Syntheses of partially hydrogenated [1,2,4]triazolo[4,5-a] pyrimidine-4-ones through cyclisation of 2-arylidenehydrazino-6-methyl-4-pyrimidones

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Abstract

3-Arylsubstituted derivatives of *2H,3H,4H,7H-* and *1H,2H,3H,4H*-[1,2,4]triazolo[4,5-a]pyrimidin-4-ones were synthesized from 2-arylidenehydrazino-6-methyl-4-pyrimidones by treatment with acetic anhydride. The structures of the starting compounds and of the isomeric di-N-acetylated reaction products were established by NMR.

Keywords: 2-Arylidenehydrazino-6-methyl-4-pyrimidones, 1,2,4]triazolo[4, 5-a]pyrimidine-4-ones, 2D NMR, HMBC, spectroscopy, structure, tautomerism

Introduction

Guanylhydrazones (alkylenaminoguanidines, carboximideamidehydrazones, diaminomethylene hydrazones) are condensation products of oxo-compounds with aminoguanidines. This class of compounds has been known for a long time[1] and is of considerable interest due to a wide variety of different pharmacological activities found with many representatives.[2,3] Further, guanylhydrazones are valuable synthetic building blocks for ring closure reactions leading to several nitrogen-containing heterocycles.[4,5]

In this context, we have published the transformation of (*E*)- aromatic aldehyde guanylhydrazones into 3-acylamino-5-aryl-1,2-diacetyl-4,5-dihydro-1,2,4-triazoles,[6] the cyclization of N[1]-glycopyranosylamino)guanidines to 3-acetylamino-N[1]-glycopyranosyl-5-methyl-1,2,4-triazoles,[7] and the synthesis of N[1]-cycloalkenyl substituted 3-acylamino-5-methyl-1,2,4-triazoles.[8] All of these cyclisations are based on the reaction of guanylhydrazones with acetic anhydride in excess and proceed via an interesting type of ring closure mechanism through an acyliminium intermediate.[5,6]

However, some related educts with a guanylhydrazone structure (e.g. 2,6-dichlorobenzaldehyde guanylhydrazone, various isatin guanylhydrazones or guanylhydrazones derived from (hetero)aryl methylketones) show different behavior and afford the corresponding N,N'-diacetyl derivatives upon treatment with acetic anhydride .[6,9,10] It should be mentioned also that the attempted ring closure reaction of 2-amino-4-aryl-1-arylideneaminoimidazoles with several acid anhydrides led only to products acylated at various positions.[11] Egyptian authors[13] investigated the reaction of 2-hydrazino-6-methyl-4-oxo-pyrimidine (**1**),[12] a cyclic aminoguanidine derivative, with aldose monosaccharides that were supposed to react in their acyclic forms like simple aldehydes. The *aldehydo*-sugar(6-methyl-4-oxo-2-pyrimidinyl)hydrazones obtained did not undergo cyclisation upon treatment with acetic anhydride.[13] Others have studied cyclisation reactions of analogous N-heterocyclic hydrazones[14-16] and have established that the ring closure can follow two different pathways to result in the formation of polyaza-heterocycles with either *linearly* or *angularly* annellated rings[14-16] (cf. Scheme 3 below). In view of the divergent results with regard to the structures of the products obtained from N-heterocyclic hydrazones under acylating conditions, we have investigated the reactions of **1** with simple aromatic aldehydes and subsequent transformations of the products upon treatment with acetic anhydride.

Results and Discussion

To study the ring closure, 2-arylidenehydrazino-6-methyl-4-oxo-pyrimidines (**3**) were prepared by the reaction of aromatic aldehydes **2** with **1**. Compounds **3a-d** were prepared in good yield with acetic acid catalysis in ethanol using a described procedure.[17] Product **3a** could be prepared also by the cyclisation of benzaldehyde-guanylhydrazone with ethyl acetoacetate catalyzed by acetic acid. The educts **3a-d** were treated with acetic anhydride under reflux and two new products could be detected after a short reaction time; these were separated by column chromatography.
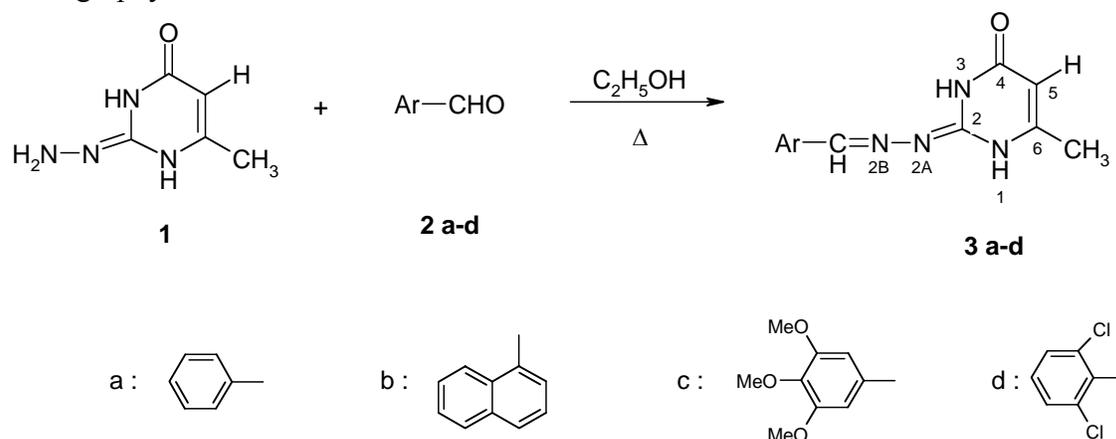
Scheme 1

