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Synthesis of 3-(Chlorosulfonylaryl)phthalides and Their Reactions with Amino Pyridines

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Certain new sulfonamido derivatives having heterocyclic moiety (2a–b and 3a–e) have been synthesised by the reaction of 3-(chlorosulfonated aryl) phthalides (1f–j) with aminopyridines in the presence of dry pyridine. The chlorosulfonated aryl phthalides were synthesised from the corresponding 3-arylphthalides (1a–e). The structures of the isolated products were confirmed from their spectral and elemental analyses data.

INTRODUCTION

3-Arylphthalides substituted with nitrogen were of interest because of their biological importance as pesticide, fungicide[1] and for their use as a precursor in the synthesis of isoindolines-1-one derivatives: the compounds which possess a biological activity as antihypertensive like chlorothalidone[2], antiarrythmic[3], antiinflammatory[4], antispasmotic[5] and in the treatment of angina pectoris.[6] On the other hand, recent interest has been developed in sulfonamide and heterocyclic compounds like pyridine, benzothiazole and their derivatives because of the biodynamic properties of the former and the wide spectrum of biological activity of the latter.[7] We thought of combining the three moieties and chlorosulfonate 3-arylphthalides with chlorosulfonic acid, then reacting the products with aminopyridines in an attempt to prepare new sulfonamide compounds. Although Giegy[8] and Giacobbe[2] obtained a patent on the synthesis of isonidiolines-1-one derivaties containing sulfonamido group, nothing has been mentioned on compounds containing a heterocyclic amine moiety. In view of these findings we report in this paper the synthesis of 3-(chlorosulfonated aryl)phthalides (1f–j) and their condensation with 2-amino- and 3-amino-pyridine which afforded in acceptable yields the corresponding sulfonamide derivatives (2a–b and 3a–e).

EXPERIMENTAL

All melting points were measured on electrothermal melting point apparatus and were uncorrected. Infrared spectra were measured using Pye-Unicam SP-300 Spectrophotometer as a potassium bromide disc. ^{1}H-NMR was measured using a Brucker WP 80 SY Spectrometer. Elemental analyses were measured at M.H.W. Laboratories, Phoenix, Arizona, USA.

Preparation of 3-(chlorosulfonyl aryl)phthalides (1f–j)

Chlorosulfonation of 3-arylphthalides[9] was carried out as reported by Giacobbe[2], but at elevated temperature. According to this procedure the following compounds were prepared. 3(4′-chlorosulfonylphenyl)phthalide (1f), 3-(4′-chloro-3′-chlorosulfonylphenyl) phthalide (1g), 3-(4′-bromo-3′-chlorosulfonyl-

phenyl) phthalide (1h), 3-(4′-methoxy-3′-chlorosulfonylphenyl) phthalide (1j) and 3-(4′-hydroxy-3′-chlorosulfonylphenyl) phthalide (1j). (See Table-1 for physical data and Table-2 for ^{1}H-NMR data.)

TABLE-1
PREPARATION AND PROPERTIES OF
3-(CHLOROSULFONYL ARYL)PHTHALIDES (1a–h)

Comp. No.	m.p. (°C)	Yield (%)	Reaction Temp. (°C)	IR absorption (cm^{-1})	Analyses %, Found (Calcd)		
					C	H	S
1e	93–95	81	60–65	1740, 1370, 1180	54.32 (54.45)	2.76 (2.91)	10.10 (10.37)
1f	159–160* Ref. 2(158–159)	84	70–75	1750, 1355, 1170	48.61 (48.97)	2.31 (2.33)	9.30 (9.32)
1g	163–165	83	70–75	1750, 1355, 1170	43.29 (43.24)	2.40 (2.31)	8.25 (8.23)
1h	102–105	80	50–55	1750, 1360, 1160	53.16 (53.25)	3.52 (3.55)	9.40 (9.46)
1i	156—158	78	50–55	1720, 1360, 1170 3000–3600	51.80 (51.85)	2.71 (2.77)	9.71 (9.87)

