Synthesis and Dimroth Rearrangement of 6-Cyano-1,2,4-triazolo-[4,3-*a*]pyrimidin-5- and 7-ones. A Novel Alkylation with Orthoesters and a New Participation of the Cyano Group in the Rearrangement

E. S. H. El Ashry*, Y. El Kilany, N. Rashed, A. Mousaad, H. Assafir

Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt

Z. Naturforsch. **53b,** 1203–1212 (1998); received June 3, 1998

Dimroth Rearrangment, Alkylation with Orthoesters, Cyano Group, Pyrimidine, Triazolopyrimidine

The cyclization products of 5-cyano-2-hydrazino-6-phenyl-3,4-dihydropyrimidin-4-one (**6**) with one carbon inserting agents have been confirmed to be of the 1,2,4-triazolo[4,3-*a*]pyrimidin-5(8*H*)-ones type and not the respective 7-ones, by comparing their alkylated derivatives **10a**, **11a**, **27** and **28** with the product from the cyclization of the 3-methyl and 3-benzyl derivatives of **6**. A novel alkylation process was found when triethyl orthoformate was used as a cyclizing agent. Dimroth rearrangement of **8**, **14**, **15**, **24**, **34** and **36** with 2% ethanolic KOH gave the respective triazolo[1,5-*a*]pyrimidinone **13**, **18**, **19**, **25**, **38** and **40,** respectively. Using 10% ethanolic KOH led to a novel participation of the cyano group in the rearrangement whereby **8a** gave 7-imino-5-phenyl-1,2,4-triazolo[1,5-*a*]pyrimidine **22**.

Introduction

The Dimroth rearrangement with certain types of compounds gives rise to unexpected products [1]. Thus, 1,2,4-triazolo[4,3-*a*]-pyrimidines undergo rearrangement to give [1,5-*a*] analogues [1,2]. There is an increasing interest in the pharmacological activity of such annelated systems. Compounds having this skeleton with a [4,3-*a*] fusion are useful as calcium channel blocking vasodilators, and have antihypertensive [3], cardiovascular[4,5] and anxiolytic [6] activities as well as a component in photographic materials [7]. The [1,5-*a*] analogues have much more biological activities. They are used as herbicides [8], fungicides [9], angiotensin II receptors antagonist [10], antianginal [11], and useful for prevention of cardiovascular diseases [12] and treatment of atherosclerosis [13]. Individuals of this class slow down the growth of *Lactobacillus casei* and *Streptococcus faecalis* and are also active against experimental tumors [14–16].

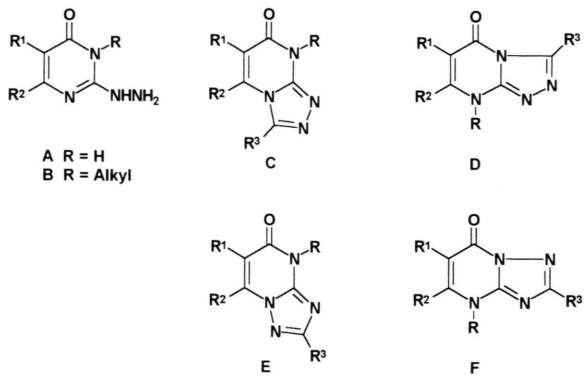
Results and Discussion

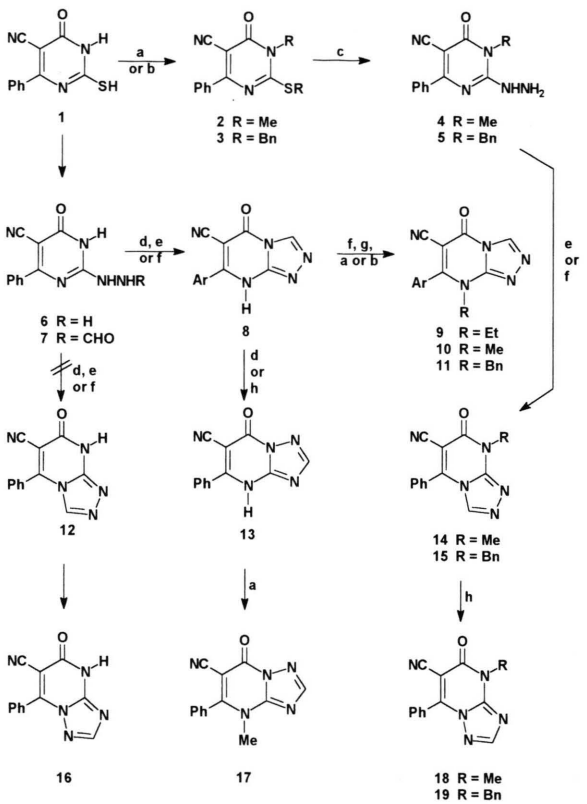
Continuing our work on the use of heterocyclic hydrazine derivatives as precursors for 1,2,4-triazolo-heterocycles and their acyclonucleoside analogues [17–27], the synthesis of 1,2,4-triazolotriazines, quinolines and quinoxalines has been reported. In the present work, the regioselective formation and Dimroth rearrangement of the annelated 6-cyano-1,2,4-triazolo[4,3-*a*]pyrimidines has been investigated. N-alkylation with triethyl orthoformate and a new rearrangement involving the participation of the nitrile group in the α-amidonitrile system have been found during this study.

Cyclization of the hydrazine derivative **A** may provide 1,2,4-triazolo[4,3-*a*]pyrimidines (**C**) or (**D**) or a mixture of both [2]. A possible Dimroth rearrangement of **C** and **D** would give 1,2,4-triazolo[1,5-*a*]pyrimidines (**E**) and (**F**), respectively. On the other hand, the cyclization of the hydrazine **B** can afford only **C** and/or its rearranged product **E**. Moreover, the products **C** and **E** from **B** can be used for deducing the site of cyclization by their comparison with the alkylated derivatives of the products from **A**. Consequently, the hydrazines **4**, **5** and **6** were selected for the present study. They were prepared [28] by the nucleophilic displacement of the SH or SR groups at C-2 of **1–3**. The displacement from **2** and **3** was more facile than that from **1**. The thioethers **2** and **3** were prepared by the alkylation of **1**. It has to be confirmed which nitrogen of the pyrimidine is the site of alkylation. The mono- and dimethylation of **1** has been reported [28]. The structure of the former

* Reprint requests to Prof. Dr. E. S. H. El Ashry.

0932–0776/98/1000–1203 $06.00





was based on the spectroscopic methods as well as its synthesis by an unambiguous method. The second methyl group has been introduced on N-3. This assignment was based [28] on a comparison of its NMR spectrum with that of the monomethylated derivative. The deshielding of the *ortho* phenyl protons in both derivatives by about 0.5 ppm relative to the *meta* and *para* protons indicated that the phenyl group is coplanar with the pyrimidine ring leading to the conclusion that N-1 is unsubstituted. Otherwise, the phenyl protons may give a compact signals indicating that the phenyl group is twisted out of plane of the pyrimidine nucleus because of the steric interaction resulting from the substituent at N-1.

