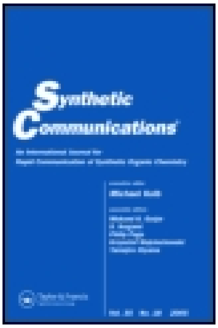

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Microwave-Induced One - Pot Synthesis of some new Spiro [Indoline-3,2′-Thiazolidine]-2,4′(1H)-Diones and Bis [Spiro [Indoline -3,2′-Thiazolidine]-2,4′(1H)-Diones]

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MICROWAVE- INDUCED ONE - POT SYNTHESIS OF SOME NEW SPIRO [INDOLINE -3,2'-THIAZOLIDINE]-2,4'*(1H)*-DIONES AND BIS [SPIRO [INDOLINE -3,2'-THIAZOLIDINE]-2,4'*(1H)*-DIONES]

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Abstract : The title compounds have been obtained thermally and under microwave irradiation by condensation of isatin, aromatic amines and mercaptoacetic acid in good to excellent yields without isolating the imine intermediates.

Domestic microwave oven is a convenient source of energy in organic synthesis which causes remarkable decrease in reaction times and provides better yields.[1,2] Owing to the medicinal importance of spiro indoles containing sulfur heterocyclic systems at C-3 of the indole ring [3-8], we studied one-pot synthesis of new spiro [indoline-3,2' -thiazolidine]-2,4' *(1H)*- diones (**1**,**2**) and bis[spiro[indoline-3,2' -thiazolidine]-2,4'*(1H)*-diones] (**3**) by the classical method and microwave irradiation.

It has been shown that isatin-3-imines (or isatin and amines) undergo thermal cyclocondensation reaction with mercaptoacetic acid to give spiro oxindoles such as **1**.[7,9-12] In this work the spiro compounds **1-3** have been prepared thermally and under microwave irradiation by condensing isatin , an

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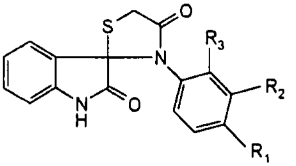
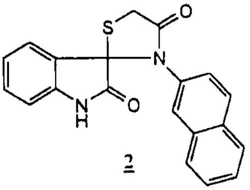
aromatic amine and mercaptoacetic acid without isolating the intermediates i.e., isatin-3-imines. Using microwave irradiation, reaction times are reduced from several hours to few minutes. Both thermal and microwave methods gave good to excellent yields.

The cycloadducts of mercaptoacetic acid with diimines of isatin (prepared *in situ* from two equivalents of isatin or *N*-methyl isatin with one equivalent phenylenediamine) to yield **3a, 3b** . Since these products possess two stereogenic centers, two diastereoisomers are possible . Howerer, on the basis of ^{1}H NMR and ^{13}C NMR spectroscopic data only one diastereomer is isolated.



1	R_1	R_2	R_3
a	H	H	H
b	OCH_3	H	H
c	CH_3	CH_3	H
d	OCH_3	H	OCH_3
e	H	NO_2	H
f	Br	H	H



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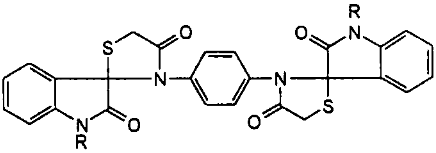

3	R
a	H
b	CH_3

The ir spectra of compounds **1- 3** gave $\nu_{C=O}$ spirothiazolidinone at 1670 - 1705 cm^{-1} and $\nu_{C=O}$ of oxindole at 1710 - 1740 cm^{-1} , along with a band at 3120 - 3300 cm^{-1} for the N-H group.

The ^{13}C NMR Spectra of compounds **1-3** showed carbonyl carbon signals at δ170-176 . The signal at 70-71 is assigned to the spiro carbon atom .

The ^{1}H NMR and elemental analyses data are in agreement with the proposed structures (see Experimental).

Experimental

Melting points were measured on a Mettler FP5 and are uncorrected. IR sprectra were recorded as KBr pellets on a Shimadzu IR-470 spectrometer . ^{1}H NMR and ^{13}C NMR spectra were determined on a Brucker 500 DRX AVANCE instrument at 500 and 125 MHz, respectively .

Microwave irradiations were carried out in a National oven, Model 5250 at 2450 MHz. Mass spectra were recorded on Shimadzu QP 1100 EX equipment . Elemental analyses were performed using a Heraeus CHN-O Rapid analyzer.

General procedure:

A: *Microwave*-A mixture of isatin (5 mmol) and an aromatic amine (5 mmol) or diamine (2.5 mmol) in dry ethanol (15 ml) or *N,N* - dimethylacetamide (DMAC) (1 ml) was placed in an erlenmeyer flask covered with a watch glass and irradiated in the microwave oven at 200 watts (for ethanol) or 400 watts (for DMAC) for 5 min. On cooling the mixture , mercaptoacetic acid (7 mmol) was added and irradiated again for 6-8 min. under the same conditions. After completion of the reaction (monitored by TLC) , ethanol (10 ml) and ice water (5 ml) were added to reaction mixture and kept at room temperature . The crystalline product was filtered, washed with light petroleum and recrystallized from ethanol.

