s-Triazines. III. Synthesis of Dihalogenoheteroaryl-s-triazines. Reaction of 2,4,6-Trichloro-s-triazine with Pyrrole, Thiophene, and Furan

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In a previous paper (1), we reported the preparation of dichloroheteroaryl-*s*-triazines by a direct coupling reaction between 2,4,6-trichloro-*s*-triazine (cyanuric chloride) and a metalated derivative of pyrrole, thiophene or furan. Due to their high reactivity, these parent five membered heterocycles are known to readily undergo electrophilic substitution reactions leading to preferential attack at the α-position. For example, acylation using an acyl-chloride or anhydride normally in presence of a catalyst under Friedel-Crafts conditions is well known. Cyanuric chloride, due to its high polarity of the C=N double bonds, resembles an acyl chloride. Its reactions with benzene and polycyclic benzenoid derivatives in the presence of aluminum chloride to yield substituted triazines are known (2). The reactions of cyanuric chloride with ambident nucleophiles, *e.g.* dialkylaniline to give 2,4-dichloro-6-(*p*-*N*,*N*-dialkylanilino)-*s*-triazines have also been reported (3).

In this report, we describe the electrophilic reactions of cyanuric chloride with various heteroaromatic ring systems to yield 2,4-dichloroheteroaryl-*s*-triazines. The reaction proceeded smoothly with various pyrroles and thiophenes. Furan, however, failed to produce any isolable product even when the reaction was carried out at elevated temperatures in a sealed tube with or without a catalyst. Factors governing these reactions, particularly in respect to substituted pyrroles, are discussed in detail. The products have been characterised on the basis of spectroscopic evidence and analyses. The results are recorded in Table I. The effect of attempted nucleophilic displacement of the triazine bound chlorines in **2** with bromines is also described.

Pyrrole and most of the *N*-alkyl as well as both *N* and *C* dialkylpyrroles underwent substitution reaction readily with cyanuric chloride in boiling benzene to produce dichloropyrrolyl-*s*-triazines in good yields. No addition of catalyst was required. The substitution always occurred at the free α-position. 1,3-Dimethylpyrrole afforded two isomeric α-substituted products **3** and **4** in the molar ratio of 3:1, the isomer *ortho* to the methyl group being predominant. Similarly, with 1-methyl-3-ethylpyrrole two α-substituted products were shown in the mixture in the ratio of 3:1 in favour of the isomer *ortho* to the ethyl group. Nmr δ 7.35 (d, H_3), 6.78 (d, H_5) J ≃ 1.5 Hz indicated the presence of the minor component. The major product **6** was isolated by crystallisation from *n*-hexane. The ratio of substitution products from these reactions indicates that the electron donating effect of methyl or ethyl groups is more pronounced than any steric factor. The reaction seemed to proceed less readily in refluxing benzene alone with 1-phenylpyrrole or 2,5-dimethyl-1-phenylpyrrole. The electron-withdrawing effect of the 1-substituent in such cases would be expected to diminish the susceptibility of the pyrrole ring to electrophilic attack. Thus, these reactions, when carried out in benzene in the presence of aluminum chloride as catalyst at 20 to 40° gave good yields of the desired products. No product, however, could be isolated in similar reactions with pyrroles substituted at position 1 with *m*-fluorophenyl, *m*-trifluoromethylphenyl or cyano-ethyl groups. It appears aluminum chloride induced much polymerisation particularly at higher temperatures leading to intractable tars. Thus, these reactions, when carried out at higher temperatures *e.g.* in boiling xylene, without any addition of catalyst, yielded the required 2-substituted pyrroles.

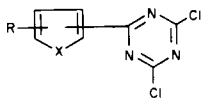
The reactivity in the thiophene series under the above conditions was found to be much reduced, so the reactions were carried out in boiling chlorobenzene in presence of aluminum chloride to give the products. Again, in the case of 3-methylthiophene, two isomeric α-substituted products **20** and **21** were obtained in the molar ratio of 4:1 favouring the substitution *ortho* to the methyl group.

The electrophilic substitution reactions of cyanuric chloride on appropriate heteroaromatic rings constitute a single step synthesis without involving any metalated derivatives as reported in our earlier paper (1). The yields in general are good and in certain cases, superior to those obtained through metalated species (Table I). Similarly, other cyanuric halides may be used to obtain the corresponding aryldihalogeno-*s*-triazines (4) otherwise obtainable only by a multistep synthesis.

