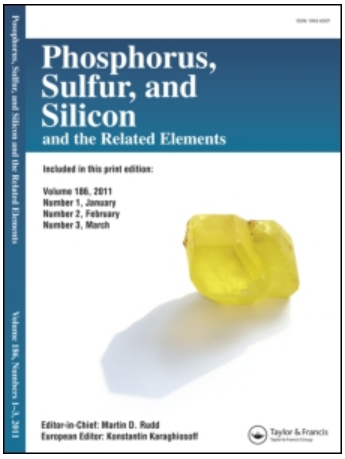


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS AND REACTIONS OF 2,3-DIHYDRO- 5-ARYL-5H,6H-THIAZOLO[3,2-b]-2,4-DIAZAFLUORENE-3,6-DIONES OF POTENTIAL BIOLOGICAL ACTIVITIES

Mohamed I. Ali[a]; Abou El-fotooh[a]; G. Hamman[a]; Salwa F. Mohamed[a]
[a] Chemistry Department, Faculty of Science, Cairo University and National Research Centre, Applied Organic Chemistry Lab., Dokki, Cairo, Egypt

To cite this Article Ali, Mohamed I. , El-fotooh, Abou , Hamman, G. and Mohamed, Salwa F.(1988) 'SYNTHESIS AND REACTIONS OF 2,3-DIHYDRO- 5-ARYL-5H,6H-THIAZOLO[3,2-b]-2,4-DIAZAFLUORENE-3,6-DIONES OF POTENTIAL BIOLOGICAL ACTIVITIES', Phosphorus, Sulfur, and Silicon and the Related Elements, 39: 3, 211 — 216
To link to this Article: DOI: 10.1080/03086648808072877
URL: http://dx.doi.org/10.1080/03086648808072877

Phosphorus and Sulfur, 1988, Vol. 39, pp. 211–216
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS AND REACTIONS OF 2,3-DIHYDRO-5-ARYL-5H,6H-THIAZOLO[3,2-b]-2,4-DIAZA-FLUORENE-3,6-DIONES OF POTENTIAL BIOLOGICAL ACTIVITIES

MOHAMED I. ALI, ABOU EL-FOTOOH, G. HAMMAN† and SALWA F. MOHAMED

Chemistry Department, Faculty of Science, Cairo University and National Research Centre, Applied Organic Chemistry Lab., Dokki, Cairo EGYPT.

(Received March 1, 1988)

1,2,3,4-Tetrahydro-1-aryl-3,9-dioxo-2,4-diazafluorenes (**2**) and 1,2,3,4-tetrahydro-1-aryl-9-oxo-3-thioxo-2,4-diazafluorenes (**3**) were newly synthesized. Compounds 3 reacted with chloroacetic acid, α-bromopropanoic acid, or B-bromopropanoic acid in the presence of fused sodium acetate and acetic anhydride to give 2,3-dihydro-5-aryl-5H,6H-thiazolo[3,2-b]2,4-diazafluorene-3,6-diones (**4**), 2-methyl-2,3-dihydro-5-aryl-5H,6H-thiazolo[3,2-b]2,4-diazafluorene-3,6-diones (**5**) and 2,3-dihydro-6-aryl-6H,7H-thiazino[3,2-b]2,4-diazafluorene-4,7-diones (**6**), respectively.

2,3-Dihydro-2-arylmethylene-5-aryl-5H,6H-thiazolo[3,2-b]2,4-diazafluorene-3,6-diones (**7**) were prepared by the reaction of compounds (**3**) with chloroacetic acid and aromatic aldehydes in the presence of fused sodium acetate and acetic anhydride or by the reactions of (**4**) with aromatic aldehydes in the presence of acetic anhydride.

2-(Arylhydroazono)-5-aryl-2,3-dihydro-5H,6H-thiazolo[3,2-b]2,4-diazafluorene-3,6-diones (**8**) were synthesized by coupling (**4**) with aryldiazonium salts in the presence of pyridine.

Key words: Thioxo-diazafluorenes, Thiazolodiazafluorenes, Thiazinodiazafluorenes.