TABLE-2
^{1}H-NMR SPECTRAL DATA OF COMPOUNDS 1(e–i) in $CDCl_3$

Comp. No.	H-3	H-5′	H-6′	H-2′	H-7	H4 +5 + 6	Others
1e	s, 6.52	m, 7.80 + H–3′	m, 7.3	m, 7.3	d, 8.01 J = 7.0 Hz	7.6–7.96	
1f	s, 6.46	d, 7.46 J = 8.5 Hz	d, 7.16 J = 8.5 Hz	s, 8.19	d, 7.96 J = 7.3 Hz	m, 7.76–78	
1g	s, 6.44	d, 7.48 J = 8.1 Hz	d, 7.11 J = 8.1 Hz	s, 8.15	d, 7.9 J = 7.0 Hz	m, 7.6–7.8	
1h	s, 6.45	d, 7.00 J = 8.2 Hz	d, 7.35 J = 8.1 Hz	s, 7.97	d, 8.01 J = 7.5 Hz	m, 7.70–7.9	s, 4.08 (OCH_3)
1i	s, 6.40	d, 7.15 J = 8.6 Hz	d, 7.20 J = 8.5 Hz	s, 7.80	d, 7.87 J = 7.8 Hz	m, 7.2–7.8	bs, 10.80 (OH)

Reactions of chlorosufonyl arylphthalides (1f–j) with aminopyridines

General method: An amine (0.001) mole was dissolved in dry pyridine (5 mL) then (0.01) mole of the corresoponding chlorosulfonyl aryl phthalide was added portion wise. The mixture was then refluxed for 3–5 h until a maximum amount of white pyridinium chloride was formed, then cooled and poured into 50 mL of ice-water. The precipitated solid was filtered and recrystallised from ethanol. According to this procedure the following compounds were prepared. 3-[4′-(2-aminopyridylsulfonyl)phenyl] phthalide (2a), 3-[4′-(3-aminopyridyl sulfonyl)phenyl] phthalide (2b), 3-[4′-chloro-3′(2-aminopridyl sulfonyl)phenyl] phthalide (3a), 3-[4′-chloro-3′ (3-aminopyridyl sulfonyl)phenyl) phthalide] (3b),

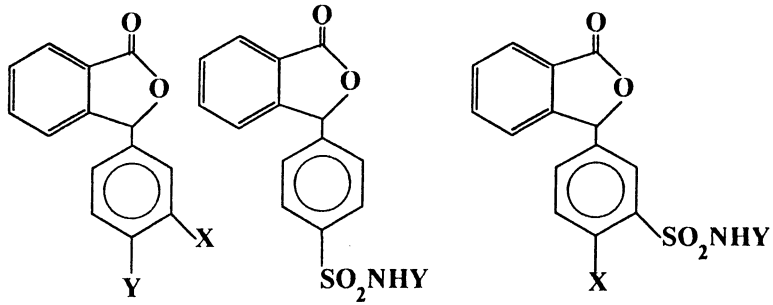
3-[4′-bromo-3′-(2-aminopyridyl sulfonyl)phenyl] phthalide (3c), 3-[4′-bromo-3′ (3-aminopyridyl sulfonyl)phenyl] phthalide (3d) and 3-[4′-methoxy-3′ (3-aminopyridyl sulfonyl)phenyl] phthalide (3e). (See Table-3 for physical data and Table-4 for ^{1}H-NMR spectral data.)