Reaction of the hydrazine **6** with formic acid in ethanol gave the formyl derivative **7** whose ring closure gave the triazole **8a** [29]. Alternatively, the latter triazole can be obtained by heating of **6** with formic acid. Moreover, the triazolopyrimidine **8a** has been also prepared by the reaction of **6** with triethyl orthoformate. Prolonged reaction of **6** with triethyl orthoformate led to the formation of a byproduct **9a** which with time became the sole product accompanied by the disappearance of **8a**. The new product was analyzed for $C_{14}H_{11}N_5O$. Its mass spectrum showed a molecular ion peak at *m/z* 265 *i.e* an increase of 28 from the anticipated product **8a**. Its ^1H NMR spectrum showed the presence of a pattern corresponding to an ethyl group as a triplet and quartet at 1.70 and 4.40 ppm, respectively. Moreover, synthesis of **9a** was achieved by the ethylation of **8a**. These data led to the conclusion that alkylation has taken place by the triethyl orthoformate to give **9a**. Alkylation with $HC(OR)_3$ have been reported before [30]. The reaction was found to be a general one whereby **8a-c** gave **9a-c**.

The formation of **8a** utilizing triethyl orthoformate indicated that the product did not undergo the Dimroth rearrangement either thermally or under the influence of formic acid (formic acid is known to induce the Dimroth rearrangement [2]). However, in our hands no such rearrangement took place even when 10% HCl in AcOH was used. To confirm this finding, the triazolopyrimidine **8a** was subjected to the action of 2% ethanolic KOH whereby compound **13** was formed. Treatment of **8a** or **13** with a more concentrated alkali (10%) gave a product whose elemental analysis and mass spectrum led to the molecular formula $C_{11}H_9N_5$, indicating the loss of a carbonyl group. Its IR spectrum showed no band around 2224 cm^{-1} (C≡N). Its mass spectrum showed a peak at *m/z* 184 due to the loss of C=NH.

The ^{1}H NMR spectrum of this new product showed the presence of a new proton signal at 6.80 ppm. Consequently, the product has been assigned the structure **22**. The mechanism of its formation may be depicted in the following scheme. It involves the attack of the hydroxide ion on the carbonyl amide of **8a** to give a Dimroth like intermediate **20**. Migration of the charge from N-4 to N-1 and rotation around the C-N bond gave **13**, when dilute alkali was used. A simultaneous isomerization of the double bond of **20** may have taken place under the strong alkalinity of the medium to give **21**, which cyclized and then decarboxylated to give **22**. Although, the addition on a nitrile group in other systems was known [31], the possible hydrolysis of the nitrile to an amide followed by cyclization can not be roled out.

This new rearrangement confirms indirectly that the site of cyclization of **6** involves N-3 to give **8a** rather than **12** or its rearranged product **16**. Comparison of the cyclized products **14** and **15** obtained from **4** and **5** (blocked at the N-3), respectively with **10a** and **11a** obtained by the derivatization of **8a** by the same blocking agents indicated which N atom of the pyrimidine is involved in the cyclization step. In order to confirm that no Dimroth rearrangement has taken place during the methylation or benzylation of **8**, methylation of the rearranged products **13** was carried out to give **17**, whereas **18** and **19** were prepared by the action of the alkali on **14** and **15,** respectively. The susceptibility of **14** and **15** for the action of alkali as well as the finding that **14** and **17** are different confirmed the assignment for the products.

Oxidative cyclization of the benzylidene derivative **23** with ferric chloride gave **24** and not **26** or **25** as indicated by the susceptibility of **24** to the action of alkali to give **25** *via* a Dimroth rearrangement.

When the cyclization of **23** was carried out with bromine in acetic acid, it gave a major product identified as **25** in addition to two minor products one of which was identified as **24**. The absence of the methine proton of the hydrazone **23** in the ^{1}H NMR spectrum of **24** confirmed the structure.

Methylation of **24** and **25** gave **27** and **29**, respectively. Benzylation of **24** gave **28**. The ^{1}H NMR spectra of the alkylated derivatives showed the presence of an alkyl group in each. The hydrazones **30-33** were cyclized to give **34-37**, respectively as the major isolated products by the action of thionyl chloride. Partial Dimroth rearrangement has taken place during this cyclization whereby **38-40**, respectively were formed as by-

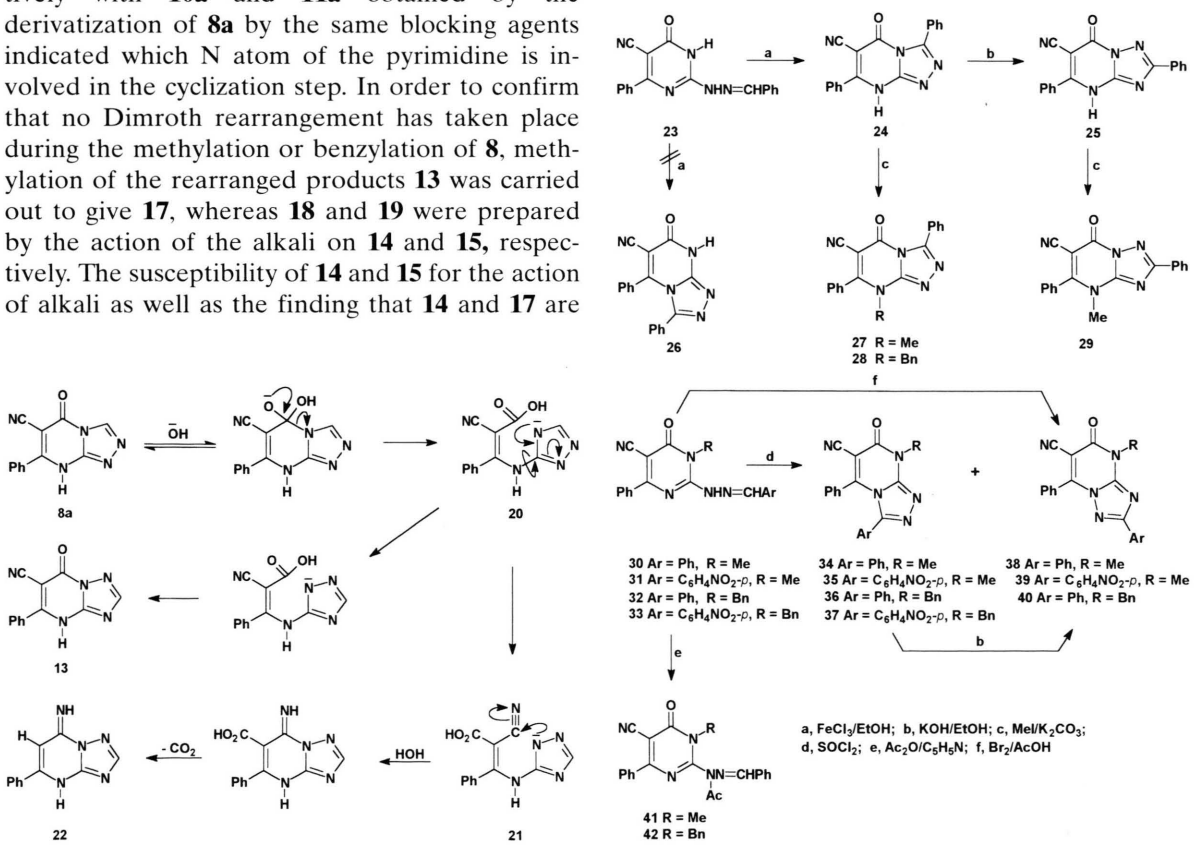


Table I. Mass spectral data.