It has been reported that 1,3-indanone derivatives are potent anticoagulants[1] and, in general have been used for the treatment of thromboembolism. Moreover, certain 1,3-dimethyl-2-azafluorenones showed interesting biological properties[2] and some thiazolopyrimidines are anticancer agents.[3]

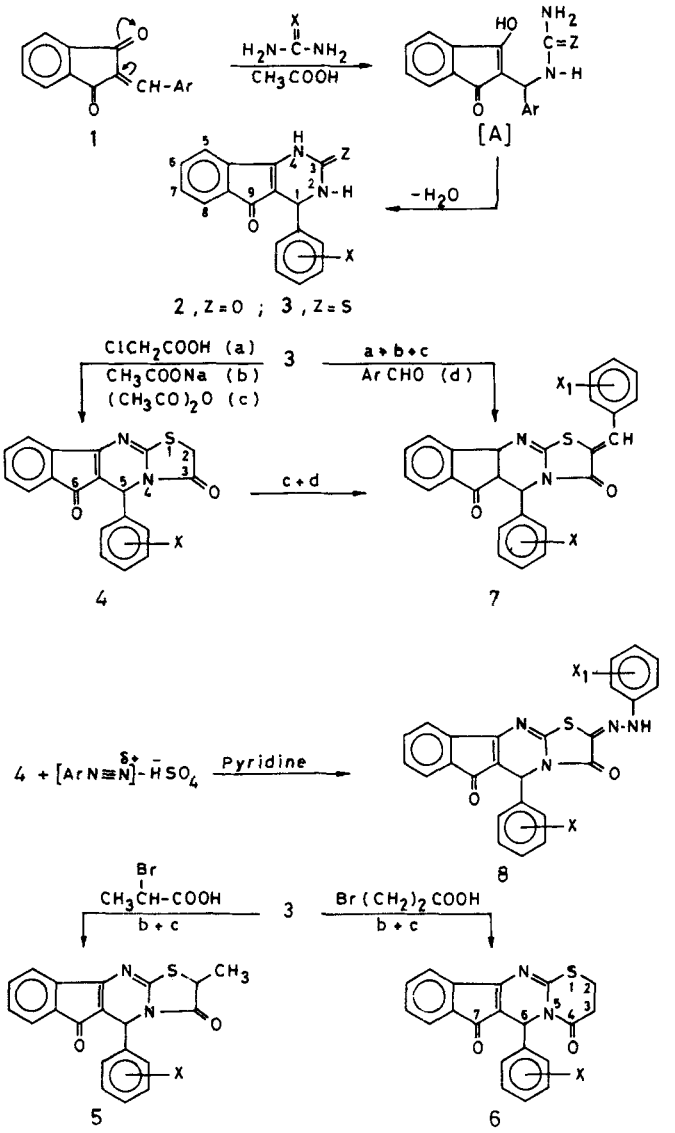
These facts led us to attempt the above reactions in order to get an indanone nucleus fused to a thiazolopyrimidine ring, a combination which is expected to possess high biological activities.

The reaction of urea or thiourea with 2-arylideneindane-1,3-dione has not been investigated.[1,2,4–6] Now we have found that urea of thiourea condenses with 2-arylidenindane-1,3-dione in boiling glacial acetic acid to give the 1,2,3,4-tetrahydro-1-aryl-3,9-dioxo-2,4-diazafluorenes (**2**) and 1,2,3,4-tetrahydro-1-aryl-9-oxo-3-thioxo-2,4-diazafluorenes (**3**), respectively.

Attempts to carry out the above reactions to give **2** and **3** in ethanol or an ethanol-piperidine mixture were not successful.

The reaction can proceed by the addition to an arylidene double bond by a Michael type addition[7,8–11] followed by cyclization of the intermediate A to (**2**) or (**3**), See the Scheme.

† To whom correspondence should be addressed at the National Research Centre.



SCHEME 1

The structures of all new compounds were confirmed by physical and chemical methods. The IR spectra of compounds I showed bands at 1725 cm^{-1} and at 1685 cm^{-1}, assignable to the two carbonyl groups (C=O); no absorption was seen at 1100 cm^{-1}.

