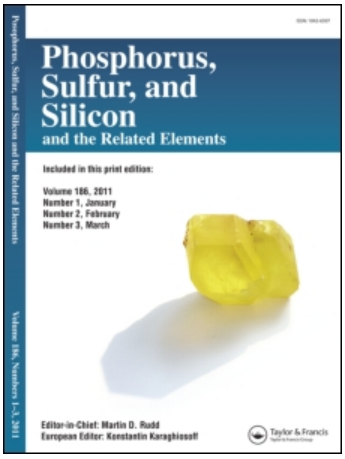

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

FUSED CYANOPYRIMIDINES: PART-I SYNTHESIS AND REACTIONS OF FUSED CYANOPYRIMIDINE DERIVATIVES AND THEIR EFFECT ON CELLOBIASE ACTIVITY

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To cite this Article Abdel-aziz, S. A.(1996) 'FUSED CYANOPYRIMIDINES: PART-I SYNTHESIS AND REACTIONS OF FUSED CYANOPYRIMIDINE DERIVATIVES AND THEIR EFFECT ON CELLOBIASE ACTIVITY', Phosphorus, Sulfur, and Silicon and the Related Elements, 116: 1, 39 — 48
To link to this Article: DOI: 10.1080/10426509608040467
URL: http://dx.doi.org/10.1080/10426509608040467

Phosphorus, Sulfur, and Silicon, 1996, Vol. 116, pp. 39–48
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FUSED CYANOPYRIMIDINES: PART-I SYNTHESIS AND REACTIONS OF FUSED CYANOPYRIMIDINE DERIVATIVES AND THEIR EFFECT ON CELLOBIASE ACTIVITY

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(Received 14 June 1995; Revised 2 April 1996; In final form 2 April 1996)

Some new fused heterotricyclic systems containing the cyanopyrimidine moiety have been synthesized from the interaction between 2-mercapto-4-arylidene-5-cyanopyrimidin-6(1*H*)one (**1**) with bifunctional halogen and nitrogen compounds. Structures of the new products have been established by elemental analyses and spectral data (UV, IR, ^{1}H NMR and mass). Effect of the newly synthesized compounds on the activity of the cellobiase produced by *Aspergillus nidulans* was studied.

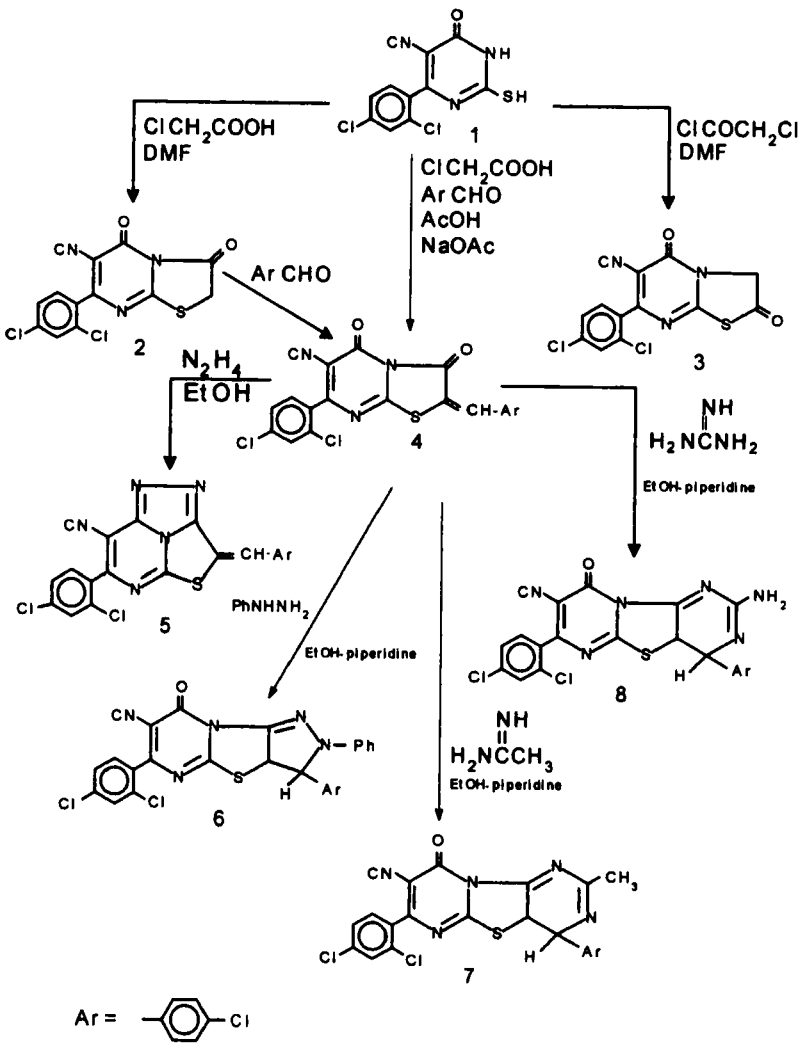
Keywords: Fused-cyanopyrimidine; heterotricyclic systems; NMR spectra; UV spectra; IR spectra; biological activity