Reaction of **2** with excess of sodium bromide or

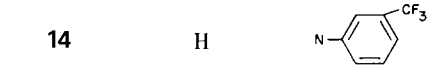
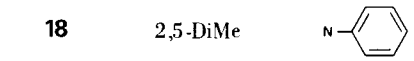
TABLE I

Aryldichloro-*s*-triazines: Synthesis and Spectra



	Compound R	Compound X	Subn.	Yield (a) (%)	M.p., °C	Microanalysis Calcd./Found % C	H	N	Cl	λ max nm (log ε)	δ ($CDCl_3$) H_2 or $_3$	H_4	H_5	J H_z
1	H	NH	2	42 (A) 45 (1)	140-142					338 (4.52)	7.41 m	6.43 m	7.17 m	
2	H	NCH_3	2	90 (A) 70 (B) 50 (1)	157	41.9 42.0	2.64 2.82	24.5 24.2		340 (4.52)	7.48 dd	6.25 dd	6.98 dd	
3(b)	3-CH_3	NCH_3	2	51 (A)	175-177	44.7 44.6	3.30 3.44	23.0 22.8	29.1 28.7	342 (4.55)		6.10 d	6.85 d	2.5
4(b)	4-CH_3	NCH_3	2	17 (A)	120-123	44.7 44.5	3.30 3.39	23.0 22.8	29.1 28.9	350 (-)	7.22 d		6.65 d	1.5
5	5-CH_3	NCH_3	2	50 (B) 15 (1)	166-168	44.7 44.4	3.30 3.26	23.0 23.0		354 (4.54)	7.48 d	6.10 d		4.0
6	3-C_2H_5	NCH_3	2	54 (A)	114-116	46.7 46.9	3.92 3.87	21.8 21.5	27.6 27.4	343 (4.55)		6.07 d	6.78 d	2.5
7	5-C_2H_5	NCH_3	2	54 (A)	118-120	46.7 46.9	3.92 3.79	21.8 21.8	27.6 27.7	353 (4.30)	7.48 d	6.12 d		4.1
8	3,5-DiMe	NCH_3	2	74 (A)	170-173	46.9 46.9	3.92 3.98	21.8 21.8	27.6 27.3	354 (4.72)		5.98 s		
9	3,5-DiMe	NC_2H_5	2	53 (A)	115-117	48.7 48.7	4.46 4.72	20.7 20.4	26.2 25.9	353 (4.59)		5.87 s		
10	H		2	63 (A)	103-105	52.5 52.8	4.74 4.96	18.9 19.1	23.9 23.7	345 (4.49)	7.57 dd	6.30 dd	7.26 dd	
11	H	$NCH_2CH{=}CH_2$	2	54 (A)	95-97	47.1 47.3	3.15 3.16	22.0 21.8	27.8 27.7	334 (4.43)	7.52 dd	6.26 dd	6.98 dd	
12	H		2	50 (B)	160-163	53.6 53.4	2.76 2.90	19.2 19.1	24.4 24.4	329 (4.40)	7.55 dd	6.37 dd	7.03 dd	
13	H		2	43 (C)	122-124	50.5 50.5	2.28 2.26	18.1 17.9	22.9 22.6	335 (4.43)	7.62 dd	6.45 dd	(e)	

TABLE I (continued)

