Studies of Pyrimidine-2,4-diones: Synthesis of Novel Condensed Pyrido[2,3-*d*]-pyrimidines *via* Intramolecular Cycloadditions

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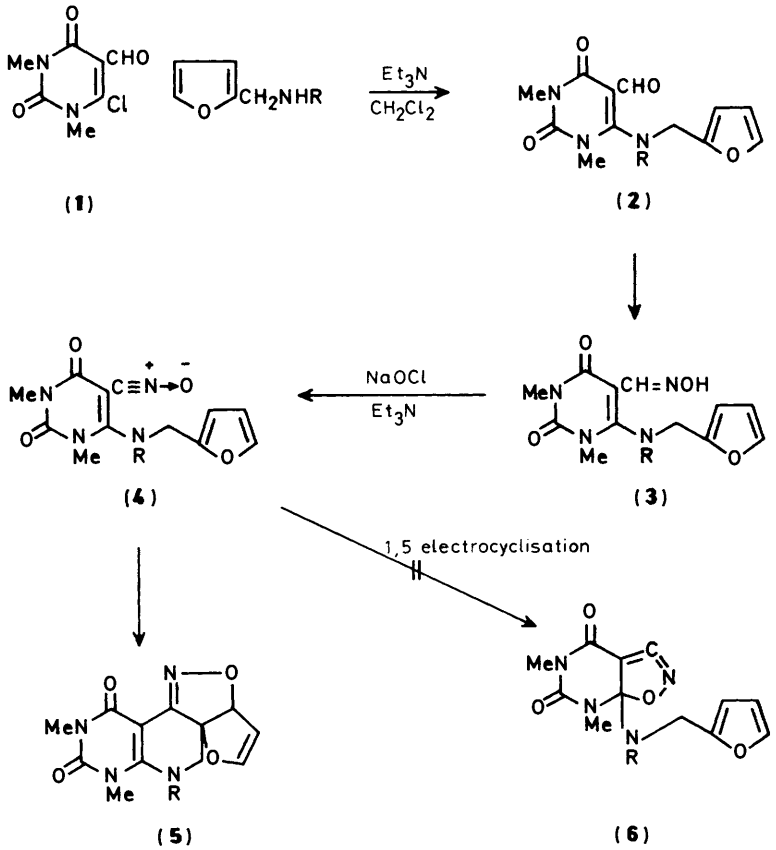
Suitably functionalised pyrimidine-2,4-diones (**1**) cyclised intramolecularly to yield the novel furo-[2″,3″:4′,5′]isoxazolo[3′,4′:4,5]pyrido[2,3-*d*]pyrimidines (**5**) and (**9**) in excellent yields. Remarkably, the pyrimidone nucleus was unaffected nor were there any side-reactions in this synthesis.

Although cycloadditions provide a powerful synthetic tool for a variety of heterocycles [1] and natural products [2] only rarely have heterocyclic dipoles or dipolarophiles been used.[3,4] Thus there appears to be only a single earlier report of true intramolecular 1,3 dipolar cycloaddition of azides under thermolytic conditions.[5] In this, the pyrimidine ring was ruptured and the parent molecule underwent rearrangement. Here we describe intramolecular cycloadditions of nitrile oxides and nitrones where the pyrimidine ring remains intact to afford the novel furo[2″,3″:4′,5′]isoxazolo[3′,4′:4,5]pyrido[2,3-*d*]pyrimidines (**5**) and (**9**).

The uracil (**1**), readily obtained from the corresponding barbituric acid *via* a Vilsmeier reaction, was treated with furfurylarylamines and allylarylamines to give the uracils (**2**) in good yields. The furfurylarylamines used were prepared from the corresponding furfurylimines by a published procedure.[6] The formation of (**2**) was thought to proceed by addition followed by elimination rather than by direct displacement of halogen from C-6 of (**1**), the formyl group activating the double bond for the addition. This postulate was supported by an improved yield of (**2**) when triethylamine was used in the reaction to capture the eliminated hydrogen chloride. The oximes (**3**) and (**7**) were prepared and characterized in the customary way (see Experimental section and Table 1).

