1735	1.18 (6H, t, J=7, $CH_2C\underline{H}_3$), 1.29 (3H, t, J=7, $CH_2C\underline{H}_3$), 3.41 (4H, s, CH_2), 4.05 (4H, q, J=7, $C\underline{H}_2CH_3$), 4.28 (2H, q, J=7, $C\underline{H}_2CH_3$), 7.46 (2H, dd, J=3, 7, ArH), 7.93 (2H, dd, J=3, 7, ArH)	$C_{20}H_{23}ClN_2O_6S$	454.0965[b] (454.0971)			454 456
19d	97		1745[a] 1735	1.17 (6H, t, J=7, $CH_2C\underline{H}_3$), 1.29 (3H, t, J=7, $CH_2C\underline{H}_3$), 3.38 (4H, d, J=2, CH_2), 4.04 (4H, q, J=7, $C\underline{H}_2CH_3$), 4.27 (2H, q, J=7, $C\underline{H}_2CH_3$), 7.59 (2H, dd, J=3, 7, ArH), 7.84 (2H, dd, J=3, 7, ArH)	$C_{20}H_{23}BrN_2O_6S$	498.0460[b] (498.0435)			498 500

a) Measured neat. *b*) Determined by high-resolution mass spectrometry (HR-MS). Upper figure, calcd for M^+; lower figure found.

TABLE II. Spectral Data for 3-[2-(4-Substituted phenyl)-1,3,4-thiadiazol-5-yl]propionic Acids (**4b—d**) and 3-[2-(4-Substituted phenyl)-1,3,4-thiadiazol-5-yl]glutaric Acids (**5b—d**)

Compd. No.	Yield (%)	mp (°C) (Recrystn. solvent)	IR (KBr) cm^{-1}		^{1}H-NMR (DMSO-d_6) δ (J=Hz)	Formula	Analysis Calcd (Found)			MS m/z (M^+)
			OH	CO			C	H	N	
4b	35	152—154 (Benzene–$CHCl_3$)	3200—2500	1700	2.82 (2H, t, J=7, CH_2), 3.36 (2H, t, J=7, CH_2), 7.48—7.65 (3H, m, ArH), 7.88—8.04 (2H, m, ArH), 8.0—11.0 (1H, br, CO_2H)	$C_{11}H_{10}N_2O_2S$	56.40 (56.48	4.30 4.18	11.96 11.84)	234
4c	94	181—182 (Benzene–$CHCl_3$)	3200—2500	1700	2.80 (2H, t, J=7, CH_2), 3.34 (2H, t, J=7, CH_2), 7.62 (2H, dd, J=2, 9, ArH), 7.98 (2H, dd, J=2, 9, ArH), 12.30 (1H, br s, CO_2H)	$C_{11}H_9ClN_2O_2S$	49.17 (48.97	3.38 3.17	10.42 10.16)	268 270
4d	81	192—193 (Benzene–$CHCl_3$)	3200—2500	1710	2.80 (2H, t, J=7, CH_2), 3.35 (2H, t, J=7, CH_2), 7.75 (2H, dd, J=2, 9, ArH), 7.91 (2H, dd, J=2, 9, ArH), 12.30 (1H, br s, CO_2H)	$C_{11}H_9BrN_2O_2S$	42.19 (42.39	2.90 2.84	8.95 8.66)	312 314
5b	59	179—181 (Acetone)	3200—2500	1720	2.86 (4H, d, J=7, CH_2), 4.00 (1H, t, J=7, CH), 7.45—7.65 (3H, m, ArH), 7.85—8.04 (2H, m, ArH), 9.0—12.5 (2H, br, CO_2H)	$C_{13}H_{12}N_2O_4S$	53.42 (53.25	4.14 4.11	9.58 9.49)	292
5c	82	186—188 ($CHCl_3$–acetone)	3150—2500	1710	2.84 (4H, d, J=7, CH_2), 3.96 (1H, t, J=7, CH), 7.60 (2H, dd, J=3, 7, ArH), 7.95 (2H, dd, J=3, 7, ArH), 12.0—12.6 (2H, br, CO_2H)	$C_{13}H_{11}ClN_2O_4S$	47.79 (47.82	3.39 3.32	8.57 8.29)	326 328
5d	65	193—195 (Benzene–acetone)	3150—2500	1705	2.84 (4H, d, J=7, CH_2), 3.97 (1H, t, J=7, CH), 7.73 (2H, dd, J=3, 7, ArH), 7.89 (2H, dd, J=3, 7, ArH), 12.0—12.6 (2H, br, CO_2H)	$C_{13}H_{11}BrN_2O_4S$	42.06 (42.17	2.99 2.87	7.55 7.29)	370 372

DMSO: dimethylsulfoxide.