NMR studies

Table 1. Relevant ^{13}C NMR and ^{15}N NMR chemical shifts (ppm) of hydrazones **3** in DMSO-d$_6$

	δ_C					δ_N			
	C-2	**C-4**	**C-5**	**C-6**	**CH=**	**N-1**	**N-2A**	**N-2B**	**N-3**
3a	152.64	162.36	101.64	163.41	144.63	186.54	166.87	320.60	145.86
3b	152.43	162.44	101.65	163.30	142.37	187.50	168.81	320.80	145.90
3c	152.44	162.30	101.42	163.45	144.95	186.15	167.20	317.90	144.60
3d	152.38	161.26	101.18	161.97	140.23	119.20	-	340.10	144.39

Table 2. Relevant ^{13}C- and ^{15}N chemical shifts (ppm) of the cyclisation products in DMSO-d$_6$ [a)] or in CDCl$_3$ [b)]

	C-3	**C-4**	**C-5**	**C-6**	**C-7a**	**N-1**	**N-2**	**N-4a**	**N-7**
4a [a)]	71.22	158.14	108.05	164.56	148.36	151.90	169.20	170.40	210.80
5a [a)]	73.43	157.69	96.40	152.76	146.47	202.60	176.40	131.30	109.82
4b [b)]	68.55	158.10	108.85	164.99	148.90	-	-	168.05	214.05
5b [a)]	72.10	157.98	96.40	152.94	146.81	-	-	156.10	110.30
4c [b)]	71.15	158.43	109.03	164.38	147.59	-	169.83	173.50	212.32
4d [a)]	70.13	157.85	107.39	164.87	148.31	-	-	164.90	208.10
5d [a)]	71.37	157.96	95.89	153.10	146.35	206.83	169.58	147.53	108.36

Arylidenehydrazones

First, we set out to establish the structures of the condensation products of **1** with the aromatic aldehydes **2a-d**. Knowledge of these structures is necessary to rationalize the subsequent reactions upon treatment with acetic anhydride. Elemental analyses and routine ^{1}H- and ^{13}C NMR spectra indicated formation of the expected hydrazone structures in the above reactions. Products **3a-d** may, however, occur in three different tautomeric forms, **I, II** or **III**, each containing two sp^2 and two sp^3 nitrogens. Full characterization of these forms was achieved by 2D NMR measurements as follows.
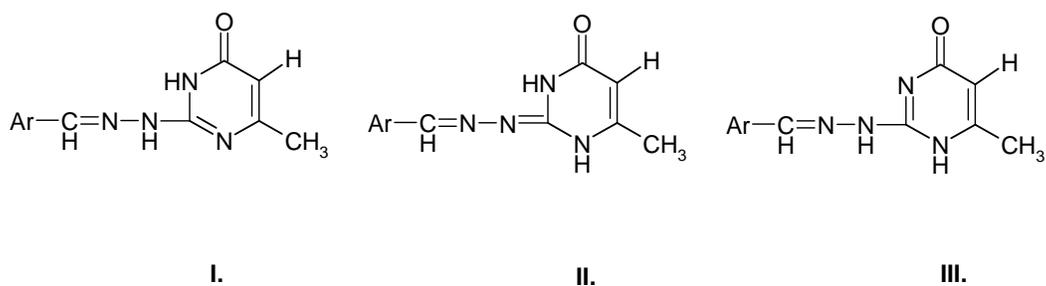
Scheme 2. Possible tautomers of arylidenehydrazones.