	Compound R	Compound X	Subn.	Yield (a) (%)	M.p., °C	Microanalysis Calcd./Found % C	H	N	Cl	λ max nm (log ε)	δ (CDCl$_3$) H_2 or $_3$	H_4	H_5	J H_z
14	H		2	10 (C)	117-118	46.8 46.7	1.96 1.81	15.6 15.4		333 (-)	(f)	6.42 dd	7.08 dd	
15	H	NCH_2CH_2CN	2	70 (C)	156-158	44.8 44.8	2.63 2.77	26.1 25.9	26.4 26.6	337 (4.48)	7.61 dd	6.35 dd	7.15 dd	
16	4,5-Benzo	NCH_3	3	36 (A)	252-253	51.6 51.4	2.86 3.00	20.1 19.8	25.4 25.3	262 (-) 276 (-) 354 (-)	8.28 s			
17	2,5-DiMe	NCH_3	3	50 (A)	203-206	46.7 46.6	3.92 3.95	21.8 21.5	27.6 27.0	292 (4.20) 341 (4.13)		6.65 s		
18	2,5-DiMe		3	45 (B)	174-176	56.4 56.6	3.79 3.71	17.6 17.6	22.0 22.3	289 (4.25) 340 (4.19)		6.76 m		
19	H	S	2	26 (D) 20 (I)	150-151 (d)	36.2 36.1	1.30 1.53	18.1 17.9		318 (4.30)	8.21 dd	7.17 dd	7.72 dd	
20 (c)	3-CH_3	S	2	52 (D) 1 (I)	172-174	39.0 39.1	2.04 1.79	17.1 16.8	28.8 28.5	323 (4.33)		6.97 d	7.55 d	5.0
21 (c)	4-CH_3	S	2	13 (D) 14 (I)	141-143	39.0 39.1	2.04 2.25	17.1 17.1		329 (4.22)	8.00 d		7.28 d	1.5
22	4,5-Benzo	S	3	5 (B)	198-200	46.8 46.5	1.79 2.00	14.9 14.6	25.1 24.9	325 (-)	9.07 s			

(a) Yield obtained by the methods shown in parenthesis. (I) refers to the method under reference (1). (b,c) Two products isolated from one reaction. (d) Lit. (13) m.p. 154°.
(e) Signal masked by phenyl protons in 6.9-7.5 δ region. (f) Signal masked by phenyl protons in 7.3-7.8 δ region.

potassium bromide in refluxing isobutylmethylketone failed to effect nucleophilic displacement of the triazine chlorines to produce the corresponding 2,4-dibromo-6-(1-methylpyrrol-2-yl)-*s*-triazine. Bromination of 2-(1-methylpyrrol-2-yl)-*s*-triazine-4,6-(3*H*,5*H*)dione (1) with phosphorylbromide and phosphorus pentabromide resulted in nuclear 4- and 5-dibromination of the pyrrole ring as well leading to 2,4-dibromo-6-(4,5-dibromo-1-methylpyrrol-2-yl)-*s*-triazine (**23**).

1,2-Dimethyl, 1,3-dimethyl, 1-methyl-2-ethyl, and 1-methyl-3-ethylpyrroles were obtained by Wolff-Kishner reduction of the respective 1-methylpyrrol-2-carboxaldehyde, 1-methylpyrrol-3-carboxaldehyde, 2-acetyl-1-methyl and 3-acetyl-1-methylpyrroles. Contrary to a literature report (5) Vilsmeier-Haack formylation of 1-methylpyrrole afforded a minor amount (*ca.* 5%) of β-substituted aldehyde which was separated by distillation from the normal α-substituted product. β-Substitution in 1-alkylpyrroles is known to be controlled mainly by steric factors (5). Nmr of the β-formylated product revealed a low field signal at δ 7.27 (m, H_2) characteristic of the ring proton in the 2-position. The reduction of this aldehyde to the known 1,3-dimethylpyrrole (6) confirmed assignment of the structure. It is also interesting to note that acylation of 1-methylpyrrole with acetic anhydride in benzene in presence of titanium tetrachloride produced both α- and β-acetylated products in the ratio 4:1 respectively. This is comparable with the Vilsmeier-Haack acylation reaction, where formation of α- and β-isomers in the ratio of 2.4:1 has been reported (7). 1-*m*-Fluorophenyl, 1-*m*-trifluoromethylphenyl, 1-cyclohexyl, and 1-allyl substituted pyrroles were prepared from appropriate amines and 2,5-dimethoxytetrahydrofuran (8). 2,4-Dimethyl-1-ethylpyrrole was made by following the method used for the preparation of 1,2,4-trimethylpyrrole (9).

EXPERIMENTAL

Melting points and boiling points are not corrected. Spectra were measured with Perkin-Elmer 457, Unicam SP800 and Varian A60-A instruments. Unless otherwise specified ir spectra were for potassium bromide discs, uv spectra for solutions in methanol, and nmr spectra for solutions in deuteriochloroform (TMS as internal reference).

