Monatshefte für Chemie 126, 733–746 (1995)

Monatshefte für Chemie
Chemical Monthly

1,4,-Diacyl-3-acylamino-5-aryl-4,5-dihydro-1*H*-1,2,4-triazoles: Ring Closure Products of Aromatic Carbaldehyde (Diaminomethylene) Hydrazones with Acylating Agents#

Z. Györgydeák[1,*], W. Holzer[2], R. W. Kunz[3], and A. Linden[3]

[1] Kossuth Lajos Tudományegyetem Szerves Kémiai Tanszék, H-4010 Debrecen, Hungary
[2] Institut für Pharmazeutische Chemie der Universität Wien, A-1090 Wien, Austria
[3] Organisch-chemisches Institut der Universität Zürich, CH-8057 Zürich, Switzerland

Summary. Treatment of aromatic carbaldehyde (diaminomethylene)hydrazones **1** with hot acetic anhydride or benzoyl chloride affords 1,4-diacyl-3-acylamino-5-aryl-4,5-dihydro-1*H*-1,2,4-triazoles **2**. In contrast, a new type of 0,N-acetal with an 1,2,4-triazole substructure (**3**) is obtained from 4-pyridine-carbaldehyde (diaminomethylene)hydrazone (**1i**) by using a similar reaction procedure. The structures of all novel compounds were confirmed by spectroscopic data (^{1}H and ^{13}C NMR, MS, IR); some representative compounds were also studied by X-ray analysis.

Keywords. 1,2,4-Triazolines; (Diaminomethylene)hydrazones; X-Ray analysis; NMR-spectroscopy.

1,4-Diacyl-3-acylamino-5-aryl-4,5-dihydro-1*H*-1,2,4-triazole: Ringschlußprodukte von aromatischen Aldehyd-dimethylaminomethylenhydrazonen mit Acylierungsmitteln

Zusammenfassung. Die Umsetzung von aromatischen Aldehyde-diaminomethylene-hydrazonen **1** mit heißem Essigsäureanhydrid oder Benzoylchloride liefert 1,4-Diacyl-3-acylamino-5-aryl-4,5-dihydro-1*H*-1,2,4-triazole **2**. Im Gegensatz dazu erhält man aus 4-Pyridinaldehyd-diaminomethylen-hydrazon (**1i**) unter den gleichen Reaktionsbedingungen einen neuen O,N-Acetaltyp mit einer 1,2,4-Triazoleinheit. Die Struktur sämtlicher neuer Produkte wurde durch spektroskopische Daten (^{1}H- und ^{13}C-NMR, MS, IR) unterstützt; einige repräsentative Vertreter wurden zusätzlich mittels Röntgenstrukturanalyse untersucht.

Introduction

"Guanylhydrazones" ((alkylenamino)guanidines, (diaminomethylene)hydrazones), a class of compounds discovered by *Thiele* [1] more than hundred years ago, are obtained usually by the reaction of carbonyl compounds with salts of amino-guanidine in slightly acidic media. Recently, we reported on investigations regarding the structure of a variety of such compounds related to the antihypertensive agent Guanabenz [2].

Dedicated to Professor Dr. *S. Makleit* on the occasion of his 65th birthday.

In consideration of the interesting biological activities of "guanylhydrazone" derivatives [2–4], in the present work we have investigated the behaviour of such compounds towards acylating agents such as acetic anhydride and benzoyl chloride.

Results and Discussion

Syntheses

As shown previously [2], acylation of "guanylhydrazones" carrying bulky substituents on the aromatic system gives rise to the formation of N_3,N_4-diacyl derivatives. Thus, for instance, the acylation product of 2,4-dichlorobenzaldehyde (diaminomethylene)hydrazone was clearly shown to be the N_3,N_4-diacetyl product on the basis of its characteristic ^{13}C NMR data (appearence of an N=CH resonance with $\delta = 150.8$ ppm and $^1J_{N=CH} = 168.0$ Hz).

