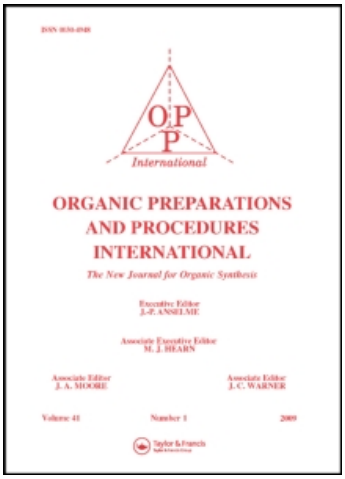

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SOLVENT-FREE SYNTHESIS OF SPIRO[3*H*-INDOLE-3,2'-THIAZOLIDINES]

Anshu Dandia[a]; Ruby Singh[a]; Kapil Arya[a]
[a] Department of Chemistry, University of Rajasthan, Jaipur, INDIA

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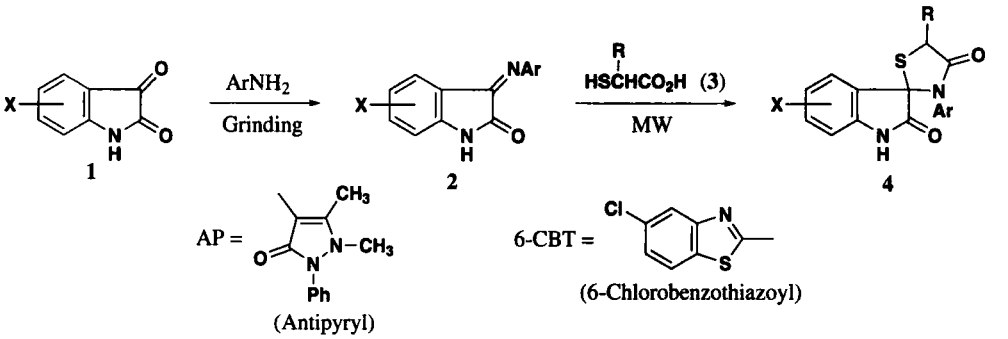
SOLVENT-FREE SYNTHESIS OF SPIRO[3*H*-INDOLE-3,2'-THIAZOLIDINES]

Submitted by Anshu Dandia*, Ruby Singh and Kapil Arya
(07/23/02)

Department of Chemistry, University of Rajasthan
Jaipur-302004, INDIA

Thiazolidinones[1-4] and spiro[indole-thiazolidines][5-8] have attracted considerable attention because of their wide biological and pharmacological activities. The spiro[indole-thiazolidinone] system has been synthesized earlier by a two-step procedure in 40-60% yield using isatin-3-imines as key intermediates, themselves obtained from substituted isatins and aromatic amines. The classical method involves either the azeotropic removal of water[9,10] or reaction in presence of dehydrating agent[11] and use of large amounts of solvents at elevated temperature for several hours. Further, the products generally have to be purified by crystallization or column chromatography. Solvent-free methods are of interest because of their high efficiency and selectivity, the easy separation and purification of products, the mild reaction conditions and environmental acceptability.[12] The potential of microwave activation coupled with dry reaction techniques is established technology.[13]

In continuation of our earlier interest,[14] we now describe a solvent-free one-pot synthesis of some new spiro derivatives (**4a-m**) incorporating three heterocyclic moieties on preparative scale in few minutes (5-8 min) in an open vessel under microwave irradiation using unmodified domestic microwave oven. This method is of general applicability. Further, indolylimines (**2**) also represent a novel class of anti-HIV agents which appear to act by



