Synthesis of 1,2,4-Triazolo[4,3-*a*]pyrimidine Derivatives by Cyclocondensation of a 2-Thioxopyrimidin-4(3*H*)-one with Hydrazonoyl Halides

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The reaction of 1,2-dihydro-6-(phenylamino)-2-thioxopyrimidin-4(3*H*)one (**16**) with *N*-arylhydrazonoyl halides **15** in $CHCl_3$ in the presence of Et_3N under reflux afforded the corresponding 1,2,4-triazolo[4,3-*a*]-pyrimidin-5-ones of type **20** in good yields (*Scheme 3*). The structure of one of the derivatives, **20d**, has been established by X-ray crystallography. Conceivable reaction mechanisms are discussed in *Schemes 3* and *4*. The products of type **20** easily undergo reactions with electrophiles such as benzenediazonium chloride, chloroacetyl chloride, and $NaNO_2$ in AcOH to give 6-phenylazo, 6-chloroacetyl, and 6-nitroso derivatives **21**, **23**, and **25**, respectively (*Scheme 5*).

Introduction. – Recently, the chemistry of 1,2,4-triazolo[4,3-*a*]pyrimidines **1** has been reviewed comprehensively [1]. The other three isomeric 1,2,4-triazolopyrimidines are **2** [2], **3** [3], and **4** [4] with [1,5-*a*], [4,3-*c*], and [1,5-*c*] fusions, respectively, of the two heterocyclic systems. As with the other classes, derivatives of **1** have found broad applications in biology and medicine as well as in photography [5].

1 **2** **3** **4**

Chemically, one of the most remarkable features of compounds of type **1** is their tendency to rearrange to give [1,5-*a*] isomers **2** under acidic and basic conditions as well as by heating [6]. This isomerization *via* ring-opening/ring-closure processes is well-known as the *Dimroth* rearrangement [7] and appears often as a difficulty in the preparation of **1**. Another problem is the selectivity of the ring closure process, *e.g.*, in the frequently used cyclizations of 2-hydrazinopyrimidines with C_1 building blocks (*Scheme 1*). For example, heating **5** in HCOOH to 50–60° for 1 h gave a mixture of the isomeric 1,2,4-triazolo[4,3-*a*]pyrimidine derivatives **6** and **7**, in addition to their

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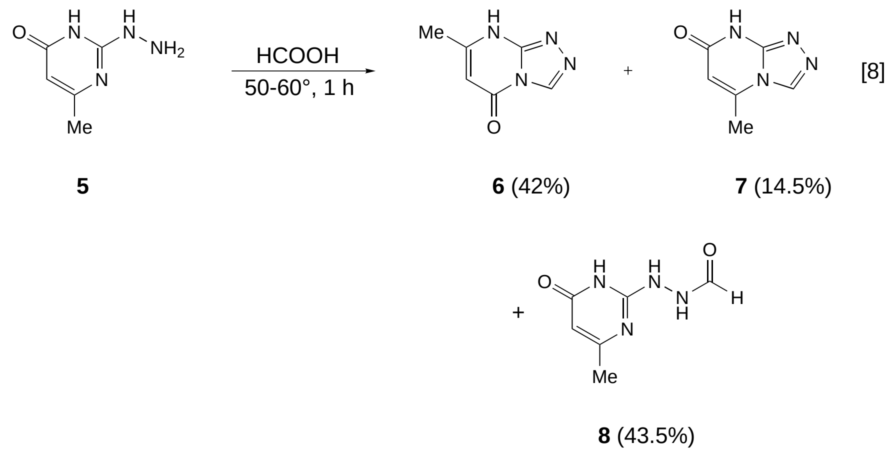
Scheme 1



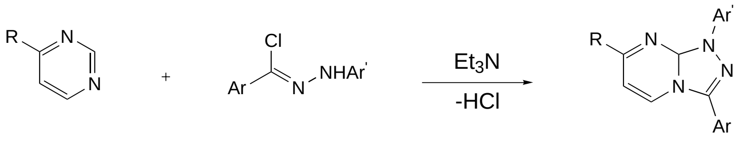
precursor **8** [8]. Cyclization of **8** by ring closure *via* N(1) or N(3) of the pyrimidine ring and dehydration leads to **7** or **6**, respectively.