The nitrile oxides (**4**), generated *in situ* by chlorination of the oximes (**3**) using aqueous sodium hypochlorite followed by



(**1**) (**2**) (**3**) (**4**) (**5**) (**6**)

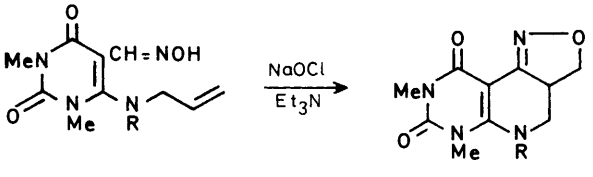
R		R	
a;	*p*-$EtOC_6H_4$	**d**;	*p*-BrC_6H_4
b;	*p*-$MeOC_6H_4$	**e**;	*p*-ClC_6H_4
c;	*p*-MeC_6H_4	**f**;	Ph

Table 1. Physical characteristics of the oximes (**3a**—**f**) and (**7a**—**c**)

Compd.	R	M.p.(°C)	Molecular Formula	% Analysis Calc. (Found) C	H	N
(**3a**)	*p*-$EtOC_6H_4$	169—171	$C_{20}H_{22}N_4O_5$	60.30	5.53	14.07
				(60.15	5.3	13.9)
(**3b**)	*p*-$MeOC_6H_4$	139—140	$C_{19}H_{20}N_4O_5$	59.38	5.21	14.58
				(59.21	5.1	14.4)
(**3c**)	*p*-MeC_6H_4	166—168	$C_{19}H_{20}N_4O_4$	61.96	5.43	15.22
				(61.75	5.4	15.1)
(**3d**)	*p*-BrC_6H_4	185—187	$C_{18}H_{17}N_4O_4Br$	49.89	3.93	12.93
				(49.81	3.85	12.85)
(**3e**)	*p*-ClC_6H_4	186—188	$C_{18}H_{17}N_4O_4Cl$	55.67	4.38	14.43
				(55.4	4.1	14.2)
(**3f**)	Ph	192—194	$C_{18}H_{18}N_4O_4$	61.02	5.09	15.82
				(59.9	4.95	15.65)
(**7a**)	Ph	180—182	$C_{16}H_{18}N_4O_3$	61.14	5.73	17.83
				(61.0	5.8	17.7)
(**7b**)	*p*-$MeOC_6H_4$	175—176	$C_{17}H_{20}N_4O_4$	59.30	5.81	16.27
				(59.2	5.7	16.25)
(**7c**)	*p*-ClC_6H_4	205—206	$C_{16}H_{17}N_4O_3Cl$	55.11	4.88	16.09
				(55.0	4.75	16.1)

Table 2. Physical characteristics for compounds (**5a**—**f**) and (**8a**—**c**)

Compd.	R	M.p.(°C)	Molecular Formula	% Analysis Calc. (Found) C	H	N
(**5a**)	*p*-$EtOC_6H_4$	194—196	$C_{20}H_{20}N_4O_5$	60.61	5.05	14.14
				(60.45	4.9	14.1)
(**5b**)	*p*-$MeOC_6H_4$	125—130	$C_{19}H_{18}N_4O_5$	59.69	4.71	14.66
				(59.5	4.65	14.35)
(**5c**)	*p*-MeC_6H_4	183—185	$C_{19}H_{18}N_4O_4$	62.30	4.92	15.30
				(62.15	4.3	15.15)
(**5d**)	*p*-BrC_6H_4	228—230	$C_{18}H_{15}N_4O_4Br$	50.12	3.48	12.99
				(50.1	3.4	12.85)
(**5e**)	*p*-ClC_6H_4	218—220	$C_{18}H_{15}N_4O_4Cl$	55.96	3.89	14.51
				(55.7	3.65	14.4)
(**5f**)	Ph	154—156	$C_{18}H_{16}N_4O_4$	61.36	4.55	15.91
				(61.3	4.5	15.8)
(**8a**)	Ph	280—282	$C_{16}H_{16}N_4O_3$	61.53	5.12	17.98
				(61.4	5.0	17.9)
(**8b**)	*p*-$MeOC_6H_4$	205—208	$C_{17}H_{18}N_4O_4$	59.64	5.26	18.71
				(59.55	5.2	18.6)
(**8c**)	*p*-ClC_6H_4	295—296	$C_{16}H_{15}N_4O_3Cl$	55.49	4.33	18.49
				(55.35	4.3	18.35)



(**7**) (**8**)

R

a; Ph

b; *p*-$MeOC_6H_4$

c; *p*-ClC_6H_4

treatment with anhydrous triethylamine, then underwent intramolecular cyclisation to give the cycloadducts (**5**) in high yields. The olefinic dipolarophiles obtainable from compounds (**7**) also cyclised to compounds (**8**) in good yields. Since the n.m.r. spectra of these cycloadducts showed no proton signals typical of a furan ring, it was clear that cycloaddition had occurred at one of the furan double bonds. Characterization data for the cycloadducts (**5**) and (**8**) are given in Tables 2 and 3. In this intramolecular capture of nitrile oxides, there was no evidence for dimer formation or any 1,5-electrocyclisations[7] as depicted in the reaction scheme.