2a) Ar = AP, X = H; 2b) Ar = AP, X = CH_3; 2c) Ar = AP, X = 5,7-diCH_3; 2d) Ar = AP, X = 5-Cl; 2e) Ar = 6-CBT, X = H; 2f) Ar = 2-pyridyl, X = 5,7-diCH_3; 2g) Ar = 3-FC_6H_4, X = 5,7-diCH_3; 2h) Ar = 4-FC_6H_4, X = 5,7-diCH_3; 2i) Ar = 3-CF_3,4-ClC_6H_3, X = 5,7-diCH_3; 2j) Ar = 4-ClC_6H_4, X = 5,7-diCH_3; 4a) Ar = AP, X = H, R = H; 4b) Ar = AP, X = 5-CH_3,R = H; 4c) Ar = AP, X = 5-CH_3, R = CH_3; 4d) Ar = AP, X = 5-Cl, R = H; 4e) Ar = AP, X = 5-Cl, R = CH_3; 4f) Ar = AP, X = 5,7-diCH_3, R = H; 4g) Ar = AP, X = 5,7-diCH_3, R = CH_3; 4h) Ar = 6-CBT, X = H, R = H; 4i) Ar =2-Pyridyl, X = 5,7-diCH_3, R = H; 4j) Ar = 3-FC_6H_4, X = 5,7-diCH_3, R = H; 4k) Ar = 4-FC_6H_4, X = 5,7-diCH_3, R = H; 4l) Ar = 3-CF_3, 4-ClC_6H_3, X = 5,7-diCH_3, R = H; 4m) 4-ClC_6H_4, X = 5,7-diCH_3, R = H

inhibiting virus-dependent cell fusion.[15] They also exhibit other diverse biological activities.[16,17] The incorporation of fluorine enhances the biological activity by increasing solubility in lipoid material and fat deposits in the body.[18] Treatment of these imines with thioacids (**3**) yielded spiro compounds (**4a-m**) using inorganic solid supports such as montmorillonite KSF, alumina (acidic, neutral, basic) or silica gel. The montmorillonite KSF is the best solid support, giving the best yields (92-97%) in the shortest time and with easiest work-up. The reaction was also carried out without adding any support (neat reaction). Although the reaction proceeded efficiently (100% conversion, indicated by TLC), the yield of isolated products were lower (70-83%) due to tedious work-up procedure which requires first trituration with petroleum ether followed by crystallization from methanol. Finally, to check the possible intervention of specific (non-thermal) microwave effects on reactivity, the reaction of compound **4a** carried out using a pre-heated oil-bath for the same duration and at the same final temperature (135°C) as measured at the end of exposure during the microwave experiment, gave only traces of products (8%), detected by TLC. Lower yield (58%) was obtained under conventional heating, even after one hour.

The structure of the products (**2a-j**) and (**4a-m**) was established by mixture mps and spectral studies (*Tables 1-3*). The IR spectra of intermediates (**2a-j**) show characteristic absorption bands at 3350-3320 (N-H), 2960-2850 (C-H), 1620-1610 (C=N) and 1730-1720 (C=O) cm^{-1}, while the compounds **2a-d** show a additional C=O absorption band at 1660-1650 cm^{-1}. The formation of spiro thiazolidinones (**4h-m**) was confirmed by the appearance of two carbonyl absorption bands at 1735-1725 and 1705-1700 cm^{-1}, while **4a-g** show three C=O absorption bands at 1735-1725, 1705-1700 and 1660-1650 cm^{-1}. The spiro compounds (**4c, 4e, 4g** where R = CH_3) contain two chiral centers, hence exist in two diastereomeric forms, which was confirmed by appearance of two sets of signals in ^1H NMR due to $CHC\underline{H}_3$, $C\underline{H}CH_3$ and N<u>H</u> protons; *e. g.* the compound **4c** exhibits two sets of doublet (J = 4.5 Hz) due to CH-$C\underline{H}_3$ at δ 1.67/1.97, quartet (J = 4.5 Hz) due $C\underline{H}CH_3$ at δ 4.69/4.35 and a broad singlet at 9.11/9.49 in 75%/25% corresponding to two diastereomeric forms **4c** and **4c'**. The positions of the other signals are given in *Table 3*. However, the complex multiplets of aromatic and other methyl protons of the two diastereomers could not be resolved. The mass spectrum of **2a** shows molecular ion peak at m/z 332 (100%) along with other fragments at 304 (28), 289 (35), 255 (41), 180 (30), 111 (21), 97 (28), 71 (18), 57 (39). The mass spectrum of spiro compound **4a** shows molecular ion peak at m/z 406 (100%) along with 378 (M^+-CO, 9.3), 332 (M^+ -C_2H_4OS, 25.5), 277 (10.2), 230 (22.5), 157 (30.4), 112 (40.3), 77 (10), 43 (75).

