ROLE OF FLUORINE IN CYCLOCONDENSATION OF 3-ARYLIMINO-2H-INDOL-2-ONES WITH o-MERCAPTOBENZOIC ACID

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Abstract : The synthesis of some new fluorinated spiro-indole derivatives is reported. Cyclocondensation of 3-arylimino-2H-indol-2-ones, prepared by the treatment of various fluorinated anilines with isatins, with *o*-mercaptobenzoic acid in acidic ethanol was investigated for the first time. A novel spiro system, spiro[2H-1,3-benzothiazine-2,3'-[3H-indole]-2',4(1'H,3H)-dione (**4**) was isolated. Further, the role of fluorine in such cyclocondensation reactions has been studied. It was observed that 3-[2,3,4,5,6-pentafluorophenyl)-imino-2H-indol-2-one, **2** afforded exclusively S-[3-(1,3-dihydro-2-oxo-(2H)indolyl)]-*o*-mercaptobenzoic acid **5** instead of the expected spiro compound as obtained with mono to tetra fluorinated imino indoles. The spiro compounds have been further subjected to methylation and morphomethylation.

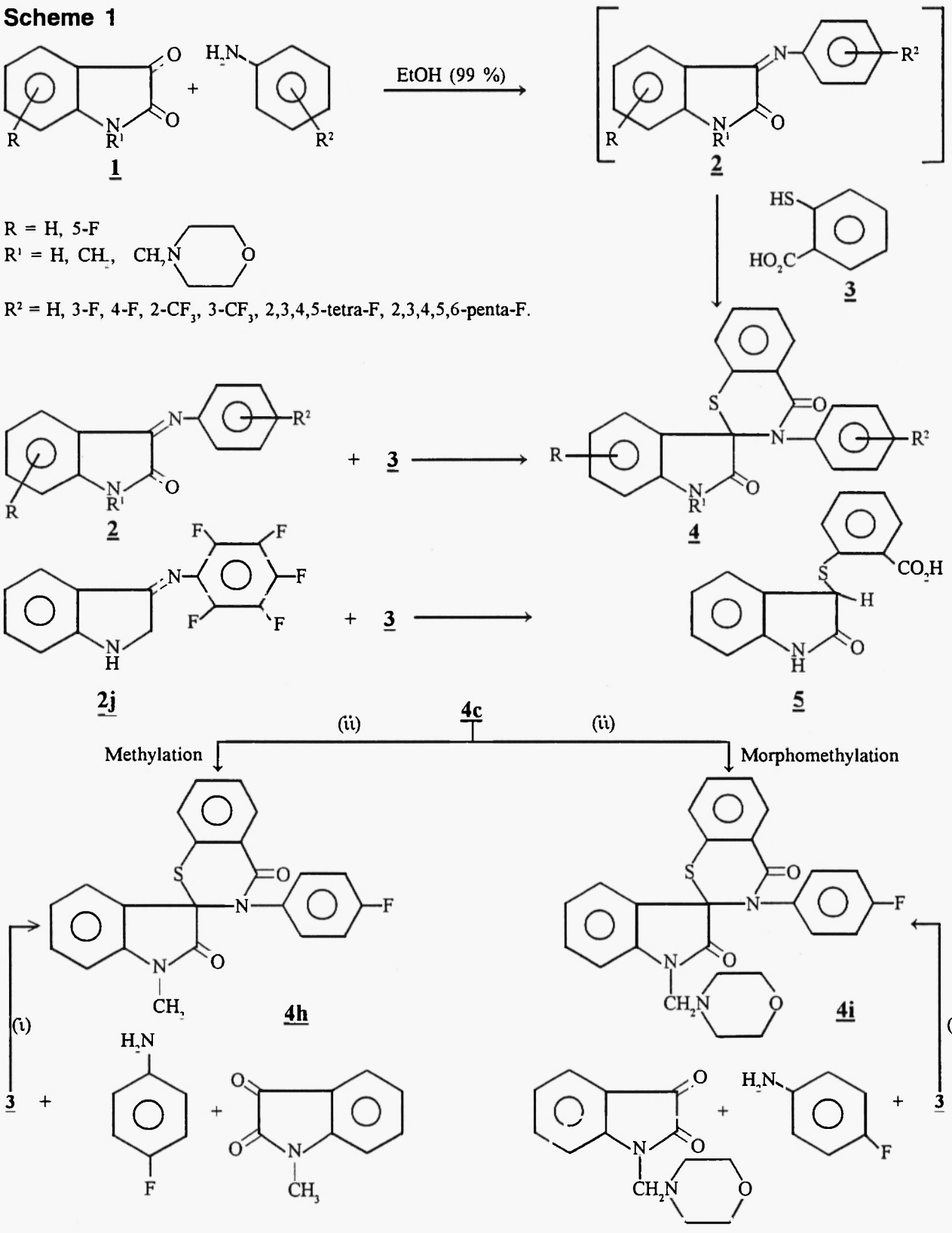
Introduction

Fluorinated indole derivatives are reported to exhibit multifaceted pharmacological and biological activities (1-3). The role of fluorine in organic compounds is noteworthy in view of profound changes which are produced in biological activities on incorporation of fluorine at critical reaction sites (4). Earlier, we had studied the cyclization reactions of 3-arylimino-2H-indol-2-ones with mercaptoacetic acid (5,6) and mercaptopropionic acid (7). In the present investigation, the role of increasing the number of fluorine atoms during the cyclocondensation has been studied by the reaction of 3-arylimino-2H-indol-2-ones with *o*-mercaptobenzoic acid.

Results and Discussion

Suitable indole-2,3-diones and anilines, with varying degrees of fluorination, were reacted in acidic ethanol to give 3-arylimino-2H-indol-2-ones which were further treated with *o*-mercaptobenzoic acid by two methods : Without isolation of *anil* (one-step) and with isolation of *anil* (two-step). Both the methods afforded the same product: 3-aryl-4,5-dihydrospiro[2H-1,3-benzothiazine-2,3'-[3H]indole]-2',4(1'H,3H)-diones (Scheme1). However, the two-step method