Use of a less reactive dipole, *i.e.* the nitrones (**2**), gave similarly successful results. Thus, compound (**2a**) was refluxed in methanol with freshly prepared phenylhydroxylamine to give the nitrone, which underwent simultaneous intramolecular cyclisation to provide compound (**9a**). The uracil (**11**) reacted similarly to give the isoxazolo[3′,4′:4,5]pyrido[2,3-*d*]pyrimidines (**12a**—**e**) in excellent yields. Characterization data for these are recorded in Tables 4 and 5. None of the reactions showed the formation of 1,5 electrocyclisation products which would have resulted from participation of the uracil carbon-carbon double bond of these conjugated dipoles used in this investigation. Further we observed no side-products arising from ring transformation of the uracils.

Table 3. Spectroscopic data for compounds (**5a**—**f**) and (**8a**—**c**)

Compd.	R	Mass (M^+) at m/z	δ (p.p.m.)*
(**5a**)	*p*-$EtOC_6H_4$	396	1.25—1.55 (3 H, t), 3.85—4.32 (4 H, m), 5.36 (1 H, dd), 5.50 (1 H, d), 6.17 (1 H, d)
(**5b**)	*p*-$MeOC_6H_4$	382	3.95, 4.15 (each 1 H, d, CH_2), 5.35 (1 H, dd), 5.47 (1 H, d), 6.15 (1 H, d)
(**5c**)	*p*-MeC_6H_4	366	4.01, 4.20 (each 1 H, d, CH_2), 5.40 (1 H, dd), 5.48 (1 H, d), 6.16 (1 H, d)
(**5d**)	*p*-BrC_6H_4	431	4.03, 4.19 (each 1 H, d, $-CH_2$), 5.37 (1 H, dd), 5.45 (1 H, d), 6.12 (1 H, d)
(**5e**)	*p*-ClC_6H_4	386	4.02, 4.18 (each, 1 H, d, $-CH_2$), 5.37 (1 H, dd), 5.44 (1 H, d), 6.13 (1 H, d)
(**5f**)	Ph	352	3.98, 4.17 (each 1 H, d, $-CH_2$), 5.35 (1 H, dd), 5.46 (1 H, d), 6.14 (1 H, d)
(**8a**)	Ph	312	3.75 (2 H, d), 3.89 (1 H, m), 4.45 (2 H, d)
(**8b**)	*p*-$MeOC_6H_4$	342	3.70 (2 H, d), 3.85 (1 H, m), 4.45 (2 H, d)
(**8c**)	*p*-ClC_6H_4	346	3.75 (2 H, d), 3.90 (1 H, m), 4.40 (2 H, d)

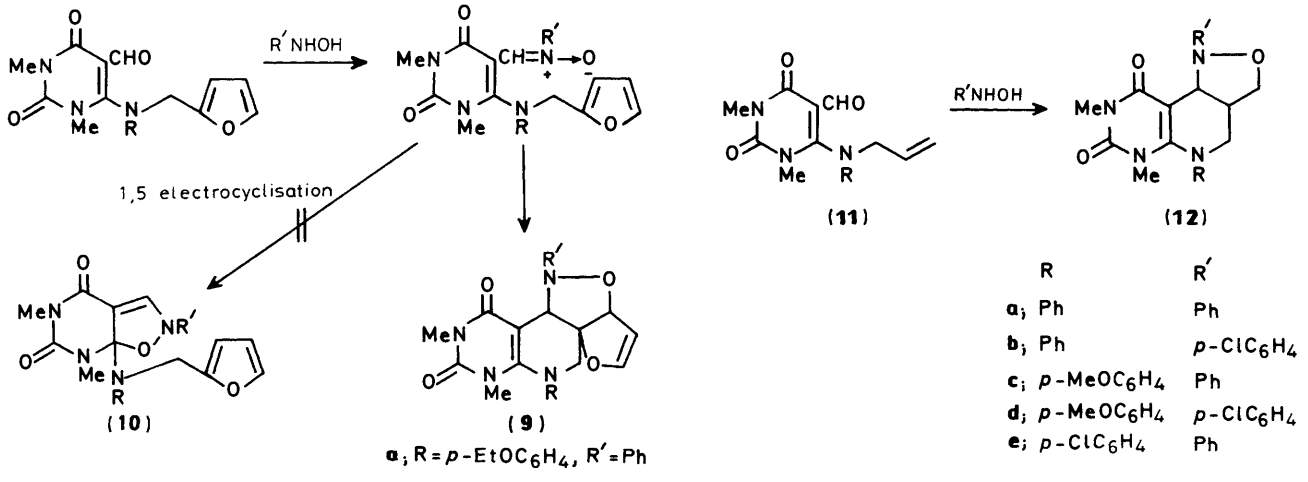
* The signals for the uracil methyl and aromatic protons, not given in the table, were present at their expected positions.