CPBA) at room temperature gave the sulfoxide **8** as a diastereoisomeric mixture[1] in 92% yield. Nucleophilic substitution of the methylsulfinyl group in **8** with ethyl acetate in the presence of lithium diisopropylamide (LDA) at −78 °C afforded the acetate derivative **9** in 97% yield. Oxidation of **9** with *m*-CPBA at room temperature gave the 2,3-dihydro-1,3,4-thiadiazole 1-oxide (**10**) in 93% yield. The oxygen atom of the sulfoxide group of **10** was assigned as being *trans* to the benzyl group.[4—6] Treatment of **10** with 4-dimethylaminopyridine (DMAP) in ethanol under reflux gave the 1,3,4-thiadiazole derivative **11** in 82% yield.[1,3g]

An attempt to obtain the 2-benzoyl-1,3,4-thiadiazole derivative **15** directly from **11** by oxidation with selenium dioxide was unsuccessful. Therefore, an alternative approach to **15** from **11** was developed, as shown in Chart 3. The reaction of **11** with N-bromosuccinimide (NBS) (2 mol eq) catalyzed by benzoyl peroxide afforded the dibromo derivative **12**, which was oxidized with chromium(VI) oxide (CrO_3) in acetic acid to give the 5-benzoyl derivative **13**. Reduction of **13** with zinc in acetic acid gave the 2-(α-hydroxybenzyl)-1,3,4-thiadiazole derivative **14**, which was oxidized with pyridinium dichromate (PDC) to furnish **15**. Treatment of **15** with potassium carbonate in aqueous ethanol gave the corresponding carboxylic acid **3a**. Compound **3a** was found to be decarboxylated on standing at room temperature,[7] probably *via* the intramolecular participation of the N-4 atom, affording the 5-methyl derivative **3b** as evidenced by ^{1}H-NMR analysis. Thus, its biological activity could not be tested.

We then directed our attention toward the synthesis of 3-(2-benzoyl-1,3,4-thiadiazol-5-yl)propionic acid (**4a**) and the 3-glutaric acid derivative **5a**. Compound **11** was used as the starting material for the synthesis of these compounds. The synthetic routes are shown in Chart 4.

Alkylation of **11** with 1 mol eq of ethyl bromoacetate in the presence of sodium hydride (NaH) at 0 °C provided the diethyl succinate derivative **18e**, whose hydrolysis with potassium hydroxide gave the carboxylic acid **4e**. This was oxidized with CrO_3 to furnish **4a**. On the other hand, alkylation of **11** with 2 mol eq of ethyl bromoacetate provided the diethyl glutarate derivative **19e**. Similarly, hydrolysis of **19e** with potassium hydroxide followed by oxidation with CrO_3 gave **5a**.

The 2-phenyl substituted compounds **4b—d** and **5b—d** were prepared by using the sulfones **16b—d**. These were obtained by the oxidation of 5-(4-substituted phenyl)-2-methylthio-1,3,4-thiadiazoles with potassium permanganate ($KMnO_4$) in acetic acid according to Fujii's method.[8] Displacement of **16—d** with ethyl acetate in the presence of LDA at −78 °C gave **17b—d**, whose conversions to the target molecules were achieved through procedures similar to those described earlier for **4a** and **5a**.

The analytical and spectral data for compounds **18b—d**, **19b—d**, **4b—d** and **5b—d** are shown in Tables I and II. Compounds **4a—d** and **5a—d** did not exhibit any significant inhibitory effect on cyclooxygenase from bovine seminal vesicles.

Experimental

Melting points were determined by the capillary method and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 215 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL PS-100 or a JEOL JNM-PMX 60_{SI} spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were measured with a JEOL D-300 instrument. For column chromatography, Silica gel 60 (230—400 mesh, Nacalai Tesque) was employed.