Table 1. Physical and Analytical Data of Compounds **(2a-j)**

Cmpd	Yield (%)	mp (°C)	Elemental Analysis (Found) C	H	N
2a	97	129-131	68.67 (68.84)	4.81 (4.80)	16.86 (16.82)
2b	96	153-155	68.36 (68.53)	5.20 (5.19)	16.18 (16.22)
2c	97	278-280	70.00 (69.80)	5.55 (5.54)	15.55 (15.58)
2d	96	245-247	62.29 (62.13)	4.09 (4.08)	15.30 (15.26)
2e	96	148-150	57.50 (57.35)	2.55 (2.54)	13.41 (13.38)
2f	97	179-181	83.72 (83.54)	6.04 (6.06)	13.02 (13.05)
2g	96	188-190	71.64 (71.48)	4.85 (4.84)	10.44 (10.42)
2h	95	223-225	71.64 (71.49)	4.85 (4.86)	10.44 (10.41)
2i	96	238-240	57.95 (57.79)	3.40 (3.41)	7.95 (7.93)
2j	97	260-262	67.60 (67.76)	4.57 (4.56)	9.85 (9.83)

Table 2. Physical and Analytical Data of Compounds **(4a-m)**

Cmpd	Yield (%)	Time (min)	mp (°C)	Elemental Analysis (Found) C	H	N
	78[a]	4[a]				
4a			305-307	62.06 (61.90)	4.43 (4.44)	13.79 (13.76)
	94[b]	6[b]				
	80[a]	5[a]				
4b			307-309	62.85 (62.69)	4.76 (4.75)	13.33 (13.30)
	95[b]	7[b]				
4c	93	6	325-327	63.59 (63.74)	5.06 (5.05)	12.90 (12.87)
4d	97	6	328-330	57.27 (57.13)	3.86 (3.85)	12.72 (12.69)
4e	96	5	323-325	58.14 (58.29)	4.18 (4.17)	12.33 (12.35)
4f	96	6	330-332	63.59 (63.43)	5.06 (5.07)	12.90 (12.87)
4g	95	5	315-317	64.28 (64.13)	5.35 (5.36)	12.50 (12.53)
	83[a]	3[a]				
4h			157-159	52.71 (52.85)	2.58 (2.57)	10.85 (10.82)
	92[b]	5[b]				
4i	90	6	214-216	62.76 (62.60)	4.61 (4.62)	12.92 (12.95)
4j	97	5	230-232	62.60 (62.45)	4.34 (4.33)	8.11 (8.09)
4k	96	6	265-267	62.60 (62.44)	4.34 (4.33)	8.11 (8.12)
4l	95	5	257-259	53.52 (53.40)	3.28 (3.27)	6.57 (6.55)
4m	93	5	276-278	60.33 (60.47)	4.18 (4.19)	7.82 (7.80)

[a]Neat Reaction; [b]Using Montmorillonite KSF

Table 3. ^{1}H and ^{13}C NMR Spectra of Compounds (**2a-j**) and (**4a-m**)

