Phenacylsulfonylacetic Acid Methyl Ester-Synthon for 1,2,3-Selena/Thiadiazoles and 2*H*-Diazaphospholes

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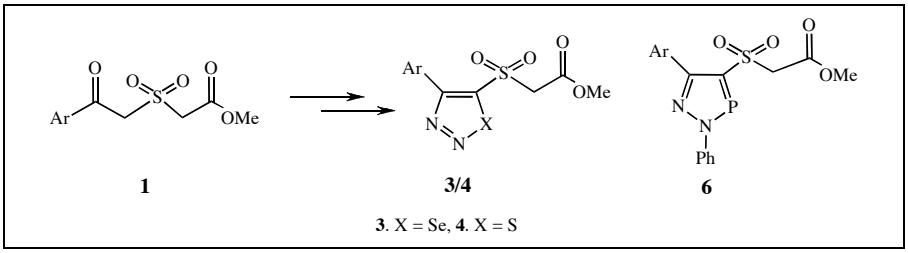
Received August 31, 2006



A new class of 1,2,3-selena/thiadiazoles and 2*H*-diazaphospholes were synthesized by exploiting α-ketomethylene group in phenacylsulfonylacetic acid methyl ester.

J. Heterocyclic Chem., **44**, 1165 (2007).

INTRODUCTION

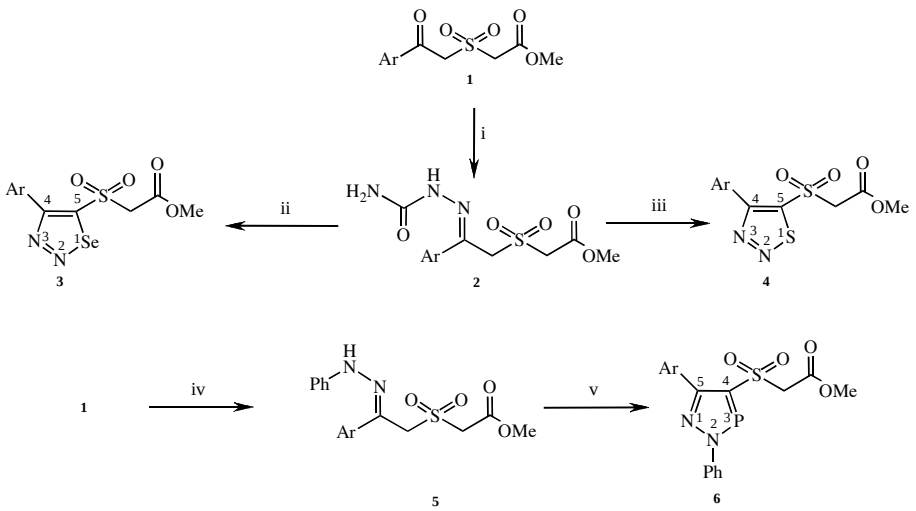
Heterocycles continue to be a major contributing nucleus in organic chemistry and have gained immense importance biologically. Amongst different heterocyclic systems, the chemistry of five membered heterocycles containing nitrogen and sulfur has gained much attention due to their varied physicochemical properties. One such class of compounds include 1,2,3-selenadiazoles, 1,2,3-thiadiazoles and 2*H*-diazaphospholes [1-4]. In general when selenium is part of a functional group, it tends to be more toxic than sulfur analogue compounds [5]. However, when selenium is part of a ring system, the toxicity of sulfur and selenium do not differ widely. This paves the way towards the development of selenium containing drugs like ^{75}Se-selenamethiomine used in pancreatic scanning [6]. Besides, the thiadiazole derivatives also possess pronounced biological activity [1,7,8]. In fact, for the last few years we have been actively involved in the synthesis of annelated heterocycles having selenadiazole, thiadiazole and diazaphosphole units [9]. In continuation of our study towards the development of biologically potent heterocycles, herein we wish to report a new class of 1,2,3-selenadiazoles, thiadiazoles and 2*H*-diazaphospholes exploiting α-ketomethylene functionality in phenacylsulfonylacetic acid methyl ester.