Phenylacetaldehyde Methylthio(thiocarbonyl)hydrazone (6) Compound

6 was prepared by the literature method.[9]

3-Benzoyl-2-benzyl-5-methylthio-2,3-dihydro-1,3,4-thiadiazole (7) A mixture of **6** (5.04 g, 22.5 mmol) and benzoyl chloride (6.2 ml, 53.41 mmol) in $CHCl_3$ was refluxed for 30 min. The mixture was neutralized with 5% aqueous sodium hydrogen carbonate and extracted with $CHCl_3$ (3×100 ml). The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was recrystallized from MeOH to give **7** (7.23 g, 98%), mp 86—88 °C. IR (KBr): 1630 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s, SCH_3), 3.08 (1H, dd, $J=8$, 14 Hz, PhCH), 3.43 (1H, dd, $J=4$, 14 Hz, PhCH), 6.55 (1H, dd, $J=4$, 8 Hz, C_2-H), 7.28 (5H, s, ArH), 7.29—7.95 (5H, m, ArH). MS *m/z*: 328 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_2OS_2$: C, 62.17; H, 4.91; N, 8.53. Found: C, 62.07; H, 4.79; N, 8.34.

3-Benzoyl-2-benzyl-5-methylsulfinyl-2,3-dihydro-1,3,4-thiadiazole (8) A solution of 80% *m*-CPBA (95 mg, 0.44 mmol) in $CHCl_3$ (3 ml) was added dropwise to a stirred solution of **7** (145 mg, 0.44 mmol) in $CHCl_3$ (1 ml) at 0 °C. After being stirred at room temperature for 30 min, the mixture was neutralized with 5% aqueous sodium hydrogen carbonate and extracted with $CHCl_3$ (3×50 ml). The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column ($CHCl_3$–acetone, 20 : 1, v/v) to give **8** (140 mg, 92%) as an inseparable diastereomeric mixture. IR (neat): 1650 (CO), 1070 (SO) cm^{-1}. Major isomer ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s, $SOCH_3$), 2.88—3.65 (2H, m, $PhCH_2$), 6.60—6.79 (1H, m, C_2-H), 7.23 (5H, s, ArH), 7.31—7.80 (5H, m, ArH). Minor isomer ^{1}H-NMR ($CDCl_3$) δ: 2.74 (3H, s, $SOCH_3$), 2.88—3.65 (2H, m, $PhCH_2$), 6.60—6.79 (1H, m, C_2-H), 7.25 (5H, s, ArH), 7.31—7.80 (5H, m, ArH). MS *m/z*: 344 (M^+).

Ethyl 3-Benzoyl-2-benzyl-2,3-dihydro-1,3,4-thiadiazol-5-ylacetate (9) A solution of ethyl acetate (0.95 ml, 9.73 mmol) in anhydrous tetrahydrofuran (THF) (3 ml) was added to a solution of LDA (9.41 mmol; prepared from a 1.65 M solution of *n*-BuLi in hexane, 5.7 ml, 9.41 mmol, and diisopropylamine, 1.4 ml, 9.99 mmol) in anhydrous THF (3 ml) at −78 °C under argon. After the mixture had been stirred at −78 °C for 30 min, a solution of **8** (1.61 g, 4.68 mmol) in anhydrous THF (10 ml) was added dropwise. After 1 min at −78 °C, the mixture was quenched with aqueous acetic acid and extracted with $CHCl_3$ (3×100 ml). The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column ($CHCl_3$–acetone, 30 : 1, v/v) to give **9** (1.67 g, 97%) as an oil. IR (neat): 1745 (CO), 1650 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 3.12 (1H, dd, $J=8$, 14 Hz, PhCH), 3.42 (1H, dd, $J=4$, 14 Hz, PhCH), 3.39 (2H, s, C_5-CH_2), 4.15 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 6.49 (1H, dd, $J=4$, 8 Hz, C_2-H), 7.25 (5H, s, ArH), 7.26—7.90 (5H, m, ArH). MS *m/z*: 368 (M^+).

Ethyl 3-Benzoyl-2-benzyl-2,3-dihydro-1,3,4-thiadiazol-1-oxide-5-ylacetate (10) A solution of 80% *m*-CPBA (937 mg, 4.34 mmol) in $CHCl_3$ (20 ml) was added dropwise to a stirred solution of **9** (1.6 g, 4.35 mmol) in $CHCl_3$ (10 ml) at 0 °C. After the mixture had been stirred at room temperature for 30 min, work-up as described for the preparation of compound **8** gave **10** (1.55 g, 93%), mp 102—103 °C. IR (KBr): 1735 (CO), 1670 (CO), 1055 (SO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.84 (1H, dd, $J=10$, 14 Hz, PhCH), 3.46 (1H, dd, $J=4$, 14 Hz, PhCH), 3.79 (2H, d, $J=7$ Hz, C_5-CH_2), 4.24 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 5.89 (1H, dd, $J=4$, 10 Hz, C_2-H), 7.32 (5H, s, ArH), 7.35—7.90 (5H, m, ArH). MS *m/z*: 384 (M^+). *Anal.* Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24; N, 7.29. Found: C, 62.18; H, 5.02; N, 6.99.

