Phenacylsulfonylacetic esters – Source for thiadiazoles, triazoles and oxadiazoles

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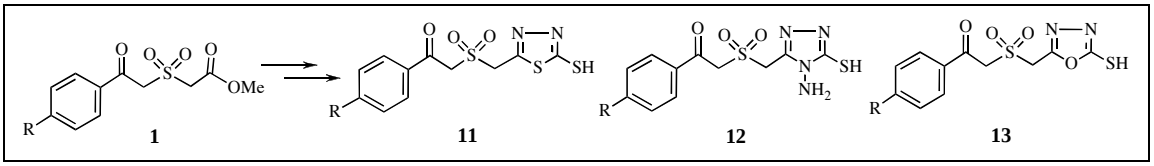
Received March 13, 2006



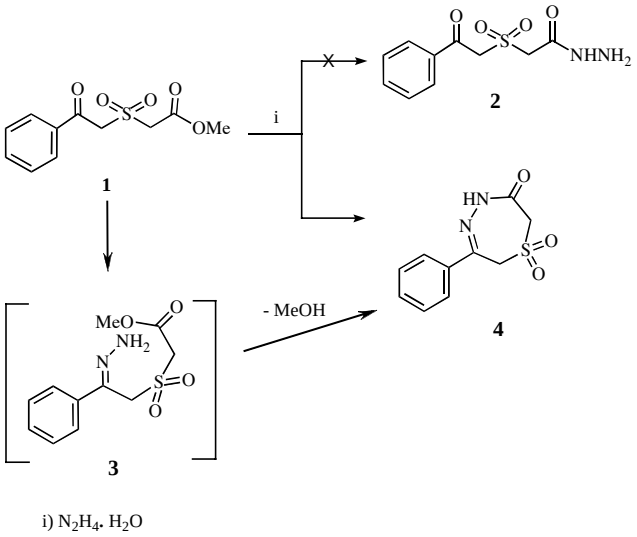
A new class of thiadiazoles, triazoles and oxadiazoles were prepared from phenacylsulfonylacetic ester by protecting the carbonyl group by oximation. Deoximation was affected by using β-cyclodextrin in the presence of an oxidizing agent.

J. Heterocyclic Chem., **44**, 93 (2007).

INTRODUCTION

The development of simple, facile and efficient methods for the synthesis of five membered heterocycles is one of the major challenges in organic synthesis. Amongst five membered heterocycles thiadiazoles, triazoles and oxadiazoles have gained importance because of their intrinsic biological activities and constitute the structural feature of many bioactive compounds. In fact, some of them have also emerged as potential drugs [1]. The molecules having triazole and thiadiazine units have a broad spectrum of antimicrobial and antiparasitic activities [2]. The 2-mercapto-5-methyl-1,3,4-thiadiazole is an intermediate for the therapeutically useful antibiotic cefazolin [3]. Our interest in the development of novel heterocycles prompted us to study the reactivity of the methyl ester of phenacylsulfonylacetic acid towards the development of five membered heterocycles *viz*., 1,3,4-thiadiazoles, 1,2,4-triazoles and 1,3,4-oxadiazoles.