Table 4. Physical characteristics for the products (**9a**) and (**12a**—**e**)

Compd.	R	R′	Yield %	M.p. (°C)	Molecular formula	% Analysis Calc. (Found) C	H	N
(**9a**)	*p*-$EtOC_6H_4$	Ph	50	236—240	$C_{26}H_{26}N_4O_5$	65.82 (65.7	5.48 5.35	11.81 11.9)
(**12a**)	Ph	Ph	75	214—215	$C_{22}H_{22}N_4O_3$	67.69 (67.55	5.64 5.6	14.35 14.3)
(**12b**)	Ph	*p*-ClC_6H_4	65	234—235	$C_{22}H_{21}N_4O_3Cl$	62.26 (62.2	4.95 4.85	13.21 13.35)
(**12c**)	*p*-$MeOC_6H_4$	Ph	68	207—208	$C_{23}H_{24}N_4O_4$	65.71 (65.65	5.71 5.75	13.33 13.3)
(**12d**)	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	72	216—218	$C_{23}H_{23}N_4O_4Cl$	60.79 (60.65	5.06 5.0	12.33 12.2)
(**12e**)	*p*-ClC_6H_4	Ph	70	229—230	$C_{22}H_{21}N_4O_3Cl$	62.26 (62.15	4.95 4.8	13.21 13.2)

Table 5. Spectroscopic data for compounds (**9a**) and (**12a**—**e**)

Compd.	R	R′	Mass (M^+) at m/z	δ (p.p.m.)
(**9a**)	*p*-$EtOC_6H_4$	Ph	474	1.22—1.61 (3 H, t), 3.20 (3 H, s), 3.45 (3 H, s), 3.75—4.21 (4 H, m), 5.04 (2 H, m), 5.31 (1 H, dd), 6.08 (1 H, dd), 6.90—7.44 (9 H, m)
(**12a**)	Ph	Ph	390	3.25 (3 H, s), 3.35 (3 H, s), 3.65 (2 H, d), 3.89 (1 H, m), 5.25 (1 H, d), 4.05 (2 H, d), 7.00—7.25 (10 H, m)
(**12b**)	Ph	*p*-ClC_6H_4	424	3.20 (3 H, s), 3.25 (3 H, s), 3.60 (2 H, d), 3.85 (1 H, m), 5.20 (1 H, d), 4.15 (2 H, d), 6.80—7.30 (9 H, m)
(**12c**)	*p*-$MeOC_6H_4$	Ph	420	3.00 (3 H, s), 3.15 (3 H, s), 3.75 (3 H, s), 3.60 (2 H, d), 3.00 (1 H, m), 4.00 (2 H, d), 5.25 (1 H, d), 7.00—7.22 (9 H, m)
(**12d**)	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	454	3.10 (3 H, s), 3.20 (3 H, s), 3.70 (3 H, s), 3.58 (2 H, d), 3.80 (1 H, m), 4.15 (2 H, d), 5.28 (1 H, d), 6.90—7.30 (8 H, m)
(**12e**)	*p*-ClC_6H_4	Ph	424	3.25 (3 H, s), 3.30 (3 H, s), 3.65 (2 H, d), 3.80 (1 H, m), 4.10 (2 H, d), 5.15 (1 H, d), 6.85—7.25 (9 H, m)



Experimental

M.p.s were determined in open capillary tubes on a Buchi apparatus and are uncorrected. The 90 MHz ^1H n.m.r. spectra were recorded by Dr. B. J. Wakefield, with $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard. The chemical shift values are recorded in δ units (p.p.m.). The i.r. spectra were recorded on a Perkin-Elmer 237B i.r. spectrometer as KBr discs. Mass spectra were recorded on an AEIMS 30 instrument by the electron impact method.