The NH-protons undergo fast exchange on the NMR time scale so they are not suitable for structural characterization. ^{15}N-HMBC connectivities were, on the other hand, instrumental in determining the prevailing tautomeric form in each of the above cases. Inspection of formulas **I-III** reveals that the ^{15}N chemical shifts of N1 and N3 in the pyrimidine ring are of diagnostic value for this purpose. Assignments of these nitrogens are straightforward from the ^{15}N-HMBC spectra; while H-5 can, in principle, be coupled to both N1 and N3, only N1 can give a cross peak to the CH_3-6 protons. In fact, H-5 shows a HMBC correlation to a nitrogen with δ_N ~145 ppm in all hydrazones **3a-d**, whereas the protons of CH_3-6 are coupled to an aromatic N (δ_N ~186 ppm) in **3a, 3b** and **3c** and to an sp^3-N (δ_N =119.2 ppm) in **3d**. These chemical shifts clearly indicate the prevalence of tautomeric forms **I** for the former three derivatives and **II** for the fourth. Furthermore, occurrence of tautomer **III** can be safely excluded in all cases investigated. The ^{15}N chemical shift values of the hydrazone nitrogens in Table 1 are in full agreement[18] with these structures. In addition to tautomerism, the *E/Z* isomerism also is of interest in describing the structure of the hydrazones. The configuration about the CH=N – bond was found to be *E* in all four derivatives **3a-d** from the fact that the $^1J_{CH}$-values were less than ~170 Hz (Experimental); these values are expected to be significantly larger for the *Z*-configuration.[20]

Products obtained by acetylation

^{13}C-HMBC spectra of the acetylation products (**4, 5**) provide clear evidence of cyclisation reactions occurring during treatment of **3a-d** with acetic anhydride. Specifically, the CH-proton at around 7 ppm in the ^{1}H NMR spectra displays long-range couplings to C-2 and C-4 pyrimidine carbons in each of the reaction products containing two acetyl groups. The ^{13}C chemical shifts of these CHs, on the other hand, are much less (~73 ppm) than that expected for a CH=N carbon (around 150 ppm) in each of the products. Therefore, the acylhydrazone structure (Scheme 3) can be safely discounted from further considerations. Furthermore, these observations eliminate structures originating from angular type ring closure (Scheme 3).