The IR spectra of compounds **2** show absorption at 3250 cm^{-1} (NH) and at 1650 cm^{-1} and 1700 cm^{-1} (C=O); the IR spectra of compounds **3** show bands at 3250 cm^{-1} and at 3285 cm^{-1} (NH), at 1685 cm^{-1} (C=O) and a very strong band at 1100 cm^{-1} assignable to [>C=S][12].

Compounds **3** reacted with chloroacetic acid in acetic acid-acetic anhydride mixture in the presence of fused sodium acetate to give 2,3-dihydro-5-aryl-

5H,6H-thiazolo[3,2-b]2,4-diazafluorene-3,6-dinones (**4**). For pertinent literature see Reference 8.

The IR spectra of compounds **4** show bands at 1735 cm^{-1} assignable to C=O of the thiazolone ring and at 1685 cm^{-1} to the C=O of the diazafluorene ring; no NH absorption. The ^1H NMR spectrum of **4a** ($CDCl_3$) showed; the Ar-H protons (9H) as a multiplet in the δ 7.5–8.0 ppm region; the methine proton (1 H) as a singlet at δ 6.0 ppm and the methylene group (CH_2) as a singlet at 3.85 ppm.

Compounds **4** contain an active methylene group. They condensed with aromatic aldehydes in the presence of acetic anhydride to yield 2-arylmethylene-2,3-dihydro-5-aryl-5H,6H-thiazolo[3,2-b]2,4-diazafluorene-3,6-diones **7**. However, the arylmethylene derivatives **7**, were prepared directly from **3** by the action of chloroacetic acid, the aromatic aldehyde and sodium acetate in the presence of acetic acid-acetic anhydride mixture. The IR spectra of compounds **7** showed absorption at 1715 cm^{-1} (thiazolo C=O) and at 1685 cm^{-1} (diazafluorene C=O). The thiazolo carbonyl absorption (1715 cm^{-1}) was shifted to lower frequency; it was 1735 cm^{-1} in compounds **4** due to conjugation with the exocyclic double bond.

The ^1H NMR spectrum of compound **7a** ($CDCl_3$) showed the Ar-H protons and the benzylic proton as a multiplet (15 H) at δ 7.5–8.0 ppm and the methine proton as a singlet at δ 6.2 ppm.

Compounds **4** coupled with aryldiazonium salts in the presence of pyridine to give 2-(arylhydrazono)-2,3-dihydro-5-aryl-5H,6H-thiazolo[3,2-b]2,4-diazafluorene-3,6-diones **8**. The IR spectrum of compounds **8** showed absorption at 3250 cm^{-1} (NH), 1710 cm^{-1} (C=O) and 1685 cm^{-1} (C=O). This shift to lower frequency is due to conjugation with the exocyclic double bond (1735 cm^{-1} to 1710 cm^{-1}).

Compounds **3** reacted with 2-bromopropanoic acid and with 3-bromopropanoic acid (under the same conditions used for the preparation of compound **4** from **3**) to yield 2-methyl-2,3-dihydro-5-aryl-5H,6H-thiazolo[3,2-b]2,4-diazafluorene-3,6-diones (**5**) and 2,3-dihydro-6-aryl-6H,7H-thiazino[3,2-b]2,4-diazafluorene-4,7-diones (**6**), respectively.

The IR spectra of compounds **5** showed absorption bands at 1730 cm^{-1} and at 1685 cm^{-1} due to two carbonyl groups. The ^1H NMR spectrum of compound **5a** ($CDCl_3$) shows the methyl group as a doublet centered at 1.8 ppm and the methine proton as a quartet centered at 4.15 ppm, the methine proton as a singlet at 6.0 ppm and the aromatic protons (9H) as a multiplet at 7.7–8.0 ppm region. The IR spectrum of compounds **6** showed absorption bands at 1712 cm^{-1} and 1685 cm^{-1} due to the two carbonyl groups. The ^1H NMR spectrum of compound **6a** ($CDCl_3$) showed the AR-H protons (9H) as a multiplet at δ 7.45–8.0 ppm region, the methine proton (1H) as a singlet at δ 6.1 ppm, and showed the protons of the thiazine ring (4H) as a multiplet at the 2.8–3.0 ppm region.

