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A MILD AND REGIOSPECIFIC SYNTHESIS OF 3-AMINO SUBSTITUTED TRIAZOLO-[4,3-c]-PYRIMIDINES BY CYCLISATION OF 4-HYDRAZINOPYRIMIDINES WITH IMINIUM CHLORIDES AND WITH N-ARYL PHOSGENIMINES.

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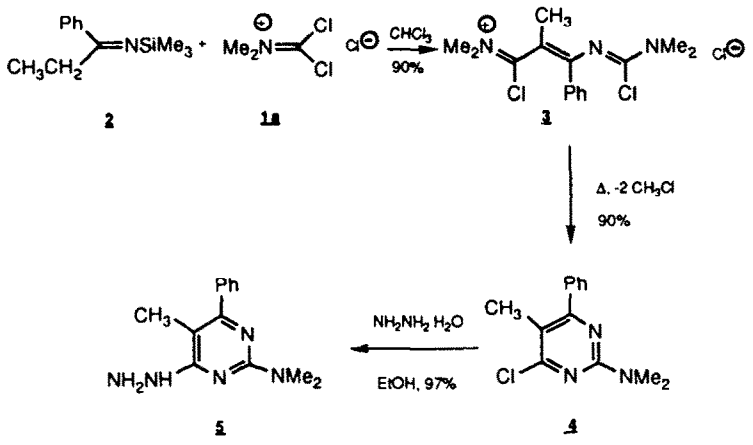
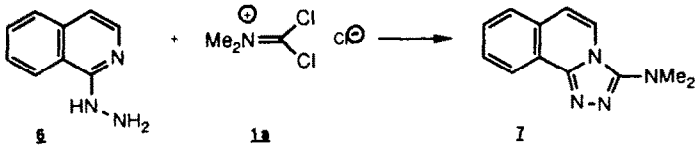
Abstract: *Phosgeniminium chloride (PI)* ***1a*** *permits the regiospecific synthesis of 3-dimethylaminotriazolo-[4,3-c]-pyrimidine* ***8a*** *from the corresponding 4-hydrazinopyrimidine* ***5*** *without Dimroth type isomerisation into its [1,5-c] isomer. This synthesis has been extended to the cyclic phosgeniminium salts* ***1b-e*** *and to the N-aryl phosgenimines (aryl isocyanide dichlorides)* ***18a,b****. The triazolopyrimidine structure was confirmed by an X-ray diffraction analysis of derivative* ***8d****. When the Vilsmeier salt* ***10****, tetramethylurea dichloride* ***11*** *or dimethyl(2,2,2-trifluoro-1,1-dichloroethyl)amine* ***12*** *were used as the electrophilic reagents, 4-methylenehydrazinopyrimidines* ***13****,* ***14*** *and* ***15*** *respectively were isolated. Thermolysis of* ***13*** *yielded with the same regiospecificity 3-unsubstituted triazolo-[4,3-c]-pyrimidine* ***16****. This compound could be rearranged to* ***17*** *in a separate step. Chlorination of hydrazidopyrimidine* ***20*** *in refluxing* $POCl_3$ *led to the isomerised triazolo-[1,5-c]-pyrimidine* ***22****, as ascertained by X-ray diffraction and* ^{13}C*-nmr analysis.*

As previously described[1,2] phosgeniminum salts are valuable synthons for heterocyclic synthesis, notably because of their ability to dechloroalkylate. Thus 2-aza-1,5-dichloropentamethine cyanine **3**, obtained by reaction of phosgeniminium salt **1a** with the N-silylated primary enamine **2**, cyclises to 4-chloro-2-dimethylamino-5-methyl-6-phenylpyrimidine **4** upon heating. This process represents a regiospecific intramolecular dechloroalkylation (Scheme 1)[2].



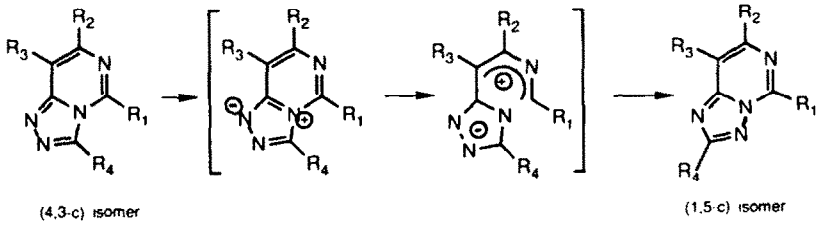
Scheme 1

The nucleophilic displacement of the chlorine atom of **4** with hydrazine hydrate yields the 4-hydrazinopyrimidine **5** (Scheme 1). A particular aspect of the reactivity of PI is its ability to condense smoothly with bisnucleophilic reagents to yield various heterocycles[3]. For example, **1a** reacts with amidrazone **6** to give the triazole **7** in high yield[4] (Scheme 2).



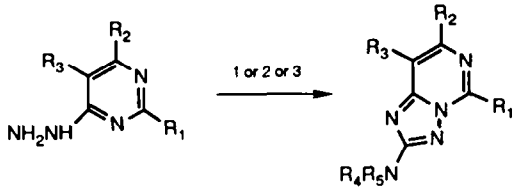
Scheme 2

When extended to 4-hydrazinopyrimidine **5**, the reaction with PI **1a** yielded regiospecifically 3-dimethylaminotriazolo-[4,3-c]-pyrimidine **8a** (Scheme 5). Under the mild conditions required for reaction no rearrangement was observed. This condensation constitutes a new entry to 3-substituted triazolo-[4,3-c]-pyrimidines. Indeed, such ring-fused s-triazoles are difficult to prepare because their ready isomerisation (usually referred to as a Dimroth-type rearrangement) is induced thermally and/or by either acids or bases. A detailed study on related systems showed that electronic and steric factors are mainly responsible for this type of rearrangement[5] (Scheme 3).