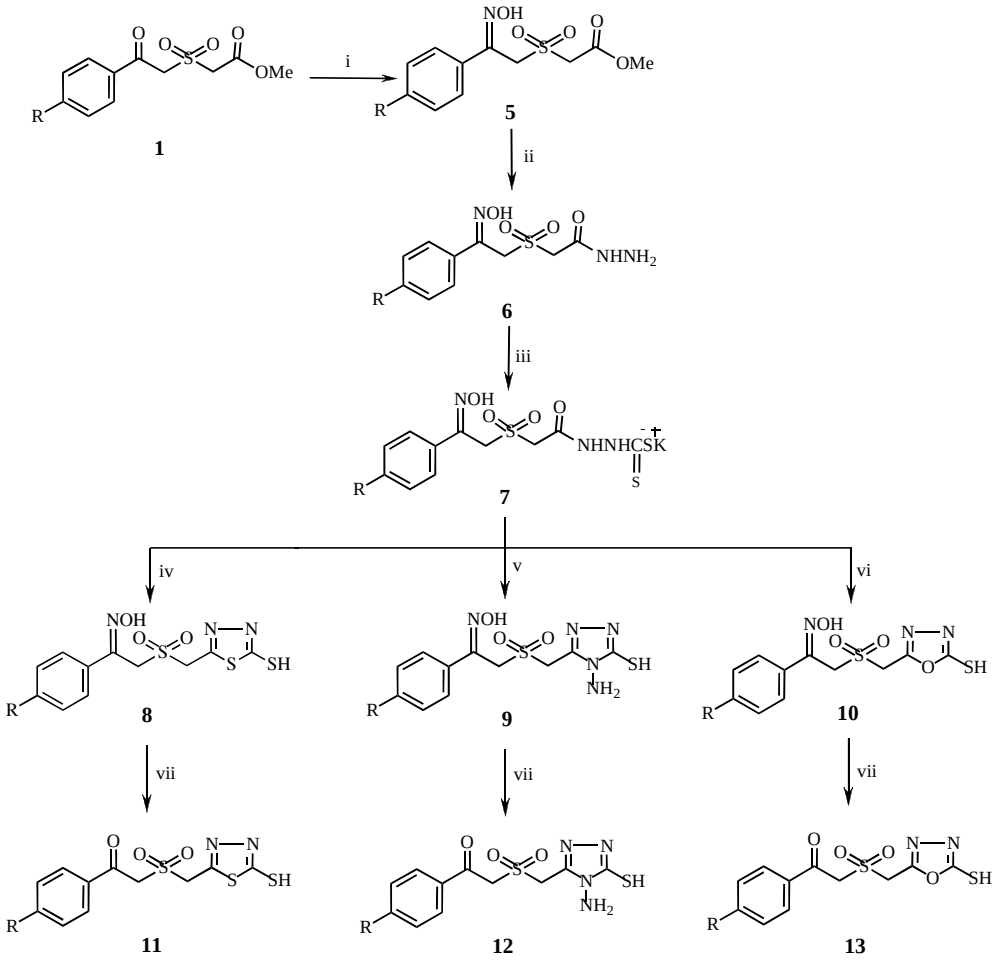
Scheme I



RESULTS AND DISCUSSION

When the methyl ester of phenacylsulfonylacetic acid (**1**) was treated with hydrazine hydrate instead of the expected (oxo-phenyl-ethanesulfonyl)-acetic acid hydrazide (**2**), a cyclic product 6-phenyl-4,7-dihydro-1*H*-1λ^6, 4,5-thiadiazepin-1,1,3(2*H*)-trione (**4**) was obtained [4] (Scheme I). The structure of this compound was established by its spectral parameters. The ^{1}H NMR spectrum of **4** showed signals at δ 4.25 and 4.89 ppm for C_2-H and C_7-H and a broad singlet at δ 10.65 ppm for NH, which disappeared on deuteration. The IR spectrum of **4** displayed bands in the regions 1650 (C=O), 1129, 1321 (SO_2), 1540 (C=N) and 3258 cm^{-1} (NH). The ^{13}C NMR spectrum of **4** showed signals at δ 67.2, 166.3, 154.8 and 61.2 ppm for C-2, C-3, C-6 and C-7. It seems that the initially formed (hydrazono-phenyl-ethanesulfonyl)-acetic acid methyl ester (**3**) undergoes an intramolecular cyclo-condensation to **4**. In order to achieve the acid hydrazide, the carbonyl group in **1** was protected by treatment with hydroxylamine hydrochloride to get hydroxyimino-phenyl-ethanesulfonyl)-acetic acid methyl ester (**5**) (Scheme II). The IR spectra of **5** showed absorption bands at 1721 (C=O of ester) and at 3338 cm^{-1} (N-OH of oxime). Then **5** was stirred with hydrazine hydrate at room temperature to get (hydroxyimino-phenyl-ethane-sulfonyl)-acetic acid hydrazide (**6**). The absence of an absorption band corresponding to the ester carbonyl group and the presence of bands at 1665 cm^{-1} for an amidic carbonyl group and at 3214 and 3229 cm^{-1} for NH and NH_2 in the IR spectrum indicates the formation of **6**. The

Scheme II



a R = H
b R = Me
c R = Cl

i) $NH_2OH.HCl$ / EtOH ii) $N_2H_4.H_2O$ / Pyridine / EtOH iii) KOH / CS_2 / EtOH
iv) AcOH v) $N_2H_4.H_2O$ vi) H^+ vii) β-CD / H_2O

potassium dithiocarbazate of the acid hydrazide (**7**) was prepared by treating **6** with carbon disulfide in the presence of potassium hydroxide under ultrasonic conditions. In refluxing acetic acid, the latter cyclized to give 1-phenyl-2-{[(5-sulfanyl-1,3,4-thiadiazol-2-yl)methyl]-sulfonyl}-1-ethanone oxime (**8**). Treatment of **7** with hydrazine hydrate produced 2-{[(4-amino-5-sulfanil-4*H*-1,2,4-triazol-3-yl)methyl]sulfonyl}-1-phenyl-1-ethanone oxime (**9**). Similarly base catalyzed hydrolysis of **7** resulted in 1-phenyl-2-{[(5-sulfanyl-1,3,4-oxadiazol-2-yl)methyl]sulfonyl}-1-ethanone oxime (**10**). The IR spectra of **8-10** displayed absorption bands around 1634 cm^{-1} for C=N apart from bands due to other functional groups. The ^1H NMR spectra showed a singlet at δ 10.23-10.43 ppm for SH apart from signals due to methylene protons. However the compound **9** exhibited signals at δ 5.60 ppm for NH_2, which disappeared on deuteration. The structures of these compounds were further confirmed by ^{13}C NMR spectra.

There were different methods in the literature for the deoximation of oxime group [5-20]. We have adopted the deoximation reaction of **8-10** using mild oxidizing agent 2-iodoxybenzoic acid catalyzed by β-cyclo-dextrin in water at room temperature. The products obtained were identified as 1-phenyl-2-{[(5-sulfanyl-1,3,4-thiadiazol-2-yl)methyl]sulfonyl}-1-ethanone (**11**), 2-{[(4-amino-5-sulfanil-4*H*-1,2,4-triazol-3-yl)methyl]-sulfonyl}-1-phenyl-1-ethanone (**12**) and 1-phenyl-2-{[(5-sulfanyl-1,3,4-oxadiazol-2-yl)methyl]sulfonyl}-1-ethanone (**13**), respectively. The IR spectra of these compounds displayed an additional band due to C=O at 1680 cm^{-1} apart from other absorption bands. The ^1H NMR spectra of these compounds displayed two singlets at δ 4.70-4.79 and 4.62-4.72 ppm due to methylene protons flanked between Ar-CO-SO_2 and SO_2-heterocyclic units. The structure of the compounds was further confirmed by ^{13}C NMR spectra.

CONCLUSION

The desired thiadiazoles, triazoles and oxadiazoles were prepared from phenacylsulfonylacetic esters by protecting the carbonyl group. Thus the oximation of carbonyl group and deoximation with β-cyclodextrin in the presence of oxidizing agent provides a simple and efficient methodology for regiospecific synthesis of heterocycles.