INTRODUCTION

The chemistry of pyrimidines is receiving much attention in recent years, principally due to the unique physical and chemical properties[1,2] of such derivatives, which have gained wide applications as anti-bacterial[3] and anti-microbial[4] agents. This together with our interest in the synthetic potential of fused pyrimidine systems, prompted us to investigate the synthesis of some new fused cyanopyrimidines of potential biological activity.

RESULTS AND DISCUSSION

The starting compound, 2-mercapto-4-(2′,4′-dichlorophenyl)-5-cyanopyrimidin-6(1*H*)one (**1**), was obtained by stirring ethyl cyanoacetate, thiourea with 2,4-dichlorobenzaldehyde in sodium ethylate at room temperature (Scheme I).

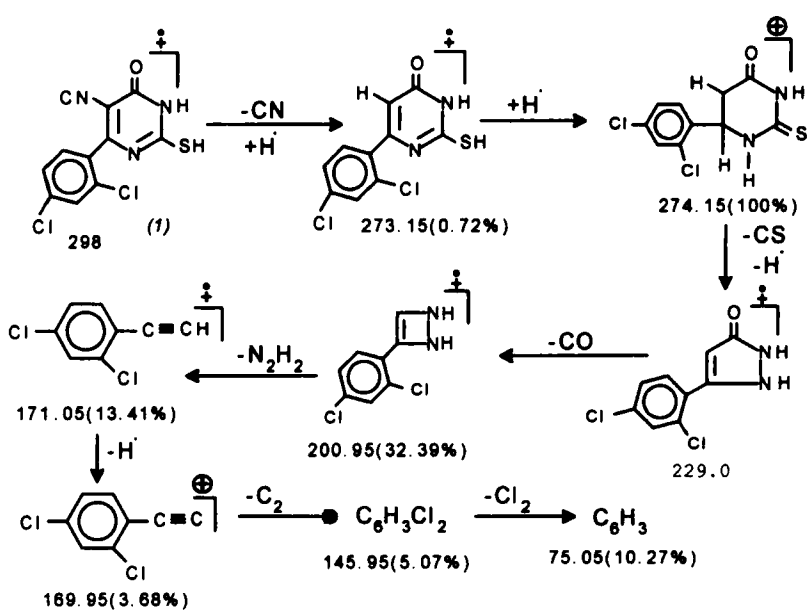


SCHEME I Representative scheme for the reactions of compound **1**.

