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An efficient one-step multicomponent synthesis of Oxopyrimidooxazine derivatives

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Abstract: A mixture of BMMM, urea and 4-substituted phenols on reflux with Dimethylformamide solvent in presence of K_2CO_3 for 5-6 hours gives 2,6-dihydro-2,6-diimino-4,8-bis(substituted) pyrimido[2,1-b][1,3] oxazine-3,7-dicarbonitrile. The synthesized compounds were characterized by elemental analysis and spectral data.
Key Words : BMMM, urea, 4-substituted phenols, dimethyl formamide, K_2CO_3.

Introduction :

Heterocyclic compounds constitute the largest, most varied family of organic compounds and are very widely distributed in nature. They play a vital role in the metabolism of all the living cells. The study of heterocycles is of great interest both from the theoretical as well as practical view. Whilst the synthesis of pteridines and related bicyclic nitrogen heterocycles is established,[1] the synthesis of their diaza analogues requires further development because most methods for the synthesis of such compounds have not been designed with the intention of creating highly diverse libraries of compounds as is required for modern medicinal chemistry in which multiple biological targets may be relevant. With emphasis on diversity oriented synthesis in our own studies, we have identified active compounds with respect to GTP cyclohydrolase-1,[2]dihydropterin diphosphokinase,[3]dihydrofolate reductase,[4]pteridine reductase-1[5] and nitric oxide synthase.[6] Several of these targets are significant clinically and the optimisation of activity requires the availability of more diverse libraries within the same basic structural skeleton.

In accordance with this invention there is provided a group of 7,8-dihydro-2,5,8-trisubstituted-7-oxopyrido[2,3-d]-pyrimidine-6-carboxylic acid derivatives which act as gastric antisecretory agents, by virtue of which they are useful in the treatment of peptic ulcer disease. Many of the compounds of this invention also exhibit anti-allergy activity, by virtue of which they are useful in the prophylactic suppression of allergic manifestations in warm-blooded animals. As anti-secretory agents, the compounds of this in-y ventionreduce, total gastric volume, hydrogen ion secretion, or hydrogen ion concentration. The reduction of any one of these parameters aids in attenuating the general debilitating influence of a peptic ulcer in humans. The use of compounds exhibiting anti-secretory activity in the curative‘ and/or prophylactic treatment of peptic ulcer disease is an established. As anti-allergy agents, the compounds of this invention suppress the manifestations of an allergic response of the atopic immediate hypersensitivity type in warm blooded, sensitized animals when administered prior to an allergic attack. Although the mechanism of action is not known, it is believed that the antiallergy agents of this invention function in the same manner as disodium cromoglycate to block reaction(s) within mast cells, thereby preventing the production and re lease of mediators such as Bradykinin, SRS-A (slow reacting substance-A), histamine and other: unknown substances. The-suppression of allergic manifestations is a desirable treatment in both human and domestic warm-blooded animals such as the mouse, rat, hamster, gerbil, dog, cat, sheep, goat horse and cow.

In the recent years, many biologically active fused benzimidazoles exhibiting interesting medicinal properties for the potential treatment of human diseases have been disclosed. For example, pyrrolobenzimidazoles,[7-11] thiazolobenzimidazoles,[12] pyrimidobenzimidazoles,[13] and pyridobenzimidazoles[14] were reported as potent antitumor agents. Furthermore, pyrrolobenzimidazoles,[15] pyridobenzimidazoles,[16] were found to be useful in treating central nervous system disorder. Pyridobenzimidazoles have also anxiolytic activity in humans, [17-19]and pyrimidobenzimidazoles were anti-rheumatic agents.[20]Also, 1,2,4-triazinobenzimidazoles were found to be aldose reductase inhibitors[21] and to possess antimicrobial activity.[22]

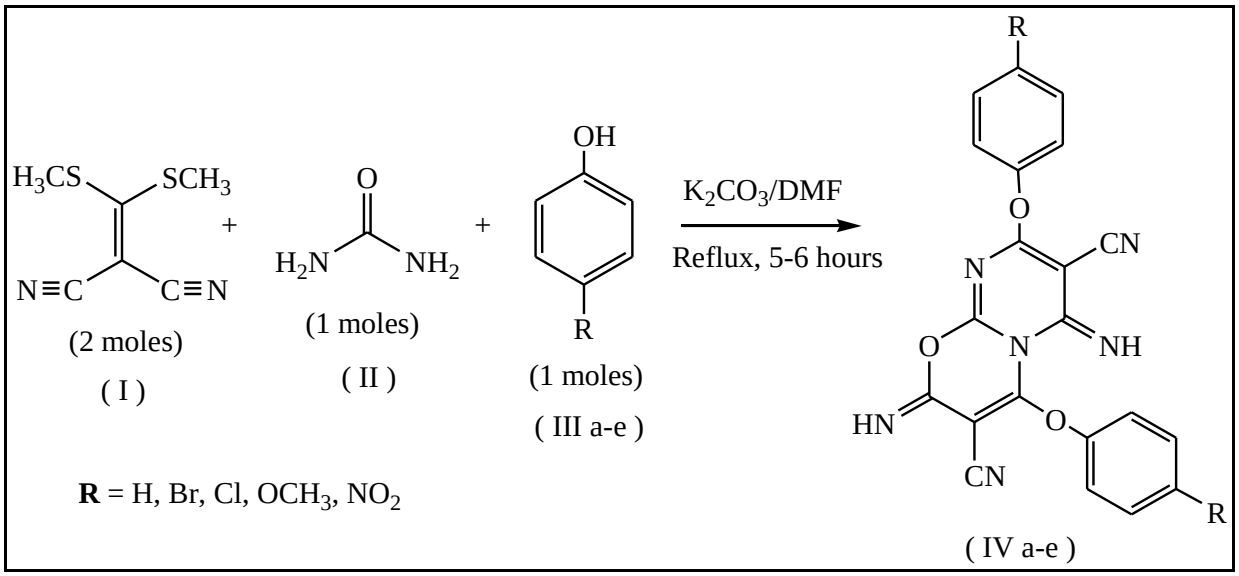
There are a large number of pharmacologically interesting benzimidazole molecules fused to a five membered rings containing one heteroatom (pyrrolobenzimidazoles), two heteroatoms (pyrazolo-, imidazo-, oxazolo-, and thiazolo-benzimidazoles) and three heteroatoms (triazolo-, thiadiazolo- and oxadiazolo-benzimidazoles). Also, several benzimidazole moieties are fused to a six membered ring containing one heteroatom (pyridobenzimidazoles), two heteroatoms (pyrimido-, pyrazino-, thiazino-benzimidazoles) and three heteroatoms (triazinobenzimidazoles). Seven membered rings fused to benzimidazole (azepino-, diazepino-, triazepino- and thiazepinobenzimidazoles) are also well known.