If benzaldehyde (diaminomethylene)hydrazone (**1a**) is treated under analogous reaction conditions, a product can be obtained, which *Thiele* [5] postulated to be the diacetyl compound.

However, in the ^{13}C NMR spectrum of this product (**2a**) the expected N=CH fragment (compare Ref. [2]) cannot be detected, whereas the signal of a C–H fragment appears at $\delta = 75.0$ ppm which is rather characteristic of an sp^3-hybridized C-atom flanked by two (electronegative) heteroatoms. Additionally, the ^{13}C NMR spectrum of **2a** clearly shows three acetyl groups, which is in accordance with the findings of *Grammaticakis* [6] who, based on elemental analysis, postulated a threefold acylated product resulting from this reaction.

These results were confirmed by the mass spectrum of **2a**, which showed M^+ to have $m/z = 288$. The ^{13}C NMR data of compound **2a** together with its carbonyl absorptions (IR: 1732, 1700, 1654 cm^{-1}; not congruent with those for acylated (diaminomethylene)hydrazones described in Ref. [2]) gave a strong indication that **2a** is a triacylated 1,2,4-triazoline derivative, apparently resulting from cyclization of the corresponding acylated (diaminomethylene)hydrazone.

Some other related ring transformation reactions of (diaminomethylene)-hydrazones into 1,2,4-triazole derivatives can be found in the literature [8–10]. It was also reported that some compounds, having the "guanylhydrazone" substructure (partially) incorporated into a heterocyclic ring system, show ring-chain tautomerism forming an anellated 1,2,4-triazoline ring [11–13]. Additionally, the formation of an 1,2,4-triazoline derivative upon reaction of aldehyde S-methyl isothiosemicarbazones with acetic anhydride should be mentioned [14].

All above mentioned ring closure products formally result from transformation of a *Schiff* base to an animal. The findings described in the literature together with the characteristic spectroscopic features of compound **2a** (particularly the signal at 75.0 ppm in the ^{13}C NMR spectrum) led to the assumption that **2a** must contain an aminal substructure and thus has to be formulated as 3-acetamido-1,4-diacetyl-2-phenyl-4,5-dihydro-1*H*-1,2,4-triazole (**2a**). It should be mentioned that the physical constants found for **2a** are in full agreement with those given in Refs. [5, 6]; however, the formation of a further isomer as mentioned in Ref. [6] could not be detected.

In order to prove the validity of this novel "5-*Endo*-*Trig*" ring closure reaction as a route to hitherto not accessible 4,5-dihydro-1,2,4-triazole derivatives [15], we similarly cyclized some additional "guanylhydrazones" (**1b–1h**) to the corresponding reaction products **2b–2h**. Direct evidence for the structure of compounds **2a** and **2b** of this series was obtained by X-ray analyses (Figs. 1 and 2).

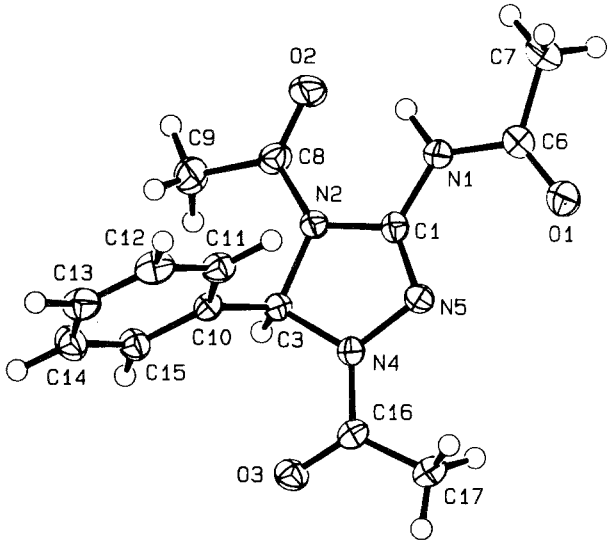


Fig. 1. Molecular structure of **1a**. Selected bond lengths (Å) and angles (°): C1–N2, 1.411(3); N2–C3, 1.477(3); C3–N4, 1.476(3); N4–N5, 1.413(3); C1–N5, 1.283(3); C1–N1, 1.379(4); N1–C6, 1.380(4); N2–C8, 1.386(4); C3–C10, 2.517(4); N4–C16, 1.361(3); N2–C1–N5, 115.3(3); C1–N2–C3, 107.7(2); N2–C3–N4, 98.4(2); C3–N4–N5, 114.0(2); C1–N5–N4, 104.2(2)