The infrared absorption spectrum of compound **1** showed ν at 3578 (OH), 3385-3178 (NH, NH), 2300 (C≡N), 1573 (C═N) and 1172 cm^{-1} (C-S). The presence of the band characteristic of a cyano group emphasizes that the cyano moiety is a reaction independent. The UV of **1** in DMF recorded λ_{max} 274.1 nm (A 3.619). ^1H NMR of **1** revealed the signals at δ 5.2, 7.2–8.0, 10.1 and 11.5 ppm attributed to SH, aromatic and NH, OH (tautomeric forms) protons. The mass spectrum of **1** showed a molecular ion peak, m/z, at 299 (1.18%) and a base peak at 274.15 (100%) which confirmed the postulated structure (Scheme II).

Alkylation of compound **1** with mono-chloroacetic acid and/or chloroacetyl chloride in DMF yielded the isomeric structures 2,3-dihydro-6-cyano-7-(2′,4′-dichlorophenyl)thiazolo[3,2-a]pyrimidin-3,5-dione (**2**) and/or 2,3-dihydro-6-cyano-7-(2′,4′-dichlorophenyl)thiazolo[3,2-a]pyrimidin-2,5-dione (**3**), respectively (Scheme I).

The structure for compound **2** was confirmed by spectral data. The IR showed strong bands at ν 3400 (OH), 3028 (aromatic CH), 2958 (aliphatic CH), 2435 (C≡N), 2099 (NCS; standard 2100)[5], 1719 (pyrimidine C═O), 1632 (thiazole C═O), 1586 (C═N) and at 1196 cm^{-1} (C-S). The UV spectrum of **2** in DMF recorded λ_{max} 272.4 nm.



SCHEME II Mass Fragmentation of compound **1**.

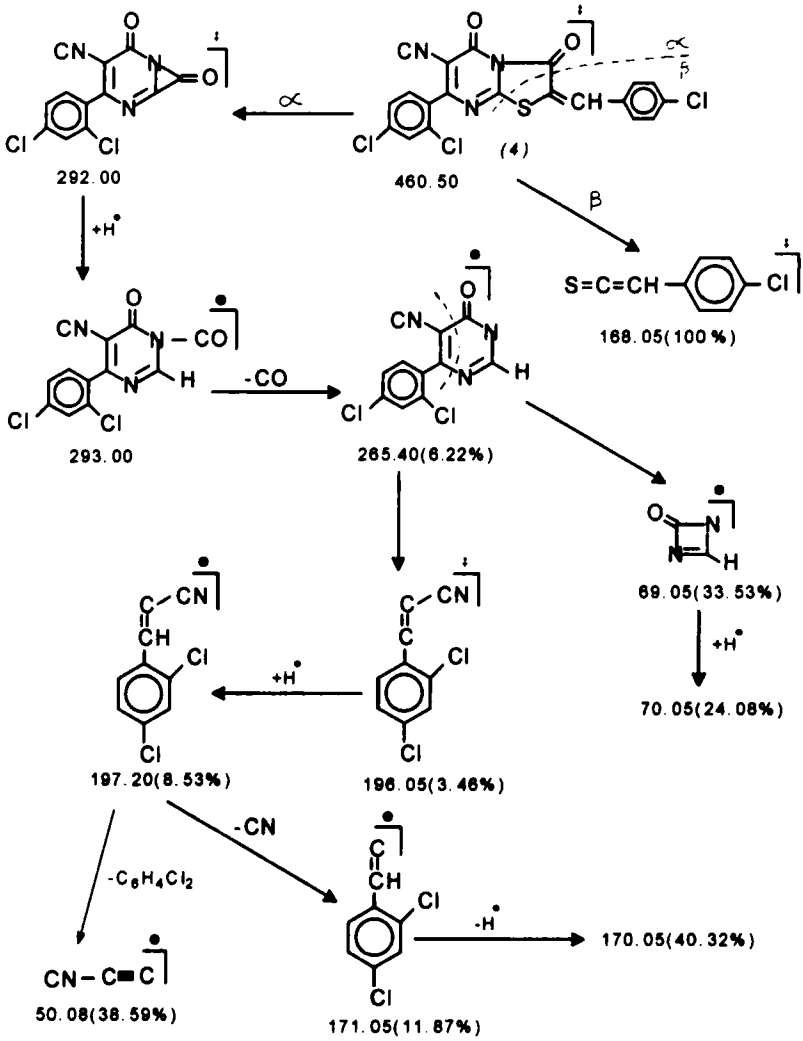
The presence of an active methylene group in compound **2** was established by the condensation with *p*-chlorobenzaldehyde in the presence of glacial acetic acid-fused sodium acetate to give 2-[(*p*-chlorophenyl)methylene]-6-cyano-7-(2′,4′-dichlorophenyl)thiazolo-[3,2-a]pyrimidin-3,5-dione (**4**). The latter compound was also produced from the interaction between compound **1** and monochloroacetic acid, *p*-chlorobenzaldehyde in glacial acetic acid-fused sodium acetate in one step. The IR spectrum of **4** showed stretching frequencies of the exocyclic C=C at ν 1643 cm^{-1} in addition to the normal frequencies of the cyclic C=O at ν 1717 and 1696 cm^{-1}. The UV spectrum gave confirming information about structure **4**. The shifts in wavelengths λ_{max} at 371.4, 298.8 and 271.9 nm are indicative of a chromophore conjugated with the thiazolone ring. Furthermore, the mass spectrum of **4** exhibited the postulated structure[6] (Scheme III).