RESULTS AND DISCUSSION

The synthetic scheme was based on the reactivity of the α-ketomethylene group in phenacylsulfonylacetic acid methyl ester (**1**). The latter was obtained by the oxidation of phenacylmercaptoacetic acid methyl ester which inturn was prepared by the reaction of phenacyl bromide with thioglycolic acid followed by esterification. The α- ketomethylene group in **1** served as a building block for the development of the desired heterocycles. Compound **1** on reaction with semicarbazide gave the semicarbazone of phenacylsulfonylacetic acid methyl ester (**2**) (Scheme I and Table **1**). The IR spectra of **2** displayed bands in the region 3365-3490 (*NH*CO and CO*NH*$_2$), 1690-1710 and 1555-1580 (*CO*NH$_2$) and 1640-1650 cm^{-1} (C=N) apart from bands at 1730-1735 (CO_2Me) and 1330-1345 & 1135-1145 cm^{-1} (SO_2) (Table 2). The ^{1}H NMR spectrum of **2a** displayed three singlets at 5.12, 4.82 and 3.52 ppm due to methylene (C*H*$_2$SO$_2$ and SO$_2$C*H*$_2$) and methoxy protons. Oxidative cyclization of **2** with selenium dioxide in acetic acid at 60–70ºC furnished (4-phenyl[1,2,3]selenadiazole-5-sulfonyl)acetic acid methyl ester (**3**). However, the Hurd-Mori [10] reaction process of **2** with excess thionyl chloride in dichloromethane at 0°C produced (4-phenyl[1,2,3]thiadiazole-5-sulfonyl)acetic acid methyl ester (**4**) (Scheme I & Table 1). In the IR spectra of **3** and **4** the absorption bands were observed in the regions 1730-1735 (CO_2Me), 1320-1340 and 1120-1155 (SO_2), 1430-1455 (N=N) and 715-730 cm^{-1} (C-Se / S) (Table **2**). The ^{1}H NMR spectra of **3a** and **4a** displayed two singlets at 4.75, 4.68 and 3.54, 3.56 ppm due to methylene protons present between SO_2 and ester group and methoxy protons of carbomethoxy group (Table **3**). The absence of a singlet around 5.0 ppm corresponding to methylene protons flanked between semicarbazone and SO_2 group substantiate that heteroannulation occurred.

The reaction of **1** with phenylhydrazine produced (1-phenylethanone-phenylhydrazone)sulfonylacetic acid methyl ester (**5**). The absorption bands in the region 3280-3300 (NH) and 1590-1600 cm^{-1} (C=N) in the IR spectra of

Scheme I



(i) $NH_2NHCONH_2$ / AcONa/MeOH (ii) SeO_2/AcOH (iii) $SOCl_2/CH_2Cl_2$
(iv) $PhNHNH_2$/MeOH (v) $PCl_3/Et_3N/Et_2O$
a: Ar = C_6H_5 ; **b**: Ar = *p*-$CH_3C_6H_4$; **c**: Ar = *p*-ClC_6H_4

Table 1

Physical and Analytical Data of Compounds **2-6**

Compound.	Mp (°C)	Ar	Yield %	Molecular Formula	Analysis % Calcd. /Found C	H	N
2a	89-91	Ph	72	$C_{12}H_{15}N_3O_5S$	46.00	4.83	13.41
					46.12	4.91	13.49
2b	98-100	4-MePh	70	$C_{13}H_{17}N_3O_5S$	47.70	5.23	12.84
					47.77	5.29	12.92
2c	113-115	4-ClPh	66	$C_{12}H_{14}N_3ClO_5S$	41.44	4.06	12.08
					41.51	4.14	12.06
3a	118-120	Ph	63	$C_{11}H_{10}N_2O_4SSe$	38.27	2.92	8.11
					38.38	2.98	8.19
3b	114-116	4-MePh	60	$C_{12}H_{12}N_2O_4SSe$	40.12	3.37	7.86
					40.08	3.32	7.80
3c	123-125	4-ClPh	74	$C_{11}H_9N_2ClO_4SSe$	34.80	2.39	7.30
					34.89	2.43	7.38
4a	132-134	Ph	62	$C_{11}H_{10}N_2O_4S_2$	44.28	3.38	9.39
					44.38	3.40	9.49
4b	127-129	4-MePh	64	$C_{12}H_{12}N_2O_4S_2$	46.14	3.87	8.97
					46.24	3.92	9.06
4c	138-140	4-ClPh	73	$C_{11}H_9N_2ClO_4S_2$	39.70	2.73	8.42
					39.62	2.71	8.49
5a	112-114	Ph	75	$C_{17}H_{18}N_2O_4S$	58.94	5.24	8.09
					59.02	5.31	8.14
5b	119-121	4-MePh	78	$C_{18}H_{20}N_2O_4S$	59.98	5.59	7.77
					59.92	5.56	7.81
5c	124-126	4-ClPh	71	$C_{17}H_{17}N_2ClO_4S$	53.61	4.50	7.36
					53.66	4.58	7.39
6a	150-152	Ph	62	$C_{17}H_{15}N_2O_4PS$	54.54	4.04	7.48
					54.65	4.00	7.55
6b	143-145	4-MePh	68	$C_{18}H_{17}N_2O_4PS$	55.67	4.41	7.21
					55.58	4.45	7.34
6c	160-162	4-ClPh	64	$C_{17}H_{14}N_2ClO_4PS$	49.95	3.45	6.85
					50.04	3.42	6.94