A different synthetic approach to the ring skeleton **1** is the heterocyclization of a pyrimidine **9** with a C–N–N building block, *e.g.*, the chemo- and regioselective 1,3-dipolar cycloaddition of diaryl-nitrile imines generated *in situ* from **10**, leading to **11** [9] (*Scheme 2*). An intramolecular variant *via* 1,5-dipolar electrocyclization of a nitrile imine is also known [10]. On the other hand, pyrimidines bearing a leaving group at C(2) react with acid hydrazides [11], semicarbazide [12], thiosemicarbazide [13], and hydrazonoyl bromides [14]. For example, the reaction of pyrimidine derivative **12** with hydrazide **13** (R = alkyl) gave, after heating the intermediate 2-hydrazinopyrimidine in the presence of phenol, 3-alkyl-7-methyl-1,2,4-triazolo[4,3-*a*]pyrimidin-5-one **14** [15] (*Scheme 2*), whereas, with benzohydrazide under the same conditions, 5-methyl-3-phenyl-1,2,4-triazolo[4,3-*a*]pyrimidin-7-one was formed [16]. Recently, 5-substituted 1,2,4-triazolo[4,3-*a*]pyrimidines of type **1** have been prepared by the reaction of a 3-(dimethylamino)prop-2-en-1-one with 3-amino-1*H*-1,2,4-triazole [17].

One of us has a long-lasting interest in using heterocyclic compounds containing a thiourea moiety in the synthesis of fused heterocycles (*cf.* [18][19]). For example, it has been shown that hydrazonoyl halides **15** react with such heterocycles to give, in general, only one of the two possible isomers of the fused products. This selectivity has been explained by the assumption that one of the two ring-N-atoms is more basic and more nucleophilic (*cf.* [20][21]). Therefore, in the case of 2-thioxopyrimidin-4-one derivatives of type **16**, the ring closure is expected to occur at N(1), as N(3) is more desactivated by the neighboring C=O group. On the other hand, the dehydrocyclization of intermediate **8** (*Scheme 1*) yielded **6** as the major product, and the expected isomer **7** was obtained as the minor one.

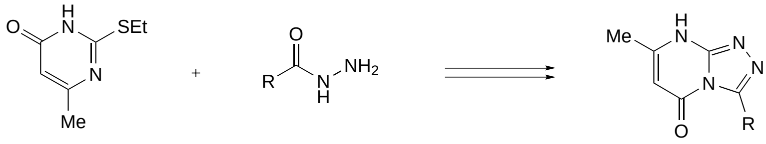
Recently, first examples of the reaction of 6-(phenylamino)-2-thioxopyrimidin-4(3*H*)-one (**16**) and C-(ethoxycarbonyl)hydrazonoyl chlorides leading to 5-oxo-1,2,4-triazolo[4,3-*a*]pyrimidine-3-carboxylates have been described [22]. In the present

Scheme 2



[9]

9 **10** **11**



[15]