The CH-proton of the triazole ring (H-3) displays long-range coupling to one of the acetyl carbonyl carbons in both products **4** and **5** (Scheme 4). H-3 is, in addition, weakly coupled (^{13}C-HMBC) to the other C=O carbon in **4a** but not in **5a**. This suggests structures for **4** and **5** as shown in Scheme 4. This hypothesis was then fully confirmed by determining the ^{15}N chemical shifts through ^{15}N-HMBC measurements. Specifically, N-7 is clearly an sp^2, aromatic type N in **4a-d** whereas ^{15}N chemical shifts indicate an sp^3 amide type N-7 in **5a-d** (Table 2). Key ^{1}H/^{15}N HMBC correlations allowing unequivocal ^{15}N assignments are shown in Scheme 4. The above data therefore provide firm evidence for the structures of the ring closure products **4** and **5**; their product distribution depending on the aryl substituent at C-3 (Experimental).
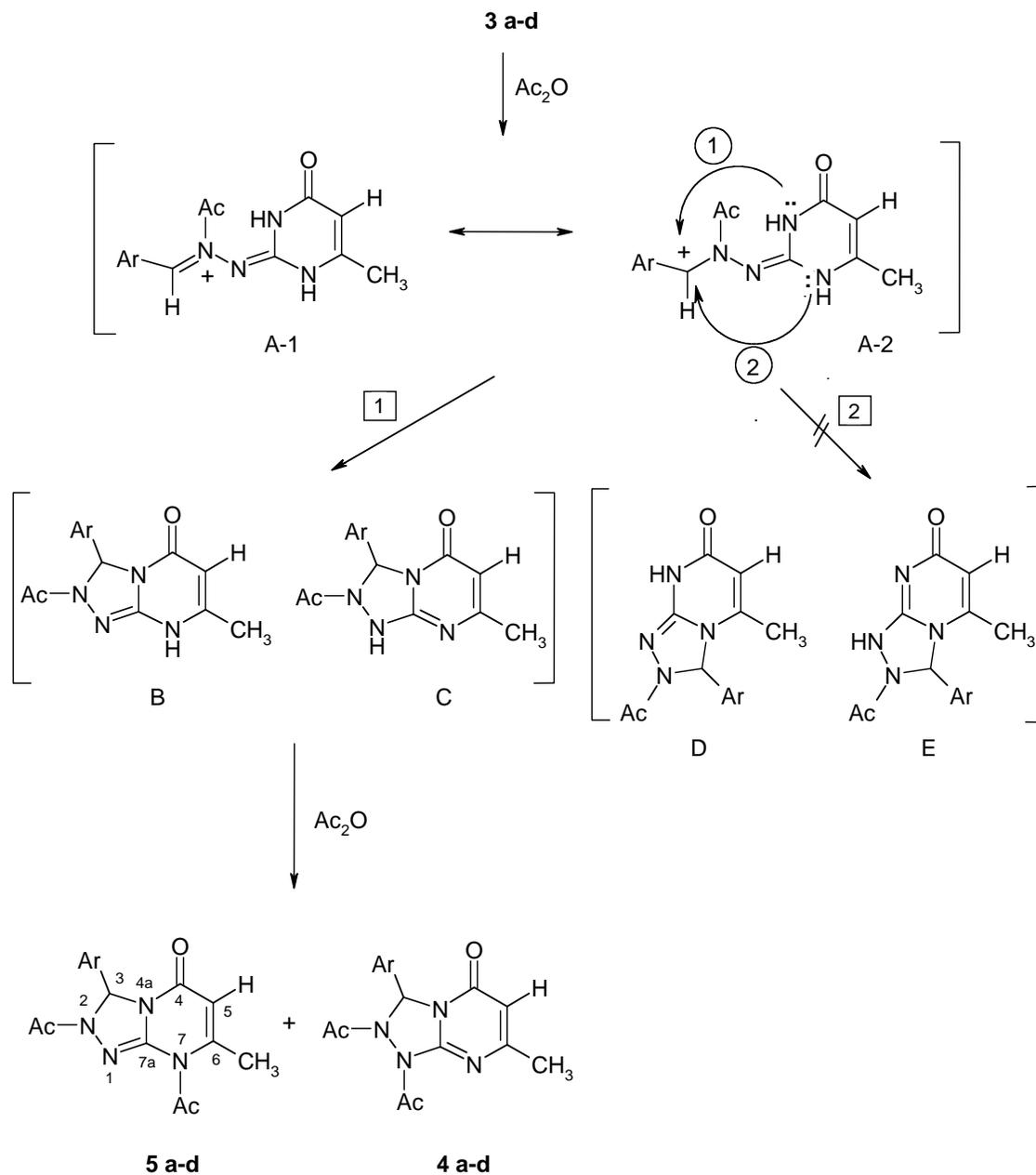
Scheme 3
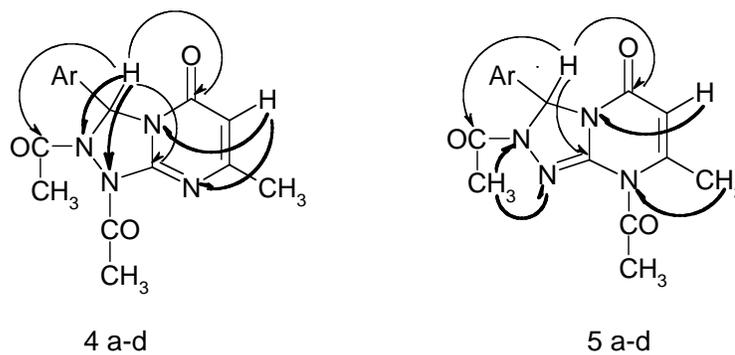
Scheme 4. Relevant ^{13}C- (thin lines) and ^{15}N-HMBC (thick lines) correlations.

A possible mechanism for the ring closure reactions is set out in Scheme 3. Acyliminium ion **A,** depicted in two mesomeric forms **A-1** and **A-2**, is supposed to form,[5,6] as a first step, from tautomeric forms **II** of arylidenehydrazones **3a-d**, via direct nucleophilic attack upon Ac$_2$O. Form **I** may tautomerize into **II** under the reaction conditions. Ring closure can be effected by intramolecular nucleophilic attack either from ring N-3 or N-1 onto the formal carbocationic center in **A-2**, followed by deprotonation, leading to products **B** and **C** (route [1]) or **D** and **E** (route [2]). The single NH group in these intermediates is acetylated in situ in the presence of excess acetic anhydride. Since we could isolate N-acetylated derivatives (**4** and **5**) of [1,2,4]triazolo[4,5-a]pyrimidine tautomers (**B** and **C**) only and no products from the alternative structures **D** and **E,** route [1] appears to be favored over route [2] under the conditions employed. Inspection of Table 2 and ^{1}H chemical shifts (see, Experimental) reveals that the chemical shifts of H-5, C-5 and C-6 are of diagnostic value in determining the positions of the N-acetyl groups and, therefore, discriminating between **4a-d** vs. **5a-d**. Namely, H-5, C-5 and C-6 are all shifted upfield significantly in the **5a-d** isomers (typical values being ~5, ~96 and ~152 ppm for H-5, C-5 and C-6, respectively) with respect to those in their **4a-d** counterparts (typical values at ~6, ~108 and ~164 ppm, respectively, for H-5, C-5 and C-6). These chemical shift changes reflect the presence vs. absence of the acetyl group at N-7 through substituent effects on the respective carbons and the neighbour anisotropy of the acetyl carbonyl on the H-5 chemical shift, respectively. These characteristic differences have, on the other hand, a welcome practical consequence in that they make it easy to identify the isomeric structures by simply relying on 1D ^{1}H- and ^{13}C-NMR spectra.