Scheme 3

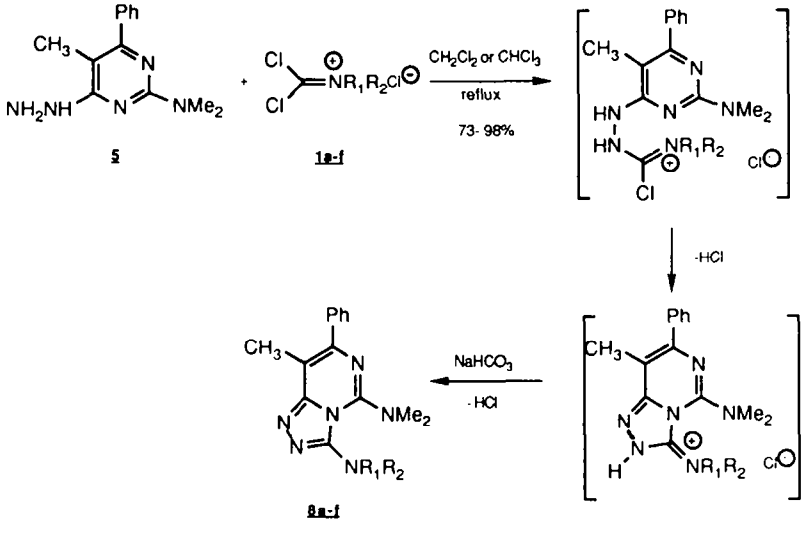
The driving force for this rearrangement is ascribed to the increased aromatic character of the [1,5-c]-heterocycle[6]. Until now no 3-dialkylamino or 3-alkylaminotriazolo-[4,3-c]-pyrimidines were known because of the harsh conditions needed for the cyclisation step, the only products isolated being 2-dialkylaminotriazolo-[1,5-c]-pyrimidines (Scheme 4)[7].



1. a) R_4NCX; b) $POCl_3$, reflux.
2. a) CS_2, BuOH, 130°C; b) Me_2SO_4, Na_2CO_3; c) $(NH_4)_2S_2O_8$, H_2SO_4; d) R_4R_5NH, 120-130°C
3. a) ClCN, HCl; b) HBr, Br_2; c) R_4R_5NH.

Scheme 4

The multifaceted biological activities of the ring-fused s-triazoles[8] led us to extend the reaction to phosgeniminium chlorides with different N-substituents (Scheme 5). The yields were excellent, as summarised in Table 1.



Scheme 5

Table 1	8	NR^1R^2	yield
	a	$N(CH_3)_2$	85%
	b		73%
	c		98%
	d		98%
	e		77%
	f	$NHCH_2Ph$	58%

The structures **8a-f** were confirmed by X-ray diffraction analysis of **8d** and by ^{13}C-nmr experiments (Table 2).The crystallographic parameters of **8d** were as follows : $C_{18}H_{22}N_6O$, Mr = 338.42, monoclinic, $P2_1/a$, a = 7.176(1), b = 18.603(5), c = 13.193(4) Å, β = 98.03(2)°, V = 1743.9(8) Å^3, Z = 4, Dx = 1.29 g.cm^{-3}, MoKα, λ= 0.71069 Å, μ = 0.92 cm^{-1}, F(000) = 720, T = 291K, R = 0.042 for 2351 observed reflections.

Figure 1 is a stereoscopic view of the molecule showing the numbering of the atoms[12]. The list of atomic coordinates and the geometrical parameters have been deposited with the Cambridge Data Centre. To our knowledge, no structure of a (1,2,4)-triazolo-[4,3-c]-pyrimidine has been reported[16]. A high degree of bond fixation is indicated by some of the bond lengths : N4-C5 (1.399(2) Å) is longer and C5-N6 (1.286(2) Å) shorter than expected for a pyrimidine[18]. Also three bond distances of 1.390(3) Å for the formal single bonds and two of 1.302(3) Å for the formal double bonds were observed in the triazole-ring. The pyrimidine ring deviates significantly from planarity, adopting a flat boat conformation with torsion angles of 6,8,-13,3,10 and -15° (σ = 0.7°). The (1,2,4)-triazine moiety is planar within experimental errors (the max. deviation from the mean plane was less than 0.02 Å)[17]. The dihedral angle between the best mean planes through the two heterocycles was 9(1)°.

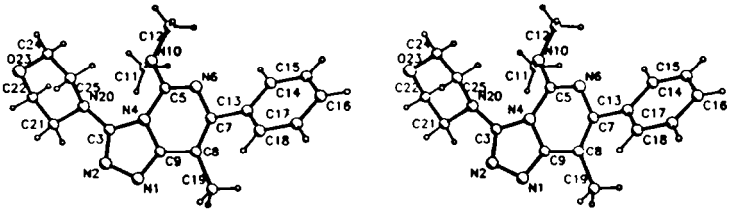
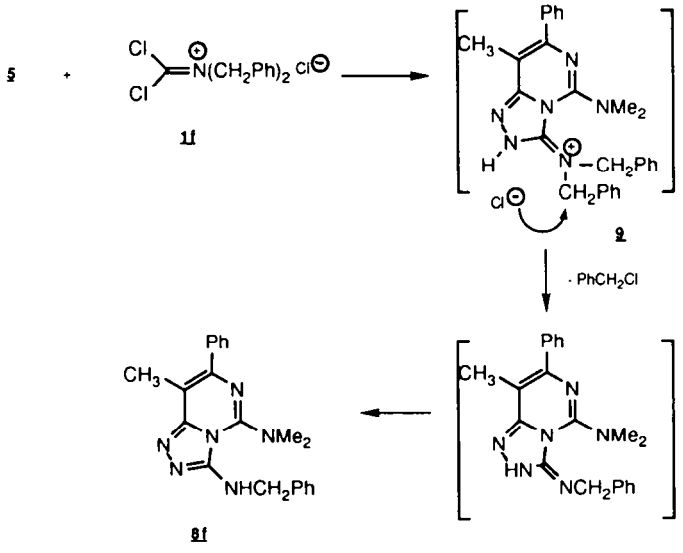