12 **13** **14**

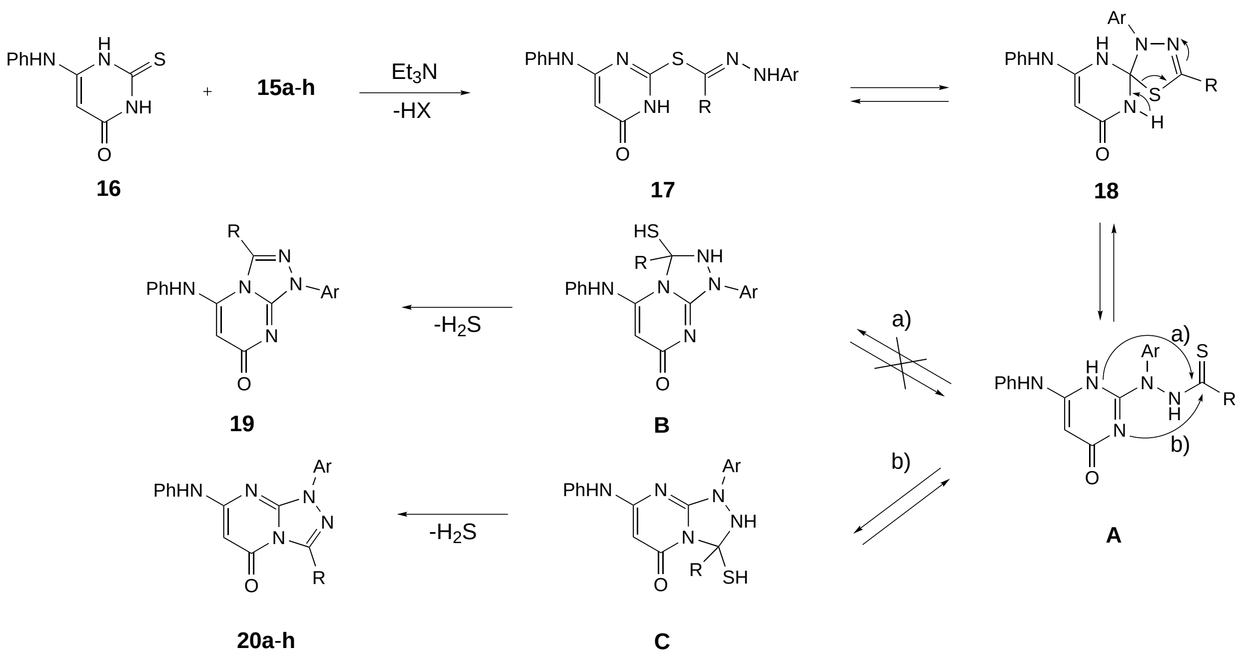
15 (X = Cl, Br) **16**

study, we report the generalization of the reaction of **16** with different hydrazonoyl halides of type **15**. The latter are known as very useful C–N–N building blocks that can react either *via* substitution by nucleophiles followed by cyclization (*cf.* [18][19][23]) or *via* intermediate nitrile imines by 1,3-dipolar cycloaddition (*cf.* [9][24–27]).

Results and Discussion. – The reactions of **16** with equimolar amounts of hydrazonoyl halides **15a**–**15h** were carried out in refluxing $CHCl_3$ in the presence of Et_3N. When all **15** had disappeared (4–6 h, TLC), the mixture was worked up by evaporating the solvent and treating the residue with MeOH. In all cases, a single product was obtained, which was recrystallized from a suitable solvent to give orange to yellow crystals. Both mass spectrometry and elemental analyses confirmed the absence of sulfur in all products (*cf.* [18][19]). Therefore, structures **17** and **18** (*Scheme 3*), which are the products of a nucleophilic substitution of X of **15** by the S-atom of **16** and the cyclization product of the intermediate[3]), respectively, were ruled out.

[3]) Formally, **18** is the product of the 1,3-dipolar cycloaddition of the corresponding nitrile imine, generated *in situ* from **15** by elimination of HX, onto the C=S group. Although nonenolizable C=S groups belong to the most reactive dipolarophiles known, and, therefore, thioketones are called 'superdipolarophiles' [28], it is rather unlikely that **18** is formed by this mechanism as nitrile imines – like other 1,3-dipoles – are easily protonated by OH, SH, and NH compounds (*cf.* [26]). For this reason, a nitrile imine and **16** would react to give the 1,3-adduct **17**.

Scheme 3



15, 20	R / Ar
a	MeOCO / Ph
b	MeOCO / 4-MeC_6H_4
c	MeOCO / 4-ClC_6H_4
d	EtOCO / 4-$MeOC_6H_4$

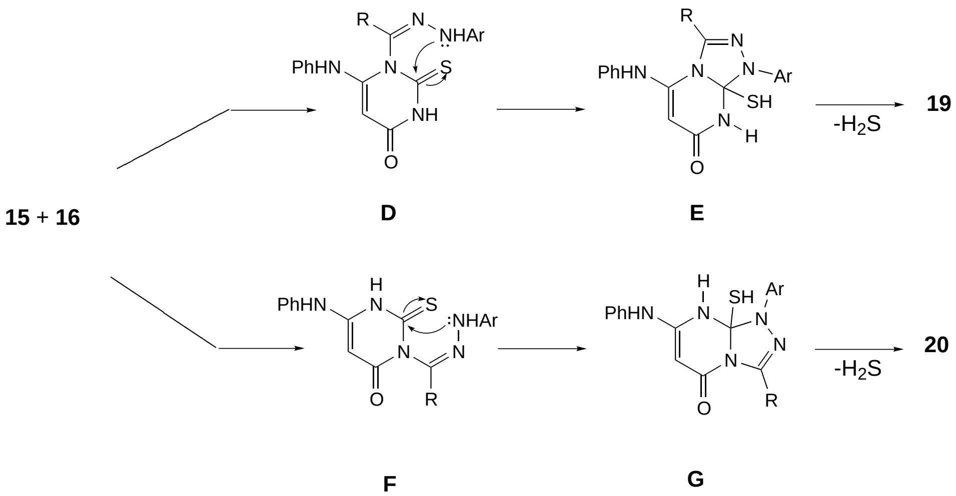
15, 20	R / Ar
e	PhCH=CH / Ph
f	MeCO / Ph
g	PhNHCO / Ph
h	2-thienyl / 4-$NO_2C_6H_4$