TABLE-3
PREPARATION AND PROPERTIES OF 3-(AMIDOSULFONYLARYL) PHTHALIDES (2a–b) and (3a–c)

Comp. No.	m.p (°C)	Yield %	Time (h)	IR absorption (cm^{-1})	Analysis %, Found (Calcd.)		
					C	H	S
2a	201–202	32	5	3220, 1740, 1330, 1160	62.06 (62.29)	3.86 (3.82)	7.45 (7.65)
2b	135–137	40	5	3100, 1750, 1340, 1150	62.13 (62.29)	3.64 (3.82)	7.52 (7.65)
3a	241–243	50	3	3220, 1750, 1340, 1130	56.50 (56.92)	3.11 (3.24)	6.93 (6.99)
3b	117–120	31	3	3100, 1760, 1320, 1160	56.48 (56.92)	3.16 (3.24)	6.88 (6.99)
3c	255–257	76	3	3200, 1750, 1340, 1130	51.60 (51.23)	2.90 (2.92)	6.20 (6.29)
3d	150–151d	35	3	3200, 1740, 1340, 1130	50.96 (51.23)	2.60 (2.92)	6.34 (6.29)
3e	224–225	36	5	3100, 1770, 1320, 1150	60.41 (60.00)	4.31 (4.07)	6.89 (7.07)

TABLE-4
^{1}H-NMR SPECTRAL DATA OF COMPOUNDS (2a–b) AND (3a–e) IN d_6-DMSO

Comp. No.	Spectral data
2a	6.85 (s, 1H, H-3), 6.72–6.94 (d, 1H, J = 6.8 Hz, H-3″), 7.50 (d, 1H, J = 6.7 Hz, H-5″), 7.62–7.95 (m, 10H) and 12.24 (b, NH)
2b	6.81 (S, 1H, H-3), 7.29–8.99 (m, 10H), 8.26 (d, 1H, H-3″ J = 5.6 Hz) and 10.59 (b, NH)
3a	6.87 (b, 1H, J = 6.3, H-5″), 6.89 (s, 1H, H-3), 7.16 (d, 1H, J =8.2, H-3″), 7.41–8.18 (m, 9H) 7.3–7.6 (b, NH)
3b	6.87 (s, 1H, H-3), 7.32–8.29 (m, 11 H) and 11.06 (b, NH)
3c	6.80 (d, 1H, J = 6.5 Hz, H-5″), 6.88 (s, 1H, H-3′), 7.25 (d, 1H, J = 5.8 Hz, H-3″), 7.3–8.5 (m, 9H) and 7.6–7.9 (b, NH)
3d	6.86 (s, 1H, H-3), 7.16–8.3 (m, 11H) and 7.5–7.8 (b, NH)
3e	3.83 (s, 3H, OCH_3), 6.76 (s, 1H, H–3), 7.2 (d, 1H, J = 8.6 Hz), 7.30–8.26 (m, 10H) and 10.38 (b, NH)



1 a Y=X=H
b Y=Cl; X=H
c Y=Br; X=H
d Y=OCH_3; X=H
e Y=OH; X=H
f Y=SO_2Cl; X=H
g Y=Cl; X=SO_2Cl
h Y=Br; X=SO_2Cl
i Y=OCH_3; X=SO_2Cl
j Y=OH; X=SO_2Cl

2 a Y=2-pyridyl
b Y=3-pyridyl

3 a X=Cl; Y=2-pyridyl
b X=Cl; Y=3-pyridyl
c X=Br; Y=2-pyridyl
d X=Br; Y=3-pyridyl
e X=OCH_3; Y=3-pyridyl