Compound No.	*m/z* (%)
8a	237(100, M $^{+}$), 209(88, M $^{+}$-CO), 182(7, M $^{+}$-(CO, HCN)), 171 (11), 155(8), 127(20, PhC≡CCN^{+}), 103(26, PhCN^{+}), and 77(38, Ph^{+}).
13	237(54, M $^{+}$), 209(27, M $^{+}$-CO), 127(100, PhC≡CCN^{+}), 77(21, Ph^{+}), and 51(25, HC≡CCN^{+}).
14	251(100, M $^{+}$), 222(31, M $^{+}$-NMe), 154(12), 141(5), 127(89, PhC≡CCN^{+}), 77(14, Ph^{+}) and 51(15, HC≡CCN^{+}).
18	251(100, M $^{+}$), 222(18, M $^{+}$-NMe), 196(16), 169(12), 154(15), 141(7), 127(17, PhC≡CCN^{+}), 77(22, Ph^{+}), and 51(28, HC≡CCN^{+}).
22	211(100, M $^{+}$), 184(15, M $^{+}$-HCN), 171(24), 128(18), 104(19), 77(24, Ph^{+}), and 51(22, HC≡CCN^{+}).
25	313(100, M $^{+}$), 285(54, M $^{+}$ CO), 181(5), 153(8), 127(89, PhC≡CCN^{+}), 104(52) and 77(31, Ph^{+}).
38	327(100, M $^{+}$), 289(9, M $^{+}$-NMe), 225(4), 169(7), 141(10), 127 (22, PhC≡CCN^{+}), 103(43, PhCN^{+}), 77(37, Ph^{+}), and 51(21, HC≡CCN^{+}).

products. On the other hand, the cyclization with Br_2/AcOH gave the Dimroth rearranged products **38-40**.

The rearrangement of **34-36** to **38-40** was achieved with alkali. Acetylation of **30** and **32** gave **41** and **42**, respectively. The ^{1}H NMR spectra of the acetyl derivatives confirmed the assigned structures by the presence of a singlet corresponding to the acetyl group in addition to the presence of the methine proton of the hydrazone residue.

Experimental

Melting points were determined on a Meltemp apparatus and are uncorrected. IR spectra were recorded with a Unicam SP 1025 Spectrometer. ^{1}H NMR spectra were recorded with Varian EM-390 spectrometer at 200 MHz. The chemical shifts are expressed in the δ scale using tetramethylsilane as a reference. Mass spectra were carried out on Tinnigan MAT 312. TLC was performed on Baker-Flex silica gel 1B-F (2.7–7.5 cm) plates. Microanalyses were performed in the unit of Microanalysis at Cairo University.

*3-Benzyl-2-benzylthio-5-cyano-6-phenyl-3,4-dihydropyrimidin-4-one (**3**)*

A suspension of **1** [32] (0.50 g, 2.18 mmol) and potassium hydroxide (0.28 g, 5.0 mmol) in *N,N*-dimethylformamide (10 ml) was cooled to 0 °C and then benzyl chloride (3.50 ml, 27.64 mmol) was added. The mixture was refluxed for 4 h, cooled and poured onto crushed ice. The product was filtered off, washed with water and crystallized from ethanol-chloroform mixture as colorless crystals (0.41 g, 46% yield); m.p. 138–140 °C. IR (KBr): 2216 (C≡N), 1657 cm^{-1} (CON). ^{1}H NMR ($CDCl_3$): δ = 4.50 (s, 2 H, SCH_2), 5.40 (s, 2 H, NCH_2), 7.40 (m, 13 H, ArH), 7.90 (m, 2 H, ArH).

$C_{25}H_{19}N_3OS$ (409.5)

Calcd	C 73.32	H 4.68	N 10.26%,
Found	C 73.30	H 4.70	N 10.50%.

*3-Benzyl-5-cyano-2-hydrazino-6-phenyl-3,4-dihydropyrimidin-4-one (**5**)*

A suspension of **3** (1.0 g, 2.44 mmol) in ethanol (20 ml) and hydrazine hydrate (4 ml) was heated under reflux for 1 h. The reaction mixture was cooled and the separated product was filtered, and crystallized from ethanol as orange crystals (0.62 g, 80% yield); m.p. 230–232 °C. IR (KBr): 3304, 3187 (NH_2 and NH), 2204 (C≡N), 1661 cm^{-1} (CON). ^{1}H NMR (DMSO-d_6): δ = 5.10 (s, 2 H, NCH_2), 7.50 (m, 5 H, ArH), 7.90 (m, 5 H, ArH), 8.80 (s, 3 H, 3 NH).

$C_{18}H_{15}N_5O$ (317.3)

Calcd	C 68.12	H 4.67	N 22.07%,
Found	C 68.40	H 4.80	N 22.10%.

*5-Cyano-2-(N-formylhydrazino)-6-phenyl-3,4-dihydropyrimidin-4-one (**7**)*

A mixture of compound **6** (0.45 g, 1.98 mmol) and formic acid (30 ml) in ethanol (20 ml) was heated under reflux for 3 h. The solid product that separated out on cooling was filtered, washed with ethanol and then crystallized from ethanol as col-

orless crystals (0.35 g, 69% yield); m.p. 244–245 °C, [Lit.[29] m.p. 243 °C].

6-Cyano-7-phenyl-1,2,4-triazolo[4,3-a]-pyrimidin-5(8H)-one (**8a**)

(a) Compound **7** (0.47 g, 1.84 mmol) was fused at 260 °C for 1 h. The solidified product was triturated with ethanol, filtered off and crystallized from ethanol into colorless crystals (0.35 g, 80% yield); m.p. 236–239 °C, [Lit.[29] m.p. 236 °C].