EXPERIMENTAL

Melting points were determined in open capillaries on a Mel-Temp apparatus. The purity of the compounds was checked by TLC (Silica gel H, BDH, ethyl acetate-hexane, 1:3). IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR in KBr pellets. ^{1}H NMR spectra were recorded at 300 MHz on a Varian EM-360 spectrometer. ^{13}C NMR spectra were run on a Varian VXR spectrometer operating at 75.5 MHz. All chemical shifts are reported in ppm from TMS as an internal standard. Mass spectra were recorded on a Joel JMS-D 300 instrument at 70 eV. Elemental analyses were performed using a Perkin-Elmer 240 C elemental analyzer. The starting compound methyl ester of phenacylsulfonylacetic acid **1** was prepared by standard procedure [21].

6-Phenyl-4,7-dihydro-1*H*-1λ^6,4,5-thiadiazepin-1,1,3(2*H*)-trione (4): General Procedure. A mixture of **1** (0.051 g, 0.2 mmol), hydrazine hydrate (0.02 ml, 0.4 mmol) and methanol (15 ml) was refluxed for 10 h after which the solution was cooled and the solid separated was collected by filtration, dried and recrystallized from methanol.

6-Phenyl-4,7-dihydro-1*H*-1λ^6,4,5-thiadiazepin-1,1,3(2*H*)-trione (4). White crystals, Yield 0.030 g (64%), mp 301-303 °C; ir: 1129, 1321(SO_2), 1540 (C=N), 1650 (C=O), 3258 (NH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 4.25 (s, 2H, C_2-H), 4.89 (s, 2H, C_7-H), 7.22-7.63 (m, 5H, Ar-H), 10.65 (bs, 1H, NH); ^{13}C nmr (DMSO-d_6): δ_C 61.2 (C_7), 67.2 (C_2), 154.8 (C_6), 166.3 (C_3); ms: m/z 238 ($M^{+\cdot}$). *Anal.* Calcd. for $C_{10}H_{10}N_2O_3S$: C, 50.41; H, 4.23; N, 11.76. Found: C, 50.50; H, 4.27; N, 11.82.

(Hydroxyimino-aryl-ethanesulfonyl)-acetic acid methyl ester (5): General Procedure. To a solution of methyl ester of phenacylsulfonylacetic acid **1** (0.26 g, 1 mmol) in ethanol, hydroxylamine hydrochloride (0.347 g, 5 mmol) and pyridine (0.2 ml) were added and refluxed for 8 h over a water bath after which the solution was poured into crushed ice and the resultant solid was purified by recrystallization from ethanol.

(Hydroxyimino-phenyl-ethanesulfonyl)-acetic acid methyl ester (5a). White solid, Yield 0.23 g (84%), mp113-115 °C; ir: 1148, 1325 (SO_2), 1625 (C=N), 1721 (C=O), 3338 (OH) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ_H 3.67 (s, 3H, OCH_3), 4.35 (s, 2H, SO_2-CH_2), 4.92 (s, 2H, CH_2-SO_2), 7.32-7.61 (m, 5H, Ar-H), 12.15 (s, 1H, OH); ^{13}C nmr ($CDCl_3$): δ_C 53.3 (OCH_3), 56.5 (SO_2-CH_2), 57.3 (CH_2-SO_2), 128.6, 129.3, 130.5, 131.4 (Ar-C), 166.3 (C=NOH), 169.2 (*C*OOCH$_3$). *Anal.* Calcd. for $C_{11}H_{13}NO_5S$: C, 48.70; H, 4.83; N, 5.16. Found: C, 48.79; H, 4.86; N, 5.22.

(Hydroxyimino-*p*-tolyl-ethanesulfonyl)-acetic acid methyl ester (5b). White solid, Yield 0.25 g (88%), mp 122-123 °C; ir: 1146, 1335 (SO_2), 1628 (C=N), 1720 (C=O), 3335 (OH) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ_H 2.31 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 4.33 (s, 2H, SO_2-CH_2), 4.89 (s, 2H, CH_2-SO_2), 7.11-7.31 (m, 4H, Ar-H), 11.93 (s, 1H, OH); ^{13}C nmr ($CDCl_3$): δ_C 20.4 (Ar-CH_3), 53.6 (OCH_3), 56.2 (SO_2-CH_2), 58.1 (CH_2-SO_2), 129.1, 130.3, 130.8, 132.6 (Ar-C), 165.9 (C=NOH), 168.6 (*C*OOCH$_3$). *Anal.* Calcd. for $C_{12}H_{15}NO_5S$: C, 50.52; H, 5.30; N, 4.91. Found: C, 50.60; H, 5.28; N, 4.96.

[(4-Chloro-phenyl)-hydroxyimino-ethanesulfonyl]-acetic acid methyl ester (5c). White solid, Yield 0.27 g (90%), mp 98-100 °C; ir: 1150, 1327 (SO_2), 1632 (C=N), 1722 (C=O), 3339 (OH) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ_H 3.69 (s, 3H, OCH_3), 4.38 (s, 2H, SO_2-CH_2), 4.95 (s, 2H, CH_2-SO_2), 7.22-7.41 (m, 4H, Ar-H), 12.26 (s, 1H, OH); ^{13}C nmr ($CDCl_3$): δ_C 54.0 (OCH_3), 56.9 (SO_2-CH_2), 58.6 (CH_2-SO_2), 129.4, 130.7, 134.8, 136.3 (Ar-C), 166.9 (C=NOH), 169.6 (*C*OOCH$_3$). *Anal.* Calcd. for $C_{11}H_{12}ClNO_5S$: C, 43.21; H, 3.96; N, 4.58. Found: C, 43.27; H, 3.91; N, 4.55.