Ethyl 2-Benzyl-1,3,4-thiadiazol-5-ylacetate (11) A mixture of **10** (5.16 g, 13.44 mmol) and DMAP (2 g, 16.37 mmol) in EtOH (10 ml) was refluxed for 30 min. The solvent was evaporated off under reduced pressure, and the residue was chromatographed on a silica gel column ($CHCl_3$–acetone, 15 : 1, v/v) to give **11** (2.9 g, 82%) as an oil. IR (neat): 1735 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 4.09 (2H, s, CH_2), 4.19 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 4.40 (2H, s, CH_2), 7.29 (5H, s, ArH). MS *m/z*: 262 (M^+). HR-MS *m/z*: Calcd for $C_{13}H_{14}N_2O_2S$: 262.0776. Found: 262.0783.

Ethyl 2-Benzyl-1,3,4-thiadiazol-5-yldibromoacetate (12) A mixture of **11** (1.39 g, 5.31 mmol), NBS (1.88 g, 10.56 mmol), and benzoyl peroxide (5 mg) in CCl_4 (10 ml) was refluxed for 1 min. The mixture was filtered and the filtrate was neutralized with 5% aqueous sodium hydrogen carbonate and extracted with $CHCl_3$ (3×100 ml). The combined extracts were washed with 5% aqueous $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column ($CHCl_3$–acetone, 30 : 1, v/v) to give **12** (1.95 g, 88%) as an oil. IR (neat): 1760 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 4.38 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 4.40 (2H, s, CH_2), 7.33 (5H, s, ArH). MS *m/z*: 418, 420, 422 (M^+).

Ethyl 2-Benzoyl-1,3,4-thiadiazol-5-yldibromoacetate (13) A mixture of **12** (100 mg, 0.24 mmol) and CrO_3 (48 mg, 0.48 mmol) in acetic acid (3 ml) was heated at 60 °C for 30 min. The mixture was poured into ice-water, neutralized with 5% aqueous sodium hydrogen carbonate, and extracted with $CHCl_3$ (3×50 ml). The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column ($CHCl_3$) to give a solid, which was recrystallized from EtOH to give **13** (95 mg, 92%), mp 105—106 °C. IR (KBr): 1735 (CO), 1645 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 4.43 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.40—7.75 (3H, m, ArH), 8.44—8.55 (2H, m, ArH). MS *m/z*: 432, 434, 436 (M^+). *Anal.* Calcd for $C_{13}H_{10}Br_2N_2O_3S$: C, 35.97; H, 2.32; N, 6.45. Found: C, 35.97; H, 2.23; N, 6.65.

Ethyl 2-(α-Hydroxybenzyl)-1,3,4-thiadiazol-5-ylacetate (14) A suspension of **13** (200 mg, 0.46 mmol) and activated zinc (120 mg, 1.84 mmol) in acetic acid (3 ml) was stirred at room temperature for 30 min. The mixture was filtered and the filtrate was neutralized with 5% aqueous sodium hydrogen carbonate, then extracted with $CHCl_3$ (3×50 ml). Work-up as described for the preparation of **13** gave the residue, which was chromatographed on a silica gel column ($CHCl_3$–MeOH, 10 : 1, v/v) to give **14** (120 mg, 94%) as an oil. IR (neat): 3300 (OH), 1740 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 4.01 (2H, s, CH_2), 4.17 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 4.52—5.20 (1H, br, OH), 6.16 (1H, s, CH), 7.20—7.50 (5H, m, ArH). MS *m/z*: 278 (M^+).