However, the analytical and spectroscopic data of the isolated products were in accordance with structures **19** or **20** formed *via* a cyclocondensation of **15** and **16** by elimination of H_2S. For example, the product from the reaction with **15a** showed two intense IR absorptions (in KBr) at 1744 and 1692 cm^{-1}, which are characteristic for an acetate and a pyrimidinone. In the ^{1}H-NMR spectrum ($CDCl_3$), three *singlets* appeared at 7.05 (NH), 5.45 (H−C(5) of pyrimidin-4-one), and 4.06 ppm (MeOCO), in addition to a *multiplet* at 8.15 – 7.3 ppm (10 arom. H). In *Scheme 3*, reaction mechanisms leading to **19** and **20** are proposed. The common intermediate **A** can be generated from the initially formed thiohydrazonate derivative **17** by an S → N migration of the pyrimidine ring *via* the spirocyclic intermediate **18**. Cyclization of **A** *via* nucleophilic attack of N(1) (*Route a*) or N(3) (*Route b*) of the pyrimidin-4-one onto the thioamide C-atom leads to **B** and **C**, respectively. Elimination of H_2S then yields either **19** or **20**.

A different reaction mechanism *via* nucleophilic attack of N(1) or N(3) of **16** at the hydrazonoyl halide **15** to give the substitution products **D** and **F**, respectively, is formulated in *Scheme 4*. Cyclization of these intermediates could lead to **E** and **G**, which, by elimination of H_2S, could give **19** and **20**, respectively. Although it is difficult to distinguish between the mechanisms in *Scheme 3* and *4*, those *via* **D**/**F** are unlikely for the following reasons: *a*) although amidrazones of type **D** and **F** are known to be stable (*cf.* [29 – 31]), all attempts to isolate them from the reaction mixture failed; *b*) reactions of 2-thiouracil derivatives with various halogen compounds gave, in all reported cases, only the S-substituted products (*cf.* [32 – 34]). Therefore, we strongly favor the mechanism depicted in *Scheme 3*.

Unfortunately, neither the spectroscopic data[4]) of the products nor the proposed reaction mechanisms allowed discrimination between structures **19** and **20**. For this

Scheme 4



[4]) All products showed a *singlet* at *ca.* 5.5 ppm in the ^{1}H-NMR spectrum, assignable to H−C(5) of the pyrimidin-4-one moiety and, in the IR spectrum, absorption bands near 3280 and 1700 cm^{-1} for an NH and amide CO group, respectively.