gave a better yield. All the compounds listed in Table 1 were synthesized via two step method. Methylation and morphomethylation yielding 1-substituted title spiro compounds **4h** & **4i** were also undertaken using two different routes : by starting with appropriate 1-substituted indole-2,3diones followed by subsequent treatments and by methylation/morphomethylation of the spiro compounds prepared.

Scheme 1


EtOH (99 %)
1
2
3
4
5
2j
4c
(ii)
(ii)
Methylation
Morphomethylation
4h
4i
(i)
(i)
R = H, 5-F
R¹ = H, CH₃, CH₂N O
R² = H, 3-F, 4-F, 2-CF₃, 3-CF₃, 2,3,4,5-tetra-F, 2,3,4,5,6-penta-F.

It was observed that while the reaction of 3-(3-F/4-F/2-CF_3/3-CF_3, 2,3,4,5-tetrafluorophenyl)imino-2H-indol-2-ones, (2) with *o*-mercaptobenzoic acid yielded a novel spiro system, spiro[2H-1,3-benzothiazine-2,3'-[3H]indole]-2',4 (1'H,3H)-dione, a similar reaction of 3-(2,3,4,5,6-pentafluorophenyl)imino-2H-indol-2-one with 3 resulted in the formation of S-[3-(1,3-dihydro-2-oxo-(2H)indolyl)]-*o*-mercaptobenzoic acid, 5 (Scheme 1). The formation of the product 5, instead of a spiro derivative obtained in other reactions, may be attributed to the deactivating effect due to increased number of fluorine atoms and thus resulting in the hydrolysis of *anil* before cyclocondensation could take place.

TABLE 1. Analytical data of 3-aryl-4,5-dihydrospiro[2H-1,3-benzothiazine-2,3'-[3H]indole]-2',4(1'H,3H)-diones

Compd. No.**	R*	R¹*	R²*	M.P. °C	Yield %	Molecular formula	Elemental analysis % Calcd. (Found) C	H	N	S
4a	5-F	H	4-F	295-6	78	$C_{21}H_{12}F_2N_2O_2S$	64.02 (64.05)	3.07 (3.03)	7.10 (7.05)	8.13 (8.11)
4b	5-F	H	H	282	80	$C_{21}H_{13}FN_2O_2S$	67.01 (66.95)	3.48 (3.50)	7.44 (7.48)	8.52 (8.49)
4c	H	H	4-F	280	78	$C_{21}H_{13}FN_2O_2S$	67.01 (67.13)	3.48 (3.44)	7.44 (7.40)	8.52 (8.44)
4d	H	H	3-F	278	78	$C_{21}H_{13}FN_2O_2S$	67.01 (67.18)	3.48 (3.51)	7.44 (7.41)	8.52 (8.55)
4e	H	H	2-CF_3	275	74	$C_{22}H_{13}F_3N_2O_2S$	61.97 (62.06)	3.07 (3.05)	6.57 (6.60)	7.52 (7.49)
4f	H	H	3-CF_3	288	79	$C_{22}H_{13}F_3N_2O_2S$	61.97 (61.86)	3.07 (3.10)	6.57 (6.55)	7.52 (7.54)
4g	H	H	2,3,4,5-tetrafluoro	288-9	81	$C_{21}H_{10}F_4N_2O_2S$	58.60 (58.54)	2.34 (2.35)	6.51 (6.48)	7.45 (7.47)