(b) A mixture of compound **6** (0.47 g, 2.07 mmol) and (20 ml) formic acid was heated under reflux for 4 h. The reaction mixture was cooled and the product that separated out was filtered, and crystallized from ethanol as colorless crystals (0.37 g, 75% yield); m.p. 236–239 °C. It is identical with the product from method a.

(c) A mixture of **6** (0.47 g, 2.07 mmol) and triethyl orthoformate (30 ml) was heated under reflux for 1 h. The product that separated out on cooling, was filtered, and crystallized from ethanol as colorless crystals (0.31 g, 63% yield); m.p. 236–239 °C. It is identical with the product from method a.

6-Cyano-8-ethyl-7-phenyl-1,2,4-triazolo[4,3-a]-pyrimidin-5-one (**9a**)

(a) A mixture of **8a** (0.47 g, 1.98 mmol) and triethyl orthoformate (10 ml) was heated under reflux for 4 h. The product that separated out was filtered and crystallized from ethanol as colorless crystals (0.30 g, 57% yield); m.p. 182–183 °C. IR (KBr): 2220 (C≡N), 1682 cm^{-1} (CON).

$C_{14}H_{11}N_5O$ (265.3)

Calcd	C 63.38	H 4.18	N 26.40%,
Found	C 63.40	H 4.20	N 26.00%.

(b) A stirred solution of **8a** (0.47 g, 1.98 mmol) in *N,N*-dimethylformamide (10 ml) was treated with sodium hydride (0.43 g, 17.92 mmol) for 20 min. Then, ethyl iodide (10 ml) was added and the mixture was stirred at room temperature for 4 h. Then, it was diluted with cold water, and the product that separated out was filtered, washed with water, and crystallized from ethanol as colorless crystals (0.39 g, 74% yield); m.p. 182–183 °C. It is identical with that obtained from a.

6-Cyano-8-ethyl-7-p-methoxyphenyl-1,2,4-triazolo[4,3-a]pyrimidin-5-one (**9b**)

(a) A mixture of **8b** (0.50 g, 1.87 mmol) and triethyl orthoformate (10 ml) was heated under reflux for 4 h. The product that separated out was filtered and crystallized from ethanol as colorless crystals (0.38 g, 69% yield); m.p. 219–220 °C. IR (KBr): 2220 (C≡N), 1680 cm^{-1} (CON).

$C_{15}H_{13}N_5O_2$ (295.3)

Calcd	C 61.01	H 4.44	N 23.72%,
Found	C 61.40	H 4.20	N 23.60%.

(b) A stirred solution of **8b** (0.50 g, 1.87 mmol) in *N,N*-dimethylformamide (10 ml) was treated with sodium hydride (0.43 g, 17.92 mmol) for 20 min. Then, ethyl iodide (10 ml) was added and the mixture was processed as above, colorless crystals (0.39 g, 71% yield); m.p. 219–220 °C. It is identical with that obtained from a.

6-Cyano-8-ethyl-7-p-chlorophenyl-1,2,4-triazolo[4,3-a]pyrimidin-5-one (**9c**)

A mixture of **8c** (0.50 g, 1.84 mmol) and triethyl orthoformate (10 ml) was heated under reflux for 4 h. The product was crystallized from ethanol as pale yellow crystals (0.39 g, 71% yield); m.p. 160–163 °C. IR (KBr): 2222 (C≡N), 1683 cm^{-1} (CON).

$C_{14}H_{10}N_5OCl$ (299.8)

Calcd	C 56.09	H 3.36	N 23.35%,
Found	C 56.30	H 3.60	N 23.60%.

6-Cyano-8-methyl-7-phenyl-1,2,4-triazolo[4,3-a]-pyrimidin-5-one (**10a**)

A suspension of **8a** (0.47 g, 1.98 mmol) and potassium carbonate (1.0 g, 7.24 mmol) in *N,N*-dimethylformamide (20 ml) was treated with methyl iodide (1.0 ml). The reaction mixture was stirred for 4 h at room temperature, and then processed as before. The product was crystallized from ethanol as colorless crystals (0.36 g, 72% yield); m.p. 230–232 °C. IR (KBr): 2218 (C≡N), 1669 cm^{-1} (CON). ^1H NMR (DMSO-d_6): δ = 3.95 (s, 3 H, NMe), 7.60 (m, 3 H, ArH), 7.90 (m, 2 H, ArH), 9.47 (s, 1 H, CH).

$C_{13}H_9N_5O$ (251.2)

Calcd	C 62.14	H 3.61	N 27.88%,
Found	C 62.30	H 3.80	N 27.50%.

6-Cyano-8-benzyl-7-phenyl-1,2,4-triazolo[4,3-a]-pyrimidin-5-one (**11a**)

A suspension of **8a** (0.47 g, 1.98 mmol) and potassium hydroxide (0.50 g, 8.93 mmol) in *N,N*-dimethylformamide (10 ml) was cooled and treated with benzyl chloride (3.5 ml). The reaction mixture was heated under reflux for 4 h, cooled and poured onto crushed ice. The product that separated was filtered, washed with water and crystal-

lized from ethanol as white crystals (0.30 g, 46% yield); m.p. 213–215 °C. IR (KBr): 2212 (C≡N), 1641 cm^{-1} (CON). ^1H NMR (DMSO-d_6): δ = 2.51 (s, 2 H, NCH_2), 7.19–7.40 (m, 6 H, ArH), 7.52 (m, 2 H, ArH), 7.83 (m, 2 H, ArH), 8.91 (s, 1 H, CH).

$C_{19}H_{13}N_5O$ (327.3)
Calcd C 69.71 H 4.00 N 21.40%,
Found C 69.90 H 3.80 N 21.60%.

6-Cyano-5-phenyl-1,2,4-triazolo[1,5-a]-pyrimidin-7(4H)-one (**13**)

(a) A mixture of **8a** (0.47 g, 1.98 mmol) and potassium hydroxide (0.50 g, 8.93 mmol) in ethanol (25 ml) was heated under reflux for 3 h. The reaction mixture was cooled and neutralized with dilute HCl. The product that separated out was filtered, and crystallized from ethanol as colorless crystals (0.32 g, 68% yield); m.p. 325–328 °C. IR (KBr): 3114 (NH), 2230 (C≡N), 1671 (CON), 1606 cm^{-1} (C=N).

$C_{12}H_7N_5O$ (237.2)
Calcd C 60.75 H 2.97 N 29.53%,
Found C 60.50 H 3.10 N 29.60%.

(b) Compound **8a** (0.47 g, 1.98 mmol) was fused above its melting point for 1 h. The solidified product was triturated with ethanol, filtered off and recrystallized from ethanol (0.32 g, 68% yield); m.p. 325–327 °C. It is identical with the product from method a.