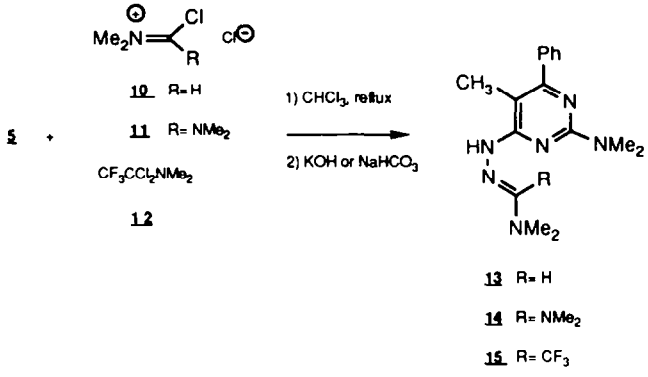
Figure 1. - Stereoscopic view of **8d**

The reaction involving the N,N-dibenzyl phosgeniminium salt **1f** merits comment because it led to 3-benzylaminotriazolo-[4,3-c]-pyrimidine **8f** *via* the loss of benzyl chloride from **9** (Scheme 6).



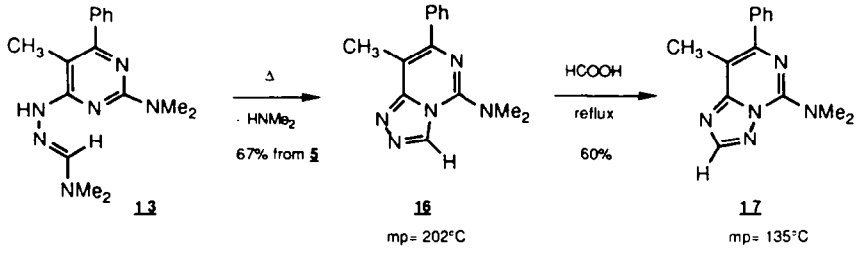
Scheme 6

The condensations between **5** and the Vilsmeier salt **10**, or tetramethylurea dichloride **11**, or dimethyl(2,2,2-trifluoro-1,1-dichloroethyl)amine **12**[9], yielded the unsubstituted amidines **13-15** respectively (Scheme 7).



Scheme 7

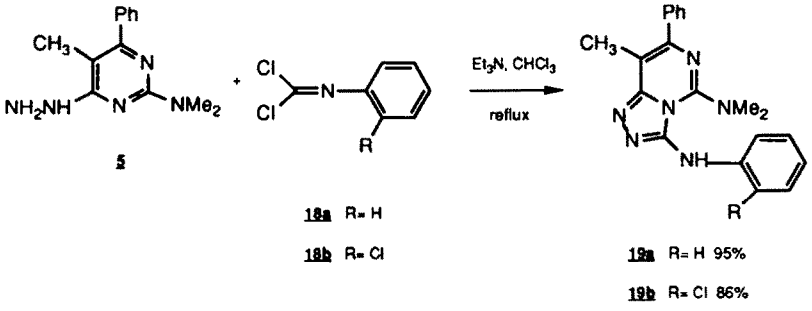
The thermolysis of neat formamidrazone **13** at 200°C or its refluxing nitrobenzene solution led, by intramolecular transamination, without isomerisation, to the 3-unsubstituted triazolo-[4,3-c]-pyrimidine **16**. Rearrangement of **16** to **17** occurred upon refluxing in formic acid[10] (Scheme 8) and this confirmed its structure.



Scheme 8

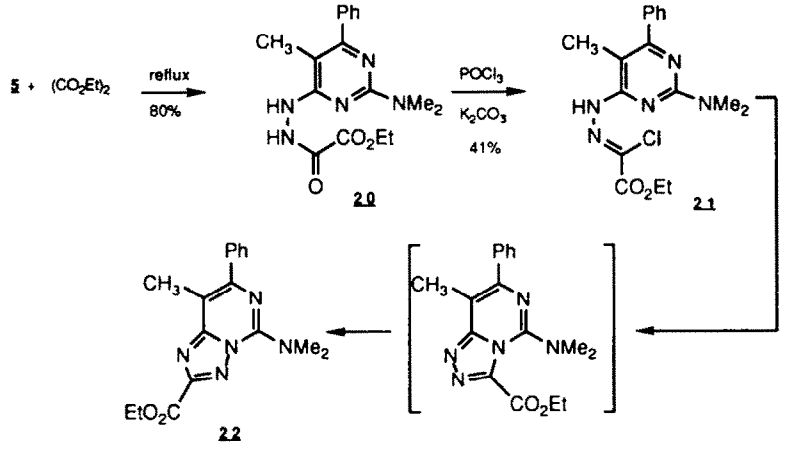
In contrast, amidines **14** and **15** remained unchanged even upon refluxing in nitrobenzene for several days, or upon thermolysis at 250°C *in vacuum*.