* Compounds 1a-g and 2a-g have same sequence of R, R¹ & R² ** New compounds

IR spectrum of compound 2 (R=5-F, R¹ = H, R² = 4-F) showed characteristic absorption peaks at 3320 (>N-H stretching), 1680 (imido >C=O) and at 1620 cm^{-1} (>C=N stretching). ^1H NMR displayed a multiplet for aromatic protons in the region δ 6.80-7.85 and a singlet at δ 9.80 for >NH proton. Fluorine attached to the indole ring appeared at δ -116 and of aryl ring at δ -119 in the ^{19}F NMR. A signal at δ -60/-61 was observed for the trifluoromethyl group attached to the aryl ring of 2 (R² = 2-CF_3/3-CF_3). Peaks at δ -138.962 (d,F²), δ-157.457 (t,F³), δ -173.782 (s,F⁴) and at δ -190.111 (d,F⁵) were obtained for the four fluorine atoms present in 2 (R = R¹ = H, R² = 2,3,4,5-tetrafluoro). The expected doublet of F² coalesced to give a broad ill defined doublet probably due to quadrupole moment of ortho nitrogen. For compound 2j (R=R¹=H, R² = 2,3,4,5-pentafluoro) a doublet at δ-140.48 for the two ortho fluorines (F² and F⁶), a triplet at δ -152.43 due to meta fluorines (F³ and F⁵) and another triplet at δ -159.50 for the para fluorine (F⁴) was observed.

The reaction of 3-(pentafluorophenyl)imino-2**H**-indol-2-one (**2**) with **3**, resulted in the formation of a product, **5**, which did not display fluorine signals in ^{19}F NMR. A different percentage of C and N (63.04 and 4.95 respectively) obtained as against the expected 56.25 and 6.25% for the spiro[benzothiazine-indole] system also indicated that a compound **5** other than the anticipated spiro product was formed with the elimination of a pentafluorophenyl ring. The presence of $[M]^+$ at m/z 285 corresponding to the formula $C_{15}H_{11}NO_3S$ instead of at m/z 448 corroborating with formula $C_{21}H_9F_5N_2O_2S$ for the corresponding spiro system further supported the formation of compound **5**. Spectral data of the synthesized compound are given in Table 2.

TABLE 2. Spectral data of 3-aryl-4,5-dihydrospiro[2**H**,1-3-benzothiazine-2,3'-[3**H**]indole]2',4(1'**H**,3**H**]-diones

Comp. No.	IR (cm^{-1}) C=O	NHC=O	N-R^1	^1H NMR(δ,ppm) Ar-H	N-R^1	^{19}F NMR (δ,ppm) R/R^2	Mass (m/z) M^+
4a	1700	1685	3310	7.17-8.24	10.20	-116.125 (5'-Fluoro), -119.11 3-(*p*-Fluoro)	394
4b	1708	1680	3320	7.10-8.24	9.88	-116.0 (5'-Fluoro)	376
4c	1700	1680	3310	7.00-8.20	9.90	-118.564 3-(*p*-Fluoro)	376
4d	1700	1685	3300	7.20-8.22	9.99	-118.60 3-(*p*-Fluoro)	376
4e	1710	1685	3330	7.19-8.25	10.10	-60.0 3-(*o*-Trifluoromethyl)	426
4f	1710	1685	3315	7.18-8.25	9.96	-61.0 3-(*m*-Trifluoromethyl)	426
4g	1712	1690	3345	7.25-8.44	10.30	-138.962 (d,F^2),-157.457 (t,F^3), 173.782 (s, F^4), -190.111 (d,F^5), 3-(2,3,4,5-Tetrafluoro)	430

Experimental

Melting points were determined in open glass capillaries and are uncorrected. TLC was performed on silica gel - G plates using EtOAc-C_6H_6 (2:3) as irrigant. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer-557 spectrophotometer. ^1H and ^{19}F NMR were recorded on Jeol-FX-90Q spectrometer at 89.55 and 84.25 MHz respectively. TMS was used as internal reference for ^1H NMR and hexafluorobenzene as external reference for ^{19}F NMR (chemical shifts in δ, ppm). Mass spectra were scanned on Kratos mass spectrometer (MS-30 and MS-50) at 70 eV.