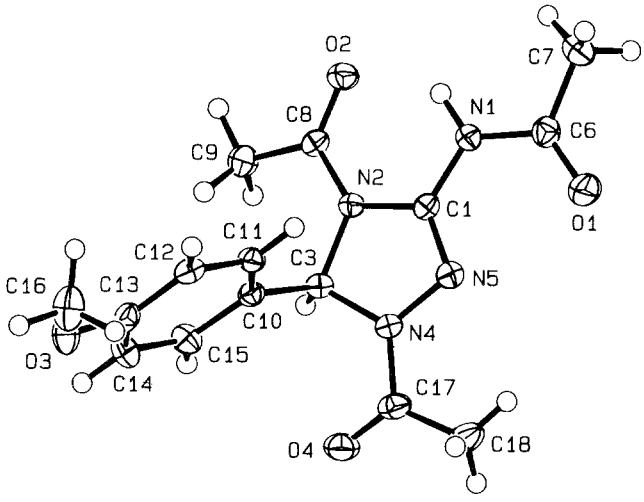
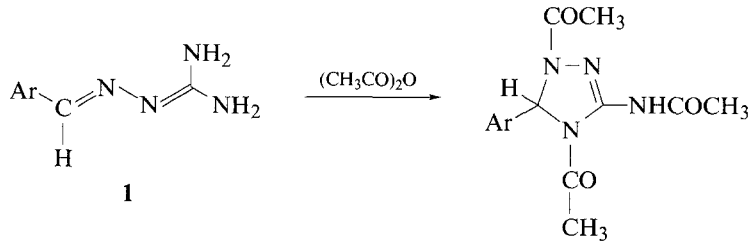


Fig. 2. Molecular structure of **1b**. Selected bond lengths (Å) and angles (°): C1–N2, 1.412(3); N2–C3, 1.482(3); C3–N4, 1.475(3); N4–N5, 1.410(3); C1–N5, 1.284(3); C1–N1, 1.380(3); N1–C6, 1.388(3); N2–C8, 1.383(3); C3–C10, 1.512(3); N4–C17, 1.365(3); N2–C1–N5, 114.5(2); C1–N2–C3, 108.0(2); N2–C3–N4, 98.2(2); C3–N4–N5, 113.7(2); C1–N5–N4, 104.9(2)

Reaction of **1a** with three equivalents of benzoyl chloride at room temperature resulted in a related triazoline derivative **2a** (C_6H_5CO instead of CH_3CO), which was mentioned as the "tribenzoylation product" of **1a** in Ref. [16].

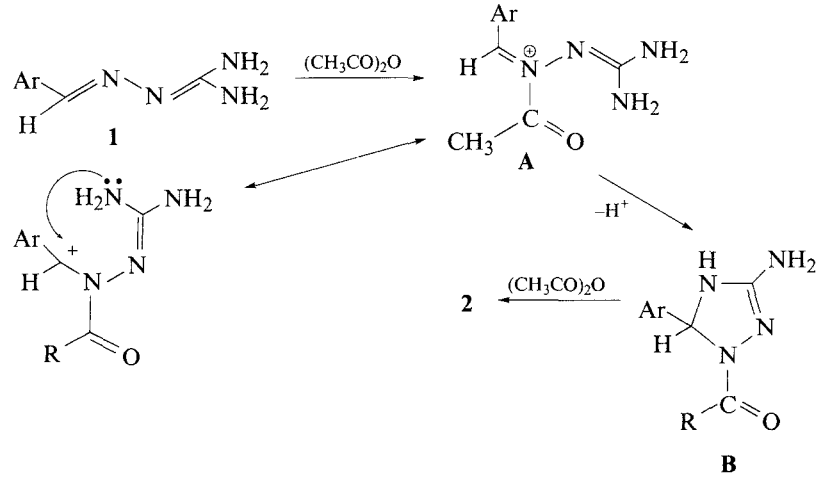
The first step in the cyclization of (diaminomethylene)hydrazones of type **1** in acetic anhydride might be the formation of an electrophilic N-acylium ion **A** (Scheme 1), which, in accordance with the