6-Cyano-8-methyl-5-phenyl-1,2,4-triazolo[4,3-a]-pyrimidin-7-one (**14**)

(a) A mixture of **4** [28] (0.48 g, 1.99 mmol) in DMF (3 ml) and triethyl orthoformate (6 ml) was heated under reflux for 1 h, whereby the product precipitated out during the heating. The product was crystallized from ethanol as pale yellow crystals (0.31 g, 62% yield); m.p. 287–289 °C. IR (KBr): 2231 (C≡N), 1677 (CON), 1621 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ = 3.70 (s, 3 H, NMe), 7.60 (s, 5 H, ArH), 8.10 (s, 1 H, CH).

$C_{13}H_9N_5O$ (251.2)
Calcd C 62.14 H 3.61 N 27.88%,
Found C 62.40 H 3.80 N 27.50%.

(b) A mixture of **4** (0.48 g, 1.99 mmol) and formic acid (60 ml) was heated under reflux for 4 h. The product that separated out on cooling was crystallized from ethanol (0.36 g, 72% yield); m.p. 287–289 °C. It is identical with the product from method a.

8-Benzyl-6-cyano-5-phenyl-1,2,4-triazolo[4,3-a]-pyrimidin-7-one (**15**)

(a) A mixture of **5** (0.60 g, 1.89 mmol) and triethyl orthoformate (6 ml) was heated under reflux for 1 h. The product was crystallized from ethanol as colorless crystals (0.45 g, 73% yield); m.p. 217–218 °C. IR (KBr): 2231 (C≡N), 1681 (CON), 1622 cm^{-1} (C=N).

$C_{19}H_{13}N_5O$ (327.3)
Calcd C 69.71 H 4.00 N 21.40%,
Found C 69.80 H 4.10 N 21.30%.

(b) A mixture of **5** (0.60 g, 1.89 mmol) and formic acid (6 ml) was heated under reflux for 1 h. The product was crystallized from ethanol (0.46 g, 74% yield); m.p. 217–219 °C. It is identical with that obtained by method a.

6-Cyano-4-methyl-5-phenyl-1,2,4-triazolo[1,5-a]-pyrimidin-7-one (**17**)

A suspension of **13** (0.47 g, 1.98 mmol) and potassium carbonate (1.0 g, 7.24 mmol) in *N,N*-dimethylformamide (20 ml) was treated with methyl iodide (1.0 ml). The reaction mixture was stirred for 6 h, and then processed as for **10**. The product was crystallized from ethanol as colorless crystals (0.31 g, 62% yield); m.p. 157–160 °C. IR (KBr): 2239 (C≡N), 1690 (CON), 1603 cm^{-1} (C=N).

$C_{13}H_9N_5O$ (251.2)
Calcd C 62.14 H 3.61 N 27.88%,
Found C 62.40 H 3.80 N 27.60%.

6-Cyano-4-methyl-7-phenyl-1,2,4-triazolo[1,5-a]-pyrimidin-5-one (**18**)

A mixture of **14** (0.50 g, 1.99 mmol) and potassium hydroxide (0.50 g, 8.92 mmol) in absolute ethanol (25 ml) was heated under reflux for 2 h. The reaction mixture was processed as for **13** and the product was crystallized from ethanol as colorless crystals (0.33 g, 66% yield); m.p. 227–228 °C. IR (KBr): 2234 (C≡N), 1674 (CON), 1620 cm^{-1} (C=N).

$C_{13}H_9N_5O$ (251.2)
Calcd C 62.14 H 3.61 N 27.88%,
Found C 62.00 H 3.60 N 28.20%.

4-Benzyl-6-cyano-7-phenyl-1,2,4-triazolo[1,5-a]-pyrimidin-5-one (**19**)

A mixture of **15** (0.30 g, 0.92 mmol) and potassium hydroxide (0.50 g, 8.92 mmol) in absolute ethanol (25 ml) was heated under reflux for 1 h.

The reaction mixture was processed as before and the product was crystallized from ethanol as colorless crystals (0.23 g, 77% yield); m.p. 190 °C. IR (KBr): 2228 (C≡N), 1670 (CON), 1619 cm^{-1} (C=N).

$C_{19}H_{13}N_5O$ (327.3)
Calcd C 69.71 H 4.00 N 21.40%,
Found C 69.60 H 4.00 N 21.20%.

*7-Imino-5-phenyl-1,2,4-triazolo[1,5-a]pyrimidine (**22**)*

A mixture of **8a** (0.47 g, 1.89 mmol) and potassium hydroxide (2.0 g, 35.71 mmol) in ethanol (20 ml) was heated under reflux for 2 h. The reaction mixture was cooled and neutralized with dilute HCl. The product that separated out was filtered, and crystallized from ethanol as colorless crystals (0.35 g, 84% yield); m.p. 303–306 °C. IR (KBr): 3314 (NH), 1606 cm^{-1} (C=N). ^1H NMR (DMSO-d_6): δ = 6.80 (s, 1 H, CH), 7.54 (m, 3 H, ArH), 8.06 (m, 2 H, ArH), 8.20 (s, 2 H, NH), 8.48 (s, 1 H, CH).

$C_{11}H_9N_5$ (211.2)
Calcd C 62.55 H 4.30 N 33.16%,
Found C 62.50 H 4.30 N 33.30%.

Attempted Dimroth rearrangement with acid

When compound **15** (0.20 g, 0.61 mmol) in acetic acid (10 ml) and HCl (1 ml) were boiled under reflux for 4 h, then diluted with water, the product formed was recovered unchanged.

*Benzaldehyde 5-cyano-4-oxo-6-phenyl-3,4-dihydropyrimidin-2-yl)hydrazone (**23**)*

A suspension of **6** [28] (0.45 g, 1.98 mmol) in ethanol (10 ml), benzaldehyde (1 ml) and 2 drops of acetic acid was heated under reflux for 1 h. During the reaction period the hydrazine dissolved with the precipitation of the hydrazone. The product was filtered and crystallized from ethanol as pale yellow crystals (0.41 g, 66% yield); m.p. 299–301 °C [Lit.[28] m.p. 299 °C].

*6-Cyano-3,7-diphenyl-1,2,4-triazolo[4,3-a]-pyrimidin-5(8H)-one (**24**)*

A solution of 2 M solution of ferric chloride in ethanol (50 ml) was added dropwise to a boiling solution of **23** (0.62 g, 1.97 mmol) in ethanol (10 ml), and heating was continued for 15 min. The reaction mixture was cooled and diluted with water. The product that separated out was filtered and crystallized from ethanol as colorless crystals (0.40 g, 65% yield); m.p. 237–239 °C [Lit.[29] m.p. 235 °C].