Ethyl 2-Benzoyl-1,3,4-thiadiazol-5-ylacetate (15) A mixture of **14** (1.1 g, 3.99 mmol) and PDC (2.97 g, 7.89 mmol) in CH_2Cl_2 (15 ml) was stirred at room temperature for 4 h, then mixed with ether, and filtered. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on a silica gel column ($CHCl_3$–acetone, 20 : 1, v/v) to give a solid, which was recrystallized from EtOH to give **15** (756 mg, 69%), mp 66—68 °C. IR (KBr): 1735 (CO), 1650 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 4.26 (2H, s, CH_2), 4.27 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.40—7.75 (3H, m, ArH), 8.44—8.53 (2H, m, ArH). MS *m/z*: 276 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14. Found: C, 56.41; H, 4.20; N, 9.92.

2-Benzoyl-1,3,4-thiadiazol-5-ylacetic Acid (3a) A suspension of **15** (125 mg, 0.45 mmol) and potassium carbonate (125 mg, 0.9 mmol) in 70% aqueous EtOH (6 ml) was heated at 60 °C for 2 h. After cooling, the mixture was acidified with 5% HCl and extracted with ethyl acetate (3×50 ml). The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated to give a solid, which was washed with $CHCl_3$ to provide **3a** (95 mg, 85%), mp 100—101 °C. IR (KBr): 2500—3100 (OH), 1720 (CO), 1665 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 4.27 (2H, s, CH_2), 7.35—7.75 (3H, m, ArH), 8.40—8.65 (2H, m, ArH). MS *m/z*: 204 ($M^+ - CO_2$). *Anal.* Calcd for $C_{11}H_8N_2O_3S$: C, 53.22; H, 3.25; N, 11.28. Found: C, 53.00; H, 3.01; N, 10.92. Decarboxylation of **3a** occurred gradually on standing at room temperature.

2-Benzoyl-5-methyl-1,3,4-thiadiazole (3b) The structure of compound **3b** was confirmed by examination of the ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$) δ: 2.90 (3H, s, CH_3), 7.50—7.72 (3H, m, ArH), 8.49—8.54 (2H, m, ArH).

Diethyl 2-Benzyl-1,3,4-thiadiazol-5-ylsuccinate (18e) A suspension of sodium hydride (76 mg, 1.91 mmol, 60% dispersion in oil, washed twice with ether) in anhydrous THF (5 ml) was added dropwise to a stirred solution of **11** (500 mg, 1.91 mmol) in THF (15 ml) at 0 °C. After being stirred at 0 °C for 1 h, the mixture was treated dropwise with a solution of ethyl bromoacetate (0.21 ml, 1.91 mmol) in THF (3 ml). After 30 min, the mixture was neutralized with aqueous acetic acid and extracted with $CHCl_3$ (3×100 ml). The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column ($CHCl_3$–acetone, 100 : 1, v/v) to give two fractions. Evaporation of the first fraction gave **18e** (443 mg, 67%). IR (KBr): 1730 (CO), 1740 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 1.22 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 3.16 (2H, dd, $J=3$, 7 Hz, CH_2), 4.10 (2H, q, $J=7$ Hz, CH_2CH_3), 4.17 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 4.35 (2H, s, C_2-CH_2), 4.51 (1H, t, $J=7$ Hz, CH), 7.29 (5H, s, ArH). MS *m/z*: 348 (M^+). HR-MS *m/z*: Calcd for $C_{17}H_{20}N_2O_4S$: 348.1143. Found: 348.1108. The starting material **11** (128 mg) was recovered from the second fraction.

3-(2-Benzyl-1,3,4-thiadiazol-5-yl)propionic Acid (4e) A solution of 85% KOH (444 mg, 6.73 mmol) in H_2O (5 ml) was added to a stirred solution of **18e** (395 mg, 1.13 mmol) in EtOH (5 ml) at room temperature. After being stirred at 50 °C for 1 h, the mixture was cooled on ice, acidified with

10% aqueous HCl, and extracted with $CHCl_3$ (3 × 100 ml). The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column ($CHCl_3$–MeOH, 20 : 1, v/v) to give a solid, which was recrystallized from isopropyl ether–acetone to give **4e** (127 mg, 45%), mp 89—90 °C. IR (KBr): 3100—2500 (OH), 1715 (CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.71 (2H, t, J=7 Hz, CH_2), 3.22 (2H, t, J=7 Hz, CH_2), 4.23 (2H, s, C_2-CH_2), 7.34 (5H, s, ArH), 11.2—12.8 (1H, br, OH). MS m/z: 248 (M^+). *Anal.* Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 58.20; H, 4.80; N, 11.32.