resonance structure shown, exhibits enhanced reactivity towards intramolecular nucleophilic attack by the NH_2 group. Reaction of the resulting monoacylated intermediate **B** with acetic anhydride (catalyzed by H^+) gives rise to the stable end products **2**. The complete process represents a new type of α-amidoalkylation [17]. It should be emphasized that conducting the reaction of **1a** with acetic anhydride in the presence of pyridine does not lead to the above ring closure reaction; instead, formation of the monoacylation product 4 (as the main component of the reaction mixture) was observed.



1,2	a	b	c	d
Ar	C_6H_5	4-$CH_3OC_6H_4$	3,4,5-$(OCH_3)_3C_6H_2$	2,4,5-$(OCH_3)_3C_6H_2$

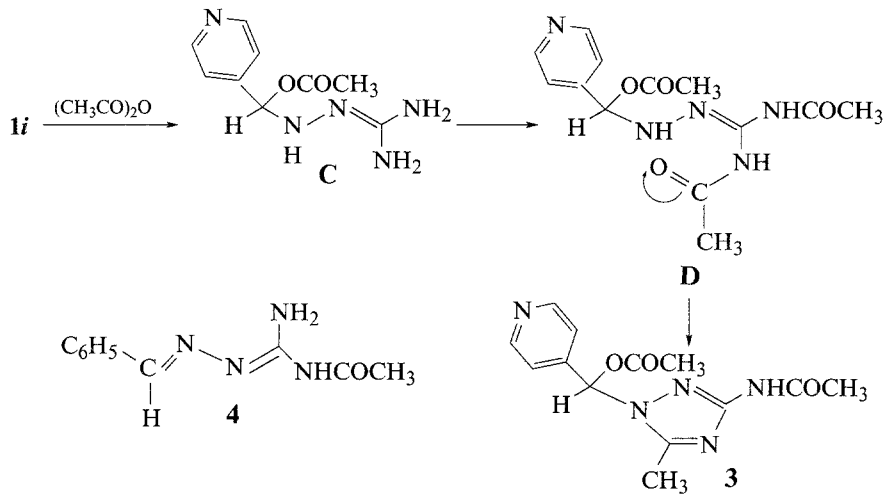
e	f	g	h	i
3-Br,4-CH_3O–C_6H_3	2-BrC_6H_4	1-$C_{10}H_7$	2-Thienyl	4-Pyridyl



Scheme 1

Surprisingly, the main product, **3**, resulting from the reaction of 4-pyridincarbaldehyde (diaminomethylene)hydrazone (**1i**) with acetic anhydride, showed a different spectroscopic behaviour as compared to compounds **2a–h** (see below). As the elemental analysis of **3** agrees with that of the expected 1,2,4-triazoline derivative **2i** ($C_{13}H_{15}N_5O_3$; MS: m/z of $M^+ = 289$), the compound must be an isomer of **2i**.

Since the spectroscopic data of **3** (^{1}H and ^{13}C NMR, IR, MS) did not permit an unambiguous determination of its structure, we turned to X-ray analysis which indicated that compound **3** is a 1,2,4-triazole derivative with the azole N-1 incorporated into an O,N-acetal substructure (Fig. 3). A possible explanation for the formation of **3** is acetoxylation of **1i** to intermediate **C** (Scheme 2), which is subsequently transformed into the ring-closure product **3**.



