A NEW SYNTHESIS OF PYRIMIDO[5,4-e]-as-TRIAZINE DERIVATIVES

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The reaction of 5-arylazo-6-arylidenehydrazino-1,3-dimethyluracils (II), prepared by the diazotization of 6-arylidenehydrazino-1,3-dimethyluracils (I), with dimethylformamide dimethylacetal afforded the corresponding 3-arylfervenulins (3-aryl-6,8-dimethylpyrimido[5,4-e]-as-triazine-5,7(6H,8H)-diones)(V).

The discovery of the triad of antibiotics fervenulin, 2-methylfervenulone (MSD-92), and toxoflavin, has stimulated recent considerable interest in the chemistry of pyrimido[5,4-e]-as-triazines.[1] In connection with our studies on the pyrimido-[5,4-e]-as-triazines as potential medicinal agents,[2] we now report a new synthetic approach to 3-arylfervenulins (3-aryl-6,8-dimethylpyrimido[5,4-e]-as-triazine-5,7(6H,8H)-diones)(Va-e) by the reaction of readily accessible 5-arylazo-6-arylidenehydrazino-1,3-dimethyluracils (IIa-h) with dimethylformamide dimethylacetal (DMFDMA).

Treatment of the appropriate 6-arylidenehydrazino-1,3-dimethyluracils (Ia-e)[3] with diazotized arylamines by the conventional method[4] gave the desired starting materials (IIa-h) in 30-56% yields. Refluxing of the appropriate uracils (IIa-e) (0.0005 mol) with DMFDMA (2 ml) at 150°C for 5 h, followed by concentration of the reaction mixture in vacuo and addition of ethanol, caused the separation of the corresponding products (Va-e)[5] in 20-60% yields. The yields of (Va-e) were depending upon the nature of arylidenehydrazino group of (IIa-e), i.e., the uracils with an electron-withdrawing arylidenehydrazino group gave better results than those with an electron-releasing group. Similar substituent effect was also observed on the arylazo group, i.e., treatment of the uracils (IIf-h), which possess a strong electron-withdrawing p-nitrophenylazo group, with DMFDMA caused pronounced improvement in the yield of (Va)(82-97%)(Table).[6]

It should be noted that the reaction of (IIa) with dimethylformamide in stead of DMFDMA under the same conditions resulted in the recovery of (IIa). Therefore, the reaction of (IIa-h) with DMFDMA leading to (Va-e) can be best explained by assuming the initial formation of the intermediate (III) through the enol form of (II), followed by 1,5-migration of the 1-methoxytrimethylamino group to give (IV), which possesses a triazahexatriene-type structure. This could undergo intramolecular cycloaddition and aromatization by loss of 1-arylamino-1-methoxytrimethylamine to give (V) as a final product. The C-O bond formation as exemplified by (III) has been speculated in the reaction of certain enols with DMFDMA[7] and the intramolecular cycloaddition of aza analogs of hexatriene has ample precedents.[8] To our knowledge, this is the first example in which 5-arylazopyrimidine was directly used as a nitrogen source for N-4 of the pyrimido[5,4-e]-as-triazine ring system (Scheme).

Scheme

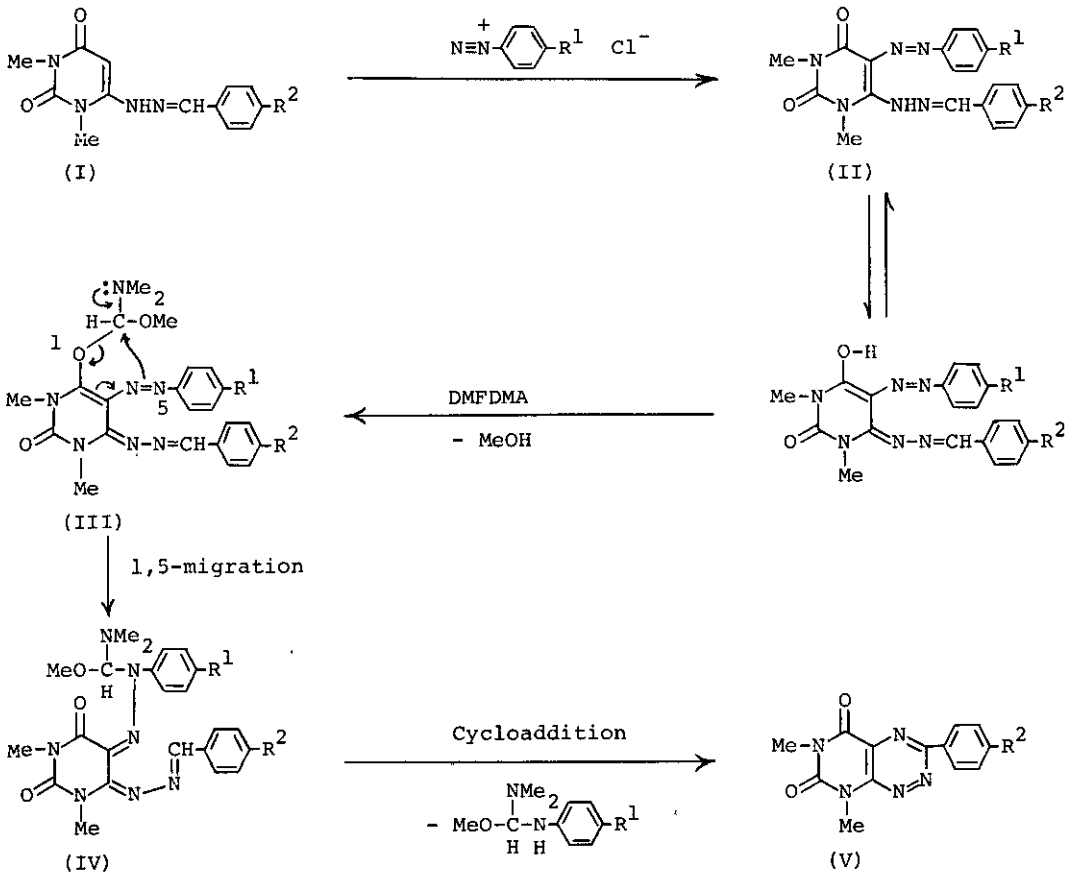

Table 5-Arylazo-6-arylidenehydrazino-1,3-dimethyluracils and 3-Arylfervenulins

5-Arylazo-6-arylidenehydrazino-1,3-dimethyluracils					3-Arylfervenulins			
Compd.[a]	R^1	R^2	Mp(°C)	Yield(%)	Compd.[b]	R^2	Mp(°C)	Yield(%)
IIa	H	H	187-188	56	Va	H	273-275	50
IIb	H	Br	213-215	47	Vb	Br	>300	60
IIc	H	Cl	200-202	56	Vc	Cl	280-283	56
IId	H	OMe	144-145	31	Vd	OMe	263-264	26
IIe	H	NMe_2	176-178	30	Ve	NMe_2	>300	20
IIf	NO_2	H	256-257	46	Va	H	——	88
IIg	NO_2	Br	235-236	42	Va	H	——	97
IIh	NO_2	Cl	223-225	34	Va	H	——	82

a) All compounds were recrystallized from DMF.

b) All compounds were recrystallized from EtOH.

REFERENCES AND NOTES

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6 Satisfactory analytical and spectral data were obtained for all compounds.

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