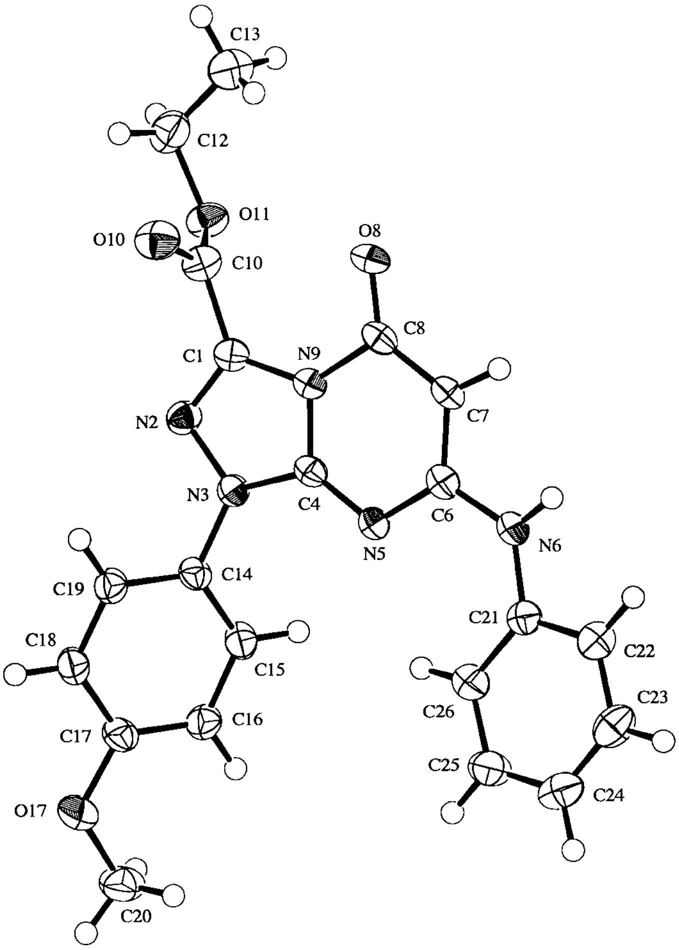


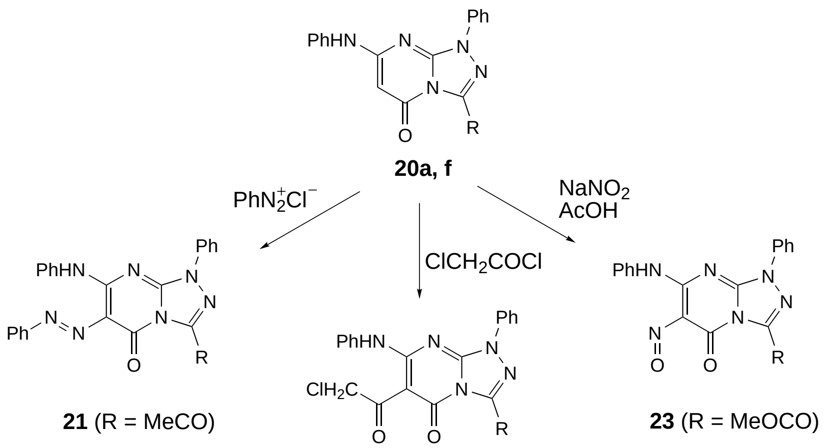
Figure. *ORTEP Plot* [35] *of the molecular structure of* **20d**: *disordered conformation A* (arbitrary numbering of the atoms; 50% probability ellipsoids)

reason, the molecular structure of the product obtained with **15d** has been established by X-ray crystallography as the 1,2,4-triazolo[4,3-*a*]pyrimidin-5-one derivative **20d** (*Fig.*).

In the structure of **20d**, the EtO atoms of the ethyl ester group are disordered over two positions that are related by a *ca.* 180° rotation about the O(11)–C(12) bond, with relative site occupation factors of 0.542 : 0.458. The plane of the O=C–O moiety is almost orthogonal to the ring plane (torsion angle O(10)–C(10)–C(1)–N(2) 76.6(3)°). The six-membered heterocyclic ring shows evidence for strong bond delocalization in that the C=O bond is slightly elongated (1.248(2) Å), and most of the lengths of the ring bonds approach those normally found in Ph rings. Neither the aromatic residue at N(3) nor PhNH at C(6) is coplanar with the heterocyclic system; the angles between the planes are 44.59(8) and 13.70(7)°, respectively. The amine group (N(6)H) of the molecule forms an intermolecular H-bond with O(8) of the amide C=O group of a neighboring molecule. The interactions link the molecules into infinite one-dimensional chains that run parallel to the *y*-axis and have a graph-set motif of C(6) [36].

In analogy to [22], the prepared 7-(phenylamino)-1,2,4-triazolo[4,3-*a*]pyrimidin-5-ones **20** undergo smooth reactions with electrophiles leading to C(6)-functionalized derivatives. For example, **20f** was readily coupled with an equimolar amount of benzenediazonium chloride to give the corresponding 6-(phenylazenyl) derivative **21** as the only product (*Scheme 5*). The structure of **21** was established on the basis of the elemental analysis and spectroscopic data (IR, ^{1}H-NMR, MS). Furthermore, the structure was confirmed by an independent synthesis *via* the reaction of 1,2-dihydro-6-(phenylamino)-5-(phenyldiazenyl)-2-thioxopyrimidin-4(3*H*)-one [37] with **15f**.

Scheme 5



22 (R = MeOCO)

Acylation of **20a** with ClCH$_2$COCl furnished the corresponding 6-(chloroacetyl) derivative **22**, and nitrosation with NaNO$_2$ in AcOH gave the corresponding 6-nitroso-1,2,4-triazolo[4,3-*a*]pyrimidine derivative **23** in excellent yield. The same compound was obtained after treatment of **16** with NaNO$_2$ in AcOH (*cf.* [37]) and reaction of the intermediate with hydrazonoyl chloride **15a** (*Scheme 5*).

In conclusion, we have shown that the reaction of **16** with differently substituted hydrazonoyl halides **15** is a general approach to 1,2,4-triazolo[4,3-*a*]pyrimidin-5-ones of type **20**, which can be further substituted at C(6) by reactions with electrophiles. The initial reaction in the formation of **20** is a nucleophilic substitution of the halide of **15** rather than a 1,3-dipolar cycloaddition of an intermediate nitrile imine, in contrast to reactions with *N*-substituted 1*H*-pyrimidinethiones [9]. The structure of **20d** was established by X-ray crystallography. The other structures of type **20** have been assigned on the basis of the similarity of spectroscopic data and under the assumption that the regioselectivity of the cyclization in intermediate **A** (*Scheme 3*) is not influenced by the variation of the substituents (*cf.* also [22]).