(Hydroxyimino-aryl-ethanesulfonyl)-acetic acid hydrazide (6): General Procedure. To a solution of **5** (0.271 g, 1 mmol) in absolute ethanol, hydrazine hydrate (0.22 ml, 4.5 mmol) and pyridine (0.4 ml) were added and stirred for 3 h at room temperature. The resultant solid was collected by filtration and recrystallized from ethanol.

(Hydroxyimino-phenyl-ethanesulfonyl)-acetic acid hydrazide (6a). White solid, Yield 0.23 g (79%), mp 165-166 °C; ir: 1135, 1312 (SO_2), 1623 (C=N), 1665 (C=O), 3214 (NH), 3229 (NH_2), 3331 (OH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 3.96 (s, 2H, SO_2-CH_2), 4.91(s, 2H, CH_2-SO_2), 5.15 (br s, 2H, NH_2), 7.25-7.31 (m, 5H, Ar-H), 9.52 (br s, 1H, NH), 12.16 (s, 1H, OH); ^{13}C nmr (DMSO-d_6): δ_C 55.8 (SO_2-CH_2), 57.7 (CH_2-SO_2), 128.7, 129.8, 130.6, 131.5 (Ar-C), 166.2 (C=NOH), 168.4 (CONHNH$_2$). *Anal.* Calcd. for $C_{10}H_{13}N_3O_4S$: C, 44.27; H, 4.83; N, 15.49. Found: C, 44.21; H, 4.80; N, 15.55.

(Hydroxyimino-*p*-tolyl-ethanesulfonyl)-acetic acid hydrazide (6b). White solid, Yield 0.23 g (76%), mp 171-173 °C; ir: 1136, 1320 (SO_2), 1626 (C=N), 1650 (C=O), 3210 (NH), 3225 (NH_2), 3330 (OH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 2.34 (s, 3H, CH_3), 3.94 (s, 2H, SO_2-CH_2), 4.80 (s, 2H, CH_2-SO_2), 4.98 (br s, 2H, NH_2), 7.16-7.23 (m, 4H, Ar-H), 9.23 (br s, 1H, NH), 11.92 (s, 1H, OH); ^{13}C nmr (DMSO-d_6): δ_C 20.6 (Ar-CH_3), 56.1 (SO_2-CH_2), 58.4 (CH_2-SO_2), 129.2, 130.4, 131.7, 132.8 (Ar-C), 166.4 (C=NOH), 168.7 (CONHNH$_2$). *Anal.* Calcd. for $C_{11}H_{15}N_3O_4S$: C, 46.30; H, 5.30; N, 14.73. Found: C, 46.35; H, 5.33; N, 14.78.

[(4-Chloro-phenyl)-hydroxyimino-ethanesulfonyl]-acetic acid hydrazide (6c). White solid, Yield 0.24 g (75%), mp 178-180 °C; ir: 1136, 1313 (SO_2), 1624 (C=N), 1655 (C=O), 3212 (NH), 3223 (NH_2), 3327 (OH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 3.99 (s, 2H, SO_2-CH_2), 4.94 (s, 2H, CH_2-SO_2), 5.21 (br s, 2H, NH_2), 7.25-7.39 (m, 4H, Ar-H), 9.66 (br s, 1H, NH), 12.25 (s, 1H, OH); ^{13}C nmr (DMSO-d_6): δ_C 56.8 (SO_2-CH_2), 58.9 (CH_2-SO_2), 129.6, 131.2, 133.2, 138.3 (Ar-C), 166.8 (C=NOH), 168.9 (CONHNH$_2$). *Anal.* Calcd. for $C_{10}H_{12}ClN_3O_4S$: C, 39.28; H, 3.96; N, 13.74. Found: C, 39.33; H, 4.00; N, 13.78.

Potassium dithiocarbazate (7): General Procedure. To a mixture of potassium hydroxide (0.112 g, 2 mmol) and **6** (0.271 g, 1 mmol) in absolute ethanol, carbon disulfide (0.24 ml, 4 mmol) was added and sonicated for 12 h. The separated solid was collected by filtration and dried.

Potassium N′-[2-(2-hydroxyimino-2-phenyl-ethanesulfonyl)-acetyl]-hydrazine carbodithioate (7a). White solid, Yield 0.28 g (72%); ir: 1137, 1315 (SO_2), 1224 (C=S), 1627 (C=N), 1671 (C=O), 3219 (NH), 3340 (OH) cm^{-1}. *Anal.* Calcd. for $C_{11}H_{12}KN_3O_4S_3$: C, 34.27; H, 3.14; N, 10.90. Found: C, 34.31; H, 3.18; N, 10.95.

Potassium N′-[2-(2-hydroxyimino-2-(4-methyl-phenyl)-ethanesulfonyl)-acetyl]-hydrazine carbodithioate (7b). White

solid, Yield 0.30 g (75%); ir: 1132, 1317 (SO_2), 1225 (C=S), 1623 (C=N), 1679 (C=O), 3221 (NH), 3332 (OH) cm^{-1}. *Anal.* Calcd. for $C_{12}H_{14}KN_3O_4S_3$: C, 36.07; H, 3.53; N, 10.52. Found: C, 36.10; H, 3.56; N, 10.57.

Potassium *N′*-[2-(2-hydroxyimino-2-(4-chloro-phenyl)-ethanesulfonyl)-acetyl]-hydrazine carbodithioate (7c). White solid, Yield 0.33 g (79%); ir: 1135, 1320 (SO_2), 1227 (C=S), 1629 (C=N), 1681 (C=O), 3225 (NH), 3342 (OH) cm^{-1}. *Anal.* Calcd. for $C_{11}H_{11}ClKN_3O_4S_3$: C, 31.46; H, 2.64; N, 10.01. Found: C, 31.48; H, 2.68; N, 10.05.