*6-Cyano-2,5-diphenyl-1,2,4-triazolo[1,5-a]-pyrimidin-7(4H)-one (**25**)*

(a) A suspension of **23** (0.62 g, 1.97 mmol) in acetic acid (10 ml), was treated with bromine (5 ml) in acetic acid (2 ml) dropwise and the reaction mixture was stirred for 4 h. Then, it was diluted with water and the product was filtered and crystallized from ethanol. TLC showed the presence of a major spot and two minor ones. One of the minor spots was identified to be for compound **24**. The major product was separated by fractional crystallization as colorless crystals (0.45 g, 73% yield); m.p. > 300 °C. IR (KBr): 3225 (NH), 2227 (C≡N), 1666 (CON), 1615 cm^{-1} (C=N). ^1H NMR (DMSO-d_6): δ = 7.62 (m, 6 H, ArH), 7.66 (s, 1 H, NH), 7.84 (m, 2 H, ArH), 8.16 (m, 2 H, ArH).

$C_{18}H_{11}N_5O$ (313.3)
Calcd C 69.00 H 3.54 N 22.35%,
Found C 68.60 H 3.80 N 22.10%.

(b) A mixture of **24** (0.30 g, 0.96 mmol) and potassium hydroxide (0.50 g, 8.93 mmol) in absolute ethanol (25 ml) was heated under reflux for 2 h. The reaction mixture was processed as for **13**. The product was crystallized from ethanol (0.20 g, 67% yield); m.p. > 300 °C. It is identical with the product from method a.

*6-Cyano-8-methyl-3,7-diphenyl-1,2,4-triazolo-[4,3-a]pyrimidin-5-one (**27**)*

A suspension of **24** (0.62 g, 1.98 mmol) and potassium carbonate (0.50 g, 3.62 mmol) in *N,N*-dimethylformamide (10 ml), was treated with methyl iodide (3 ml). The reaction mixture was processed as before and the product was crystallized from ethanol as colorless crystals (0.40 g, 62% yield); m.p. 175–178 °C. IR (KBr): 2216 (C≡N), 1680 cm^{-1} (OCN). ^1H NMR ($CDCl_3$): δ = 4.08 (s, 3 H, NMe), 7.55 (m, 6 H, ArH), 7.84 (m, 2 H, ArH), 8.02 (m, 2 H, Ar-H).

$C_{19}H_{13}N_5O$ (327.3)
Calcd C 69.71 H 4.00 N 21.40%,
Found C 69.40 H 4.10 N 21.10%.

*8-Benzyl-6-cyano-3,7-diphenyl-1,2,4-triazolo-[4,3-a]pyrimidin-5-one (**28**)*

A suspension of **24** (0.62 g, 1.98 mmol) and potassium hydroxide (0.28 g, 5.0 mmol) in *N,N*-dimethylformamide (10 ml), was cooled and treated

with benzyl chloride (3.5 ml). The reaction mixture was processed as before and the product was crystallized from ethanol as colorless crystals (0.46 g, 58% yield); m.p. 213–215 °C. IR (KBr): 2213 (C≡N), 1698 cm^{-1} (CON).

$C_{25}H_{17}N_5O$ (403.4)
Calcd C 74.43 H 4.25 N 17.35%,
Found C 74.10 H 4.30 N 17.00%.

6-Cyano-4-methyl-2,5-diphenyl-1,2,4-triazolo-[1,5-a]pyrimidin-7-one (**29**)

A suspension of **25** (0.62 g, 1.98 mmol) and potassium carbonate (0.50 g, 3.62 mmol) in *N,N*-dimethylformamide (10 ml), was treated with methyl iodide (3 ml). The reaction mixture was processed as before and the product was crystallized from ethanol as colorless crystals (0.40 g, 62% yield); m.p. 299–301 °C. IR (KBr): 2210 (C≡N), 1697 cm^{-1} (CON). ^1H NMR ($CDCl_3$): δ = 3.77 (s, 3 H, NMe), 7.52 (m, 6 H, ArH), 7.70 (m, 2 H, ArH), 8.40 (m, 2 H, ArH).

$C_{19}H_{13}N_5O$ (327.3)
Calcd C 69.71 H 4.00 N 21.40%,
Found C 69.50 H 4.20 N 21.20%.

Benzaldehyde (5-cyano-3-methyl-4-oxo-6-phenyl-3,4-dihydropyrimidin-2-yl) hydrazone (**30**)

A suspension of **4** [28] (0.48 g, 2.11 mmol) in ethanol (10 ml) and benzaldehyde (1 ml) with 2 drops of acetic acid was heated under reflux for 1 h. During the reaction period the hydrazine dissolved with the formation of the hydrazone. The product was filtered and crystallized from ethanol as yellow crystals (0.42 g, 60% yield); m.p. 220–221 °C [Lit.[28] m.p. 220 °C].

p-Nitrobenzaldehyde (5-cyano-3-methyl-4-oxo-6-phenyl-3,4-dihydropyrimidin-2-yl)hydrazone (**31**)

A suspension of **4** (0.48 g, 2.11 mmol) in ethanol (10 ml) and *p*-nitrobenzaldehyde (0.30 g, 1.99 mmol) with 2 drops of acetic acid was heated under reflux for 1 h. The mixture was processed as before. The product was crystallized from ethanol as yellow crystals (0.42 g, 53% yield); m.p. 253–254 °C. IR (KBr): 2220 (C≡N), 1678 (CON), 1620 cm^{-1} (C=N).

$C_{19}H_{14}N_6O_3$ (374.4)
Calcd C 60.96 H 3.77 N 22.45%,
Found C 60.80 H 3.90 N 22.70%.

Benzaldehyde (3-benzyl-5-cyano-4-oxo-6-phenyl-3,4-dihydropyrimidin-2-yl)hydrazone (**32**)

A suspension of **5** (0.60 g, 1.89 mmol) in ethanol (10 ml) and benzaldehyde (1 ml) with 2 drops of acetic acid was heated under reflux for 1 h. The reaction was processed as before. The product was crystallized from ethanol as yellow needles (0.56 g, 73% yield); m.p. 220–222 °C. IR (KBr): 3311 (NH), 2222 (C≡N), 1684 (CON), 1623 cm^{-1} (C=N).

$C_{25}H_{19}N_5O$ (405.4)
Calcd C 74.06 H 4.72 N 17.28%,
Found C 74.30 H 4.80 N 17.00%.

p-Nitrobenzaldehyde (3-benzyl-5-cyano-4-oxo-6-phenyl-3,4-dihydropyrimidin-2-yl)hydrazone (**33**)

A suspension of **5** (0.60 g, 1.89 mmol) in ethanol (10 ml) and *p*-nitrobenzaldehyde (0.30 g, 1.99 mmol) with 2 drops of acetic acid was heated under reflux for 1 h. The product was crystallized from ethanol as yellow crystals (0.52 g, 61% yield); m.p. 289–292 °C. IR (KBr): 3310 (NH), 2223 (C≡N), 1685 (CON), 1625 cm^{-1} (C=N).

$C_{25}H_{18}N_6O_3$ (450.4)
Calcd C 66.66 H 4.03 N 18.66%,
Found C 66.80 H 4.20 N 18.40%.