The reactivity of the α,β-unsaturated carbonyl moiety in compound **4** was arrived us to synthesize new fused heterotricyclic systems in order to give a conclusive proof for structure **4**. This has been carried out by reaction of **4** with some nucleophile nitrogen moieties, such as, hydrazine hydrate, phenylhydrazine, acetamidine hydrochloride and/or guanidine hydrochloride, which involves condensation with carbonyl group of thiazolidine followed by the addition to exocyclic C=C with ring closure reaction.

Thus, compound **4** reacted with hydrazine hydrate[7] in absolute ethanol to give the corresponding *s*-triazolo[4,3-c]thiazolo[3,2-a]pyrimidine (**5**) and with phenylhydrazine in ethanol-piperidine[8] to give 1,2-dihydro-1, 7-diaryl-6-cyanopyrazolo [5,4-d]thiazolo[3,2-a]pyrimidin-5-one(6) (Scheme I). The suggested structure of compound **5** was based on the following evidences: a) the IR spectrum showed a lack of absorption bands due to C=O with the appearance of $\nu_{exocyclic}$ C=C and C≡N groups, and b) the UV spectrum of **5** gave more support for its structure which showed λ_{max} at 271.9 nm (A 1.617) with absence of the chromophoric shifts of the conjugation system.

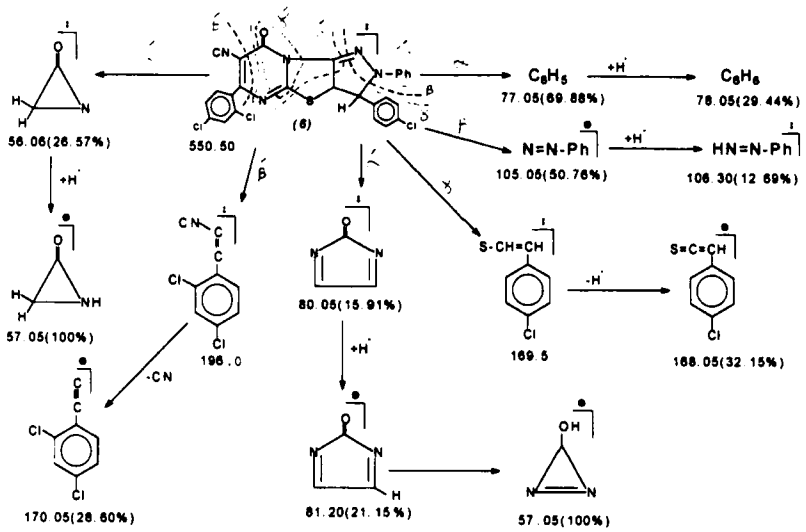
The structure of compound **6** was based on: a) the results of the molecular weight determination of mass spectrum, 551 (2.37%) and a base peak at 57 (100%) agreed with the molecular structure (Scheme IV), b) the UV absorption spectrum showed a band at 273 nm, and c) the IR spectrum showed absorption bands at ν 3067 (aromatic CH), 2223 (C≡N), 1692 (C=O), 1590 (cyclic C=C), 1556 (C=N) and 1538 cm^{-1} (C=N). The ^1H NMR spectrum of compound **6** showed signals at δ 2.61, 3.46 and 6.50–7.74 ppm which are attributed to the two CH protons of the pyrazolo moiety and aromatic protons, respectively.