Cmpd	^{1}H NMR (δ)	^{13}C NMR (δ)
2a	2.04 (s, 3H, CH_3), 3.08 (s, 3H, N-CH_3), 6.81-7.80 (m, 9H, Ar-H), 9.05 (bs, 1H, NH*)	11.1 (C-CH_3), 33.6 (N-CH_3), 122.2, 123.4, 124.8, 125.2, 126.7, 128.4, 129.1, 130.9, 132.7, 135.3, 138.4, 144.6, 147.8, 148.5 (14 aromatic carbons), 158.2 (C=N), 171.7, 176.9 (two C=O).
2b	2.03 -2.28 (bs, 6H, 2 x CH_3), 3.12 (s, 3H, N-CH_3), 6.83-7.79 (m, 8H, Ar-H), 9.08 (bs, 1H, NH*)	
2c	2.02 - 2.48 (bs, 9H, 3 x CH_3), 3.14 (s, 3H, N-CH_3), 6.79- 7.70 (m, 7H, Ar-H), 9.10 (bs, 1H, NH*)	
2d	2.05 (s, 3H, CH_3), 3.17 (s, 3H, N-CH_3), 6.81- 7.70 (m, 8H, Ar-H), 9.12 (bs, 1H, NH*)	
2e	6.89- 7.88 (m, 7H, Ar-H), 9.10 (bs, 1H, NH*)	121.4, 123.8, 126.2, 127.1, 128.9, 130.2, 132.8, 135.6, 136.1, 141.2, 142.3, 143.9 (12 aromatic carbons), 159.4, 160.2 (two C=N), 169.1 (C=O)
2f	2.17 - 2.31 (bs, 6H, 2 x CH_3), 6.81-7.85 (m, 6H, Ar-H), 9.12 (bs, 1H, NH*)	
2g	2.18 -2.34 (bs, 6H, 2 x CH_3), 6.89-7.65 (m, 6H, Ar-H), 9.13 (bs, 1H, NH*)	
2h	2.16 -2.32 (bs, 6H, 2 x CH_3), 6.85-7.70 (m, 6H, Ar-H), 9.14 (bs, 1H, NH*).	
2i	2.17 -2.34 (bs, 6H, 2 x CH_3), 6.88-7.70 (m, 5H, Ar-H), 9.15 (bs, 1H, NH*)	
2j	2.15- 2.35 (bs, 6H, 2 x CH_3), 6.84-7.55 (m, 6H, Ar-H), 9.13 (bs, 1H, NH*)	
4a	2.09 (s, 3H, CH_3), 3.24 (s, 3H, N- CH_3), 3.80-4.48 (dd, 2H, J=14.8 Hz, -CH_2-), 6.86-7.90 (m, 8H, Ar-H), 9.13 (bs, 1H, NH*)	10.5 (C-CH_3), 32.5 (N-CH_3), 34.9 (-CH_2), 72.6 (spiro carbon), 115.7, 116.9, 117.3, 117.9, 124.3, 124.8, 125.1, 127.3, 129.1, 134.4, 134.8, 153.7, 156.2, 159.9 (14 aromatic carbons), 170.7, 171.7, 176 (three C=O)
4b	2.11-2.28 (bs, 6H, 2 x CH_3), 3.21 (s, 3H, N-CH_3) 3.78-4.45 (dd, 2H, J=14.6 Hz, -CH_2-) 6.85-7.92 (m, 8H, Ar-H), 9.16 (bs, 1H, NH*)	

Table 3. Continued...