B: *Thermal* - A mixture of isatin (10 mmol) and an aromatic amine (10 mmol) or diamine (5 mmol) was refluxed in toluene (100 ml) for one hr using Dean-Stark aparatus and the water formed was removed azeotropically . On cooling the mixture , mercaptoacetic acid (15 mmol) was added and refluxed again for 8-15 hr.

The reaction mixture was then allowed to cool down to room temperature , toluene was evaporated *in vacuo* and the residue was recrystallized from ethanol .

1a: White crystals. Yield 81% (thermal 68%): mp 233 °C (lit.[10] 235 °C) :ν max/cm^{-1} 3285 (N-H) , 1730 , 1683 (C=O): δ_H ($CDCl_3$) 3.7-4.4 (dd. 2H. CH_2). 6.6-7.5 (m. 9 H). 7.8 (s. 1 H. NH): δ_C ($CDCl_3$) 177.12 (C=O). 172.96 (C=O). 111.08-140.86 (12 signals , arom). 70.58 (spiro carbon). 33.33 (CH_2): MS (*m/z* , %) 296 (M^+ , 75). 268 (M^+ -CO. 70). 222 (M^+ -C_2H_2OS. 100). 194 (M^+-$C_3H_2O_2S$. 80) (Found: C.64.5: H. 4.1: N. 9.1. $C_{16}H_{12}N_2O_2S$ requires C. 64.85: H. 4.08 : N. 9.45 %) .

1b: White crystals . Yield 88% (thermal 74%): mp 206 °C (lit.[10] 210 °C) : ν max/cm^{-1} 3290 (N-H) . 1735, 1681 (C=O): δ_H ($CDCl_3$) 3.6 (s. 3H. OCH_3). 3.7- 4.4 (dd. 2 H. CH_2). 6.6 - 7.5 (m. 8H.). 7.7 (s.1 H.NH). δ_C ($CDCl_3$) 177.23 (C=O). 173.05 (C=O). 111.14-140.87 (12 signals . arom). 70.65 (spiro carbon). 33.38 (CH_2): 55.68 (OCH_3):MS (*m/z* . %) 326 (M^+ . 100). 298 (M^+ -CO. 60). 252 (M^+ -C_2H_2OS. 50). 224 (M^+ -$C_3H_2O_2S$. 50) (Found: C.62.3: H, 4.1; N. 8.4. $C_{17}H_{14}N_2O_3S$ requires C. 62.56; H. 4.32 ; N. 8.58 %) .

1c : White crystals . Yield 79% (thermal 64%) : mp 222°C: ν max/cm^{-1} 3250 (N-H). 1734 , 1700 (C=O) : δ_H ($CDCl_3$) 3.7-4.3 (dd. 2 H. CH_2). 6.6 - 7.4 (m. 7H.). 8.3 (s.1 H.NH). 2.1 (s.6 H.CH_3): δ_C ($CDCl_3$) 177.36 (C=O).173.15 (C=O). 111.28 -140.90 (12 signals , arom). 70.82 (spiro carbon). 33.40 (CH_2). 20.14 (CH_3). 19.81 (CH_3);MS (*m/z* . %) 324 (M^+ . 100). 296 (M^+ -CO. 75). 251 (M^+ -C_2H_2OS. 75). 223 (M^+ -$C_3H_2O_2S$. 75) (Found: C. 66.6 ;H. 4.7: N. 8.6. $C_{18}H_{16}N_2O_2S$ requires C. 66.65: H. 4.97 : N. 8.63 %) .

1d : White crystals .Yield 82% (thermal 69%) : mp 192 °C: ν max/cm^{-1} 3270 (N-H), 1720 .1682 (C=O) : δ_H ($CDCl_3$)3.6 (s. 6 H. OCH_3). 3.9 - 4.5 (dd.2H . CH2). 6.3-7.4 (m. 7 H). 7.9 (s.1 H.NH): δ_C ($CDCl_3$) 176.91 (C=O).172.62 (C=O). 111.23-141.24 (12 signals . arom).

70.44 (spiro carbon). 32.92 (CH_2). 55.33 (OCH_3). 56.74 (OCH_3);MS (*m/z* . %) 356 (M^+ , 100). 328 (M^+ -CO. 60). 282 (M^+ -C_2H_2OS. 50). 254 (M^+ -$C_3H_2O_2S$. 25) (Found: C, 60.5; H, 4.5; N. 7.7. $C_{18}H_{16}N_2O_4S$ requires C. 60.66; H. 4.53 ; N. 7.86 %) .