Indole-2,3-diones, **1**

5-Fluoro,1-methyl and 1-morpholinomethylindole-2,3-diones were prepared by literature methods (8-10) using appropriate anilines.

3-Arylimino-2H-indol-2-ones, **2**

5-Fluoro-3-(4-fluorophenyl)iminoindol-2-one, 5-fluoro-3-phenyliminoindol-2-one, 3-(4-fluorophenyl)imino-indol-2-one, 3-(3-fluorophenyl)iminoindol-2-one, 3-(2-trifluoromethylphenyl)-iminoindol-2-one, 3-(3-trifluoromethylphenyl)iminoindol-2-one, 3-(2,3,4,5-tetrafluorophenyl)iminoindol-2-one, 3-(2,3,4,5,6-pentafluorophenyl)iminoindol-2-one, 1-methyl-3-(4-fluorophenyl)iminoindol-2-one and 1-morpholinomethyl-3-(4-fluorophenyl)iminoindol-2-one were prepared by literature method (10).

4,5-Dihydro-5'-fluoro-3-(4-fluorophenyl) spiro[2H-1,3-benzothiazine-2,3'-[3H]indole]-2',4(1'H,3H)-dione, (**4a**)

Compound **4a** was prepared by two different methods viz: (i) *In situ* without isolation of the intermediate Schiff's base (one-step). (ii) By isolation of Schiff's base and subsequent cyclization with *o*-mercaptobenzoic acid (two-step).

(i) A mixture of 5-fluoroindole-2,3-dione (1.65g, 0.01 mol) and 4-fluoroaniline (1.61g, 0.01 mol) and 4-fluoro aniline was refluxed in alcohol (60 ml) in presence of 2,3 drops of glacial acetic acid for 2 hours. The reaction mixture was cooled, *o*-mercaptobenzoic acid (1.696 g, 0.011 mol) was added and refluxed again for 10 hours. The crystals obtained on cooling were filtered and crystallized from ethanol. M.P. 295-6°C, Yield 70%.

(ii) A mixture of 5-fluoro-3-(4-fluorophenyl)imino-2H-indol-2-one (2.58 g, 0.01 mol) and *o*-mercaptobenzoic acid (1.696g, 0.011 mol) was refluxed in absolute ethanol-glacial acetic acid (5:1) for 10 hours. The crystals obtained on cooling were filtered, washed successively with ethanol, water and ethanol, dried and recrystallized from ethanol. M.P. 295-6°C, Yield 78%. Compounds **4a-i** were homogeneous on TLC plate run in C_6H_6: EtOAc (3:2).

4,5-Dihydro-3-(4-fluorophenyl)-1'-methyl-spiro[2H-1,3-benzothiazine-2,3'-[3H]indole]2',4 (1'H,3H)-dione, **(4h)**

This was synthesized by two pathways. The latter method gave higher yields.

(i) A mixture of 1-methylindole-2,3-dione (0.01 mol, 1.11 g) was refluxed in acidified absolute ethanol for 2 hrs. Red crystals of 3-(4-fluorophenyl)-1-methylimino-2H-indoi-2-one were isolated, recrystallized from ethanol and it (0.01 mol, 2.54 g) was subsequently treated with *o*-mercaptobenzoic acid (0.011 mol, 1.696g) in absolute ethanol-glacial acetic acid (5:1) for 10 hrs. The crystals obtained were filtered, washed successively with water and ethanol, dried and recrystallized from ethanol. M.P. 283°C, Yield 73%.

