FLUORINE CONTAINING BIOACTIVE HETEROCYCLES PART III : SYNTHESIS OF SOME NEW FLUORINE CONTAINING PHENYLGLYOXALS AND 1,2,4-TRIAZINE DERIVATIVES

Krishna C. Joshi*, (Miss) Kalpana Dubey and (Mrs.) Anshu Dandia
Department of Chemistry, University of Rajasthan,
Jaipur-302004 (India)

Abstract - Some medicinally important new fluorine containing phenylglyoxals have been synthesized by selenium dioxide oxidation of appropriate fluorinated acetophenones and characterized by spectral studies. The phenylglyoxals were treated with thiosemicarbazide to give corresponding thiosemicarbazones (III) which were cyclized, in situ, to yield 5-(fluorophenyl)-1,2,4-triazine-3(2H)-thiones. The 5-(4-fluorophenyl)-1,2,4-triazine-3-(2H)-thione(IV) undergoes nucleophilic displacement when refluxed with hydrazine hydrate to give corresponding 3-hydrazino-5-(4-fluorophenyl)-1,2,4-triazine. The hydrazino derivative reacts with fluorinated 1,3-diketones, in glacial acetic acid yielding 5-(4-fluorophenyl)-3-[1-(3,5-disubstituted) pyrazolyl]-1,2,4-triazines(VII). All synthesized compounds have been characterized on the basis of elemental analyses, ir, pmr and ^{19}F nmr studies.

Phenylglyoxals find very useful applications in medicinal chemistry in view of a wide variety of biological activities associated with their derivatives, viz., antiviral[1], antifungal[2], antibacterial[3], neoplasm inhibitor[4], hypoglycemic[5] and antifertility[6]. Some derivatives of phenylglyoxals also act as plant growth stimulators[7] and also have an effect on blood vessels[8] and marked central vegal action[9].

Scanty information is available in literature concerning the chemistry and pharmacology of fluorine containing phenylglyoxals. The synthesis of only 4-fluorophenylglyoxal was reported in 1955 and some of its derivatives like oxime and hydrazone were reported later on, but no attention seems to have been given to biological activity of such compounds.

These observations prompted us to synthesize various new fluorine containing phenylglyoxals(IIb-e) by the oxidation of fluorinated acetophenones(I) with selenium dioxide. The glyoxals were purified by distillation under reduced pressure and preserved in the form of hydrates. Only IIe, pentafluorophenylglyoxal did not form a hydrate, which may be due to its high polarity[10,11]. Formation of phenylglyoxal hydrates was confirmed by elemental analyses and spectral studies. In ir spectra, two ketonic absorptions at 1730 and 1680 cm^{-1}, a broad hydroxyl absorption of hydrate at 3280-3350 cm^{-1} and $\geqslant$C-F absorptions at 1130-1300 cm^{-1} provide support for their formation. The pmr spectra exhibit aromatic protons at δ 6.9-7.3 ppm, aldehydic -$\overset{O}{\overset{\|}{C}}$H signals downfield at δ 8.3-8.5 ppm and OH protons of water at δ 3.6-3.7 ppm. Disappearance of methyl proton signal of acetophenone provides further support for the formation of phenylglyoxals.

The phenylglyoxals were treated with thiosemicarbazide to give corresponding thiosemicarbazones (III) which were cyclised, in situ, to yield 5-(fluoro phenyl)-1,2,4-triazine-3(2H)-thiones (IV). In preparing these triazine derivatives, we have been prompted by the observations that different types of biological activities are associated with triazine derivatives, viz. antihypertensive[12], antidepressant[13], analgesic[14], hypnotic[15], antibacterial[16], antifungal[16], antiinflammatory[17] and anticancer[18] and introduction of fluorine in such derivatives may lead to new medicinally important compounds.