Typical examples of the different experimental methods are given below:

2,4-Dichloro-6-(5-ethyl-1-methylpyrrol-2-yl)-*s*-triazine (**7**).

Method A.

A mixture of 2-ethyl-1-methylpyrrole (4.8 g., 0.044 mole) and cyanuric chloride (8.0 g., 0.043 mole) in benzene (30 ml.) (dried over sodium) was refluxed for 2 hours. The reaction mixture was filtered through a pad of silica gel (30 g., 100-200 mesh) and the pad was thoroughly washed with dichloromethane. The filtrate was evaporated to a yellow solid which after removal of unreacted cyanuric chloride by sublimation at 60°/10 mm, and crystallisation from acetonitrile gave 6.1 g. of product as pale yellow crystals.

2,4-Dichloro-6-(1,5-dimethylpyrrol-2-yl)-*s*-triazine (**5**).

Method B.

To a well stirred mixture of 1,2-dimethylpyrrole (3.5 g., 0.035 mole) and cyanuric chloride (5.4 g., 0.03 mole) in dry benzene (60 ml.) was added aluminium chloride (4.7 g., 0.036 mole). The mixture was stirred for 90 minutes at 40°, poured onto ice-water and stirred for 5 minutes. The benzene phase was separated, washed with water, dried (sodium sulfate) and evaporated to give a yellow solid which after removal of cyanuric chloride was crystallised from *n*-hexane to yield 4.2 g. of the product.

2,4-Dichloro-6-[1-(2-cyanoethyl)pyrrol-2-yl)]-*s*-triazine (**15**).

Method C.

A mixture of 1-(2-cyanoethyl)pyrrole (1.2 g., 0.01 mole) and cyanuric chloride (1.84 g., 0.01 mole) in xylene (20 ml.) (dried over sodium) was refluxed for 20 hours. Work up and purification of the product as described in method A gave 1.9 g. of pale yellow crystals.

2,4-Dichloro-6-[3(4)-methylthiophen-2-yl]-*s*-triazine (**20**, **21**).

Method D.

A mixture of 3-methylthiophene (0.98 g., 0.01 mole), cyanuric chloride (1.84 g., 0.01 mole) and aluminium chloride (1.3 g., 0.01 mole) in chlorobenzene (25 ml.) was refluxed for 5 hours. The mixture was filtered and the black sticky mass was repeatedly extracted with hot benzene and the extracts, combined with the chlorobenzene, were passed through a short column of alumina (activity grade 1) to remove insoluble polymeric material. The filtrate was evaporated to a yellow solid 1.6 g.; nmr (carbon tetrachloride): δ 2.71 (s, C-CH_3), 2.32 (s, C-CH_3) indicated a mixture of 2,4-dichloro-6-(3-methylthiophen-2-yl)-*s*-triazine (**20**) and 2,4-dichloro-6-(4-methylthiophen-2-yl)-*s*-triazine (**21**) in the molar ratio of 4:1 respectively. The isomers were separated by fractional crystallisation from carbon tetrachloride and characterised.

2,4-Dibromo-6-(4,5-dibromo-1-methylpyrrol-2-yl)-*s*-triazine (**23**).

A mixture of 2-(1-methylpyrrol-2-yl)-*s*-triazine-4,6-(3*H*,5*H*)-dione (1) (5.3 g., 0.0275 mole), phosphorus pentabromide (23.8 g., 0.055 mole) and phosphorus oxybromide (15.8 g., 0.055 mole) was stirred at 120-140° for 18 hours. The mixture was poured onto crushed ice and the resulting solid filtered off and dried over phosphorus pentoxide under vacuum. The dried solid was extracted in a Soxhlet with *n*-hexane and the extract evaporated to a yellow solid 4.0 g., (31%). Crystallised from acetonitrile, m.p. 226-230°; nmr (DMSO-d_6): δ 4.00 (s, 3H, NCH_3), 7.50 (s, H_3).

Anal. Calcd. for $C_8H_4Br_4N_4$: C, 20.19; H, 0.84; N, 11.77; Br, 67.18. Found: C, 19.56; H, 0.73; N, 11.95; Br, 66.83.

1,2(3)-Dimethylpyrrole.