(ii) 4,5-Dihydro-3-(4-fluorophenyl)spiro[2H-1,3-benzothiazine-2,3'-[3H]indole]-2',4(1'H,3H)-dione (**4c**; 0.0025 mol, 1.0 g) in absolute ethanol (20 ml) was treated dropwise with ethanolic KOH (5 ml, 10%) while stirring. Dimethyl sulphate (freshly distilled) was subsequently added at 60°C with vigorous shaking to the above suspension and stirred for one and a half hour (5). The residue obtained was filtered and recrystallized from ethanol. M.P. 283°C, Yield 81%. IR (KBr) : 2910, 2850, 1690, 1675, 1570, 1530, 1470, 1420, 1400, 1380, 1350, 1260, 1240, 1160, 1150, 1120, 1080, 1060, 1035, 1000, 980, 950cm^{-1}; ^{1}H NMR : δ 2.01 (s, 3H, -CH_3) and 7.10-8.21 (m, 12H, arom.); ^{19}F NMR (CH_3OH) : δ -118.211; Anal. found C, 67.76; H, 3.91; N, 7.21; S, 8.19; $C_{22}H_{15}FN_2O_2S$ requires C, 67.68; H, 3.87; N, 7.18; S, 8.21%.

4,5-Dihydro-3-(4-fluorophenyl)-1'-morpholinomethyl-spiro[2H-1,3-benzothiazine-2,3'-[3H]indole]-2',4(1'H,3H)-dione, **4i**

This was also prepared by two routes. The latter method gave higher yields.

(i) A mixture of 1-morpholinomethylindole-2,3-dione (0.01 mol, 2.46 g) and 4-fluoroaniline (0.01 mol, 1.11 g) was refluxed in absolute ethanol containing 2-3 drops of glacial acetic acid for two hrs. The crystals separated on cooling were filtered and recrystallized from ethanol. 3-(4-Fluorophenyl)-1'-morpholinomethylimino-2H-indol-2-one (0.01 mol, 3.39 g) thus prepared was treated with (0.011 mol, 1.696 g) *o*-mercaptobenzoic acid in absolute ethanol - glacial acetic acid (5:1) for 10 hrs. The compound obtained was isolated, washed successively with ethanol, water and ethanol, dried and crystallized from ethanol. M.P. 291, Yield 68%.

(ii) 4,5-Dihydro-3-(4-fluorophenyl)-spiro[2H-1,3-benzothiazine-2,3'-[3H]indole]-2',4(1'H,3H)-dione (**4c**; 0.0025 mol, 1.0 g) was morphomethylated using morpholine (0.003 mol, 0.26 g) and 40% formaldehyde (0.0038 mol, 0.114 g) by literature method (10). M.P. 291°C, Yield 72%; IR (KBr) : 2900, 2860, 1685, 1670, 1560, 1540, 1480, 1450, 1415, 1395, 1350, 1275, 1240, 1210, 1175, 1145, 1105, 1090, 1035, 1010 cm^{-1}; ^1H NMR : δ 2.90 (m, 4H, CH_2-N-CH_2), 3.31 (m, 4H, CH_2-O-CH_2), 3.70 (s, 2H, N-CH_2-N) and 6.28-7.45 (m, 12H, arom.); ^{19}F NMR : δ -118.00; Anal. found C, 65.74; H, 4.68; N, 8.88; S, 6.70; $C_{26}H_{22}FN_3O_3S$ requires C, 65.67; H, 4.66; N, 8.84; S, 6.74%.

S-[3-(1,3-Dihydro-2-oxo-(2H)indolyl]-o-mercaptobenzoic acid, **5**

A mixture of 3-(2,3,4,5,6-pentafluorophenyl)imino-2H-indol-2-one (3.12 g, 0.01 mol) and *o*-mercaptobenzoic acid (1.696 g, 0.011 mol) was refluxed in absolute ethanol - glacial acetic acid (5:1) for 12 hrs. The compound obtained was filtered, washed with ethanol, water and finally with ethanol, dried and recrystallized from ethanol. M.P. 190°C, Yield 85%, IR (KBr) : 3480-3530 (-OH in CO_2H), 3260 (>N-H), 2560-2750 (CO_2H), 1680 (imido >C=O), 1660 cm^{-1} (CO in CO_2H); ^1H-NMR (DMSO-d_6) : δ 5.10 (s, -CH, 1H), 6.65-7.90 (m, H_{arom}, 8H), 8.80 (s, >NH, 1H), 9.88 (s, -OH, 1H). MS : m/z 285. Anal. found C, 63.04; H, 3.85; N, 4.95; S, 11.3; $C_{15}H_{11}NO_3S$ requires C, 63.14; H, 3.89; N, 4.90; S, 11.24%.

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