In summary, we have determined the tautomeric forms and the configuration of the CH=N bond in pyrimidine hydrazones **3** by NMR. It has been established that cyclisation of hydrazones **3** with acetic anhydride results in the exclusive formation of the linear type of heterobicycles featuring different acetylation patterns (**4, 5**).

Experimental Section

General Procedures. Melting points were determined with a hot stage microscope F. Küstner & Nachf., Dresden. Column chromatography was performed on silica gel (Merck 40, 70-230 mesh) using ethyl acetate – ethanol = 70:1 as eluent. NMR spectra were recorded on a Bruker Avance DRX 500 (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C and 50.69 MHz for ^{15}N) spectrometer. Chemical shifts (δ in ppm) are referenced to internal TMS for ^{1}H NMR, [13]CDCl$_3$ (77.0) or DMSO-d$_6$ (39.51) for ^{13}C NMR and external nitromethane converted to external liquid ammonia scale (0.0) for ^{15}N NMR.

2-Arylidenehydrazino-6-methyl-4-pyrimidones (3a-d). The procedure of Doyle[17] was modified as in reference 19: a mixture of aldehyde (10 mmol) and 2-hydrazino-6-methyl-4-pyrimidone (1.40 g, 10 mmol) in ethanol (17 mL) was heated with 3 drops of acetic acid for the

given time. The product was filtered from the cooled reaction mixture and was dried under an infrared lamp.

2-Benzylidenehydrazino-6-methyl-4-pyrimidone (3a). a., Using the general procedure, after 40 min reaction time the yield was 2.05 g (89.8%), m.p.: 244-7°C (2-propanol). Anal. Calcd. for $C_{12}H_{12}N_4O$ (228.25): C, 63.14; H, 5.30; N, 24.54. Found: C, 62.89; H, 5.23; N, 24.42. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 10.35 (2H, NH); 8.05 (1H, CH=); 7.95-7.45 (3H, aromatic); 5.51 (1H, H-5); 2.09 (3H, CH$_3$); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ 163.41 (C-6); 162.36 (C-4); 152.64 (C-2); 144.63 (CH=, $^1J_{CH}$ =166Hz); 134.63 (C-1'); 129.67 (C-4'); 128.62 (C-2'); 127.62 (C-3'); 101.64 (CH-5); 22.76 (CH$_3$); ^{15}N-NMR (DMSO-d_6, 50.68 MHz): δ 320.60 (N-2B); 186.54 (N-1); 166.87 (N-2A); 145.86 (N-3).

b., Benzaldehyde guanylhydrazone (1.50 g, 10 mmol), ethyl acetoacetate (1.26 ml, 10 mmol) and 1 drop of acetic acid in ethanol (6.5 ml) were refluxed for 6 h. The precipitate (0.9 g, 39 %) was recrystallized from 2-propanol, m.p.: 244-6°, Lit.[17]: 209°C.

2-(1'-Naphthylidenehydrazino)-6-methyl-4-pyrimidone (3b). Using the general procedure, after 45 min reaction time the yield was 2.60 g (87.7 %), m.p.:202-203°C (ethanol). Anal. Calcd. for $C_{16}H_{14}N_4O·H_2O$ (296.32): C, 64.85; H, 5.44; N, 18.91. Found: C, 64.69; H, 5,61; N, 18.97. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.38 (2H, NH); 8.91 (1H, CH=); 8.55-7.54 (7H, aromatic); 5.58 (1H, H-5); 2.08 (3H, 6-CH3); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ 163.30 (C-6); 162.44 (C-4); 152.43 (C-2); 142.37 (CH=, $^1J_{CH}$ =161Hz); 133.35; 130.36; 129.46 (Cq-aromatic); 129.86; 128.80; 126.94; 125.96; 125.75; 125.55; 122.59 (CH-aromatic); 101.65 (CH-5); 22.63 (CH3); ^{15}N-NMR (DMSO-d_6, 50.68 MHz): δ 320.80 (N-2B); 187.50 (N-1); 168.81 (N-2A); 145.90 (N-3).