Although aryl isocyanide dichlorides (N-aryl phosgenimines) **18a,b** are less electrophilic than phosgeniminium and Vilsmeier salts, they can still participate in the cyclisation with bisnucleophilic reagents[11]. Thus, **18a,b** react, in the presence of triethylamine, with the 4-hydrazinopyrimidine **5** in refluxing chloroform. The 3-anilinotriazolo-[4,3-c]-pyrimidines **19a,b** were obtained in high yields. Their structure was established by comparison of their ^{13}C-nmr spectra with those of the triazolopyrimidines **8** (Scheme 9, Table 2).



Scheme 9

Refluxing hydrazinopyrimidine **5** in diethyl oxalate, followed by chlorination with phosphorus oxychloride of the carbazate **20**, yielded the rearranged (2-ethoxycarbonyl)triazolo-[1,5-c]-pyrimidine **22**. Its structure was confirmed by X-ray diffraction analysis (Scheme 10).



Scheme 10

The intermediate hydrazidoyl chloride **21** could, however, be isolated under milder conditions : $POCl_3$, reflux 1h and $H_2O/NaHCO_3$ work up.

The crystallographic parameters of $C_{17}H_{19}N_5O_2$ **22** are : Mr = 325.37, triclinic, $P\bar{1}$, a = 9.341(3), b = 14.146(5), c = 14.139(4) Å, α = 111.23(3), β = 99.23(3), γ = 101.22(3)°, V = 1652.8(8) Å^3, Z = 4, Dx = 1.31 g.cm^{-3}, CuKα, λ = 1.54178 Å, μ = 7.42 cm^{-1}, F(000) = 688, T = 291K, R = 0,071 for 5196 observed reflections.

The atomic parameters of the two independent molecules in the unit cell have been deposited with the Cambridge Data Centre. They differ only by the orientation of the ester group (N1-C2-C20-O21 was -9° in A, 178° in B). Figure 2 is a stereoscopic view of molecule **22A** showing the numbering of the atoms[12]. Only two structures containing the (1,2,4)-triazolo-[1,5-c]-pyrimidine skeleton have been previously reported[16,19,20]. The bond lengths in the triazole moiety of **22** indicate a greater degree of conjugation than in **8d**. In both of the structures A and B, the pyrimidine and the triazole-rings are planar within experimental errors (max. deviation from mean planes less than 0.04 Å)[17]. The dihedral angles between the best mean planes are 5(1)° and 1(1)° respectively for A and B.

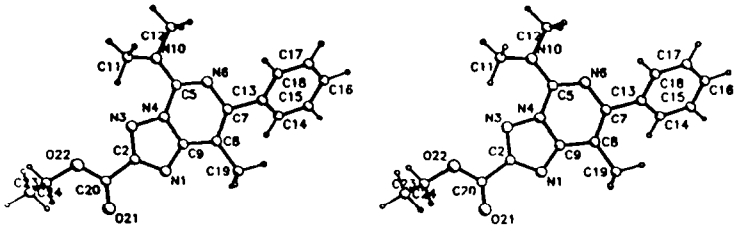


Figure 2. - Stereoscopic view of **22A**

In conclusion, we have shown that N-silylated primary enamine **2** and phosgeniminum salts **1a-f** give ring-fused triazolopyrimidines smoothly and regiospecifically in three steps.

Experimental

IR and mass spectra were measured on a Perkin Elmer 1710 and a Varian 44SEI apparatus respectively. 200 MHz ^{1}H NMR and 50 MHz ^{13}C NMR spectra were recorded on a Varian XL200 or Varian Gemini 200 spectrometers in deuteriochloroform using TMS as internal standard; chemical shifts are expressed in δ(ppm) and the coupling constants, J, are measured in Hz. All the melting points were determined on a Buchi apparatus and are uncorrected. The following abbreviations are used : S,s : singlet, D,d : doublet, T,t : triplet, Q,q : quartet, bs : broad singlet, m : multiplet.

The starting phosgeniminium salts **1a-f** were obtained by chlorination of the corresponding dithiurames[1]. The commercially available phenyl- and *ortho* -chlorophenyl isocyanide dichlorides were distilled before use.

2-dimethylamino-4-hydrazino-5-methyl-6-phenyl pyrimidine 5:

A solution of 4-chloro-2-dimethylamino-5-methyl-6-phenyl pyrimidine **5**[1] (4.95 g; 0.02 mol) and hydrazine hydrate (4.0 g; 0.08 mol) in ethanol (4.7 ml; 0.08 mol) was refluxed for 5 h. After cooling, the precipitate was filtered, washed with ether and dried. Pyrimidine **5** was recrystallised from ethanol. Yield : 97 %; m.p. 169°C; IR ($CHCl_3$): 3456, 3326, 1589, 1574, 1498, 1409, 1389 and 705 cm^{-1}; ^{1}H NMR δ : 1.91 (3H,s,CH_3), 3.18 (6H,s,$N(CH_3)_2$), 4.05(2H,bs,NH_2), 6.13 (1H,bs,NH), 7.36-7.54 (5H,m,Ph); ^{13}C NMR δ : 11.2 (Qs,^{1}J = 127,CH_3), 36.7 (Qq,^{1}J = 137, ^{3}J = 3.5,$N(CH_3)_2$), 97.7 (Sq,^{2}J = 6,C5), 127.9 (Dd,^{1}J = 161,^{3}J = 7.8,C3-Ph), 128.2 (Dt,^{1}J = 161,^{3}J = 7.5,C4-Ph), 129.2 (Dt,^{1}J = 160.2, ^{3}J = 6.5,C2-Ph), 140.0 (Sm,C1-Ph), 160.4 (Sm,C2), 126.9 (Sm,C6), 163.9 (Sm,C4); Anal. calc. for $C_{13}H_{17}N_5$: C, 64.17; H, 7.04; N, 28.78; Found : C, 64.20; H, 7.08; N, 28.85 %; MS (m/z): 243 ($m^{+\cdot}$).