RESULTS AND DISCUSSION

The reactions of chlorosulfonic acid with 3-arylphthalides (1a–e) were conducted at a temperature between 50–75°C, yield a solid product. The IR spectra of the crude products show strong absorptions in the range of 1750–1750 and 1370–1360, 1180–1160 cm^{-1} indicating the presence of lactonic and chlorosulfonyl groups; such absorptions confirm that the lactonic groups persist ring opening and the reactions occur smoothly at the aryl group attached to position-3 of the phthalide. The position of chlorosulfonation was checked by the ^{1}H-NMR spectra of all products, which shows the presence of one proton singlet at δ 6.40–6.52 assigned to H–3. The appearance of this proton at such chemical shift in $CDCl_3$ indicates clearly that this proton is unaffected either electronically or sterically by any substituent on the aryl group[9], indicating no chlorosulfonation occurs at position 2′. On the other hand, the appearance of one proton singlet at δ 7.8–8.19 in case of (1b–e) suggests that the aromatic electrophilic substitution reaction occurs regioselectively at position 4′ in case of (1a), and at position 3′ *ortho* to the substituent in case of (1b–e) giving rise to products (1f–j) respectively. See Table-2 for spectral data. The reactions of 2-amino- and 3-aminopyridines with chlorosulfonylaryl phthalides were conducted in dry pyridine under reflux condition. The reaction of (1f) as an example with 2-aminopyridines afforded a solid product. The IR spectra of the products shows the following absorptions: 3220–3100, 1750–1740 and 1340–1330, 1160–1150 cm^{-1} indicating the presence

of NH, lactonic and sulfonamido groups, respectively. The ^{1}H-NMR spectra in d^6-DMSO shows one proton singlet at δ 6.81–85 assigned to the phthalidyl proton H-3. The indication of product formation was also conducted from the chemical shifts of the two protons, *ortho* and *para* to the NH_2 group in the starting amines, since it was expected that these two protons will be slightly deshielded in the product due to the formation of SO_2NHR group, and this was actually the case, and a deshielding of about 0.6–0.4 pm was noticed. See Table-4 for ^{1}H-NMR spectral data. In a similar manner the structures of the sulfonamido arylphthalides (2a), (3a–e) were confirmed.

The reaction of 3-(4′-hydroxy-3′-chlorosulphonylphenyl)phthalide (1j) with both amines afforded a product whose structures are entirely different from the others. From their spectral data, it seems that some elimination reactions might happen. The antimicrobial activity of compounds (2a, 3a–e) is understudy and the reuslts will be communicated later.

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REFERENCES

1. D.D. Wheeler and D.C. Young, US Pat 2, 904, 556 (Sept. 15, 1959); *Chem. Abstr.*, **55**, 2556 (1961); US Pat. 2, 905, 865 (July, 19, 1960); *Chem. Abstr.*, **55**, 2557 (1961).
2. T.J. Giacobbe and H.C. White, US Pat. 4, 188, 330 (Feb. 12, 1980); *Chem. Abstr.*, **92**, 19825f (1980).
3. K. Okazaki, E. Oshima, H. Obse, Y. Oiji, M. Nito and K. Kubo, Eur. Pat. EP 273, 401 (1988); *Chem. Abstr.*, **109**, 170232p.
4. S.J. Foster, P. Bruneau, E. Walker and R. McMillans, *British Journal of Pharmacology*, **99**, 113 (1990).
5. J.R. Giegy, Swiss Pat. 374, 071 (1974); *Chem. Abstr.*, **62**, 104166 (1965).
6. Y. Morisaw, M. Kataoka, H. Ngahori, F. Saito and H. Koke, Jap. Kokai Tokkyo Koho Jp 62, 185, 070 (13, Aug. 1987); *Chem. Abstr.*, **108**, 186566r.
7. B.H. Trivedi and V.H. Shah, *Indian Drugs*, **29**, 262 (1992); J. Patrick, J. Leblevee and Nemecek, Cur. Pat. Appl. EP 409, 692; *Chem. Abstr.*, **114**, 228902d (1991).
8. J.R. Giegy, British Pat. 914, 613 (1963); *Chem. Abstr.*, **59**, 7492e (1963); J.R. Giegy, French. Pat. 1, 297, 110 91962; *Chem. Abstr.*, **58**, 9028c (1963).
9. R. Al-Hamdany, J. Al-Rawi and S. Ibrahim, *J. Prakt. Chem.*, **329**, 126 (1987).

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