1-Aryl-2-{[(5-sulfanyl-1,3,4-thiadiazol-2-yl)methyl]sulfonyl}-1-ethanone oxime (8): General Procedure. A mixture of **7** (0.371 g, 1 mmol) and acetic acid (4 ml) were refluxed for 24 h. The contents of the flask were cooled and poured into crushed ice. The solid obtained was collected by filtration, dried and recrystallized from 2-propanol.

1-Phenyl-2-{[(5-sulfanyl-1,3,4-thiadiazol-2-yl)methyl]-sulfonyl}-1-ethanone oxime (8a). White solid, Yield 0.21 g (65%), mp 192-194 °C; ir: 1128, 1330 (SO_2), 1633 (C=N), 2559 (SH), 3336 (OH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 4.65 (s, 2H, SO_2-CH_2), 4.92 (s, 2H, CH_2-SO_2), 7.31-7.62 (m, 5H, Ar-H), 10.23 (s, 1H, SH), 12.21 (s, 1H, OH); ^{13}C nmr (DMSO-d_6): δ_C 55.8 (SO_2-CH_2), 58.6 (CH_2-SO_2), 128.6, 129.5, 130.8, 131.2 (Ar-C), 159.8 (C_5), 166.1 (C=NOH), 169.1 (C_2); ms: m/z 329 ($M^{+\cdot}$). *Anal.* Calcd. for $C_{11}H_{11}N_3O_3S_3$: C, 40.11; H, 3.37; N, 12.76. Found: C, 40.15; H, 3.34; N, 12.83.

1-*p*-Tolyl-2-{[(5-sulfanyl-1,3,4-thiadiazol-2-yl)methyl]-sulfonyl}-1-ethanone oxime (8b). White solid, Yield 0.25 g (69%), mp 210-212°C; ir: 1130, 1332 (SO_2), 1634 (C=N), 2562 (SH), 3334 (OH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 2.24 (s, 3H, CH_3), 4.63 (s, 2H, SO_2-CH_2), 4.89 (s, 2H, CH_2-SO_2), 7.29-7.42 (m, 4H, Ar-H), 10.28 (s, 1H, SH), 11.89 (s, 1H, OH); ^{13}C nmr (DMSO-d_6): δ_C 20.2 (CH_3), 55.6 (SO_2-CH_2), 58.4 (CH_2-SO_2), 128.2, 129.1, 131.2, 134.6 (Ar-C), 158.2 (C_5), 163.7 (C=NOH), 167.6 (C_2). *Anal.* Calcd. for $C_{12}H_{13}N_3O_3S_3$: C, 41.97; H, 3.82; N, 12.23. Found: C, 41.88; H, 3.86; N, 12.31.

1-(4-Chlorophenyl)-2-{[(5-sulfanyl-1,3,4-thiadiazol-2-yl)-methyl]sulfonyl}-1-ethanone oxime (8c).White solid, Yield 0.23 g (63%), mp 204-206 °C; ir: 1132, 1335 (SO_2), 1638 (C=N), 3332 (OH), 2564 (SH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 4.68 (s, 2H, SO_2-CH_2), 4.95 (s, 2H, CH_2-SO_2), 7.34-7.68 (m, 4H, Ar-H), 10.43 (s, 1H, SH), 12.31 (s, 1H, OH); ^{13}C nmr (DMSO-d_6): δ_C 55.9 (SO_2-CH_2), 58.8 (CH_2-SO_2), 128.9, 129.3, 130.4, 135.9 (Ar-C), 161.5 (C_5), 164.9 (C=NOH), 167.6 (C_2). *Anal.* Calcd. for $C_{11}H_{10}ClN_3O_3S_3$: C, 36.31; H, 2.77; N, 11.55. Found: C, 36.36; H, 2.82; N, 11.63.

2-{[(4-Amino-5-sulfanil-4*H*-1,2,4-triazol-3-yl)methyl]sulfonyl}-1-aryl-1-ethanone oxime (9): General Procedure. To a solution of **7** (0.37 g, 1 mmol) in 6 ml of water, hydrazine hydrate (0.1 ml, 2 mmol) was added and refluxed for 8-9 h. The contents of the flask were cooled, diluted with water and acidified with 2 ml of acetic acid. The separated solid was collected by filtration, dried and recrystallized from 2-propanol.

2-{[(4-Amino-5-sulfanil-4*H*-1,2,4-triazol-3-yl)methyl]sulfonyl}-1-phenyl-1-ethanone oxime (9a). White solid, Yield 0.22 g (66%), mp 165-167 °C; ir: 1141, 1337 (SO_2), 1628 (C=N), 2624 (SH), 3280 (NH_2), 3335 (OH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 4.73 (s, 2H, SO_2-CH_2), 4.91 (s, 2H, CH_2-SO_2), 5.60 (br s, 1H, NH_2), 7.32-7.68 (m, 5H, Ar-H), 10.41 (s, 1H, SH), 12.36 (s, 1H, OH); ^{13}C nmr (DMSO-d_6): δ_C 48.4 (SO_2-CH_2), 59.6 (CH_2-SO_2), 128.5, 129.0, 130.8, 131.4 (Ar-C), 149.3 (C_5), 164.9 (C=NOH), 167.4 (C_3); ms: m/z 327 ($M^{+\cdot}$). *Anal.* Calcd. for $C_{11}H_{13}N_5O_3S_2$: C, 40.36; H, 4.00; N, 21.39. Found: C, 40.25; H, 3.95; N, 21.46.