6-Cyano-8-methyl-3,5-diphenyl-1,2,4-triazolo-[4,3-a]pyrimidin-7-one (**34**)

A mixture of **30** (0.50 g, 1.52 mmol) and thionyl chloride (0.5 ml) was heated under reflux for 3 h. The reaction mixture was cooled and poured onto crushed ice. The product separated was filtered, washed with water and crystallized from ethanol as colorless crystals (0.30 g, 60% yield); m.p. 181–183 °C. IR (KBr): 2237 (C≡N), 1698 (CON), 1630 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ = 3.85 (s, 3 H, NMe), 6.96–7.30 (m, 10 H, ArH).

$C_{19}H_{13}N_5O$ (327.3)
Calcd C 69.71 H 4.00 N 21.40%,
Found C 69.70 H 4.10 N 21.00%.

6-Cyano-8-methyl-3-p-nitrophenyl-1,2,4-triazolo[4,3-a]pyrimidin-7-one (**35**)

A mixture of **31** (0.55 g, 1.47 mmol) in thionyl chloride (5 ml) was heated under reflux for 3 h. The reaction mixture was processed as above and the product was crystallized from ethanol as pale yellow crystals (0.30 g, 55% yield); m.p. 264–265 °C. IR (KBr): 2238 (C≡N), 1682 (CON), 1624 cm^{-1} (C=N).

$C_{19}H_{12}N_6O_3$ (372.3)
Calcd C 61.29 H 3.25 N 22.56%,
Found C 61.10 H 3.30 N 22.30%.

8-Benzyl-6-cyano-3,5-diphenyl-1,2,4-triazolo-[4,3-a]pyrimidin-7-one (**36**)

A mixture of **32** (0.60 g, 1.48 mmol) in thionyl chloride (5 ml) was heated under reflux for 3 h. The reaction mixture was processed as before. The product was crystallized from ethanol as colorless crystals (0.35 g, 58% yield); m.p. 140–143 °C. IR (KBr): 2235 (C≡N), 1683 (CON), 1621 cm^{-1} (C=N).

$C_{25}H_{17}N_5O$ (403.4)
Calcd C 74.42 H 4.25 N 17.36%,
Found C 74.50 H 4.20 N 17.40%.

8-Benzyl-6-cyano-3-p-nitrophenyl-5-phenyl-1,2,4-triazolo[4,3-a]pyrimidin-7-one (**37**)

A suspension of **33** (0.60 g, 1.33 mmol) in thionyl chloride (5 ml) was heated under reflux for 3 h. The reaction mixture was processed as before. The product was crystallized from ethanol as colorless crystals (0.38 g, 64% yield); m.p. 210–212 °C. IR (KBr): 2240 (C≡N), 1694 (CON), 1627 cm^{-1} (C=N).

$C_{25}H_{16}N_6O_3$ (448.4)
Calcd C 66.96 H 3.60 N 18.73%,
Found C 67.10 H 3.70 N 18.30%.

6-Cyano-4-methyl-2,7-diphenyl-1,2,4-triazolo-[1,5-a]pyrimidin-5-one (**38**)

(a) A suspension of **30** (0.50 g, 1.52 mmol) in acetic acid (10 ml), was treated with bromine (5 ml) in acetic acid (20 ml) dropwise addition and the reaction mixture was stirred for 4 h. Then, it was diluted with water and the product formed was filtered and crystallized from ethanol as colorless crystals, m.p. 286–288 °C (0.35 g, 70% yield). IR (KBr): 2235 (C≡N), 1684 (CON), 1631 cm^{-1} (C=N).

$C_{19}H_{13}N_5O$ (327.3)
Calcd C 69.71 H 4.00 N 21.40%,
Found C 69.90 H 3.80 N 21.00%.

(b) A mixture of **34** (0.60 g, 1.83 mmol) and potassium hydroxide (0.50 g, 8.93 mmol) in absolute ethanol (25 ml) was heated under reflux for 2 h. The reaction mixture was processed as for **13**. The product was filtered crystallized from ethanol as colorless crystals (0.43 g, 72% yield); m.p. 286–288 °C. IR (KBr): 2234 (C≡N), 1684 (CON), 1631 cm^{-1} (C=N).

6-Cyano-4-methyl-2-p-nitrophenyl-7-phenyl-1,2,4-triazolo[1,5-a]pyrimidin-5-one (**39**)

(a) A suspension of **31** (0.37 g, 1.0 mmol) in acetic acid (10 ml), was treated with bromine (5 ml) in acetic acid (20 ml) dropwise addition and the reaction mixture was stirred for 4 h. Then, it was processed as before. The product was crystallized from ethanol as pale yellow crystals, m.p. 260 °C (0.29 g, 78% yield). IR (KBr): 2234 (C≡N), 1689 (CON), 1629 cm^{-1} (C=N).

$C_{19}H_{12}N_6O_3$ (372.3)
Calcd C 61.29 H 3.25 N 22.56%,
Found C 61.40 H 3.20 N 22.80%.

(b) A mixture of **35** (0.74 g, 1.99 mmol) and potassium hydroxide (0.50 g, 8.93 mmol) in absolute ethanol (25 ml) was heated under reflux for 2 h. The reaction mixture was processed as before. The product crystallized from ethanol as colorless crystals; m.p. 260 °C. It was found to be identical with the product from method a.

4-Benzyl-6-cyano-2,7-diphenyl-1,2,4-triazolo-[1,5-a]pyrimidin-5-one (**40**)

(a) A suspension of **32** (0.60 g, 1.48 mmol) in acetic acid (10 ml), was treated with bromine (5 ml) in acetic acid (20 ml) dropwise addition and the reaction mixture was processed as before. The product was crystallized from ethanol as colorless crystals (0.45 g, 75% yield); m.p. 245–247 °C. IR (KBr): 2226 (C≡N), 1674 (CON), 1620 cm^{-1} (C=N).

$C_{25}H_{17}N_5O$ (403.4)
Calcd C 74.42 H 4.25 N 17.36%,
Found C 74.20 H 4.00 N 17.40%.

(b) A mixture of **36** (0.40 g, 0.99 mmol) and potassium hydroxide (0.50 g, 0.93 mmol) in absolute ethanol (25 ml) was heated under reflux for 2 h. The reaction mixture was processed as before; m.p. 245–247 °C. IR (KBr): 2226 (C≡N), 1674 (CON), 1620 cm^{-1} (C=N). The product was found to be identical with that obtained by method a.