EXPERIMENTAL

1-Aryl-1,2,3,4-tetrahydro-9-oxo-3-thiooxo-2,4-diazafluorenes (**3**). A solution of 0.01 mol of aryl-ideneindane-1,3-dione[4], in 15 ml of glacial acetic acid, was treated at the b.p. with 0.01 mol of thiourea; a deep red colour immediately developed, followed after 25 min. of boiling by the

TABLE I

Compd.	M.p. solvent	Yield %	X	X_1	Formula m.w.	Analysis % calcd./found C	H	N	S
2a	225	65	H	—	$C_{17}H_{12}N_2O_2$	73.92	4.38	10.14	—
	A				(276.28)	73.75	4.23	10.00	—
b	240		Cl-2	—	$C_{17}H_{11}ClN_2O_2$	65.71	3.57	9.01	—
	A				(310.7)	65.60	3.44	8.91	—
c	300	60	Cl-4	—	$C_{17}H_{11}ClN_2O_2$	65.71	3.57	9.01	—
	A				(310.7)	65.64	3.48	8.88	—
d	181	80	NO_2-4	—	$C_{17}H_{11}N_3O_4$	63.56	3.45	13.08	—
	A				(321.2)	63.37	3.28	12.79	—
3a	265	80	H	—	$C_{17}H_{12}N_2OS$	69.84	4.13	9.58	10.97
	A				(292.3)	69.79	4.20	9.49	11.00
b	210	75	Cl-2	—	$C_{17}H_{11}ClN_2OS$	62.47	3.39	8.57	9.81
	A				(326.8)	62.27	3.54	8.40	9.70
c	240	80	Cl-4	—	$C_{17}H_{11}ClN_2OS$	62.47	3.39	8.57	9.81
	A				(326.8)	62.43	3.20	8.51	9.60
d	262	80	Br-4	—	$C_{17}H_{11}BrN_2OS$	54.99	2.98	7.53	8.64
	A				(371.3)	54.75	3.10	7.43	8.50
e	250	65	NO_2-4	—	$C_{17}H_{11}N_3O_3S$	60.35	3.28	12.42	9.48
	A				(337.3)	60.23	3.37	12.29	9.30
f	260	60	OH-2,3	—	$C_{17}H_{12}N_2O_3S$	62.38	3.73	8.64	9.38
	A				(324.3)	62.17	3.68	8.55	9.50
g	225	50	$(OCH_3)_3$	—	$C_{20}H_{18}N_2O_4S$	62.83	4.73	7.32	8.38
	A		3,4,5		(382.3)	62.72	4.81	7.40	8.20
4a	164	76	H	—	$C_{19}H_{12}N_2O_2S$	68.65	3.64	8.43	9.64
	E				(332.4)	69.0	3.58	8.2	9.50
b	180	65	Cl-2	—	$C_{19}H_{11}ClN_2O_2S$	62.21	3.02	7.64	8.74
	M				(366.8)	62.00	3.00	7.48	8.63
c	240	75	Cl-4	—	$C_{19}H_{11}ClN_2O_2S$	62.21	3.02	7.64	8.74
	D				(366.8)	62.10	2.95	7.49	8.54
d	198	75	Br-4	—	$C_{19}H_{11}BrN_2O_2S$	55.48	2.69	6.81	7.79
	D				(411.3)	55.30	2.80	6.75	7.81
5a	180	75	H	—	$C_{20}H_{14}N_2O_2S$	69.34	4.07	8.08	9.26
	M				(346.4)	69.10	4.00	7.89	9.05
b	250	65	Cl-2	—	$C_{20}H_{13}ClN_2O_2S$	63.07	3.43	7.36	8.42
					(380.8)	63.00	3.38	7.21	8.33
c	210	70	Cl-4	—	$C_{20}H_{13}ClN_2O_2S$	63.07	3.43	7.36	8.42
					(380.8)	63.10	3.45	7.10	8.24
d	250	65	Br-4	—	$C_{20}H_{13}BrN_2O_2S$	56.48	3.08	6.58	7.54
					(425.3)	56.38	3.00	6.48	7.36
6a	198	60	H	—	$C_{20}H_{14}N_2O_2S$	69.34	4.07	8.08	9.26
	M				(346.4)	68.98	4.10	7.98	9.13
b	245	60	Cl-2	—	$C_{20}H_{13}ClN_2O_2S$	63.07	3.43	7.36	8.42
					(380.8)	62.90	3.30	7.25	8.19
c	215	65	Cl-4	—	$C_{20}H_{13}ClN_2O_2S$	63.07	3.43	7.36	8.42
	E				(380.8)	63.10	3.40	7.20	8.35
d	255	70	Br-4	—	$C_{20}H_{13}BrN_2O_2S$	56.48	3.08	6.58	7.54
	M				(425.3)	56.70	3.00	6.44	7.55
7a	264	90	H	H	$C_{26}H_{16}N_2O_2S$	74.26	3.84	6.66	7.62
	Ac				(420.5)	74.10	3.78	6.70	7.64
b	298	90	H	F-4	$C_{26}H_{15}FN_2O_2S$	71.06	3.67	6.37	7.29
	D				(438.5)	71.00	3.66	6.25	7.38
c	245	80	H	Br-4	$C_{26}H_{15}BrN_2O_2S$	62.40	3.02	5.60	6.70
	D				(499.4)	62.00	2.88	5.55	6.55
d	158	70	Cl-2	F-4	$C_{26}H_{14}ClFN_2O_2S$	66.03	2.98	5.92	6.78
					(472.9)	66.0	2.80	5.86	6.76
e	272	75	Cl-2	Br-4	$C_{26}H_{14}BrClN_2O_2S$	58.49	2.64	5.24	6.00
	Ac				(533.8)	58.30	2.53	5.09	5.89