Table 2

IR Data of Compounds **2-6**

Compound	IR (cm^{-1})						
	C-Se/S	SO_2	N=N	C=O	C=N	*CO*NH_2	NH&NH_2
2a	-	1331 1147	-	1730	1635	1710 1555	3470 3374
2b	-	1328 1134	-	1733	1642	1690 1562	3450 3365
2c	-	1343 1142	-	1735	1650	1704 1580	3491 3379
3a	723	1335 1121	1440	1729	-	-	-
3b	725	1332 1139	1435	1734	-	-	-
3c	728	1321 1153	1453	1731	-	-	-
4a	716	1330 1149	1450	1732	-	-	-
4b	721	1332 1137	1430	1736	-	-	-
4c	724	1339 1132	1445	1734	-	-	-
5a	-	1328 1148	-	1729	1600	-	3300
5b	-	1338 1147	-	1733	1598	-	3280
5c	-	1326 1133	-	1737	1590	-	3290
6a	-	1336 1143	-	1732	1580	-	-
6b	-	1338 1148	-	1734	1585	-	-
6c	-	1342 1139	-	1731	1600	-	-

Table 3

^{1}H and ^{13}C NMR Data of Compounds **2-6**

Compound	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
2a	3.52 (s, 3H, -OCH_3), 4.82 (s, 2H, SO_2-CH_2), 5.12 (s, 2H, CH_2-SO_2), 6.67 (bs, 2H, NH_2), 7.38-7.93 (m, 5H, Ar-H), 9.72 (bs, 1H, NH)	-
2b	2.32 (s, 3H, Ar-CH_3), 3.48 (s, 3H, -OCH_3), 4.86 (s, 2H, CH_2-SO_2), 5.00 (s, 2H, SO_2-CH_2), 6.58 (bs, 2H, NH_2), 7.32-7.89 (m, 4H, Ar-H), 9.69 (bs, 1H, NH)	-
2c	3.56 (s, 3H, -OCH_3), 4.92 (s, 2H, CH_2-SO_2), 5.05 (s, 2H, SO_2-CH_2), 6.69 (bs, 2H, NH_2), 7.42-7.94 (m, 4H, Ar-H), 9.78 (bs, 1H, NH).	-
3a	3.54 (s, 3H, -OCH_3), 4.75 (s, 2H, SO_2-CH_2), 7.42-7.94 (m, 5H, Ar-H)	52.8 (-OCH_3), 59.2 (SO_2-CH_2), 155.7 (C-5), 156.1 (C-4), 160.4 (C=O), 126.6, 130.2, 132.2, 135.4 (aromatic carbons)
3b	2.35 (s, 3H, Ar-CH_3), 3.54 (s, 3H, -OCH_3), 4.52 (s, 2H, SO_2-CH_2), 7.38-7.92 (m, 4H, Ar-H)	20.1 (Ar-CH_3), 52.4 (-OCH_3), 58.2 (SO_2-CH_2), 156.8 (C-5), 157.1 (C-4), 161.4 (C=O), 126.8, 127.6, 134.2, 137.2 (aromatic carbons)
3c	3.58 (s, 3H, -OCH_3), 4.78 (s, 2H, SO_2-CH_2), 7.63-7.84 (m, 4H, Ar-H)	52.9 (-OCH_3), 60.6 (SO_2-CH_2), 158.0 (C-5), 159.1 (C-4), 162.4 (C=O), 128.6, 129.2, 132.2, 135.4 (aromatic carbons)
4a	3.56 (s, 3H, -OCH_3), 4.68 (s, 2H, SO_2-CH_2), 7.38-7.92 (m, 5H, Ar-H)	51.8 (-OCH_3), 57.2 (SO_2-CH_2), 154.3 (C-5), 155.1 (C-4), 158.4 (C=O), 125.6, 127.2, 131.2, 134.4 (aromatic carbons)
4b	2.28 (s, 3H, Ar-CH_3), 3.59 (s, 3H, -OCH_3), 4.74 (s, 2H, SO_2-CH_2), 7.32-7.82 (m, 4H, Ar-H)	21.8 (Ar-CH_3), 51.7 (-OCH_3), 58.2 (SO_2-CH_2), 156.5 (C-5), 157.7 (C-4), 161.2 (C=O), 126.7, 128.5, 131.7, 134.8 (aromatic carbons)
4c	3.54 (s, 3H, -OCH_3), 4.72 (s, 2H, SO_2-CH_2), 7.65 -7.82 (m, 4H, Ar-H)	52.8 (-OCH_3), 59.2 (SO_2-CH_2), 157.6 (C-5), 158.7 (C-4), 163.2 (C=O), 128.7, 129.4, 132.7, 134.8 (aromatic carbons)