General procedure for the preparation of 3-dialkylaminotriazolo-[4,3-c]-pyrimidines 8:

A solution of 4-hydrazino pyrimidine **5** (2.43 g; 0.01 mol) in 10 ml dry dichloromethane was added dropwise to a stirred suspension of PI chloride (0.01 mol) in dry dichloromethane (20 ml) at 20°C. The resulting mixture was then refluxed for about one hour in order to achieve complete dissolution of PI and until the HCl evolution stopped. The solvent was removed *in vacuo* and the residue was treated with saturated $NaHCO_3$ solution. After extraction with dichloromethane, the organic phases were washed with brine and dried ($MgSO_4$). After evaporation of solvent, the residue was purified either by recrystallisation from ethanol (**8c, 8d**), or by filtration on short silicagel column using ethyl acetate : ethanol (95 : 5) as eluents, and then recrystallised from CH_2Cl_2/hexane (**8a, 8b**).

3,5-bis-(dimethylamino)-8-methyl-7-phenyl-(1,2,4)-triazolo-[4,3-c]-pyrimidine 8a: Yield : 85 %; m.p. 161-162°C (from CH_2Cl_2/hexane); IR ($CHCl_3$): 1607, 1581, 1562, 1544, 1507, 1446, 1420, 1363, 698 and 666 cm^{-1}; ^1H NMR δ: 2.51 (3H,s,CH_3), 3.01 (6H,s,$N(CH_3)_2$), 3.03 (6H,s,$N(CH_3)_2$), 7.40-7.69 (5H,m,Ph); Anal. calc. for $C_{16}H_{20}N_6$: C, 64.84; H, 6.80; N, 28.35; Found : C, 65.0; H, 6.89; N, 28.58 %; MS (m/z): 296 ($m^{+\cdot}$), 267 ($m^{+\cdot}$-NCH_3), 252 ($m^{+\cdot}$-$(CH_3)_2N$), 224, 115, 49.

5-dimethylamino-8-methyl-7-phenyl-3-pyrrolidino-(1,2,4)-triazolo-[4,3-c]-pyrimidine 8b: Yield : 73 %; m.p. 189-190°C (from CH_2Cl_2/hexane); IR ($CHCl_3$): 3053, 1606, 1580, 1539, 1505, 1460, 1445, 1366, 705 and 666 cm^{-1}; ^1H NMR δ: 1.98 (4H,m), 2.49 (3H,s,CH_3), 2.99 (6H,s,$N(CH_3)_2$), 3.55 (4H,m), 7.38-7.7 (5H,m,Ph); Anal. calc. for $C_{18}H_{22}N_6$: C, 67.05; H, 6.88; N, 26.0; Found : C, 67.05; H, 6.91; N, 26.10 %; MS (m/z): 322 ($m^{+\cdot}$), 293 ($m^{+\cdot}$-NCH_3), 252 ($m^{+\cdot}$-C_4H_8N), 224, 115, 55 (C_4H_7), 43.

5-dimethylamino-8-methyl-7-phenyl-3-piperidino-(1,2,4)-triazolo-[4,3-c]-pyrimidine 8c: Yield : 98 %; m.p. 184.5-185°C (from EtOH); IR ($CHCl_3$): 3019, 1606, 1559, 1531, 1503, 1445, 1384, 1363, 701 and 663 cm^{-1}; ^1H NMR δ: 1.65 (2H,m), 1.76 (4H,m), 2.53 (3H,s,CH_3), 3.02 (6H,s,$N(CH_3)_2$), 3.33 (4H,m), 7.35-7.70 (5H,m,Ph); Anal. calc. for $C_{19}H_{24}N_6$: C, 67.83; H, 7.19; N, 24.98; Found : C, 67.78; H, 7.29; N, 25.02 %; MS (m/z): 336 ($m^{+\cdot}$), 307 ($m^{+\cdot}$-NCH_3), 281, 224, 115, 84 ($C_5H_{10}N$); 43.

5-dimethylamino-8-methyl-3-morpholino-7-phenyl-(1,2,4)-triazolo-[4,3-c]-pyrimidine 8d: Yield : 98 %; m.p. 223.5-226°C (from EtOH); IR ($CHCl_3$): 3012, 1608, 1580, 1558, 1531, 1503, 1451, 1418, 1361, 702 and 664 cm^{-1}; ^1H NMR δ: 2.52 (3H,s,CH_3), 3.04 (6H,s,$N(CH_3)_2$), 3.44 (4H,m,NCH_2), 3.90 (4H,m,CH_2O), 7.37-7.68 (5H,m,Ph); Anal. calc. for $C_{18}H_{22}N_6O$: C, 63.89; H, 6.55; N, 24.83; Found : C, 63.95; H, 6.51; N, 24.94 %; MS (m/z): 338 ($m^{+\cdot}$), 309 ($m^{+\cdot}$-NCH_3), 281, 252, ($m^{+\cdot}$-C_4H_8NO), 224, 115, 43.

5-dimethylamino-8-methyl-3-perhydroazepinyl-7-phenyl-(1,2,4)-triazolo-[4,3-c]-pyrimidine 8e: Yield : 77 %; m.p. 163.5-164.5°C (from hexane); IR ($CHCl_3$): 3062, 1606, 1560, 1528, 1503, 1445, 708 and 669 cm^{-1}; ^1H NMR δ: 1.75-1.81 (8H,m), 2.51 (3H,s,CH_3), 2.99 (6H,s,$N(CH_3)_2$), 3.54 (4H,m,NCH_2), 7.42-7.71 (5H,m,Ph); Anal. calc. for $C_{20}H_{26}N_6$: C, 68.54; H, 7.48;N, 23.98; Found : C, 68.60; H, 7.52; N, 24.02 %; MS (m/z): 350 ($m^{+\cdot}$), 321 ($m^{+\cdot}$-NCH_3), 307 ($m^{+\cdot}$-CH_2NCH_3), 281, 252 ($m^{+\cdot}$-$C_6H_{12}N$), 224, 115, 98 ($C_6H_{12}N$), 43.