2-{[(4-Amino-5-sulfanil-4*H*-1,2,4-triazol-3-yl)methyl]-sulfonyl}-1-*p*-tolyl-1-ethan-one oxime (9b). White solid, Yield 0.23 g (67%), mp 153-155 °C; ir: 1144, 1329 (SO_2), 1631 (C=N), 2631 (SH), 3284 (NH_2), 3340 (OH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 2.26 (s, 3H, CH_3), 4.67 (s, 2H, SO_2-CH_2), 4.87 (s, 2H, CH_2-SO_2), 5.54 (br s, 1H, NH_2), 7.27-7.52 (m, 4H, Ar-H), 10.31 (s, 1H, SH), 12.28 (s, 1H, OH); ^{13}C nmr (DMSO-d_6): δ_C 20.6 (CH_3), 48.6 (SO_2-CH_2), 59.1 (CH_2-SO_2), 128.2, 129.1, 130.3, 140.1 (Ar-C), 148.4 (C_5), 165.2 (C=NOH), 166.9 (C_3). *Anal.* Calcd. for $C_{12}H_{15}N_5O_3S_2$: C, 42.22; H, 4.43; N, 20.51. Found: C, 42.19; H, 4.40; N, 20.55.

2-{[(4-Amino-5-sulfanil-4*H*-1,2,4-triazol-3-yl)methyl]-sulfonyl}-1-(4-chloro-phenyl)-1-ethanone oxime (9c). White solid, Yield 0.26 g (71%), mp 174-176 °C; ir: 1146, 1339 (SO_2), 1634 (C=N), 2644 (SH), 3287 (NH_2), 3337 (OH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 4.77 (s, 2H, SO_2-CH_2), 4.93 (s, 2H, CH_2-SO_2), 7.40-7.82 (m, 4H, Ar-H), 5.63 (br s, 1H, NH_2), 10.36 (s, 1H, SH), 12.44 (s, 1H, OH); ^{13}C nmr (DMSO-d_6): δ_C 49.1 (SO_2-CH_2), 59.9 (CH_2-SO_2), 129.0, 129.3, 130.6, 136.3 (Ar-C), 150.1 (C_5), 166.1 (C=NOH), 167.8 (C_3). *Anal.* Calcd. for $C_{11}H_{12}ClN_5O_3S_2$: C, 36.51; H, 3.34; N, 19.36. Found: C, 36.46; H, 3.30; N, 19.42.

1-Aryl-2-{[(5-sulfanyl-1,3,4-oxadiazol-2-yl)methyl]sulfonyl}-1-ethanone oxime (10): General Procedure. Potassium salt **7** (0.371 g, 1 mmol) was dissolved in 6 ml of water and acidified with 1-2 ml of con. hydrochloric acid. The regenerated solid was collected by filtration, dried and purified by recrystallization from 2-propanol.

1-Phenyl-2-{[(5-sulfanyl-1,3,4-oxadiazol-2-yl)methyl]-sulfonyl}-1-ethanone oxime (10a). White solid, Yield 0.23 g (74%), mp 185-187 °C; ir: 1125, 1328 (SO_2), 1630 (C=N), 2578 (SH), 3339 (OH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 4.72 (s, 2H, SO_2-CH_2), 4.89 (s, 2H, CH_2-SO_2), 7.28-7.59 (m, 5H, Ar-H), 10.28 (s, 1H, SH), 12.39 (s, 1H, OH); ^{13}C nmr (DMSO-d_6): δ_C 54.8 (SO_2-CH_2), 58.9 (CH_2-SO_2), 128.5, 129.1, 130.6, 131.3 (Ar-C), 158.7 (C_5), 165.2 (C=NOH), 166.2 (C_2); ms: m/z 313 ($M^{+\cdot}$). *Anal.* Calcd. for $C_{11}H_{11}N_3O_4S_2$: C, 42.16; H, 3.54; N, 13.41. Found: C, 42.11; H, 3.56; N, 13.35.

1-*p*-Tolyl-2-{[(5-sulfanyl-1,3,4-oxadiazol-2-yl)methyl]-sulfonyl}-1-ethanone oxime (10b). White solid, Yield 0.25 g (76%), mp 194-196 °C; ir: 1129, 1330 (SO_2), 1626 (C=N), 2580 (SH), 3341 (OH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 2.25 (s, 3H, CH_3), 4.69 (s, 2H, SO_2-CH_2), 4.86 (s, 2H, CH_2-SO_2), 7.30-7.68 (m, 4H, Ar-H), 10.30 (s, 1H, SH), 11.91 (s, 1H, OH); ^{13}C nmr (DMSO-d_6): δ_C 20.4 (CH_3), 55.1 (SO_2-CH_2), 59.2 (CH_2-SO_2), 128.2, 129.1, 130.2, 139.8 (Ar-C), 157.9 (C_5), 164.1 (C=NOH), 165.8 (C_2). *Anal.* Calcd. for $C_{12}H_{13}N_3O_4S_2$: C, 44.02; H, 4.00; N, 12.84. Found: C, 43.95; H, 3.98; N, 12.75.

1-(4-Chloro-phenyl)-2-{[(5-sulfanyl-1,3,4-oxadiazol-2-yl)-methyl]sulfonyl}-1-ethanone oxime (10c). White solid, Yield 0.26 g (75%), mp 198-200 °C; ir: 1132, 1340 (SO_2), 1623 (C=N), 2584 (SH), 3338 (OH) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ_H 4.74 (s, 2H, SO_2-CH_2); 4.91 (s, 2H, CH_2-SO_2); 7.40-7.71 (m, 4H, Ar-H); 10.32 (s, 1H, SH); 12.48 (s, 1H, OH); ^{13}C nmr (DMSO-d_6): δ_C 54.3 (SO_2-CH_2), 58.5 (CH_2-SO_2), 128.9, 129.2, 130.2, 135.2 (Ar-C), 159.2 (C_5), 164.6 (C=NOH), 166.9 (C_2). *Anal.* Calcd. for $C_{11}H_{10}ClN_3O_4S_2$: C, 37.99; H, 2.90; N, 12.08. Found: C, 38.07; H, 2.93; N, 12.03.