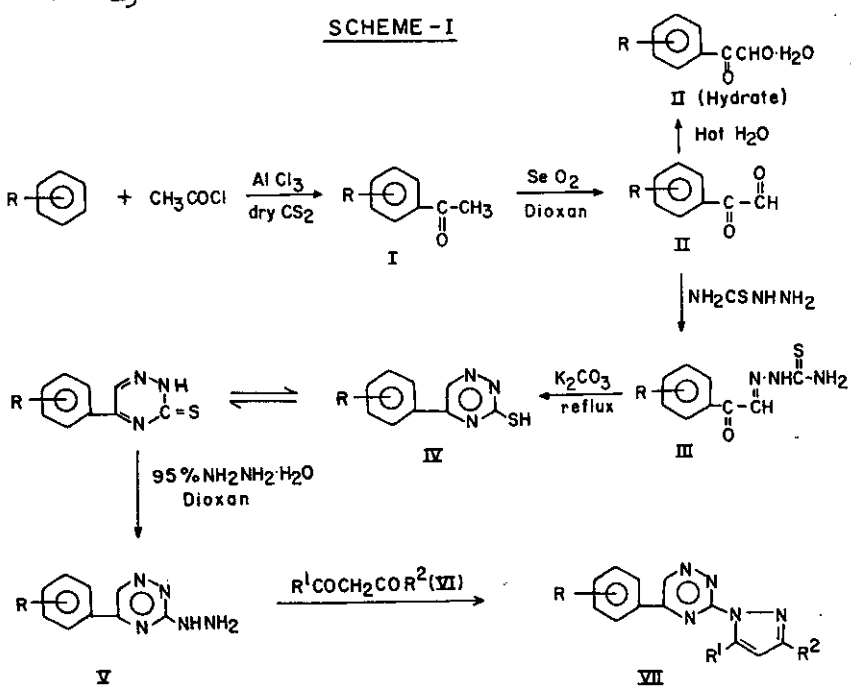
The 1,2,4-triazines(IV) obtained have been characterized by ir and pmr spectra. Disappearance of ketonic absorption peak in ir spectra and the appearance of new bands at 1640 cm^{-1} (N=N) and 1600 cm^{-1} (C=N) provide support for the formation of 5-(fluoroaryl)-3-mercapto-1,2,4-triazines. Further, a characteristic methine proton (N=CH) resonance signal at δ 8.8-9.1, a thiol proton resonance signal at 3.4-3.5, and aromatic signals at 7.0 to 8.4 ppm in pmr are noted. Triazine derivatives(IV) exist as keto-enol tautomers and spectral evidence points to predominance of thione form in solid state and an enol form in solution.

Presence and position of fluorine in these compounds (II and IV) have been confirmed by ^{19}F nmr. A sharp singlet of fluorine (IVa) attached to phenyl ring was observed at δ 39.65 ppm (TFA as external standard). Position of o-F, p-F, m-F in perfluoroaryl group of IIf and IVf were observed at δ 62.02, 80.4, 85.4 ppm, respectively. A preliminary screening of phenylglyoxals and 3-mercapto-1,2,4-

triazines indicates that these compounds exhibit CNS depressant activity. A detailed pharmacological study will be reported elsewhere.

5-(4-Fluorophenyl)-3-hydrazino-1,2,4-triazine has been prepared by nucleophilic displacement of 3-mercapto group by hydrazino group. Formation of V has been confirmed by the appearance of characteristic band in the region of 3260-3450 cm^{-1} ($-NHNH_2$) in the ir spectrum. Condensation of V with fluorinated 1,3-diketones(VI) in the presence of glacial acetic acid yielded 5-(4-fluorophenyl)-3-[1-(3,5-disubstituted)pyrazolyl]-1,2,4-triazines(VII) and the compounds characterized by elemental analysis, ir, pmr and ^{19}F nmr spectral studies. The pmr spectra of VII exhibits a characteristic pyrazolyl methine proton ($-C\underline{H}=C$) resonance signal at δ 6.2 ppm. In ^{19}F nmr spectrum of VIIc fluorine in benzene ring was observed at δ35.6 ppm and two sharp singlets of $-CF_3$ groups were observed at δ -5.2 ($\underline{F}_3C-\overset{\overset{\|}{N}}{C}-N$) and -6.8 ppm ($\underline{F}_3C-\overset{\overset{|}{N}}{C}=N$).

SCHEME-I



I, R = 4-F, 2-CH_3 ; 4F; 3,4-F_2 ; 2,4-F_2 ; 2-F, 5-CH_3 ; 3-Cl, 4-F.