3-benzylamino-5-dimethylamino-8-methyl-7-phenyl-(1,2,4)-triazolo-[4,3-c]-pyrimidine 8f:

Chromatography was performed with ethyl acetate as eluent.

Yield : 58 %; m.p. 163.5-164.5°C (from EtOH); IR ($CHCl_3$): 3378, 3066, 1614, 1583, 1550, 1495, 1454, 1371, 702, 669 and 637 cm^{-1}; ^1H NMR δ: 2.50 (3H,s,CH_3), 2.84 (6H,s,$N(CH_3)_2$), 4.75 (2H,d,J = 6,NCH_2Ph), 5.74 (1H,t,J = 5.9,NH), 7.26-7.64 (10H,m,Ph); Anal. calc. for $C_{21}H_{22}N_6$: C, 70.36; H, 6.18; N, 23.44; Found : C, 70.35; H, 6.21; N, 23.61 %; MS (m/z): 358 ($m^{+\cdot}$), 314 ($m^{+\cdot}$-$N(CH_3)_2$), 267 (m^{+}-$PhCH_2$), 115, 91, 65.

5-dimethylamino-8-methyl-7-phenyl-(1,2,4)-triazolo-[4,3-c]-pyrimidine 16:

A solution of 4-hydrazino pyrimidine **5** (1.0 g; 4.1 mmol) in 15 ml dry chloroform was slowly added to a solution of Vilsmeier salt **10** prepared *in situ* from dimethylformamide (0.315 g; 4.3 mmol) and oxalyl chloride (0.55 g; 4.3 mmol) in 10 ml dry $CHCl_3$. The resulting mixture was refluxed for 3 h and then treated with 5 ml 2N KOH solution. After extraction, the combined organic phases were dried over $MgSO_4$, and the solvent was removed to give the formamidrazone **13** : ^1H NMR δ: 1.95 (3H,s,CH_3), 2.90 (6H,s,$N(CH_3)_2$), 3.10 (6H,s,$N(CH_3)_2$), 6.4 (1H,bs,NH), 7.4-7.6 (5H,m,Ph), 7.76 (1H,s,H).

13 was thermolysed by distillation in a Kugelrohr apparatus at 200°C/0.01 Torr. The product was washed with ether and recrystallised from CH_2Cl_2/hexane.

Yield : 67 %; m.p. 202-203°C; IR ($CHCl_3$): 1610, 1557, 1514, 1443, 1426, 1381, 704 and 668 cm^{-1}; ^1H NMR δ: 2.58 (3H,s,CH_3), 3.20 (6H,s,$N(CH_3)_2$), 7.39-7.66 (5H,m,Ph), 8.88 (1H,s,H_3); Anal. calc. for $C_{14}H_{15}N_5$: C, 66.38; H, 5.97; N, 27.65; Found : C, 66.40; H, 5.93; N, 27.74 %; MS (m/z): 253 ($m^{+\cdot}$), 224 ($m^{+\cdot}$-NCH_3), 209 ($m^{+\cdot}$-$N(CH_3)_2$), 184, 140, 127, 115, 77, 44.

3-dimethylamino-8-methyl-7-phenyl-(1,2,4)-triazolo-[1,5-c]-pyrimidine 17:

A solution of triazolo-[4,3-c]-pyrimidine **16** (0.4 g; 1.58 mmol) in formic acid (10 ml) was refluxed for 26 h. The solvent was removed and the residue washed with ether. The ethereal solution was evaporated and the residue was chromatographed on silicagel column with ethyl acetate : hexane (50 : 50) as eluent (Rf = 0.52).

Yield : 60 %; m.p. 135°C; IR ($CHCl_3$): 3063, 1608, 1561, 1524, 1497, 1474, 1443, 1420, 1394, 701 and 649 cm^{-1}; ^1H NMR δ: 2.52 (3H,s,CH_3), 3.42 (6H,s,$N(CH_3)_2$), 7.37-7.70 (5H,m,Ph), 8.24 (1H,s,H_2)

4-[bis-(dimethylamino)methylenehydrazino]-2-dimethylamino-5-methyl-6-phenyl pyrimidine 14:

A solution of 4-hydrazino pyrimidine **5** (1.0 g; 4.1 mmol) in 15 ml dry chloroform was added to a solution of tetramethylurea dichloride (0.71 g; 4.1 mmol) in 10 ml dry chloroform. The resulting mixture was refluxed for 20 min. The solvent was removed and the residue was treated with saturated $NaHCO_3$ solution. After extraction with dichloromethane, the organic phases were dried over $MgSO_4$. After evaporation of the solvent, the oil obtained was washed with ether to induce the crystallisation of **14**.

Yield : 92 %; m.p. > 250°C; IR ($CHCl_3$): 3193, 2950, 1618, 1557, 1518, 1496, 1452, 1407, 1390, 705 and 663 cm^{-1}; ^1H NMR δ: 2.12 (3H,s,CH_3), 2.97 (6H,s,$N(CH_3)_2$), 3.07 (6H,s,$N(CH_3)_2$ pyrimidine), 3.26 (6H,s,$N(CH_3)_2$).