1-Aryl-2-{[(5-sulfanyl-1,3,4-thiadiazol-2-yl)methyl]sulfonyl}-1-ethanone (11); 2-{[(4-Amino-5-sulfanil-4*H*-1,2,4-triazol-3-yl)methyl]sulfonyl}-1-aryl-1-ethanone (12); 1-Aryl-2-{[(5-sulfanyl-1,3,4-oxadiazol-2-yl)methyl]sulfonyl}-1-ethanone (13):

General Procedure. To a solution of β-cyclodextrin (0.1134 g, 0.1 mmol) in distilled water (15 ml), appropriate oxime **8** or **9** or **10** (1 mmol) dissolved in acetone (2 ml) and 2-iodoxy-benzoic acid (0.28 g, 1 mmol) were added and stirred at room temperature for 14-16 h. The reaction mixture was extracted with ethyl acetate, and concentrated under vacuum. The crude product obtained was purified by column chromatography on silica gel (60-120 mesh) using ethyl acetate -hexane (9:1).

1-Phenyl-2-{[(5-sulfanyl-1,3,4-thiadiazol-2-yl)methyl]sulfonyl}-1-ethanone (11a). White solid, Yield 0.24 g (77%), mp 214-216 °C; ir: 1130, 1335 (SO_2), 1628 (C=N), 1680 (C=O), 2561 (SH) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 4.62 (s, 2H, SO_2-CH_2), 4.70 (s, 2H, CO-CH_2-SO_2), 7.37-7.79 (m, 5H, Ar-H), 10.24 (s, 1H, SH); ^{13}C nmr (DMSO-d_6): δ_C 52.8 (SO_2-CH_2), 61.8 (CH_2-SO_2), 128.4, 129.3, 132.9, 137.5 (Ar-C), 164.1 (C_5), 166.8 (C_2), 196.6 (C=O); ms: m/z 314 ($M^{+\cdot}$). *Anal.* Calcd. for $C_{11}H_{10}N_2O_3S_3$: C, 42.02; H, 3.21; N, 8.91. Found: C, 42.11; H, 3.24; N, 8.97.

1-*p*-Tolyl-2-{[(5-sulfanyl-1,3,4-thiadiazol-2-yl)methyl]-sulfonyl}-1-ethanone (11b). White solid, Yield 0.24 g (73%), mp 222-224 °C; ir: 1127, 1332 (SO_2), 1625 (C=N), 1676 (C=O), 2560 (SH) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 2.29 (s, 3H, CH_3), 4.69 (s, 2H, SO_2-CH_2), 4.72 (s, 2H, CH_2-SO_2), 7.40-7.68 (m, 4H, Ar-H), 10.26 (s, 1H, SH); ^{13}C nmr (DMSO-d_6): δ_C 21.2 (CH_3), 51.9 (SO_2-CH_2), 60.7 (CH_2-SO_2), 128.6, 129.2, 134.2, 142.1 (Ar-C), 163.6 (C_5), 165.6 (C_2), 196.2 (C=O). *Anal.* Calcd. for $C_{12}H_{12}N_2O_3S_3$: C, 43.88; H, 3.68; N, 8.53. Found: C, 43.79; H, 3.72; N, 8.59.

1-(4-Chloro-phenyl)-2-{[(5-sulfanyl-1,3,4-thiadiazol-2-yl)-methyl]sulfonyl}-1-ethanone (11c). White solid, Yield 0.25 g (69%), mp 209-211 °C; ir: 1122, 1335 (SO_2), 1627 (C=N), 1681 (C=O), 2563 (SH) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 4.70 (s, 2H, SO_2-CH_2), 4.73 (s, 2H, CH_2-SO_2), 7.36-7.79(m, 4H, Ar-H), 10.22 (s, 1H, SH); ^{13}C nmr (DMSO-d_6): δ_C 52.4 (SO_2-CH_2), 61.3 (CH_2-SO_2), 128.8, 129.6, 135.4, 138.2 (Ar-C), 159.8 (C_5), 167.5 (C_2), 197.1 (C=O). *Anal.* Calcd. for $C_{11}H_9ClN_2O_3S_3$: C, 37.87; H, 2.60; N, 8.03. Found: C, 37.95; H, 2.63; N, 8.07.

2-{[(4-Amino-5-sulfanil-4*H*-1,2,4-triazol-3-yl)methyl]-sulfonyl}-1-phenyl-1-ethanone (12a). White solid, Yield 0.23 g (75%), mp 157-159 °C; ir: 1142, 1338 (SO_2), 1633(C=N), 1683 (C=O), 2621(SH), 3269 (NH_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 4.68 (s, 2H, SO_2-CH_2), 4.79 (s, 2H, CH_2-SO_2), 5.61 (br s, 2H, NH_2), 7.41-7.78 (m, 5H, Ar-H), 10.24 (s, 1H, SH); ^{13}C nmr (DMSO-d_6): δ_C 43.4 (SO_2-CH_2), 61.2 (CH_2-SO_2), 128.4, 128.6, 132.8, 137.4 (Ar-C), 144.1 (C_5), 168.1 (C_3), 196.4 (C=O); ms: m/z 312 ($M^{+\cdot}$). *Anal.* Calcd. for $C_{11}H_{12}N_4O_3S_2$: C, 42.30; H, 3.87; N, 17.94. Found: C, 42.35; H, 3.92; N, 17.88.