We thank the analytical units of our institutes for spectra and analyses. *E.M.A.* thanks the *Swiss Federal Government* for the provision of a *National Scholarship for Foreign Students.*

Experimental Part

1. *General*. See [23]. IR Spectra: in KBr. ^{1}H-NMR Spectra: in $CDCl_3$. Hydrazonoyl halides (chlorides or bromides) **15a – 15c**, [38], **15d** [39], **15e** [40], **15f** [41], **15g** [42], and **15h** [43], and *1,2-dihydro-6-(phenylamino)-2-thioxopyrimidin-4(3*H*)-one* (**16**) [37] were prepared according to the procedures indicated in the literature.

2. *Synthesis of 1,2,4-Triazolo[4,3-*a*]pyrimidin-5-ones* **20**. *General Procedure.* To a stirred soln. of **16** (1.1 g, 5 mmol) and the appropriate hydrazonoyl halide **15** (5 mmol) in $CHCl_3$ (40 ml), Et_3N (0.7 ml, 5 mmol) was added at r.t. The mixture was refluxed until **16** disappeared (4 – 6 h; TLC). The solvent was evaporated under reduced pressure, and the residue was treated with MeOH (10 ml). The solid formed was collected and crystallized from a suitable solvent to give the corresponding 1,2,4-triazolo[4,3-*a*]pyrimidine derivative **20**.

*Methyl 5-Oxo-1-phenyl-7-(phenylamino)-1,2,4-triazolo[4,3-*a*]pyrimidine-3-carboxylate* (**20a**). Yield 1.26 g (70%). M.p. 196° (AcOH). IR: 3287 (NH), 1744 (CO), 1692 (CO). ^{1}H-NMR: 4.06 (*s*, MeO); 5.45 (*s*, H–C(6)); 7.05 (*s*, NH); 7.3 – 8.15 (*m*, 10 arom. H). EI-MS: 361 (100, $M^{+\cdot}$), 303 (16), 213 (46), 193 (23), 144 (73), 117 (46), 77 (76). Anal. calc. for $C_{19}H_{15}N_5O_3$ (361.35): C 63.15, H 4.18, N 19.38; found: C 63.21, H 4.35, N 19.30.

*Methyl 1-(4-Methylphenyl)-5-oxo-7-(phenylamino)-1,2,4-triazolo[4,3-*a*]pyrimidine-3-carboxylate* (**20b**). Yield 1.41 g (75%). M.p. 225° (EtOH/DMF). IR: 3281(NH), 1746 (CO), 1691 (CO). ^{1}H-NMR: 2.45 (*s*, Me); 4.10 (*s*, MeO); 5.49 (*s*, H–C(6)); 6.80 (*s*, NH); 7.2 – 8.0 (*m*, 9 arom. H). EI-MS: 375 (100, $M^{+\cdot}$), 316 (8), 259 (14), 227 (62), 207 (43), 144 (59), 105 (37), 73 (85). Anal. calc. for $C_{20}H_{17}N_5O_3$ (375.38): C 63.99, H 4.57, N 18.66; found: C 64.20, H 4.25, N 18.59.

*Methyl 1-(4-Chlorophenyl)-5-oxo-7-(phenylamino)-1,2,4-triazolo[4,3-*a*]pyrimidine-3-carboxylate* (**20c**). Yield 1.39 g (70%). M.p. 232° (AcOH). IR: 3284 (NH), 1755 (CO), 1693 (CO). ^{1}H-NMR: 4.10 (*s*, MeO); 5.45 (*s*, H–C(6)); 6.82 (*s*, NH); 7.2 – 8.2 (*m*, 9 arom. H). EI-MS: 395 (0.4, $M^{+\cdot}$), 368 (1), 313 (1), 271 (2), 236 (9), 185 (7), 149 (11), 97 (52), 57 (100). Anal. calc. for $C_{19}H_{14}N_5O_3Cl$ (395.81): C 57.66, H 3.57, N 17.69; found: C 57.36, H 3.29, N 17.57.

*Ethyl 1-(4-Methoxyphenyl)-5-oxo-7-(phenylamino)-1,2,4-triazolo[4,3-*a*]pyrimidine-3-carboxylate* (**20d**). Yield 1.62 g (80%). M.p. 186° (EtOH). IR: 3280 (NH), 1740 (CO), 1690 (CO). ^{1}H-NMR: 1.45 (*t, J* = 7, Me); 3.85 (*s*, MeO); 4.55 (*q, J* = 7, CH_2O); 5.45 (*s*, H–C(6)); 6.91 (*s*, NH); 7.05 – 8.0 (*m*, 9 arom. H). EI-MS: 406 (43), 405 (100, $M^{+\cdot}$), 333 (4), 262 (5) 243 (7), 223 (8), 148 (4), 144 (9), 77 (7). Anal. calc. for $C_{21}H_{19}N_5O_4$ (405.42): C 62.21, H 4.72, N 17.28; found: C 62.12, H 4.65, N 17.21.