3-(2-Benzoyl-1,3,4-thiadiazol-5-yl)propionic Acid (4a) A suspension of CrO_3 (40 mg, 0.4 mmol) in acetic acid (2 ml) was added to a stirred solution of **4e** (50 mg, 0.2 mmol) in acetic acid (2 ml) at room temperature. After being stirred at 60 °C for 1 h, the mixture was cooled on ice, treated with water (5 ml), and extracted with $CHCl_3$. Work-up as described for the preparation of **4e** gave **4a** (38 mg, 72%), mp 117—118 °C (acetone). IR (KBr): 3200—2500 (OH), 1720 (CO), 1690 (CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.85 (2H, t, J=7 Hz, CH_2), 3.43 (2H, t, J=7 Hz, CH_2), 7.50—7.85 (3H, m, ArH), 8.25—8.45 (2H, m, ArH), 12.42 (1H, br s, OH). MS m/z: 262 (M^+). *Anal.* Calcd for $C_{12}H_{10}N_2O_3S$: C, 54.95; H, 3.84; N, 10.68. Found: C, 55.09; H, 3.70; H, 10.68.

Diethyl 3-(2-Benzyl-1,3,4-thiadiazol-5-yl)-3-ethoxycarbonylglutarate (19e) Compound **19e** was obtained from **11** (3 g, 11.44 mmol) and ethyl bromoacetate (2.52 ml, 22.78 mmol) in a similar manner to that described for compound **18e**. Yield 3.26 g (66%). IR (KBr): 1750 (CO), 1740 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (6H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.23 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.32 (4H, s, CH_2), 3.99 (4H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.19 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.34 (2H, s, C_2-CH_2), 7.27 (5H, s, ArH). MS m/z: 434 (M^+). HR-MS m/z: Calcd for $C_{21}H_{26}N_2O_6S$: 434.1511. Found: 434.1501.

3-(2-Benzyl-1,3,4-thiadiazol-5-yl)glutaric Acid (5e) Compound **5e** was obtained from **19e** (559 mg, 1.29 mmol) and 85% KOH (434 mg, 6.57 mmol) in a similar manner to that described for compound **4e**. Yield 275 mg (70%), mp 96—98 °C (acetone). IR (KBr): 3100—2500 (OH), 1730 (CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.77 (4H, d, J=7 Hz, CH_2), 3.88 (1H, t, J=7 Hz, CH), 4.40 (2H, s, C_2-CH_2), 7.35 (5H, s, ArH), 9.0—12.0 (2H, br s, OH). MS m/z: 306 (M^+). *Anal.* Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61; N, 9.14. Found: C, 54.99; H, 4.55; N, 9.11.

3-(2-Benzoyl-1,3,4-thiadiazol-5-yl)glutaric Acid (5a) Compound **5a** was obtained from **5e** (150 mg, 0.49 mmol) and CrO_3 (98 mg, 0.98 mmol) in a similar manner to that described for compound **4a**. Yield 119 mg (76%), mp 157—158 °C (acetone). IR (KBr): 3200—2500 (OH), 1720 (CO), 1705 (CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.91 (4H, d, J=7 Hz, CH_2), 4.07 (1H, t, J=7 Hz, CH), 7.50—7.90 (3H, m, ArH), 8.28—8.46 (2H, m, ArH), 9.0—12.0 (2H, br s, OH). MS m/z: 320 (M^+). *Anal.* Calcd for $C_{14}H_{12}N_2O_5S$: C, 52.50; H, 3.78; N, 8.75. Found: C, 52.58; H, 3.76; N, 8.51.

2-Methylsulfonyl-5-phenyl-1,3,4-thiadiazole (16b) Compound **16b**[8] was prepared by the literature method.

5-(4-Chlorophenyl)-2-methylsulfonyl-1,3,4-thiadiazole (16c) Compound **16c** was prepared by the literature method.[8] mp 189—190 °C (lit.,[3g] mp 189—190 °C). IR (KBr): 1325, 1150 (SO_2) cm^{-1}.

5-(4-Bromophenyl)-2-methylsulfonyl-1,3,4-thiadiazole (16d) Compound **16d** was prepared by the literature method.[8] mp 186—187 °C. IR (KBr): 1330, 1160 (SO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.52 (3H, s, CH_3), 7.69 (2H, dd, J=2, 9 Hz, ArH), 7.93 (2H, dd, J=2, 9 Hz, ArH). MS m/z: 318, 320 (M^+). *Anal.* Calcd for $C_9H_7BrN_2O_2S_2$: C, 33.87; H, 2.21; N, 8.78. Found: C, 33.89; H, 2.13; N, 8.82.