Cmpd	^{1}H NMR (δ)	^{13}C NMR (δ)
4c/4c'	Diastereomeric ratio (3 : 1) 1.67/1.97 (d, 3H, CH-CH_3, J=4.5 Hz), 2.08-2.39 (bs, 9H, 3 x CH_3), 3.22 (s, 3H, N-CH_3), 4.69/4.34 (q, 1H, J=4.5Hz, -CH-CH_3), 6.70-7.89 (m, 8H, Ar-H), 9.11/9.49 (bs, 1H, NH*)	
4d	2.08 (s, 3H, CH_3), 3.19 (s, 3H, N-CH_3), 3.81-4.42 (dd, 2H, -CH_2-, J=14.2 Hz), 6.84-7.90 (m, 8H, Ar-H), 9.19 (bs, 1H, NH*)	10.3 (C-CH_3), 32.1 (N-CH_3), 35.1 (-CH_2), 72.9 (spiro carbon), 116.8, 117.9, 118.3, 123.6, 124.4, 125.7, 126.8, 128.1, 129.7, 134.8, 135.1, 154.2, 155.9, 159.4 (14 aromatic carbons), 171.2, 172.4, 177.4 (three C=O)
4e/4e'	Diastereomeric ratio (3:1) 1.70 /1.99 (d, 3H, CH-CH_3, J=4.7 Hz), 2.06 (s, 3H, CH_3), 3.18 (s, 3H, N-CH_3), 4.71/4.38 (q, 1H, J=4.7 Hz, -CH-CH_3), 6.68-7.91 (m, 8H, Ar-H), 9.21/9.43 (bs, 1H, NH*)	
4f	2.12-2.56 (bs, 9H, 3 x CH_3), 3.21 (s, 3H, N-CH_3) 3.82-4.58 (dd, 2H, J=14.8 Hz, -CH_2-), 6.84-7.93 (m, 7H, Ar-H), 9.15 (bs, 2H, J= 14.8 Hz, -CH_2-), 6.85-7.93 (m, 7H, Ar-H), 9.15 (bs, 1H, NH*)	
4g/4g'	Diastereomeric ratio (3:1) 1.64/1.91 (d, 3H, CH-CH_3, J=4.6 Hz), 2.08-2.53 (bs, 9H, 3 x CH_3), 3.19 (s, 3H, N-CH_3), 4.72/4.35 (q, 1H, J=4.6 Hz, -CH-CH_3), 6.69-7.88 (m, 8H, Ar-H), 9.19/9.45 (bs, 1H, NH*)	
4h	3.84-4.51 (dd, 2H, J=15.1 Hz, -CH_2-), 6.80-7.81(m, 7H, Ar-H), 9.14 (bs, 1H, NH*).	34.2 (-CH_2), 73.1 (spiro carbon), 122.9, 124.4, 126.2, 127.4, 128.5, 129.8, 130.1, 132.4, 135.8, 136.7, 142.1, 144.2 (12 aromatic carbons), 168.2, 170.1, 176.8 (two C=O and N-C=N)
4i	2.17- 2.33 (bs, 6H, 2 x CH_3), 3.82-4.55 (dd, 2H, J=13.9 Hz, -CH_2-), 6.84-7.86 (m, 6H, Ar-H), 9.13 (bs, 1H, NH*)	
4j	2.16-2.30 (bs, 6H, 2 x CH_3) , 3.83-4.56 (dd, 2H, J=13.6 Hz, -CH_2-), 6.85-7.88 (m, 6H, Ar-H), 9.16 (bs, 1H, NH*)	12.1, 21.5 (two CH_3), 33.1 (-CH_2), 72.9 (spiro carbon), 113.1, 115.4, 119.2, 123.7, 126.8, 129.2, 130.3, 133.7, 134.5, 139.8, 143.4, 150.3 (12 aromatic carbons), 169.9, 175.7 (two C=O)
4k	2.15-2.29 (bs, 6H, 2 x CH_3) , 3.86-4.59 (dd, 2H, J=13.7 Hz, -CH_2-), 6.89-7.90 (m, 6H, Ar-H), 9.18 (bs, 1H, NH*)	

Table 3. Continued...

Cmpd	^{1}H NMR (δ)	^{13}C NMR (δ)
4l	2.16-2.31 (bs, 6H, 2 x CH_3) , 3.85-4.61 (dd, 2H, J=13.8 Hz, -CH_2-), 6.90 -7.92 (m, 5H, Ar-H), 9.15 (bs, 1H, NH*)	
4m	2.18-2.33 (bs, 6H, 2 x CH_3), 3.85-4.60 (dd, 2H, J=13.9 Hz, -CH_2-), 6.86-7.88 (m, 6H, Ar-H), 915 (bs, 1H, NH*)	

* D_2O exchangeable NH.