*1-Phenyl-7-(phenylamino)-3-(2-phenylethenyl)-1,2,4-triazolo[4,3-*a*]pyrimidin-5-one* (**20e**). Yield 1.58 g (78%) M.p. 265° (AcOH). IR: 3315 (NH), 1668 (CO). EI-MS: 406 (24), 405 (100, $M^{+\cdot}$), 328 (48), 289 (18), 261 (24), 219 (16), 144 (19), 129 (18), 91 (53). Anal. calc. for $C_{25}H_{19}N_5O$ (405.46): C 74.06, H 4.72, N 17.28; found: C 74.35, H 4.54, N 17.10.

*3-Acetyl-1-phenyl-7-(phenylamino)-1,2,4-triazolo[4,3-*a*]pyrimidin-5-one* (**20f**). Yield 1.30 g (75%). M.p. 269° (EtOH/DMF). IR: 3282 (NH), 1731 (CO), 1682 (CO). EI-MS: 345 (100, $M^{+\cdot}$), 229 (22), 193 (13), 144 (40), 117 (17), 77 (41). Anal. calc. for $C_{19}H_{15}N_5O_2$ (345.35): C 66.07, H 4.38, N 20.28; found: C 66.00, H 4.21, N 20.05.

N*-Phenyl 5-Oxo-1-phenyl-7-(phenylamino)-1,2,4-triazolo[4,3-*a*]pyrimidine-3-carboxamide* (**20g**). Yield 1.48 g (70%). M.p. 285° (DMF). IR: 3250 (NH), 3214 (NH), 1703 (CO), 1645 (CO). EI-MS: 423 (7, $[M+1]^+$), 408 (15), 338 (19), 297 (13), 251 (21) 193 (33), 152 (27), 97 (72), 57 (100). Anal. calc. for $C_{24}H_{18}N_6O_2$ (422.43): C 68.23, H 4.29, N 19.90; found: C 68.15, H 4.25, N 19.77.

*1-(4-Nitrophenyl)-7-(phenylamino)-3-(thiophen-2-yl)-1,2,4-triazolo[4,3-*a*]pyrimidin-5-one* (**20h**). Yield 1.61 g (75%). M.p. 290° (EtOH/DMF). IR: 3285 (NH), 1687 (CO). EI-MS: 430 (100, $M^{+\cdot}$), 314 (26), 287 (45), 144 (44), 77 (29). Anal. calc. for $C_{21}H_{14}N_6O_3S$ (430.43): C 58.59, H 3.28, N 19.53, S 7.45; found: C 58.55, H 3.12, N 19.20, S 7.30.

3. *Synthesis of 3-Aceytyl-1-phenyl-7-(phenylamino)-6-(phenylazenyl)-1,2,4-triazolo[4,3-*a*]pyrimidin-5-one* (**21**). *Method A*. To a soln. of **20f** (5 mmol) in EtOH (100 ml), NaOH (0.2 g, 5 mmol) was added. A soln. of benzenediazonium chloride (prepared from aniline (0.5 ml, 5 mmol) and the appropriate quantities of aq. HCl

and $NaNO_2$) was then added to the stirred mixture at r.t. The product precipitated on standing and was collected by filtration and crystallized from DMF to give **21**. Yield 1.75 g (78%). M.p. 248° (AcOH). IR: 3363 (NH), 1726 (CO), 1695 (CO). ^{1}H-NMR: 2.88 (*s*; Me): 7.18 – 8.18 (*m*, 15 arom. H); 13.90 (*s*, NH). Anal. calc. for $C_{25}H_{19}N_7O_2$ (449.46): C 66.80, H 4.26, N 21.82; found: C 66.65, H 4.10, N 21.64.

Method B. Compound **21** was prepared by the same method described for the synthesis of **20** with 1,2-dihydro-6-(phenylamino)-5-(phenylazenyl-2-thioxopyrimidin-4(3*H*)-one [37] in place of **16**. The product was identical to that obtained by *Method A*.