1,8-Diaryl-3-methyl-7-cyanopyrimidino[4,5-d]thizolo[3,2-a]pyrimidin-6-one (**7**) was synthesized by refluxing a mixture of **4** and acetamidine hydrochloride



SCHEME III Mass Fragmentation of compound **4**.

in ethanol-piperidine[9]. The structure of compound **7** was confirmed as follows: a) the UV absorption spectrum in DMF recorded the λ_{max} at 333.5 nm (A 1.995) due to n-π^* and π-π^* transitions of C=N groups of the new pyrimidine synthesized, b) the IR spectrum showed ν at 2219 (C≡N), 1692 (C=O) and 1608-1589 cm^{-1} (C=N), and c) the ^1H NMR spectrum of compound **7** showed signals at δ 1.34, 2.74–2.99, 4.68 and a broad signal at δ 7.70–8.20 ppm corresponding to methyl, two CH protons of pyrimidino moiety and aromatic protons,



SCHEME IV Mass Fragmentation of compound **6**.

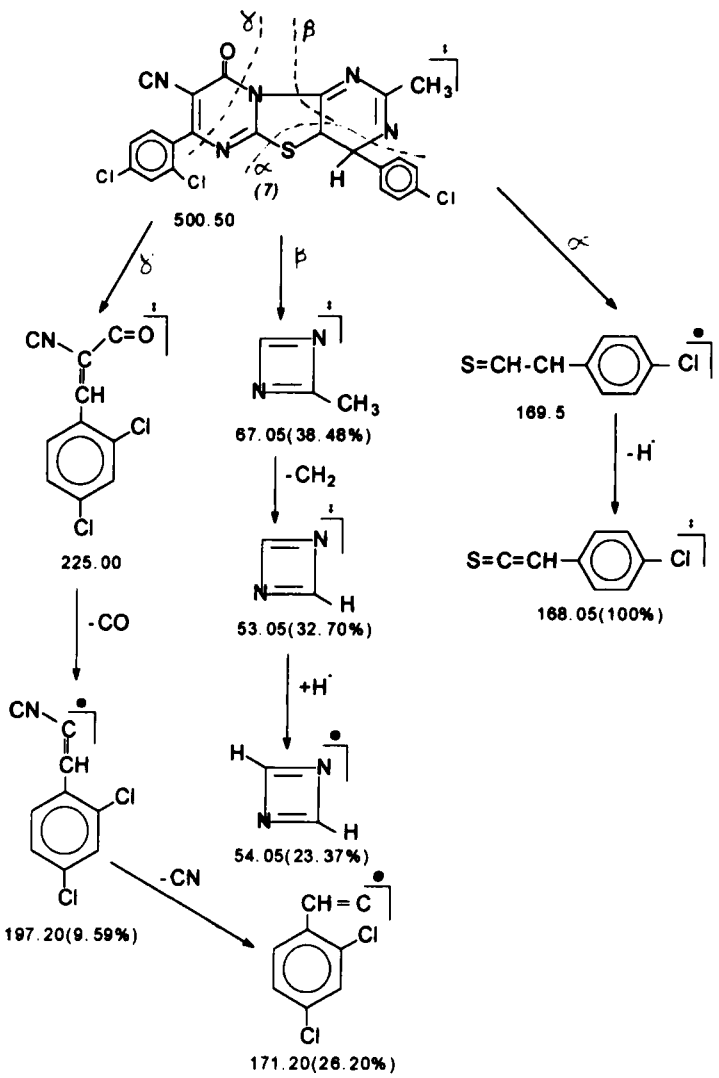
respectively. Finally, the mass spectrum of **7** showed a molecular ion peak at m/z 501 (1.71%). The base peak was shown at m/z 168 (100%) corresponding to the thioether moiety (Scheme V).