EXPERIMENTAL SECTION

Mps were determined in open glass capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer (model-577) in KBr pellets. ^{1}H NMR ($CDCl_3$ + TFA) and ^{13}C NMR (DMSO-d_6) were obtained on Jeol (model FX 90Q) at 89.55 and 22.49 MH_z, respectively, using TMS as internal reference for ^{1}H NMR and ^{13}C NMR. Mass spectra of representative compounds (**2a** and **4a**) were recorded on MS-50 Kratos mass spectrometer at 70 eV. Elemental analyses for C, H and N were performed on a Heraeus Carlo Erba 1108 analyzer. All compounds were found homogeneous by TLC in various solvent systems. The induced microwave convection system operated at a frequency of 2450 MHz. The oven has a range of microwave output energy of 700 Watts. Indole-2,3-diones[20] and 2-amino-6-chloro-benzothiazole were prepared according to the literature procedures[21]. Montmorillonite KSF and thioacids viz. mercapto acetic acid/2-mercapto propionic acid were Aldrich products and used as received.

Synthesis of 3-Heteroaryl Imino-2*H*-indol-2-ones and 3-(fluoroaryl) imino-2*H*-indol-2-ones (2a-j).- An equimolar (0.01 mole) mixture of appropriate indole-2,3-dione (**1**) and the amine was ground thoroughly in an agate mortar. Grinding was continued until the completion of reaction (1-2 min). Complete conversion was determined by TLC, which also showed the formation of a single product. The intermediates **2,** obtained in reasonable purity (TLC), were used as such for the next step without further purification. For spectral studies, elemental analyses and biological screening the compounds **2** were crystallized from methanol.

Synthesis of 3'-Substituted Spiro[3*H*-indole-3,2'-thiazolidine]-2(1*H*)-4'-diones (4a-m).- Spiro compounds (**4a-m**) were synthesized by (a) neat reaction or (b) using montmorillonite KSF as inorganic solid support.

Neat Reaction.- An equimolar mixture (0.01 mole) of appropriate intermediate anil (**2**) and thioacid (**3**) was irradiated at 640 watts in a microwave oven until the completion of the reaction (TLC). To the cream colored solid mass was added methanol (5 mL) and the resultant shiny crystals were collected and found to be pure by TLC.

Using Montmorillonite.- Appropriate anil (**2,** 0.01 mole) and thioacid (**3,** 0.01 mole) were introduced in a beaker (100 mL) and dissolved in methanol (5 mL). Montmorillonite KSF (5 gm) was then added and the mixture was swirled for a while followed by removal of solvent under gentle

vacuum. The dry powder thus obtained was irradiated in a microwave oven at power output of 640 watts for an appropriate time (monitored by TLC, Table 2). The product was extracted with methanol and the excess solvent was removed on a rotary evaporator to give shiny crystals which were found to be pure by TLC.

Synthesis of 3-(4-Chloro-3-trifluoromethylphenyl)-2-(4-fluorophenyl)thiazolidine-4-one.- An equimolar mixture (0.01 mole) of 4-fluorobenzaldehyde and 5-amino-2-chlorobenzotrifluoride was ground thoroughly in an agate mortar until (1-2 min) a solid mass was obtained (TLC, single spot). To the intermediate imine so obtained mercapto acetic acid (0.01 mole) was added and the mixture was adsorbed on montmorillonite KSF. The dry mixture was irradiated in a microwave oven for the appropriate time (5 min). The product was extracted with methanol and found to be pure on TLC, mp = 270°C, yield = 92%, molecular formula $C_{16}H_9ClF_4NOS$, ^1H NMR ($CDCl_3$ + TFA): δ 3.98 (dd, 2H, J=13.7 Hz, $-CH_2-$), 5.02 (s, 1H, CH), 7.01-8.52 (m, 7H, Ar-H), IR (cm^{-1}) : 3030, 2950, 2870, 1710, 1560, 1450.

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