2-(3',4',5'-Trimethoxybenzylidenehydrazino)-6-methyl-4-pyrimidone (3c). Using the general procedure, after 2 hours reaction time the yield was 2.22 g (69 %), m.p.: 207-8°C (2-propanol).Anal. Calcd. for $C_{15}H_{18}N_4O_4$ (318.32): C, 56.59; H, 5.70; N, 17.60. Found: C, 56.38; H, 5.61, N, 17.64. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.30 (2H, NH); 8.01 (1H, CH=); 7.20 (2H, aromatic); 5.50 (1H, H-5); 3.82 (6H, 2x OCH$_3$) ; 3.68 (3H, OCH$_3$); 2.06 (3H, 6-CH$_3$); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ 163.45 (C-6); 162.68 (C-4); 153.25 (C-4'); 152.44 (C-2); 144.95 (CH=); 139.11 (2x C-3'); 130.01 (C-1'); 105.04 (2x C-2'); 101.42 (CH-5); 60.19 (OCH$_3$); 55.26 (2x OCH$_3$); 22.66 (6-CH$_3$); ^{15}N-NMR (DMSO-d_6, 50.68 MHz): δ 317.90 (N-2B); 186.15 (N-1); 167.20 (N-2A); 144.60 (N-3).

2-(2',6'-Dichlorobenzylidenehydrazino)-6-methyl-4-pyrimidone (3d). Using the general procedure, after 10 min reaction time the yield was 2.72 g (91.5 %), m.p.: 230-31°C (ethyl acetate), lit.[17] m.p.: 237-9°C. Anal. Calcd. for $C_{12}H_{10}Cl_2N_4O$ (297.15): Cl, 23.86; N, 18.85. Found: Cl, 24.03; N, 18.82. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 11.10 (2H, NH); 8.31 (1H, CH=, $^1J_{CH}$ =167Hz); 7.53-7.38 (3H, aromatic); 5.54 (1H, H-5); 2.10 (3H, 6-CH$_3$); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ 161.97 (C-6); 161.26 (C-4); 152.38 (C-2); 140.23 (CH=, $^1J_{CH}$ =163Hz); 133.83 (2x C-2'); 130.57 (C-4'); 129.91 (C-1'); 128.78 (2x C-3'); 101.18 (CH-5); 21.05 (6-CH$_3$); ^{15}N-NMR (DMSO-d_6, 50.68 MHz): δ 340.10 (N-2B); 144.39 (N-3); not observed (N-2A); 119.20 (N-1).

General procedure for cyclization of 3a-d.

Compound 3 (2 mmol) was refluxed in acetic anhydride (1.6 mL) for 10-25 min. The volatiles were evaporated in vacuo. Codistillation with toluene (3 x 12 ml) gave rise to the crude products. Pure 4 and 5 were obtained by crystallization or column chromatographic separation (ethyl acetate : ethanol = 80:1).

(3*R*,*S*)-1*H*,2*H*,3*H*,4*H*-Tetrahydro-1,2-diacetyl-3-phenyl-6-methyl-[1,2,4]triazolo[4,5-a]pyrimidin-4-one (4a). Using the general procedure with **3a**, the crude product was separated by column chromatography. The first fraction contained **4a**, yield: 0.394 g (63 %), mp.: 150-52°C. Anal. Calcd. for $C_{16}H_{16}N_4O_3$ (312.32): C, 61.53; H, 5.16; N, 17.94. Found: C, 61.65; H, 5.07; N, 17.88. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 7.45-7.30 (3H, aromatic); 7.05 (1H, H-3); 5.05 (1H, H-5); 2.64 (3H, 2-CH$_3$); 2.28 (3H, 6-CH$_3$); 2.07 (3H, 1-CH$_3$); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ 174.05 (CO-Ac-1); 167.90 (CO-Ac-2); 164.56 (C-6); 158.14 (C-4); 148.36 (C-7a); 137.41 (C-1'); 129.50 (C-4'); 128.72 (C-2'); 128.28 (C-3'); 108.05 (CH-5); 71.22 (CH-3); 23.47 (CH$_3$-Ac-2); 22.46 (CH$_3$-Ac-1); 20.65 (6-CH$_3$); ^{15}N-NMR (DMSO-d_6, 50.68 MHz): δ 210.80 (N-7); 170.40 (N-4a); 169.20 (N-2); 151.90 (N-1).