The synthesis of 3-amino-1,8-diaryl-7-cyanopyrimidino[4,5-d]thiazolo[3,2-a]pyrimidin-6-one (**8**) was accomplished by reacting of compound **4** with guanidine hydrochloride in ethanol with a few drops of piperidine[9] (Scheme 1). The structure of compound **8** was deduced from elemental analysis and IR spectrum. The IR spectrum revealed the presence of characteristic bands at 3430 (NH_2), 2221 (C≡N), 1691 (C═O), 1609-1557 (C═N), 1144 (C-S) and at 663 cm^{-1} (C-Cl).

BIOLOGICAL ACTIVITY

The effect of the newly synthesized compounds on the activity of cellobiase produced by *Aspergillus nidulans* was studied. The fungus was grown on Czapeck's medium fortified with cellulose as a carbon source and incubated for 8 days at 45°C. The filtrate was then assayed for cellobiase activity according to the method described[10].

Each compound was dissolved in an appropriate amount of DMF to give different concentrations (Table I) and then added separately to the assay mixture consisting of the enzyme solution and the substrate (cellobiase) dissolved in



SCHEME V Mass Fragmentation of compound **7**.

citrate phosphate buffer at pH 4.8 and incubated at 50°C for one hour. The released reducing sugar was estimated colorimetrically at 540 nm as an indication for the enzyme activity. The results were recorded in Table I.

We concluded that increasing the reducing sugar in the case of compound **4** at high concentration, and in the case of compound **6** at low concentration is due to the presence of thiazolopyrimidine moiety.

EXPERIMENTAL

Melting points reported are uncorrected. UV spectra were recorded in pure DMF on a Perkin-Elmer, Lambda 4B Controller Accessory Interface, uv-vis spectrophotometer (λ_{max} in nm), IR spectra in KBr on a Perkin-Elmer, 1430 Ratio Recording spectrophotometer (ν_{max} in cm^{-1}). ^1H NMR spectra were recorded on Bruker 200 MHz/52 MM spectrometer using DMSO-d_6 as a solvent and TMS as an internal reference (chemical shifts in δ, ppm). Mass spectra were recorded using a Hewlett-Packard model: MS 5988 spectrometer (70 eV).

Synthesis of 2-mercapto-4-arylidene-5-cyanopyrimidin-6(1H)one (1)

A mixture of ethyl cyanoacetate (0.01 mole), thiourea (0.01 mole), 2,4-dicholrobenzaldehyde (0.01 mole) and sodium ethylate (0.5 g Na/20 mL abs. ethanol) was stirred for 1 h at room temperature. The reaction mixture was poured gradually onto HCl-ice. The solid thus separated was filtered off and recrystallized to give **1** (Table II).

Alkylation of 1 with Mono-Chloroacetic Acid: Synthesis of 2

An equimolar mixture of **1** and mono-chloroacetic acid in DMF (20 mL) was heated under reflux for 4 h. The reaction mixture was poured onto ice, then filtered off and the solid obtained was recrystallized to give **2** (Table II).

Alkylation of 1 with Chloroacetyl Chloride: Synthesis of 3

A suspension of compound **1** (0.01 mole) and chloroacetyl chloride (0.01 mole) in DMF (20 mL) was refluxed for 4 h. The reaction mixture was poured onto ice,

TABLE I Effect on cellobiase activity produced by *Aspergillus nidulans*

Compd. No.	*1000 μg/mL*	*100 μg/mL*	*10 μg/mL*
1	0.17	0.17	0.35
4	0.41	0.35	0.35
5	0.34	0.33	0.33
6	0.35	0.35	0.42
7	0.35	0.36	0.32

Blank: 0.35 μg/mL (without substance or DMF).
DMF: 0.04 μg/mL.