The "ideal synthesis" should lead to the desired product. In as few steps as possible, in good overall yield and by using environmentally compatible reagents. The synthetic variables that have to be optimized are time, costs, overall yield, simplicity of performance, safety, and environmental acceptability. In multistep syntheses the temporal and preparative complexity increases in proportion to the number of steps. It is reflected in many isolation and purification operations, such as crystallization, extraction, distillation, or chromatography.

Experimental Section :

All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded with potassium bromide pellets technique, ^{1}H NMR spectra were recorded on AVANCE 300 MHz Spectrometer in DMSO using TMS as internal standard. Mass spectra were recorded on a FT VG-7070 H Mass Spectrometer using EI technique at 70 eV. All the reactions were monitored by Thin layer chromatography.

Materials and Method :



Experimental :

1) Synthesis of 2,6-dihydro-2,6-diimino-4,8-diphenoxypyrimido[2,1-b][1,3]oxazine-3,7-dicarbonitrile (IVa).

A mixture of BMMM (2 moles), urea (1 mole) and phenol (1 moles) on reflux with dimethylformamide solvent in presence of K_2CO_3 for 5-6 hours gives 2,6-dihydro-2,6-diimino-4,8-diphenoxypyrimido[2,1-

b][1,3]oxazine-3,7-dicarbonitrile. The product was filtered, washed with water and then dried.The product recrystallized from ethyl alcohol.

Yield : 62 %, M.P. : 161 ^{0}C.

2) Synthesis of 4,8-bis(4-bromophenoxy)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3]oxazine-3,7-dicarbonitrile (IVb).

A mixture of BMMM (2 moles), urea (1 mole) and 4-bromophenol (1 moles) on reflux with dimethylformamide solvent in presence of K_2CO_3 for 5-6 hours gives 4,8-bis(4-bromophenoxy)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3]oxazine-3,7-dicarbonitrile. The product was filtered, washed with water and then dried.The product recrystallized from ethyl alcohol.

Yield : 66 %, M.P. : 185^{0}C.

3) Synthesis of 4,8-bis(4-chlorophenoxy)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3] oxazine-3,7-dicarbonitrile (IVc).

A mixture of BMMM (2 moles), urea (1 mole) and 4-methoxy phenol (1 moles) on reflux with dimethylformamide solvent in presence of K_2CO_3 for 5-6 hours gives 4,8-bis(4-chloro phenoxy)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3]oxazine-3,7-dicarbonitrile. The product was filtered, washed with water and then dried. The product recrystallized from ethyl alcohol.

Yield : 62 %, M.P. : 170 ^{0}C.

4) Synthesis of 4,8-bis(4-methoxyphenoxy)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3] oxazine-3,7-dicarbonitrile (IVd).

A mixture of BMMM (2 moles), urea (1 mole) and 4-methoxy phenol (1 moles) on reflux with dimethylformamide solvent in presence of K_2CO_3 for 5-6 hours gives 4,8-bis(4-methoxy phenoxy)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3]oxazine-3,7-dicarbonitrile. The product was filtered, washed with water and then dried. The product recrystallized from ethyl alcohol.

Yield : 55 %, M.P. : 155 ^{0}C.

5) Synthesis of 4,8-bis(4-nitrophenoxy)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3] oxazine-3,7-dicarbonitrile (IVe).

A mixture of BMMM (2 moles), urea (1 mole) and 4-methoxy phenol (1 moles) on reflux with dimethylformamide solvent in presence of K_2CO_3 for 5-6 hours gives 4,8-bis(4-nitro phenoxy)-2,6-dihydro-2,6-diiminopyrimido[2,1-b][1,3]oxazine-3,7-dicarbonitrile. The product was filtered, washed with water and then dried. The product recrystallized from ethyl alcohol.

Yield : 67 %, M.P. : 198^{0}C.

Result and Discussion :

The objectives of the present work are to synthesize certain pyrimidooxazine derivatives and study their biological properties. Thus an attempt has been made in this direction. As expected substituted pyrimidooxazine exhibited antibacterial, anti allergic, anti inflammatory, antitumor activities.

Conclusion :

In conclusion, we have synthesized simple and efficient novel fused bicyclic heterocycles pyrimido-oxazine having bis-electrophilic species reacting with various nucleophiles.

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