2-dimethylamino-5-methyl-6-phenyl-4-(trifluoromethyl-dimethylaminomethylene-hydrazino)-pyrimidine 15:

A solution of 4-hydrazino pyrimidine **5** (1.0 g; 4.1 mmol) in 15 ml dry chloroform was added at 0°C to a stirred solution of **12**[9] (0.77 g; 3.9 mmol) in 10 ml dry chloroform. The resulting mixture was then stirred for 20 h at 20°C After treatment with saturated $NaHCO_3$ solution, pyrimidine **15** was extracted into chloroform. Organic phases were washed with brine and dried over $MgSO_4$. Filtration through silicagel column using ethyl acetate : hexane (10 : 90) gave 0.97 g of **15.**

Yield : 68 %; m.p. 135.5-136.5°C; IR ($CHCl_3$): 3340, 2988, 1592, 1576, 1543, 1499, 1459, 1408, 1351, 702 and 647 cm^{-1}; ^1H NMR δ: 2.14 (3H,s,CH_3), 2.73 (6H,s,$N(CH_3)_2$), 3.20 (6H,s,$N(CH_3)_2$ pyrimidine), 7.39-7.58 (5H,m,Ph), 8.57 (1H,br,NH); ^{19}F NMR ($CFCl_3$-$CDCl_3$) δ: -65.15 (s,CF_3); Anal. calc. for $C_{17}H_{21}F_3N_6$: C, 55.73; H, 5.78; N, 22.94; F, 15.55; Found : C, 55.26; H, 5.95; N, 22.56; F, 15.48 %; MS (m/z): 366 ($m^{+\cdot}$), 347 ($m^{+\cdot}$-F), 322 ($m^{+\cdot}$-$N(CH_3)_2$), 227, 140, 115; ^{13}C NMR δ: 13.0 (Qs,^1J = 128,CH_3), 36.6 (Qq,^1J = 137,^3J = 3.3,$N(CH_3)_2$ pyrimidine), 39.7 (Qq,^1J = 137.6,^3J = 4.2,$N(CH_3)_2$), 99.2 (Sqd,^2J = 5.9,^3J = 2.1,C5), 120.3 (Sq,$^1J_{C\text{-}F}$ = 279.3, CF_3), 127.9 (Dd,^1J = 161,^3J = 7,C-3Ph), 128.5 (Dt,^1J = 161,^3J = 7.4,C4-Ph), 129.3 (Dt,^1J = 160,^3J = 7,C2-Ph), 137.2 (Sqm,$^2J_{C\text{-}F}$ = 33.4,^3J = 2.4,C-CF_3), 139.8 (Sm,C1-Ph), 159.3 (Sm,C6), 160.4 (Sm,C2), 166.5 (Sm,C4).

General procedure for the preparation of 3-anilinotriazolo-[4,3-c]-pyrimidines 19a,b:

A solution of 4-hydrazino pyrimidine **5** (1.0 g; 4.1 mmol) and triethylamine (0.83 g; 8.2 mmol) in 20 ml dry chloroform was added to a stirred solution of N-aryl isocyanide dichloride **18a,b** (4,1 mmol) in 20 ml dry chloroform. The resulting mixture was refluxed for 5 h (R = H) or 6.5 h (R = Cl). The solution was then washed with brine and the organic phases were dried over $MgSO_4$. After removal of the solvent the solid was recrystallised from ethanol.

3-anilino-5-dimethylamino-8-methyl-7-phenyl-(1,2,4)-triazolo-[4,3-c]-pyrimidine 19a : Yield : 95 %; m.p. 200-201°C (EtOH); IR ($CHCl_3$): 3351, 3020, 1616, 1599, 1574, 1500, 1366, 703 and 695 cm^{-1}; ^1H NMR δ: 2.53 (3H,s,CH_3), 2.92 (6H,s,$N(CH_3)_2$), 6.95-7.71 (10H,m,Ph), 8.24 (1H,bs,NH); Anal. calc. for $C_{20}H_{20}N_6$: C, 69.75; H, 5.85; N, 24.40; Found : C, 69.79; H, 5.88; N, 24.41 %; MS (m/z) : 334 ($m^{+\cdot}$), 315 ($m^{+\cdot}$-NCH_3), 300 ($m^{+\cdot}$-$N(CH_3)_2$), 252 ($m^{+\cdot}$-NHPh), 225, 115.

3-(2-chloro)-anilino-5-dimethylamino-8-methyl-7-phenyl-(1,2,4)-triazolo-[4,3-c]-pyrimidine 19b: Yield : 86 %; m.p. 196-196.5°C (from EtOH); IR ($CHCl_3$): 3295, 3010, 1619, 1598, 1571, 1552, 1529, 1497, 1474, 1365, 706, 666 cm^{-1}; ^1H NMR δ: 2.56 (3H,s,CH_3), 2.96 (6H,s,$N(CH_3)_2$), 6.93 (1H,bt,H_4), 7.31-7.65 (7H,m,Ph), 8.81 (1H,bd,H_2), 9.33 (1H,bs,NH); Anal. calc. for $C_{20}H_{19}ClN_6$: C, 63.40; H, 5.05; N, 22.18; Found : C, 62.73; H, 5.06; N, 21.99 %; MS (m/z): 378 ($m^{+\cdot}$), 349 ($m^{+\cdot}$-NCH3), 314 ($m^{+\cdot}$-Cl), 252 ($m^{+\cdot}$-NHPhCl), 115.

2-dimethylamino-4-[2-ethoxycarbonyl-hydrazido]-5-methyl-6-phenyl pyrimidine 20: A solution of hydrazino pyrimidine **5** (1.0 g; 4 1 mmol) in diethyl oxalate (10 ml) was refluxed for 1.5 h. After cooling the resulting mixture to 0°C, the yellow solid obtained was filtered, washed several times with ether, dried and recrystallised from isopropanol.