1,3 *Dimethylbarbituric Acid.*—Acetic anhydride (120 ml) was added dropwise during 3 h to a well stirred mixture of 1,3-dimethylurea (32 g) and malonic acid (36 g) in glacial acetic acid (80 ml). During the addition, and for a further 30 min thereafter, the reaction mixture was kept at 65 ± 5 °C it was then raised rapidly to 90 °C at which temperature it was stirred for 4 h. The solution was evaporated under reduced pressure and the residue boiled for 10 min with ethanol (200 ml). On cooling 1,3-dimethylbarbituric acid[8] crystallised out (33—35 g, 60%) and this gave white crystals from ethanol m.p. 121—123 °C. Refrigeration of the mother liquors gave an additional 8 g of the product, total yield 68%.

6-*Chloro*-5-*formyl*-1,3-*dimethyluracil.*—Phosphorus oxychloride (23 ml) was dissolved quite slowly in freshly distilled *N,N*-dimethylformamide (6 ml) to avoid a sudden rise in temperature, and then the solution was allowed to return to room temperature. Barbituric acid (2 g) was added (portionwise) and the mixture refluxed gently for 45 min. The excess of phosphorus oxychloride was distilled off under reduced pressure and the residue poured into ice-cold water (100 ml) with ice cooling. The mixture was then allowed to warm to room temperature when it was extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give 6-chloro-5-formyl 1,3-dimethyluracil which was crystallised from light petroleum.

5-*formyl*-6-(N-*Furfurylaryl*)-1,3-*Dimethyluracils and* 6-(N-*Allylaryl*)-5-*formyl*-1,3-*dimethyluracils.*—2-Furfuryl-*p*-phenetidine (10 mmol, 2.17 g), triethylamine (1 g), and compound (**1**) were added slowly to a magnetically stirred solution of 6-chloro-5-formyl-1,3-dimethyluracil (*ca.* 10 mmol, 2.02 g) in dry dichloromethane. Stirring was continued for 12—16 h after which the mixture was evaporated under reduced pressure. The residue was purified by column chromatography using dichloromethane as eluant; yield 25—30%, m.p. 130—132 °C. 6-(*N*-allylaryl)-5-formyl-1,3-dimethyluracils were prepared similarly.

Preparation of the Oximes (**3a—f**) *and* (**7a—c**).—The uracil (**2a**), (478 mg, 1.25 mmol) in ethanol (10 ml) was added dropwise to a well stirred solution of hydroxylamine hydrochloride (86 mg, 1.25 mmol) and sodium hydroxide (100 mg, 2.5 mmol) in water (3 ml); stirring was continued for 10—12 h. The precipitated oxime was filtered off, washed with water, and dried. On concentration of the mother liquor an additional 10% yield of oxime was obtained, m.p. 169—171 °C; total yield 60%. Similarly, the other oximes (**3b—f**) and (**7a—c**) were prepared and their characteristics are recorded in Table 1.

Reaction of the Oximes (**3a—f**) *and* (**7a—c**) *with Sodium Hypochlorite.*—To a mixture of the oxime (**3a**), 398 mg, 1 mmol and triethylamine (202 mg, 2 mmol) in dichloromethane (20 ml), 10% aqueous sodium hypochlorite (5 ml) was added dropwise at 0—10 °C. After the reaction had been vigorously stirred for 3 h, the reaction phases were separated and the aqueous phase was extracted with dichloromethane (20 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue on treatment with ether followed by light petroleum (b.p. 40—60 °C) crystallised, m.p. 194—196 °C; yield 80%. Similarly compounds (**5b—f**) and (**8a—c**) were prepared and their characteristics are recorded in Tables 2 and 3.

Reaction of 5-*Formyl*-6-(N-*furfurylaryl*)- *and* 6-(N-*Allylaryl*)-5-*formyl*-1,3-*dimethyluracils with Arylhydroxylamines.*—To a solution of the uracil (**2a**), (383 mg, 1 mmol) in absolute methanol (15 ml), phenylhydroxylamine (109 mg, 1 mmol) dissolved in absolute methanol (5 ml) was added. The resulting mixture was then refluxed gently for 2—3 h. The precipitated white crystalline material (**9a**) was filtered off, washed with dichloromethane and dried, m.p. 236—240 °C; yield 50%. The product was further purified by recrystallisation from dichloromethane. ^1H n.m.r. (90 MHz, $CDCl_3$) δ_H 3.75—4.21 (4 H, m), 5.04 (2 H, m), 5.31 (1 H, dd), 6.08 (1 H, dd), 1.22—1.61 (3 H, f), 3.20 (3 H, s), 3.45 (3 H, s), and 6.90—7.44 (9 H, m). Similarly compounds (**12a—e**) were prepared in good yields. The physical and spectral data of these compounds are recorded in Tables 4 and 5.

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