(3*R*,*S*)-2*H*,3*H*,4*H*,7*H*-Tetrahydro-2,7-diacetyl-3-phenyl-6-methyl-[1,2,4]triazolo[4,5-a]pyrimidin-4-one (5a). The second fraction in the foregoing reaction contained amorphous product **5a**, yield 0.013 g (2.0 %), mp.: 217-24 °C. Anal. Calcd. for $C_{16}H_{16}N_4O_3$ (312.32): C, 61.53; H, 5.16; N, 17.94. Found: C, 61.65; H, 5.08, N, 17.76. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 6.87 (1H, H-3); 7.45-7.30 (3H, aromatic); 5.10 (1H, H-5); 2.05 (3H, 6-CH$_3$); 2.02 (3H, CH$_3$-Ac-2); 1.92 (3H, CH$_3$-Ac-7); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ 171.97 (CO-Ac-7); 165.16 (CO-Ac-2); 167.69 (C-4); 152.76 (C-6); 146.47 (C-7a); 137.59 (C-1'); 128.61 (C-4'); 128.47 (C-2'); 126.92 (C-3'); 96.40 (CH-5); 73.62 (CH-3); 20.95 (6-CH$_3$ and CH$_3$-Ac-7)*;* 18.40 (CH$_3$-Ac-2);^{15}N-NMR (DMSO-d_6, 50.68 MHz): δ 202.60 (N-1); 176.40 (N-2); 131.30 (N-4a); 109.82 (N-7).

(3*R*,*S*)-1*H*,2*H*,3*H*,4*H*-Tetrahydro-1,2-diacetyl-3-(1'-naphthyl)-6-methyl-[1,2,4]triazolo[4,5-a]pyrimidin-4-one (4b). Using the general procedure with **3b**, the crude product was crystallized from ethanol, to give pure **4b**, yield 0.50 g (69 %), mp.: 202-204°C. Anal. Calcd. for $C_{20}H_{18}N_4O_3$ (362.25): C, 66.31; H, 4.97, N, 15.47. Found: C, 66.17; H, 4.99; N, 15.53. ^{1}H-NMR (CDCl$_3$, 500 MHz): δ 8.65-6.66 (7H, aromatic); 8.21 (1H, H-3); 6.12 (1H, H-5); 2.30 (3H, 6-CH$_3$); 2.10 (6H, CH$_3$-Ac-1 and -2); ^{13}C-NMR (CDCl$_3$, 125 MHz): δ 175.75 (7-CO); 164.99 (C-6); 158.00 (C-4); 148.90 (C-7a); 133.66; 129.98; 127.75 (Cq-aromatic); 130.58; 128.28; 126.97; 126.20; 124.20; 122.94; 121.28 (CH-aromatic); 108.85 (CH-5); 68.55 (CH-3); 23.57 (6-CH$_3$); 20.56 (CH$_3$-Ac-1 and-2); ^{15}N-NMR (CDCl$_3$, 50.68 MHz): δ 214.05.10 (N-7); 168.05 (N-4a); 166.10 (N-2); 151.50 (N-1).

(3*R*,*S*)-2*H*,3*H*,4*H*,7*H*-Tetrahydro-2,7-diacetyl-3-(1'-naphthyl)-6-methyl-[1,2,4]triazolo[4,5-a]pyrimidin-4-one (5b). The mother liquor from **4b** was evaporated to dryness and the residue purified by column chromatography to produce 0.07 g (1 %) of **5b** as an amorphous product. Anal. Calcd. for $C_{20}H_{18}N_4O_3$ (362.25). C, 66.31; H, 4.97; N, 15.47. Found: C, 66.24; H, 4.82; N,

15.34. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 8.41-7.35 (7H, aromatic); 7.58 (1H, H-3); 5.02 (1H, H-5); 2.01 (6H, 6-CH_3 and CH_3-Ac-7); 1.92 (3H, CH_3-Ac-2); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ 172.17 (7-CO); 165.49 (2-CO); 157.98 (C-4); 152.94 (C-6); 146.81 (C-7a); 134.40; 133.29; 129.57 (Cq-aromatic); 128.72; 126.47; 125.83; 125.53; 123.41 (CH-aromatic); 96.40 (CH-5); 72.10 (CH-3); 21.20 (CH_3-Ac-2); 20.99 (CH_3-Ac-7); 18.50 (6-CH_3); ^{15}N-NMR (DMSO-d_6, 50.68 MHz): δ 156.10 (N-4a); 110.30 (N-7); not observed (N-1), (N-2).