Table 3 (continued)

Compound	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
5a	3.46 (s, 3H, -OCH_3), 4.72 (s, 2H, SO_2-CH_2), 4.85 (s, 2H, CH_2-SO_2), 7.38-7.93 (m, 10H, Ar-H), 9.72 (bs, 1H, NH)	-
5b	2.34 (s, 3H, Ar-CH_3), 3.36 (s, 3H, -OCH_3), 4.68 (s, 2H, SO_2-CH_2), 4.78 (s, 2H, CH_2-SO_2), 7.32-7.84 (m, 9H, Ar-H), 9.68 (bs, 1H, NH)	-
5c	3.48 (s, 3H, -OCH_3), 4.79 (s, 2H, SO_2-CH_2), 4.91 (s, 2H, CH_2-SO_2), 7.40-7.94 (m, 9H, Ar-H), 9.78 (bs, 1H, NH)	-
6a	3.51 (s, 3H, -OCH_3), 4.68 (s, 2H, SO_2-CH_2), 7.62-7.82 (m, 10H, Ar-H)	53.8 (-OCH_3), 60.2 (SO_2-CH_2), 146.1 (C-5), 158.7 (C-4), 164.4 (C=O), 128.6, 129.2, 129.8, 130.2, 132.4, 133.1, 134.6, 134.9 (aromatic carbons)
6b	2.32 (s, 3H, Ar-CH_3), 3.48 (s, 3H, -OCH_3), 4.56 (s, 2H, SO_2-CH_2), 7.64-7.89 (m, 9H, Ar-H)	21.8 (Ar-CH_3), 52.8 (-OCH_3), 57.2 (SO_2- CH_2), 148.7 (C-5), 159.4 (C-4), 164.2 (C=O), 127.9, 128.7, 129.7, 130.4, 131.2, 131.8, 132.6, 133.1 (aromatic carbons)
6c	3.53 (s, 3H, -OCH_3), 4.59 (s, 2H, SO_2-CH_2), 7.38-7.92 (m, 9H, Ar-H)	53.8 (-OCH_3), 59.2 (SO_2-CH_2), 147.2 (C-5), 156.6 (C-4), 162.2 (C=O), 127.6, 128.3, 128.9, 129.6, 131.5, 132.6, 133.4, 134.8 (aromatic carbons)

5 were due to phenylhydrazone moiety. The ^{1}H NMR spectrum of **5a** displayed three singlets at 4.85 (CH_2-SO_2), 4.72 (SO_2-C*H*$_2$-CO_2Me) and 3.46 ppm (OCH_3). When **5** was subjected to cyclocondensation with phosphorus trichloride in anhydrous diethyl ether in the presence of triethylamine at -5 to 10°C, (2,5-diphenyl-2*H*-[1,2,3]-diazaphosphole-4-sulfonyl)acetic acid methyl ester (**6**) was obtained (Scheme I and Table 1). The absence of the NH band and the presence of bands around 1730-1735 (CO_2Me), 1335-1345, 1140-1150 (SO_2) and 1580-1600 cm^{-1} (C=N) in the IR spectra indicates the formation of **6** (Table **2**). The ^{1}H NMR spectrum of **6a** showed a singlet at 4.68 ppm for methylene protons and another singlet at 3.51 ppm for methoxy protons of carbomethoxy group. The structure of the compounds **3**, **4** and **6** was further confirmed by ^{13}C NMR spectra (Table **3**).