TABLE II Characterization data of the prepared compounds

Compd.	*Solvent*	*M.P.* °C	*Yield* %	*Molecular formula*	*Molecular weight**
1	EtOH-DMF	250–51	75	$C_{11}H_5N_3OSCl_2$	298
2	DMF	214–15	40	$C_{13}H_5N_3O_2SCl_2$	338
3	Dil. AcOH	224–25	70	$C_{13}H_5N_3O_2SCl_2$	338
4	Dil. AcOH	240	80	$C_{20}H_8N_3O_2SCl_3$	460.5
5	Dil. Dioxane	296–97	40	$C_{20}H_8N_5SCl_3$	456.5
6	Dil. AcOH	190–91	60	$C_{26}H_{14}N_5OSCl_3$	550.5
7	Dil. DMF	292–93	50	$C_{22}H_{12}N_5OSCl_3$	500.5
8	EtOH-DMF	196–97	40	$C_{21}H_{10}N_6OSCl_3$	500.5

*All the compounds were also analyzed for C, H, N, S, Cl and the analytical results were within ± 0.4–0.5%.

then filtered off and thus the solid obtained was recrystallized to give **3** (Table II).

Synthesis of 2[(p-chlorophenyl)methylene]-6-cyano-7-(2′,4′-dichlorophenyl)thiazolo[3,2-a]-pyrimidin-3,5-dione (4)

a) A mixture of compound **2** (0.01 mole), *p*-chlorobenzaldehyde (0.01 mole) and sodium acetate (2 gm) in glacial acetic acid (20 ml) was heated under reflux for 4 h, cooled, then triturated with methanol. The separated solid was recrystallized to give **4** (Table II).

b) An equimolar mixture of compound **1**, mono-chloroacetic acid, p-chlorobenzaldehyde and sodium acetate (2 gm) in glacial acetic acid (20 ml) was refluxed for 4 h, cooled, then poured onto ice. The resultant solid was recrystallized to give **4**. M.p. and mixed m.p. were 240°C (Table II).

Reaction of 4 with hydrazine hydrate: Synthesis of s-triazolo[4,3-c]thiazolo[3,2-a]pyrimidine (5)

A mixture of **4** (0.01 mole) and hydrazine hydrate (0.01 mole) in abs. ethanol (20 mL) was heated under reflux for 4 h, cooled, then evaporated to half volume. The remaining solid was filtered off and recrystallized to give **5** (Table II).

Reaction of 4 with phenylhydrazine: Synthesis of 6

A mixture of an equimolar amounts of **4** and phenylhydrazine in ethanol (20 mL), piperidine (0.5 mL) was refluxed for 4 h. The reaction mixture was concentrated to half volume. The resultant solid was filtered off and recrystallized to give **6** (Table II).

Synthesis of 1,8-diaryl-3-methyl-7-cyanopyrimidino[4,5-d]thiazolo[3,2-a]pyrimidin-6-one (7)

A mixture of **4** (0.01 mole) and acetamidine hydrochloride (0.01 mole) in ethanol (20 mL), piperidine (0.5 mL) was heated under reflux for 4 h, cooled, then evaporated to half volume. The separated solid was filtered off and recrystallized to give **7** (Table II).

Synthesis of 8

A mixture of an equimolar amounts of **4** and guanidine hydrochloride in ethanol (20 mL) with a few drops of piperidine (0.5 mL) was refluxed for 4 h. The reaction mixture was concentrated to half volume. The separated solid was filtered off and recrystallized to give **8** (Table II).

Acknowledgment

The author is greatful to Dr. Usama F. Ali, Department of Biology, Faculty of Education, AinShams University, for his help in antimicrobial screening.

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