Yield : 80 %; m.p. 148.5-150°C; IR ($CHCl_3$): 3391, 2999, 2871, 1763, 1695, 1593, 1578, 1551, 1497, 1450, 1409, 1390, 705, 666 and 647 cm^{-1}; ^1H NMR δ : 1.41 (3H,t,J = 7.05,$\underline{CH_3}CH_2$), 2.00 (3H,s,CH_3), 3.17 (6H,s,$N(CH_3)_2$), 4.41 (2H,q,J = 7.05,$CH_3\underline{CH_2}$), 7.36-7.50 (5H,m,Ph), 8.0 (1H,bs,NH), 10.48 (1H,bs,NHCO); MS (m/z): 343 ($m^{+\cdot}$), 314 ($m^{+\cdot}$-C_2H_5), 270 ($m^{+\cdot}$-CO_2Et), 254, 242, 227, 213 , 115, 43; ^{13}C NMR δ: 11.2 (Qs,^1J = 128,CH_3), 13.7 (Qt,^1J = 128,^3J = 2.7,$\underline{CH_3}CH_2O$), 36.7 (Qq,^1J = 137,^3J = 3.3,$N(CH_3)_2$), 63.2 (Tq,^1J = 149.6,^3J = 4.5,$\underline{CH_2}CH_3$), 98.7 (Sm,C5), 128.0 (Dm,^1J = 161,C3 or C2-Ph), 128.5 (Dt,^1J = 161,^3J = 7.7,C4-Ph), 129.1 (Dm,^1J = 159,C3 or C2-Ph), 138.9 (Sm,C1-Ph), 150.9 (Ss,NH$\underline{C}$O), 158.3 (Sm,C6), 159.0 (Sm,C2), 159.5 (St,^3J = 3,$\underline{C}O_2Et$), 163.9 (Sm,C4).

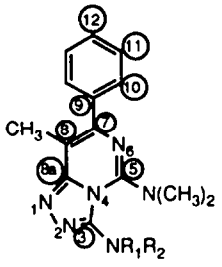
5-dimethylamino-2-ethoxycarbonyl-8-methyl-7-phenyl-(1,2,4)-triazolo-[1,5-c] pyrimidine 22:

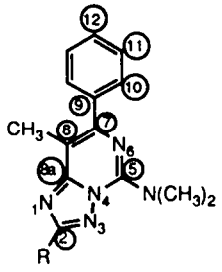
A solution of hydrazido pyrimidine **20** (0.7 g; 2.04 mmol) in 5 ml phosphorous oxychloride was refluxed for 3 h. Excess $POCl_3$ was then removed in vacuum. The residue was treated with K_2CO_3 solution. After extraction with chloroform, organic phases were dried over $MgSO_4$. The product was purified by chromatography on silicagel with ethyl acetate/hexane (40 : 60) as eluent. The oil obtained precipitated upon washing with hexane.

Yield : 74 %; m.p. 117.5-118°C; IR ($CHCl_3$): 3034, 1739, 1612, 1561, 1527, 1481, 1442, 1423, 1233, 1201, 701 and 663 cm^{-1}; ^1H NMR δ: 1.49 (3H,t,J = 7.12,$\underline{CH_3}CH_2$), 2.57 (3H,s,CH_3), 3.49 (6H,s,$N(CH_3)_2$), 4.56 (2H,q,J = 7.14,$CH_3\underline{CH_2}$), 7.43-7.69 (5H,m,Ph); Anal. calc. for $C_{17}H_{19}N_5O_2$: C, 62.75; H, 5.88; N, 21.52; Found : C, 62.80; H, 5.92; N, 21.64 %; MS (m/z) : 325 ($m^{+\cdot}$), 296 ($m^{+\cdot}$-C_2H_5), 280 ($m^{+\cdot}$-EtO), 252 (m-CO_2Et), 225, 115, 43.

Characteristics of hydrazonoyl chloride 21 : IR ($CHCl_3$): 3200, 1750, 1635, 1544, 1495, 1164, 698 cm^{-1}; ^1H NMR, δ: 1.39 (3H,t,J = 7.1,$\underline{CH_3}CH_2$), 2.21 (3H,s,CH_3), 3.20 (6H,s,$N(CH_3)_2$), 4.38 (2H,q,J = 7.1,$\underline{CH_2}CH_3$), 7.40-7.59 (5H,m,Ph), 8.86 (1H,br,NH).

Table 2: ^{13}C NMR of triazolo-[4,3-c]-pyrimidines synthetized in this work.





	NR^1R^2/R	C_3	C_5	C_7	C_8	C_{8a}	C_9	C_{10}	C_{11}	C_{12}
8a	$N(CH_3)_2$	152.4	146 0	145.1	109.6	153 2	137.7	129 2	127 7	127.9
8b		151.0	146.2	144.8	109.9	153.0	138.0	129.3	127.9	128.1
8c		152.2	146.2	145.3	110.1	153.1	137 8	129 3	127.8	128.0
8d		151 1	146.0	145 5	110.4	153 5	137 7	129 3	127.9	128.2
8e		152.4	146.2	145 0	109.9	152.7	137.8	129.2	127.7	127.9
8f	$NHCH_2Ph$	148.4	147.1	144.5	112.5	150.6	137 7	129 2	127.9	128 0
16	H	133.4	144.3	148 2	107.8	153.8	138 0	129 4	128 0	128 4
19a	NHPh	144.2	147.1	145 5	113 1	150.0	137 5	129 4	128.1	128.5
19b	NHPh(Cl)	143 9	147 3	145 7	113.4	150 1	137 5	129 4	128 1	128.2
17	H	153.0	145 8	151 3	107.5	156 4	138 5	129 2	127 8	128 2
22	CO_2Et	155.6	146 0	152.6	108.1	157 7	138.5	129 4	128 1	128.7

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