Ethyl 2-Phenyl-1,3,4-thiadiazol-5-ylacetate (17b) A solution of ethyl acetate (1.64 ml, 16.8 mmol) in anhydrous THF (3 ml) was added to a solution of LDA (16.8 mmol; prepared from a 1.68 M solution of *n*-BuLi in hexane, 10 ml, 16.8 mmol, and diisopropylamine, 2.36 ml, 16.8 mmol) in anhydrous THF (10 ml) at −78 °C under argon. The mixture was stirred at −78 °C for 30 min, then a solution of **16b** (2.02 g, 8.42 mmol) in anhydrous THF (20 ml) was added dropwise. After 1 h at −78 °C, the reaction was quenched with aqueous acetic acid and the mixture was extracted with ethyl acetate (2 × 100 ml). The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column ($CHCl_3$–acetone, 50 : 1, v/v) to give a solid, which was recrystallized from EtOH to give **17b** (1.96 g, 94%), mp 87—88 °C (lit.,[7] 88—89 °C). IR (KBr): 1730 (CO) cm^{-1}.

Ethyl 2-(4-Chlorophenyl)-1,3,4-thiadiazol-5-ylacetate (17c) Compound **17c** was obtained from **16c** (450 mg, 1.64 mmol) and ethyl acetate (0.48 ml, 4.91 mmol) in a similar manner to that described for compound **17b**. Yield 454 mg (98%), mp 105—106 °C (EtOH). IR (KBr): 1730 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.18 (2H, s, CH_2), 4.23 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.43 (2H, dd, J=2, 9 Hz, ArH), 7.90 (2H, dd, J=2, 9 Hz, ArH). MS m/z: 282, 284 (M^+). *Anal.* Calcd for $C_{12}H_{11}ClN_2O_2S$: C, 50.98; H, 3.92; N, 9.91. Found: C, 50.97; H, 3.85; N, 9.98.

Ethyl 2-(4-Bromophenyl)-1,3,4-thiadiazol-5-ylacetate (17d) Compound **17d** was obtained from **16d** (523 mg, 1.64 mmol) and ethyl acetate (0.48 ml, 4.91 mmol) in a similar manner to that described for compound **17b**. Yield 481 mg (90%), mp 105—106 °C (EtOH). IR (KBr): 1725 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.19 (2H, s, CH_2), 4.24 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.60 (2H, dd, J=2, 9 Hz, ArH), 7.83 (2H, dd, J=2, 9 Hz, ArH). MS m/z: 326, 328 (M^+). *Anal.* Calcd for $C_{12}H_{11}BrN_2O_2S$: C, 44.05; H, 3.39; N, 8.56. Found: C, 44.09; H, 3.21; N, 8.49.

Diethyl 2-(4-Substituted phenyl)-1,3,4-thiadiazol-5-ylsuccinates (18b—d) Compounds **18b—d** were obtained from **17b—d** and ethyl bromoacetate in a similar manner to that described for compound **18e**. Yields, melting points, recrystalization solvents, and analytical and spectral data for compounds **18b—d** are given in Table I.

3-[2-(4-Substituted phenyl)-1,3,4-thiadiazol-5-yl]propionic Acids (4b—d) Compounds **4b—d** were obtained from **18b—d** and potassium hydroxide in a similar manner to that described for compound **4e**. Yields, melting points, recrystallization solvents, and analytical and spectral data for compounds **4b—d** are given in Table II.

Diethyl 3-[2-(4-Substituted phenyl)-1,3,4-thiadiazol-5-yl]-3-ethoxycarbonylglutarates (19b—d) Compounds **19b—d** were obtained from **17b—d** and ethyl bromoacetate in a similar manner to that described for compound **19e**. Yields, and analytical and spectral data for compounds **19b—d** are given in Table I.

3-[2-(4-Substituted phenyl)-1,3,4-thiadiazol-5-yl]glutaric Acids (5b—d) Compounds **5b—d** were obtained from **19b—d** and potassium hydroxide in a similar manner to that described for compound **5e**. Yields, melting points, recrystallization solvents, and analytical and spectral data for compounds **5b—d** are given in Table II.

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