II, III, IV, R=4-F, 2-CH_3 ; 4F; 3,4-F_2 ; 2,4-F_2 ; 2-F, 5-CH_3 ; 3-Cl, 4-F; Pentafluoro

V, VII, R = 4-F

VI, VII, $R^1 = R^2 = CH_3$; R^1 = 4-F, C_6H_4, $R^2 = C_6H_5$; $R^1 = R^2 = CF_3$

Experimental Procedure - Melting points are uncorrected. All synthesized compounds were routinely checked by elemental analyses. Tlc was done on silica gel plates using benzene-ethyl acetate 1:1 as solvent system. Ir spectra were recorded on Perkin Elmer IR-337 spectrophotometer (KBr-pellet). The pmr spectra were recorded at 60 MHz in DMSO-d_6 using tetramethylsilane (TMS) as internal reference standard and ^{19}F nmr at 56.4 MHz using trifluoroacetic acid (TFA) as external standard. The chemical shifts in ^{19}F nmr are expressed in δ (ppm) upfield from TFA.

4-Fluoro-2-methylacetophenone - It was prepared by following the method of Buu Hoi et al.[19] from 3-fluorotoluene (22.0 g, 0.20 mole) and acetyl chloride (19.28 g, 0.25 mole) in presence of anhydrous $AlCl_3$ (16.0 g, 0.32 mole) in dry carbon disulphide, b.p. 206°C, yield 31.7 g (76.4 %). All other fluorinated acetophenones (Ia-g) were prepared by acylation of appropriately substituted benzene or toluene.

4-Fluoro-2-methylphenylglyoxal (IIa) - A solution of acetophenone Ia (1.53 g, 0.01 mole) in dioxan (15 ml) was added to selenium dioxide (1.1 g, 0.01 mole) dissolved in dioxan : water (4:1). The mixture was stirred and refluxed for 6 hr, when it formed a red oil and black elemental selenium. The latter settled down and was removed by filtration. The oil was then concentrated under reduced pressure and purified by distillation. It was then converted into shining white needles of its hydrate, m.p. 90°C, yield 1.48 g (80 %) (Found : C, 58.66; H, 4.76. $C_9H_9FO_3$ requires C, 58.69; H, 4.89 %). $\nu_{max}^{cm^{-1}}$ 3280-3350 (OH), 1680, 1730 ($>C=O$), 1000-1100 ($\geqslant C-F$). Pmr: 8.3(1H, $\overset{O}{\overset{\|}{C}}-\underline{H}$), 3.6 (2H, $-O\underline{H}$), 6.9-7.3 (3H, aromatic protons), 2.55 (3H, $C\underline{H}_3$).

All other compounds (IIb-g, Table I) were prepared in a similar manner.

5-(4-Fluoro-2-methylphenyl)-3-mercapto-1,2,4-triazine(IVa) - A reaction mixture of 4-fluoro-2-methylphenylglyoxal(IIa, 1.66 g, 0.01 mole), thiosemicarbazide (1.01 g, 0.01 mole), water (20 ml) and ethanol (60 ml) was refluxed for 10 minutes to give corresponding thiosemicarbazone (IIIa) which, in situ, was cyclized by refluxing with potassium carbonate (2.1 g, 0.015 mole) for 8 hr. The solution was cooled, filtered and filtrate was acidified with HCl to afford IVa. It was purified by recrystallization from ethyl acetate, m.p. 175°C, yield 1.79 g (81 %) (Found : N, 19.10; S, 14.43, $C_{10}H_8FN_3S$ requires N, 19.00; S, 14.47 %). $\nu_{max}^{cm^{-1}}$ 3140 (NH), 1600-1640 (C=N, N=N), 1100-1280 (C-F). Pmr (DMSO d_6): 2.75 (3H, $C\underline{H}_3$), 3.5 (1H, $S\underline{H}$), 7.2-7.8 (3H, aromatic protons), 8.85 (1H, $\geqslant C\underline{H}$).

All other compounds (IVb-g, Table II) were prepared in a similar manner.

5-(4-Fluorophenyl)-3-hydrazino-1,2,4-triazine(Va) - 5-(4-Fluorophenyl)-3-mercapto-1,2,4-triazine (2.07 g, 0.01 mole), dissolved in dioxan, was added to 2 M excess of 95 % $NH_2NH_2.H_2O$ and the mixture refluxed for 10 hr, cooled and poured into ice, giving a solid, which was filtered and purified by recrystallization from the ethanol, m.p. 230°C, yield 1.0 g (50 %) (Found : N, 34.29, $C_9H_8FN_5S$ requires N, 34.31). $\nu_{max}^{cm^{-1}}$ 3200-3400 ($NHNH_2$), 1600-1640 (C=N, N=N).