TABLE I (Contd)

Compd.	M.p. solvent	Yield %	X	X_1	Formula m.w.	Analysis % calcd./found C	H	N	S
f	250	85	Cl-2	$CHMe_2$-4	$C_{29}H_{21}ClN_2O_2S$	70.07	4.25	5.63	6.45
	D				(497.0)	69.90	4.10	5.54	6.35
g	300	80	Cl-4	NMe_2-4	$C_{28}H_{20}ClN_3O_2S$	67.53	4.05	8.43	6.43
	Ac				(497.9)	67.40	4.00	8.33	6.27
h	299	75	Br-4	H	$C_{26}H_{15}BrN_2O_2S$	62.40	3.02	5.60	6.40
					(499.4)	62.25	3.00	5.54	6.28
i	286	85	Br-4	$CHMe_2$-4	$C_{29}H_{21}BrN_2O_2S$	64.32	3.91	5.17	5.92
					(541.5)	64.20	3.80	5.08	5.78
8a	178	60	H	CH_3-p	$C_{26}H_{18}N_4O_2S$	69.23	4.03	12.44	7.81
	E				(450.5)	69.00	4.00	12.35	7.78
b	156	65	H	NO_2-p	$C_{25}H_{15}N_5O_4S$	62.36	3.14	14.54	6.66
	E				(481.5)	62.12	3.10	14.43	6.73
c	196	70	Cl-2	CH_3-p	$C_{26}H_{17}ClN_4O_2S$	64.38	3.53	11.55	6.61
	D				(485.0)	64.20	3.44	11.36	6.50

Keys of Solvents
A = Acetic acid D = Dioxane
E = Ethyl alcohol M = Methyl alcohol

separation of red crystals. The reaction mixture was left at room temperature for 2 h. and the solid formed was collected and crystallized from the proper solvent (see Table).