1-Methylpyrrole (81 g., 1.0 moles) was subjected to formylation (10). Distillation of the crude product gave two fractions: (a) 1-methylpyrrole-2-carboxaldehyde 93.6 g., (85%), b.p. 68-75°/10 mm (Lit. (10) 72-75°/11 mm); ir: ν max (neat) 1660 cm^{-1}; nmr (neat): δ 3.82 (s, 3H, NCH_3), 6.13 (dd, H_4), 6.8-6.95 (m, 2H, H_3 and H_5), 9.52 (s, CHO). (b) 1-Methylpyrrole-3-carboxaldehyde 5.2 g. (5%), b.p. 91-93°/3 mm; ir: ν max (neat)

1660 cm^{-1}; nmr: δ 3.68 (s, 3H, NCH_3), 6.12 (m, 2H, H_4 and H_5), 7.27 (m, H_2), 9.70 (s, CHO).

The above mentioned aldehydes were submitted to Wolff-Kishner reduction to give the corresponding 1,2-dimethyl pyrrole, b.p. 74°/65 mm (Lit. (11) 138°/760 mm) and 1,3-dimethyl pyrrole, b.p. 45-50°/30 mm (Lit. (6) 130-131°/760 mm).

2(3)-Ethyl-1-methylpyrrole.

1-Methylpyrrole (32.4 g., 0.4 mole), acetic anhydride (40.8 g., 0.4 mole) and titanium tetrachloride (76 g., 0.4 mole) in benzene (100 ml.) was stirred for 90 minutes at 35°. Normal workup and distillation gave two products: (a) 2-Acetyl-1-methylpyrrole 19.2 g., (39%) b.p. 86-88°/16 mm (Lit. (7) 48-49°/1.5 mm); ir and nmr consistent with the literature values (7) and (b) 3-acetyl-1-methylpyrrole 5.1 g., (10%) b.p. 82-90°/1 mm (Lit. (7) 88-89°/1.5 mm); ir and nmr consistent with the literature values (7). These two ketones on Wolff-Kishner reduction gave the corresponding alkylpyrroles: 2-Ethyl-1-methylpyrrole, b.p. 60-62°/17 mm (Lit. (12) 58.5-59.5°/15 mm); nmr (carbon tetrachloride): δ 1.2 (t, 3H, CH_2CH_3), 2.49 (q, 2H, CH_2-), 3.39 (s, 3H, NCH_3), 5.70 (m, H_3), 5.83 (dd, H_4), 6.30 (dd, H_5). 3-Ethyl-1-methylpyrrole, b.p. 62-64°/28 mm; nmr (carbon tetrachloride): δ ~3.42 (s, 3H, NCH_3), 5.70 (m, H_4), 6.20-6.30 (m, 2H, H_2/H_5).

1-(*m*-Trifluoromethyl)phenylpyrrole.

This compound was made from *m*-trifluoromethylaniline (16.1 g., 0.1 mole) and 2,5-dimethoxytetrahydrofuran (13.2 g., 0.1 mole). Distillation at 106-110°/12 mm gave 16.9 g. (80%) of a colourless oil which rapidly crystallised, m.p. 50°; nmr: δ 6.27 (dd, 2H, H_3 and H_4), 6.98 (dd, 2H, H_2 and H_5), 7.47-7.58 (4H, phenyl).

Anal. Calcd. for $C_{11}H_8F_3N$: C, 62.55; H, 3.81; N, 6.63. Found: C, 62.72; H, 3.78; N, 6.60.

1-(*m*-Fluoro)phenylpyrrole.

This compound was made from *m*-fluoroaniline (11.1 g., 0.1 mole) and 2,5-dimethoxytetrahydrofuran (13.2 g., 0.1 mole). Distillation at 127°/27 mm gave 9.8 g. (61%) of a colourless oil (crystalline at 0°).

Anal. Calcd. for $C_{10}H_8FN$: C, 74.51; H, 5.00; N, 8.69. Found: C, 74.80; H, 4.87; N, 8.71.

2,4-Dimethyl-1-ethylpyrrole.

This compound was prepared by reacting 4,5-dichloro-4-methylpentan-2-one (9) (18.1 g., 0.11 mole) with ethylamine (45 g., 1 mole). Distillation at 56-58°/10 mm (Lit. (14) b.p. 40-41°/4 mm) yielded the product 5.2 g. (38%).

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