EXPERIMENTAL

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate-hexane, 0.5:2). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Varian EM-360 spectrometer (300 MHz). The ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Varian VXR spectrometer operating at 75.5 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The microanalyses were performed on Perkin-Elmer 240C elemental analyzer. The starting compound phenacylsulfonylacetic acid methyl ester (**1**) was prepared by the literature procedure [11].

(1-Phenyl-ethanonesemicarbazone)sulfonylacetic acid methyl ester (2). General Procedure. A mixture of semicarbazide hydrochloride (0.134 g, 1.2 mmol) and sodium acetate trihydrate (0.272 g, 2 mmol) was dissolved in methanol (20 ml) and the residue (NaCl) was filtered off. Compound **1** (0.254 g, 1 mmol) in methanol (10 ml) was added to the filtrate and the contents were heated on a water bath for 3-5 hours. The reaction mixture was concentrated, cooled and poured onto crushed ice. The solid obtained was collected by filtration, dried and recrystallized from ethanol.

(4-Phenyl[1,2,3]selenadiazole-5-sulfonyl)acetic acid methyl ester (3). General Procedure. The semicarbazone **2** (0.936 g, 3 mmol) was dissolved in glacial acetic acid (20 ml) and warmed gently with stirring until a clear solution was obtained. Selenium dioxide (0.332 g, 3 mmol) was then added in portions over a period of 30 mins. with stirring. The contents were stirred at 60-70°C until the evolution of gas ceased and the deposited selenium was removed by filtration. The filtrate was poured onto crushed ice and the collected solid was washed with cold water and saturated sodium bicarbonate solution. The crude material was purified by column chromatography (silica gel, 60-120 mesh, hexane: ethyl acetate, 2:0.5) affording the titled compound.

(4-Phenyl[1,2,3]thiadiazole-5-sulfonyl)acetic acid methyl ester (4). General Procedure. To a well cooled (0°C) solution of semicarbazone **2** (0.936 g, 3 mmol) in dichloromethane (20 ml), an excess of thionyl chloride (3 ml) was added in portions while stirring. The mixture was then allowed to reach room temperature over 2-3 hours. Excess reagent was decomposed with cold saturated sodium carbonate solution. The organic layer was separated, washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* produced a residue, which was purified by column chromatography (silica gel, 60-120 mesh, hexane: ethyl acetate, 2:1).

(1-Phenyl-ethanonephenylhydrazone)sulfonylacetic acid methyl ester (5). General Procedure. To compound **1** (1.27 g, 5 mmol) dissolved in methanol (15 ml), phenylhydrazine (0.72 g, 5 mmol) was added and refluxed for 2-3 hours. Then the reaction mixture was concentrated and cooled (0°C). The solid was collected by filtration, washed with water, dried and recrystallized from ethanol.

(2,5-Diphenyl-2*H*-[1,2,3]diazaphosphole-4-sulfonyl)acetic acid methyl ester (6). General Procedure. Phosphorus tri-

chloride (0.206 g, 1.5 mmol) was added to anhydrous diethyl ether at -5 to –10°C under a nitrogen atmosphere with stirring. To this, **5** (0.346 g, 1 mmol) dissolved in anhydrous diethyl ether, was added slowly (dropwise) followed by triethylamine (0.121 g, 1.2 mmol). Stirring was continued for 2-3 hours and the contents were brought to room temperature. Evaporation of the ethereal layer under reduced pressure produced a solid, which was purified by filtration through a column of silica gel (60-120 mesh, BDH) with hexane: ethyl acetate (1.5:1) as eluent.

Acknowledgement. The authors are grateful to DST, New Delhi for financial assistance under major research project.

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