(3*R,S*)-1*H*,2*H*,3*H*,4*H*-Tetrahydro-1,2-diacetyl-3-(3',4',5'-trimethoxyphenyl)-6-methyl-[1,2,4] triazolo -[4,5-a]pyrimidin-4-one (4c). Using the general procedure with **3c**, the reaction mixture contained only **4c**, yield 0.70 g (91 %), mp.: 173-176°C (Ethyl acetate - hexane). Anal. Calcd. for $C_{18}H_{22}N_4O_6$ (384.39): C, 61.00; H, 5.76; N, 14.57. Found: C, 60.93; H, 5.67; N, 14.50. ^{1}H-NMR (CDCl$_3$, 500 MHz): δ 7.40 (1H, H-3); 6.90 (2H, aromatic); 6.05 (1H, H-5); 3.78 (6H, OCH$_3$); 3.74 (3H, OCH$_3$); 2.67 (3H, CH_3-Ac-2); 2.21 (3H, 6-CH_3); 2.19 (3H, CH_3-Ac-1); ^{13}C-NMR (CDCl$_3$, 125 MHz): δ 173.46 (2-CO); 167.58 (1-CO); 164.38 (C-6); 158.43 (C-4); 153.31 (C-3'); 147.59 (C-7a); 138.52 (C-4'); 128.92 (C-1'); 109.03 (CH-5); 103.09 (C-2'); 71.15 (CH-3); 60.37 (OCH$_3$); 55.83 (2x OCH$_3$); 23.53 (6-CH_3); 22.44 (CH_3-Ac-1); 20.29 (CH_3-Ac-2); ^{15}N-NMR (CDCl$_3$, 50.68 MHz): δ not observed (N-1); 212.32 (N-7); 173.50 (N-4a); 169.83 (N-2).

(3*R,S*)-2*H*,3*H*,4*H*,7*H*-Tetrahydro-2,7-diacetyl-3-(2',6'-dichlorophenyl)-6-methyl-[1,2,4]triazolo [4,5-a]pyrimidin-4-one (5d). The crude product obtained from **3d**, using the general procedure, was crystallized from ethanol to yield **5d,** 0.46 g (60.4 %). Mp.: 286-291°C. Anal. Calcd. for $C_{16}H_{14}Cl_2N_4O_3$ (381.22): C, 50.40; H, 3.70; N, 14.70. Found: C, 50.29; H, 3.65; N, 14.62. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 7.49 (1H, H-3); 7.45-7.34 (3H, aromatic); 5.03 (1H, H-5); 2.01 (6-CH_3); 1.99 (CH_3-Ac-2 and 7); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ 171.84 (7-CO); 162.51 (2-CO); 157.96 (C-4); 153.10 (C-6); 146.35 (C-7a); 137.07 (C-1'); 132.95 (C-2'); 130.25 (C-6'); 130.85; 129.98; 128.82 (CH-aromatic); 95.89 (CH-5); 71.37 (CH-3); 20.74 (6-CH_3); 18.55 (CH_3-Ac-2 and 7); ^{15}N-NMR (DMSO-d_6, 50.68 MHz): δ 206.83 (N-1); 169.58 (N-2); 147.53 (N-4a); 108.36 (N-1).

(3*R,S*)-1*H*,2*H*,3*H*,4*H*-Tetrahydro-1,2-diacetyl-3-(2',6'-dichlorophenyl)-6-methyl-[1,2,4]triazolo -[4,5-a]pyrimidin-4-one (4d). The mother liquor from **5d** was evaporated to dryness and the residue purified by column chromatography to produce **4d** as an amorphous product, yield 0.10 g (13 %). ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 7.45 (1H, H-3); 7.35-7.40 (3H, aromatic); 6.10 (1H, H-5); 2.27 (3H, 6-CH_3); 2.19 (3H, CH_3-Ac-1); 2.01 (3H, CH_3-Ac-2); ^{13}C-NMR (CDCl$_3$, 125 MHz): δ 171.52 (2-CO); 164.87 (1-CO); 157.85 (C-6); 152.82 (C-4); 148.31 (C-7a); 136.76 (C-1'); 133.93 (C-2'); 133.10 (C-6'); 130.30; 129.65; 129.34 (CH-aromatic); 107.39 (CH-5); 70.13 (CH-3); 23.54 (6-CH_3); 22.99 and 20.29 (CH_3-Ac-1,-2); ^{15}N-NMR (CDCl$_3$, 50.68 MHz): δ not observed (N-1); (N-2); 208.10 (N-7); 164.90 (N-4a);

Acknowledgements

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