4. *Synthesis of 6-(Chloroacetyl)-5-oxo-1-phenyl-7-(phenylamino)-1,2,4-triazolo[4,3-*a*]pyrimidine-3-carboxylate* (**22**). A soln. of **20a** (5 mmol) in $ClCH_2COCl$ (10 ml) was heated to reflux for 3 h. Then, the mixture was cooled to r.t., the precipitate was collected and crystallized from AcOH to give **22**. Yield 1.64 g (75%). M.p. 232° (AcOH). IR: 3062 (NH), 1766 (CO), 1700 (CO), 1689 (CO). ^{1}H-NMR: 4.10 (*s*, MeO); 5.05 (*s*, CH_2Cl); 7.2 – 8.1 (*m*, 10 arom. H); 12.80 (*s*, NH). EI-MS: 439 (8), 402 (63), 388 (100), 328 (21), 288 (7), 213 (13), 170 (4), 144 (14), 77 (30). Anal. calc. for $C_{21}H_{16}N_5O_4Cl$ (437.83): C 57.60, H 3.68, N 16.00; found: C 57.50, H 3.52, N 16.21.

5. *Synthesis of Methyl 6-Nitroso-5-oxo-1-phenyl-7-(phenylamino)-1,2,4-triazolo[4,3-*a*]pyrimidine-3-carboxylate* (**23**). *Method A.* To a stirred soln. of **20a** (5 mmol) in AcOH (10 ml), a conc. soln. of $NaNO_2$ (2 g in 5 ml H_2O) was added. The solid formed was collected and crystallized from EtOH to give **23**. Yield 1.37 g (70%). M.p. 173° (AcOH). ^{1}H-NMR: 4.00 (*s*, MeO); 7.3 – 8.1 (*m*, 10 arom. H); 11.90 (*s*, NH). EI-MS: 391 (0.6, $M^{+\bullet}$), 359 (1), 346 (41), 288 (10), 244 (3), 213 (2), 144 (17), 129 (20), 91 (100). Anal. calc. for. $C_{19}H_{14}N_6O_4$ (390.35): C 58.46, H 3.61, N 21.53; found: C 58.30, H 3.55, N 21.31.

Method B. Compound **23** was prepared by the same method described for the synthesis of **20** with 1,2-dihydro-5-nitroso-6-(phenylamino)-2-thioxopyrimidin-4(3*H*)-one [37] in place of **16**. The product was identical to that obtained by *Method A*.

Table. *Crystallographic Data of Compound* **20d**

Crystallized from		$CHCl_3$/i-PrOH
Empirical formula		$C_{21}H_{19}N_5O_4$
Formula weight [g mol^{-1}]		405.41
Crystal color, habit		orange, prism
Crystal dimensions [mm]		$0.32 \times 0.45 \times 0.50$
Temp. [K]		173(1)
Crystal system		monoclinic
Space group		$P2_1/c$
Z		4
Reflections for cell determination		25
2θ Range for cell determination [°]		38 – 40
Unit-cell parameters	a [Å]	13.150(1)
	b [Å]	8.057(1)
	c [Å]	19.165(1)
	β [°]	107.155(7)
	V [Å^3]	1940.2(3)
D_x [g cm^{-3}]		1.388
μ(MoK_α) [mm^{-1}]		0.0992
Scan type		$\omega/2\theta$
$2\theta_{(max)}$ [°]		55
Total reflections measured		4969
Symmetry-independent reflections		4450
Reflections used [$I > 2\sigma(I)$]		3324
Parameters refined		299
Final R		0.0438
wR ($w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$)		0.0429
Goodness-of-fit		2.104
Secondary extinction coefficient		$1.50(9) \times 10^{-6}$
Final Δ_{max}/σ		0.0003
$\Delta\rho$(max; min) [e Å^{-3}]		0.23; – 0.21

6. *Crystal-Structure Determination of* **20d** (see the *Table* and *Fig.*[5]). All measurements were performed on a *Rigaku AFC5R* diffractometer with graphite-monochromated MoK_α radiation ($\lambda = 0.71069$ Å) and a 12-kW rotating anode generator. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. The structure was solved by direct methods with SHELXS86 [44], which revealed the position of all non-H-atoms. The EtO atoms of the ethyl ester group are disordered over two orientations with relative site-occupation factors of 0.542 : 0.458. All of the H-atoms bonded to C-atoms were fixed in geometrically calculated positions (d(C−H) = 0.95 Å). The amine H-atom was fixed in the position indicated by a difference-electron-density map. Each H-atom was assigned a fixed isotropic displacement parameters with a value equal to 1.2 U_{eq} of its parent atom. Refinement of the structure was carried out on F by full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o| - |F_c|)^2$. A correction for secondary extinction was applied. Neutral atom scattering factors for non-H-atoms were taken from [45a], and the scattering factors for H-atoms were taken from [46]. Anomalous dispersion effects were included in F_{calc} [47]; the values for f' and f'' were those of [45b]. All calculations were performed with the TEXSAN crystallographic software package [48].

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[5]) CCDC-181576 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, U.K.: fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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