1-(4-Fluorophenyl)-3-phenylpropane-1,3-dione(VIb) - It was prepared according to literature method[20] from 4-fluoroacetophenone (13.8 g, 0.1 mole) and ethyl benzoate (30.0 g, 0.2 mole) in presence of sodamide (7.8 g, 0.2 mole) in dry ether and recrystallized from petroleum ether, m.p. 80° (Lit.[20], m.p. 81°C), yield 16.0 g (66 %).

5-(4-Fluorophenyl)-3-[1-(3,5-dimethyl pyrazolyl)]-1,2,4-triazine (VIIa) - A mixture of Va (2.04 g, 0.01 mole) and acetylacetone (1.0g, 0.01 mole) was refluxed in glacial acetic acid for 1 hr, cooled and poured into ice. The solid obtained was filtered and recrystallized from acetone, m.p. 95°C, yield 2 g (66%) (Found N, 23.21. $C_{14}H_{12}FN_5S$ requires N, 23.25 %). $\nu_{max}^{cm^{-1}}$ 1600-1650 (C=N, N=N), 1100-1300(C-F). Pmr ($CDCl_3$): 9.55 (1H, triazine C<u>H</u>), 6.2 (1H, pyrazolyl C<u>H</u>), 7.7-8.3 (4H, aromatic), 2.35-2.45 (6H, both C<u>H</u>$_3$).

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TABLE -I : Physical Data of Fluorinated Phenylglyoxal hydrates(II).

Compound No.	R 	Yield %	M.P. °C	Mol. Formula	Analysis			
					Calcd.		Found	
					C %	H %	C %	H %
IIa	4-F.2-CH_3	80	90	$C_9H_9FO_3$	58.69	4.89	58.56	4.96
b	3,4-F_2	80	63	$C_8H_6F_2O_3$	51.06	3.19	51.22	3.21
c	3-Cl.4-F	73	71	$C_8H_6ClFO_3$	47.05	2.94	47.12	2.80
d	2,4-F_2	79	66	$C_8H_6F_2O_3$	51.06	3.19	51.15	3.31
e	2-F. 5-CH_3	83	82	$C_9H_9FO_3$	58.69	4.89	58.81	4.99
f	Pentafluoro	70	121/0.5mm (bp)	$C_8HF_5O_2$	42.85	-	42.79	-

TABLE -II: Physical data of triazines (IV and V)*

Compound No.	R	R'	Yield %	M.P. °C	Recrystallization solvent	Formula	Analysis Calcd. N%	Calcd. S%	Found N%	Found S%
IVa	4-F.2-CH_3	SH	81	175	benzene	$C_{10}H_8FN_3S$	19.00	14.47	18.92	14.35
b	3,4-F_2	SH	82	172	ethyl acetate	$C_9H_5F_2N_3S$	18.66	14.22	18.54	14.31
c	3-Cl.4-F	SH	75	93	benzene-pet. ether	$C_9H_5ClFN_3S$	17.42	13.27	17.34	13.31
d	2,4-F_2	SH	80	164	benzene	$C_9H_5F_2N_3S$	18.66	14.22	18.60	14.10
e	2-F.5-CH_3	SH	85	192	ethyl acetate	$C_{10}H_8F_2N_3S$	19.00	14.47	19.12	14.39
f	Pentafluoro	SH	71	202	methanol	$C_9H_2F_5N_3S$	15.05	11.46	15.13	11.32
g	4-F	SH	84	188	ethyl acetate	$C_9H_6FN_3S$	20.28	15.45	20.16	15,32
Va	4-F	$NHNH_2$	50	225	methanol	$C_9H_8FN_5$	34.46	-	34.38	-

TABLE -III: Physical data of 3-pyrazolyl-triazines(VII)*

Compound No.	R	R^1	R^2	Yield	M.P. °C	Solvent	Formula	Analysis Calcd. N %	Found N%
VIIa	4-F	CH_3	CH_3	66	95	acetone	$C_{14}H_{12}FN_5$	26.02	26.15
b	4-F	4-F.C_6H_4	C_6H_5	68	260	ethyl acetate	$C_{27}H_{15}F_2N_5$	15.67	15.72
c	4-F	CF_3	CF_3	64	145	benzene-pet. ether	$C_{14}H_6F_7N_5$	18.56	18.45

• Satisfactory C and H analyses were obtained in all cases.

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