1-*Aryl*-1,2,3,4-*tetrahydro*-3,9-*dioxo*-2,4-*diazafluorenes* (**2**). Compounds **2** were prepared by the same procedure used above for compounds **3** using urea instead of thiourea (see Table).

Tricyclic Heterocycles (**4**, **5** *and* **6**). A mixture of 0.01 mol of compounds **3** with 0.01 mol of chloroacetic acid, 0.01 mol of 2-bromopropanoic acid, or 0.01 mol of 3-bromopropanoic acid and 6 g of fused sodium acetate in 30 ml of glacial acetic acid and 15 ml of acetic anhydride was refluxed for 2 h, left to cool, then poured gradually into cold water. The solid obtained was filtered off, washed with water and crystallized from the proper solvent (see Table).

(2-*Arylmethylene*)-2,3-*dihydro*-5-*aryl*-5*H*,6*H*-*thiazolo*[3,2-*b*]-2,4-*diazafluorene*-3,6-*diones* (**7**). (a) A mixture of 1 g of **4**, an equimolecular amount of the appropriate aldehyde and 3 ml of acetic anhydride was refluxed for 1 h, left to cool, then poured into cold water. The solid formed was collected and crystallized from the proper solvent.

(b) A mixture of 0.05 mol of **3**, 1 g of chloroacetic acid, 2 g of fused sodium acetate, 20 ml of acetic acid, 10 ml of acetic anhydride and an equimolecular amount of appropriate aldehyde was refluxed for 3 h. The reaction mixture was cooled and poured into cold water. The precipitate formed was collected and crystallized (see Table).

Method (b) gave better yields than method (a).

(2-*Arylhydrazono*)-2,3-*dihydro*-5-*aryl*-5*H*,6*H*-*thiazolo*[3,2-*b*]-2,4-*diaza*-*fluorene*-3,6-*diones* (8). The aromatic amine (0.01 mol) was dissolved in 3 ml of sulphuric acid (70%), cooled to 0°C and treated with 0.7 g sodium nitrite in 2 ml of water. The diazonium salt was cooled for 15 minutes and then added gradually with stirring to a cooled solution of 0.01 mol in 10 ml of pyridine. The reaction mixture was cooled for 30 min. and poured into 100 ml of water. The solid formed was collected and crystallized (see Table).

BIOLOGICAL RESULTS

The newly synthesized compounds have been tested for biological activity as herbicidal, insecticidal, antimicrobial and plant health agents. The preliminary

tests of some compounds reported in this paper showed that compounds **2c**, **4b** and **4c** showed pronounced herbicidal activity. Other biological tests after completion will be published separately.

REFERENCES

1. K. C. Murdock, *J. Org. Chem.*, **24,** 845 (1959).
2. R. L. Horoton and K. C. Murdock, *J. Org. Chem.*, **25,** 938 (1960).
3. M. I. Ali, M. A. F. Elkaschef, A. G. Hammam and S. A. Khallaf, *J. Chem. Eng. Data,* **24,** 377 (1979).
4. V. Petrow; J. Saper and B. Sturgeon, *J. Chem. Soc.*, 2134 (1949).
5. A. Mustafa and M. K. Helmy, *J. Chem. Soc.*, 1434 (1952).
6. W. A. Mosher, *J. Org. Chem.*, **35,** 2109 (1970).
7. R. M. Acheson, An Introduction to the Chemistry of Heterocyclic Compounds, 3rd ed., J. Wiley & Sons, New York, 1977, p. 405.
8. M. I. Ali, M. A. F. Elkaschef and A. G. Hammam, *J. Chem. Eng. Data,* **20,** 128 (1975).
9. A. G. Hammam and M. I. Ali, *J. Chem. Eng. Data,* **26,** 99 (1981).
10. A. G. Hammam and M. I. Ali, *J. Chem. Eng. Data,* **26,** 101 (1981).
11. M. I. Ali and A. G. Hammam, *J. Chem. Eng. Data,* **26,** 342 (1981).
12. D. H. Williams and L. Fleming; Spectroscopic Methods in Org. Chem. 2nd. ed McGraw-Hill Book Company (U.K.), 1973, p. 64.