2-(N-Acetylbenzylidenehydrazino)-5-cyano-3-methyl-6-phenyl-3,4-dihydropyrimidin-4-one (**41**)

A cold solution of **30** (0.50 g, 1.52 mmol) in dry pyridine (5 ml), was treated with acetic anhydride (4 ml). The reaction mixture was kept overnight

at 20 °C with occasional stirring and then poured onto crushed ice. The product that separated was filtered, washed with water and dried. It was crystallized from ethanol as yellow crystals (0.46 g, 82% yield); m.p. 222 °C. IR (KBr): 2228 (C≡N), 1697 and 1640 cm^{-1} (CON). ^1H NMR ($CDCl_3$): δ = 2.20 (s, 3 H, COMe), 3.47 (s, 3 H, NMe), 6.81 (m, 2 H, ArH), 6.90 (s, 1 H, N=CH), 7.20 (m, 5 H, ArH), 7.52 (m, 3 H, ArH).

$C_{21}H_{17}N_5O_2$ (371.4)
Calcd C 67.91 H 4.61 N 18.86%,
Found C 67.90 H 5.00 N 18.50%.

2-(N-Acetylbenzylidenehydrazino)-3-benzyl-5-cyano-6-phenyl-3,4-dihydropyrimidin-4-one (**42**)

A cold solution of **32** (0.40 g, 0.99 mmol) in dry pyridine (5 ml), was treated with acetic anhydride (4 ml). The reaction mixture was processed as before. The product was crystallized from ethanol as yellow crystals (0.32 g, 72% yield); m.p. 131–134 °C. IR (KBr): 2226 (C≡N), 1696 and 1650 cm^{-1} (CON).

$C_{27}H_{21}N_5O_2$ (447.5)
Calcd C 72.47 H 4.73 N 15.65%,
Found C 72.20 H 5.00 N 15.40%.

(b) A suspension of **32** (0.40 g, 0.99 mmol) in acetic anhydride (4 ml) was heated under reflux on a boiling water bath for 3 h. The reaction mixture was cooled and poured onto crushed ice. The product that separated was filtered, washed, dried and crystallized from ethanol as yellow crystals, m.p. 131–134 °C. It was found to be identical with **42**.

Acknowledgment

Thanks are due to Klaus Hagele, Universitat Konstanz for making available the mass spectra.

[1] E. S. H. El Ashry, Y. El Kilany, N. Rashed, H. Assafir, Adv. Hetrocycl. Chem., in press.
[2] E. S. H. El Ashry, N. Rashed, Adv. Heterocycl. Chem. **72**, 127 (1999).
[3] K. Awal, Ger. Pat. 3,839,711, (1989); [Chemical Abstracts **112**, 55902 (1990)].
[4] G. Barthelemy, A. Hallot, J. N. Vallat, Fr. Pat. 2,549,834 (1985); [Chemical Abstracts **103**, 71335 (1985)].
[5] N. Bru-Magniez, T. Guengor, J. M. Teulon, U. S. Pat. 5,387,747 (1995); [Chemical Abstracts **123**, 228204 (1995)].
[6] J. D. Albright, J. P. Dusza, R. A. Hardy (Jr.), U. S. Pat. 4,209,621 (1980); [Chemical Abstracts **93**, 168298 (1980)].
[7] H. Nakamura, Y. Hosoi, J. Fukawa, Jpn. Kokai Pat. 0,313,934 (1991); [Chemical Abstracts **115**, 60769 (1991)].
[8] M. J. Costales, J. C. Van Heertum, W. A. Kleschik, R. J. Ehr, P. G. Ray, U. S. Pat. 5,201,938 (1993); [Chemical Abstracts **119**, 180806 (1993)].
[9] K. J. Pees, H. M. Becher, PCT Pat. 9,420,501 (1994); [Chemical Abstracts **122**, 133227 (1995)].
[10] N. Bru-Magniez, E. Nicolai, J. M. Teulon, U. S. Pat. 5,358,950 (1994); [Chemical Abstracts **122**, 314561 (1995)].
[11] Y. Qu, W. Zhang, Zhonguo Yiyao Gongye Zazhi **23**, 538 (1992); [Chemical Abstracts **119**, 117200 (1993)].
[12] G. Jaerecke, L. Meister, L. Dressel, R. Richter, H. Voigt, Z. Chem. **29**, 378 (1989).
[13] A. Eriguchi, T. Mimura, M. Tomikawa, K. Nishida, Jpn. Kokai Pat. 03,118,383 (1991); [Chemical Abstracts **115,** 208011 (1991)].
[14] H. Kano, Y. Makisumi, Chem. Pharm. Bull. **7**, 907 (1959).
[15] H. Kano, Y. Makisumi, Chem. Pharm. Bull. **6**, 583 (1958).
[16] Y. Makisumi, H. Kano, S. Takahashi, Jap. Pat. 949862 (1958); [Chemical Abstracts **59**, 5178 (1963)].
[17] A. Mousaad, N. Rashed, E. Ramadan, E. S. H. El Ashry, Spectrosc. Lett. **27**, 677 (1994).
[18] K. F. Atta, A. M. El Massry, H. Abdel Hamid, E. S. H. El Ashry, A. Amer, J. Heterocycl. Chem. **31**, 549 (1994).
[19] N. Rashed, E. I. Ibrahim, E. S. H. El Ashry, Carbohydr. Res. **254**, 295 (1994).
[20] N. Rashed, M. Shoukry, E. S. H. El Ashry, Bull. Chem. Soc. Jpn. **67**, 149 (1994).
[21] E. S. H. El Ashry, N. Rashed, A. Mousaad, E. Ramadan, Adv. Heterocycl. Chem. **59**, 394 (1994).
[22] N. Rashed, A. El Nemr, E. S. H. El Ashry, Spectrosc. Lett. **26**, 1817 (1993).
[23] A. Mousaad, H. Abdel Hamid, A. El Nemr, E. S. H. El Ashry, Bull. Chem. Soc. Jpn. **65**, 546 (1992).
[24] N. Rashed, A. El Nemr, E. S. H. El Ashry, Arch. Pharm. **326**, 153 (1992).
[25] E. S. H. El Ashry, A. Mousaad, N. Rashed, Adv. Heterocycl.Chem. **53**, 234 (1992).
[26] E. S. H. El Ashry, Y. El Kilany, Adv. Heterocycl. Chem. **67**, 391 (1996)
[27] E. S. H. El Ashry, Y. El Kilany, Adv. Heterocycl. Chem. **68**, 1 (1997).
[28] S. M. Hussain, A. A. El-Barbary, S. A. Mansour, J. Heterocycl. Chem. **22**, 169 (1985).
[29] Z. H. Khalid, A. A. Abdel Hafez, A. A. Ahmed, Phosphorus, Sulfur and Silicon **45**, 81 (1989).
[30] S. Guccione, A. Raffaelh, G. U. Barretta, L. M. Scolaro, S. Pucci, F. Russo, J. Heterocycl. Chem. **32,** 1149 (1995).
[31] D. J. Brown, M. N. Paddon-Row, J. Chem. Soc. (C) 164 (1966).
[32] S. Kambe, K. Saito, H. Kishi, Synthesis **4**, 287 (1979).