1e : White crystals. Yield 76% (thermal 54%) ; mp 214 °C; ν max/cm^{-1} 3190 (N-H), 1713 ,1689 (C=O): δ_H (aceton d_6) 3.8- 4.4 (dd, 2H, CH2). 6.8-8.1 (m, 7 H), 9.6 (s,1 H,NH); δ_C (aceton d6) ,177.42 (C=O). 173.31 (C=O),111.83 -141.47 (12 signals , arom), 70.95 (spiro carbon). 33.61 (CH_2) ;MS (*m/z* . %) 341 (M^+ , 35). 313 (M^+ -CO. 35), 267 (M^+ -C_2H_2OS, 100), 239 (M^+ -$C_3H_2O_2S$. 40) (Found: C, 56.3 ;H, 3.2; N, 12.3. $C_{16}H_{11}N_3O_4S$ requires C, 56.30; H, 3.25 ; N, 12.31 %) .

1f : Light yellow crystals . Yield 78% (thermal 65%) ; mp 209 °C (lit.[9] 212 °C); ν max/cm^{-1} 3150 (N-H). 1726 ,1682 (C=O): δ_H ($CDCl_3$) 3.7- 4.4 (dd, 2H, CH2), 6.6-7.4 (m, 8 H). 7.9 (s, 1 H,NH); δ_C ($CDCl_3$) 177.39 (C=O),173.26 (C=O). 111.73 -141.37 (12 signals , arom). 70.88 (spiro carbon). 33.58 (CH_2) ;MS (*m/z* , %) 374 (M^+ , 75), 346 (M^+ -CO, 80), 300 (M^+ -C_2H_2OS. 100), 272 (M^+ -$C_3H_2O_2S$, 75) (Found: C, 51.2; H, 2.9; N, 7.4. $C_{16}H_{11}BrN_2O_2S$ requires C. 51.21; H. 2.95 ; N. 7.46 %) .

2 : Light yellow powder ,Yield 79% (thermal 52%) ; mp 238 °C; ν max/cm^{-1} 3210 (N-H), 1734 ,1671 (C=O): δ_H (aceton d6) 3.8- 4.4 (dd, 2H, CH2), 6.6-7.8 (m, 11 H). 9.5 (s, 1 H,NH); δ_C (Aceton d_6) 176.93 (C=O).172.40 (C=O), 111.05 -142.20 (16 signals , arom), 70.26 (spiro carbon). 32.78 (CH_2) ;MS (*m/z* . %) 346 (M^+ , 100). 318 (M^+ -CO. 60). 274 (M^+ -C_2H_2OS. 50). 244 (M^+ -$C_3H_2O_2S$. 85) (Found: C, 69.3; H, 4.1; N,8.1. $C_{20}H_{14}N_2O_2S$ requires C, 69.35; H. 4.07 ; N, 8.09 %) .

3a : White powder . Yield 74% (thermal 52%) ; mp 302 °C; ν max/cm^{-1} 3270 (N-H), 1725 , 1690 (C=O): δ_H (DMSO d_6) 3.7- 4.2 (dd, 4H, CH_2), 6.6-7.4 (m, 12 H). 10.7 (s, 2 H,NH); δ_C

(DMSO d_6). 176.87 (C=O).172.47 (C=O). 111.55 -142.17 (9 signals . arom). 70.06 (spiro carbon). 33.14 (CH_2) :MS (*m/z* . %) 514 (M^+ .50). 486 (M^+ -CO. 25). 366 (M^+ -$2C_2H_2OS$. 25). 309 (M^+ -$2C_3H_2O_2S$. 20) (Found: C. 59.9; H. 3.9; N. 10.7. $C_{26}H_{18}N_4O_4S_2$ requires C. 60.69; H. 3.52 ; N. 10.89 %) .

3b : Light yellow powder . Yield 78% (thermal 55%) : mp 308 °C: ν max/cm^{-1} 1714 , 1695 (C=O): δ_H ($CDCl_3$) 3.0 (s. 6 H. CH_3) . 3.6-4.4 (dd. 4 H . CH_2). 6.6 -7.4 (m . 12 H) ; δ_C ($CDCl_3$). 175.07 (C=O).172.62 (C=O). 109.43 -143.60 (9 signals . arom). 70.26 (spiro carbon). 33.25 (CH_2). 27.05 (CH_3):MS (*m/z* . %) 542 (M^+ .60). 514 (M^+ -CO. 15). 468 (M^+ -C_2H_2OS. 50). 395 (M^+ -$2C_2H_2OS$. 30) . 337 (M^+ -$2C_3H_2O_2S$. 15) (Found: C. 61.4; H. 4.2; N. 10.1. $C_{28}H_{22}N_4O_4S_2$ requires C. 61.98; H. 4.09 ; N, 10.32 %) .

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