2-{[(4-Amino-5-sulfanil-4*H*-1,2,4-triazol-3-yl)methyl]-sulfonyl}-1-*p*-tolyl-1-ethanone (12b). White solid, Yield 0.25 g (76%), mp 165-167°C; ir: 1140, 1329 (SO_2), 1630 (C=N), 1686 (C=O), 2626(SH), 3278 (NH_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 2.32 (s, 3H, CH_3), 4.64 (s, 2H, SO_2-CH_2), 4.74 (s, 2H, CH_2-SO_2), 5.56 (br s, 2H, NH_2), 7.48-7.68 (m, 4H, Ar-H), 10.34 (s, 1H, SH); ^{13}C nmr (DMSO-d_6): δ_C 20.8 (CH_3), 42.6 (SO_2-CH_2), 59.8 (CH_2-SO_2), 128.5, 129.2, 134.5,142.3 (Ar-C), 143.8 (C_5), 167.9 (C_3), 195.8 (C=O). *Anal.* Calcd. for $C_{12}H_{14}N_4O_3S_2$: C, 44.16; H, 4.32; N, 17.17. Found: C, 44.19; H, 4.38; N, 17.25.

2-{[(4-Amino-5-sulfanil-4*H*-1,2,4-triazol-3-yl)methyl]-sulfonyl}-1-(4-chloro-phenyl)-1-ethanone (12c). White solid, Yield 0.24 g (68%), mp 184-186°C; ir: 1132, 1320 (SO_2), 1631 (C=N), 1682 (C=O), 2644 (SH), 3275 (NH_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 4.72 (s, 2H, SO_2-CH_2), 4.78 (s, 2H, CH_2-SO_2), 5.67 (br s, 2H, NH_2), 7.53-7.79 (m, 4H, Ar-H), 10.30 (s, 1H, SH); ^{13}C nmr (DMSO-d_6): δ_C 43.1 (SO_2-CH_2), 60.8 (CH_2-SO_2), 128.8, 130.0, 135.5, 138.2 (Ar-C), 144.5 (C_5), 169.1 (C_3), 196.1 (C=O). *Anal.* Calcd. for $C_{11}H_{11}ClN_4O_3S_2$: C, 38.09; H, 3.20; N, 16.15. Found: C, 38.00; H, 3.23; N, 16.24.

1-Phenyl-2-{[(5-sulfanyl-1,3,4-oxadiazol-2-yl)methyl]sulfonyl}-1-ethanone (13a). White solid, Yield 0.20 g (68%), mp199-201 °C; ir: 1123, 1331 (SO_2), 1626 (C=N), 1684 (C=O), 2579 (SH) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 4.63 (s, 2H, SO_2-CH_2), 4.75 (s, 2H, CH_2-SO_2), 7.38-7.65 (m, 5H, Ar-H), 10.25 (s, 1H, SH); ^{13}C nmr (DMSO-d_6): δ_C 54.8 (SO_2-CH_2), 58.4 (CH_2-SO_2), 128.6, 129.0, 130.6, 131.2 (Ar-C), 158.7 (C_5), 166.4 (C_2), 196.2 (C=O); ms: m/z 298 ($M^{+\cdot}$). *Anal.* Calcd. for $C_{11}H_{10}N_2O_4S_2$: C, 44.28; H, 3.38; N, 9.39. Found: C, 44.34; H, 3.42; N, 9.45.

1-*p*-Tolyl-2-{[(5-sulfanyl-1,3,4-oxadiazol-2-yl)methyl]sulfonyl}-1-ethanone (13b). White solid, Yield 0.19 g (64%), mp 205-207 °C; ir: 1134, 1328 (SO_2), 1631 (C=N), 1682 (C=O), 2581 (SH) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 2.28 (s, 3H, CH_3), 4.66 (s, 2H, SO_2-CH_2), 4.71 (s, 2H, CH_2-SO_2), 7.59-7.73 (m, 4H, Ar-H), 10.28 (s,1H, SH); ^{13}C nmr (DMSO-d_6): δ_C 20.8 (CH_3), 54.9 (SO_2-CH_2), 58.8 (CH_2-SO_2), 128.3, 129.2, 131.2, 141.9 (Ar-C), 159.2 (C_5), 166.8 (C_2), 193.2 (C=O). *Anal.* Calcd. for $C_{12}H_{12}N_2O_4S_2$: C, 46.14; H, 3.87; N, 8.97. Found: C, 46.09; H, 3.91; N, 9.05.

1-(4-Chloro-phenyl)-2-{[(5-sulfanyl-1,3,4-oxadiazol-2-yl)-methyl]sulfonyl}-1-ethanone (13c). White solid, Yield 0.24 g (71%), mp 212-214 °C; ir: 1126, 1338 (SO_2), 1628 (C=N), 1685 (C=O), 2600 (SH) cm^{-1}; ^1H nmr (DMSO-d_6): δ_H 4.69 (s, 2H, SO_2-CH_2), 4.77 (s, 2H, CH_2-SO_2), 7.29-7.58 (m, 4H, Ar-H), 10.30 (s, 1H, SH); ^{13}C nmr (DMSO-d_6): δ_C 55.1 (SO_2-CH_2), 59.1 (CH_2-SO_2), 128.8, 130.0, 135.5, 138.2 (Ar-C), 161.3 (C_5), 167.2 (C_2), 194.4 (C=O). *Anal.* Calcd. for $C_{11}H_9ClN_2O_4S_2$: C, 39.70; H, 2.73; N, 8.42. Found: C, 39.77; H, 2.69; N, 8.54.

Acknowledgements. The authors are thankful to DST, New Delhi, India for the financial assistance under major research project.

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