Scheme 2

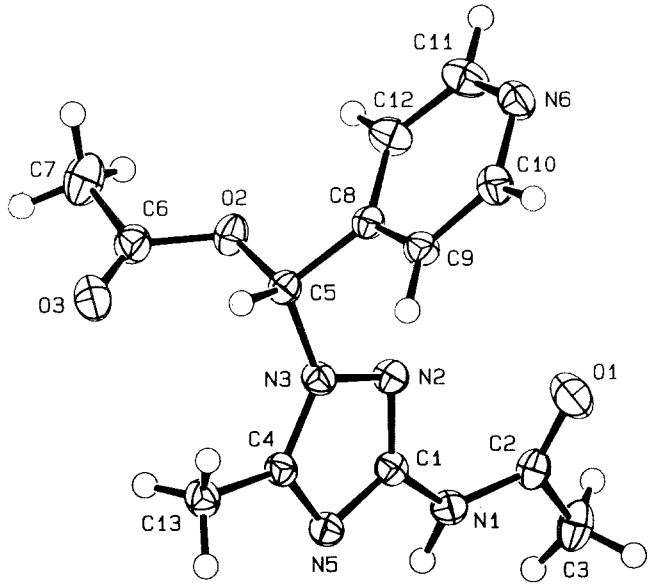


Fig. 3. Molecular structure of **3**. Selected bond lengths (Å) and angles (°): C1–N2, 1.321(2); N2–N3, 1.390(2); N3–C4, 1.359(2); C4–N5, 1.326(2); C1–N5, 1.364(2); C1–N1, 1.391(3); N3–C5, 1.446(2); C4–C13, 1.482(3); N2–C1–N5, 116.5(2); C1–N2–N3, 100.7(2); N2–N3–C4, 110.2(1); N3–C4–N5, 109.5(2); C1–N5–C4, 103.0(1)

NMR Spectroscopic Investigations

The ^{1}H NMR and ^{13}C NMR data of "guanylhydrazones" **1a–1i** are summarized in Tables 1 and 3, respectively. The structure elucidation of these compounds was performed in a similar manner to that described for related structures in Ref. [2]. Thus, ^{1}H NMR and ^{13}C NMR data in *DMSO*-d_6 solution together with $^1H\{^1H\}$ NOE difference experiments enabled us to assign **1a–1i** to the structures displayed in Scheme 1.

The NMR-spectroscopic data of 1,2,4-triazolines **2a–2h** (*DMSO*-d_6) are presented in Table 2 (^{1}H NMR) and Table 4 (^{13}C NMR). Apart from signals due to protons of the aromatic (or heteroaromatic) system (and attached methoxy functions, if present), the similarities among the ^{1}H and ^{13}C NMR spectra of structures **2a–2h** clearly suggest close structural similarity; the remarkably large chemical shifts of the triazoline protons ($\delta = 6.97$–7.78 ppm) are in good accordance with those of related compounds described in the literature [15, 19]. Unambiguous assignments of all acetyl group resonances could be achieved by NOE difference experiments (significant nuclear *Overhauser* enhancement on the signal of N^4-COCH_3 upon irradiation of the triazoline-H resonance) together with HMQC spectra (or 1D HETCOR spectra with selective excitation) and long-range INEPT experiments with selective excitation.

Compounds **2a** and **2c** were also investigated in $CDCl_3$ solution in the same way as described above (for spectral data, see Experimental). A comparison of these data with those obtained for *DMSO*-d_6 solution shows the most striking differences for the signals due to the acetyl groups which can be explained by the assumption that in $CDCl_3$ solution the oxygen atom of the N4-acetyl function and the NH-proton are linked by an intramolecular hydrogen bond as shown by the X-ray data for the solid state (see Figs. 1 and 2), whereas in the strong hydrogen acceptor *DMSO*-d_6 this interaction is diminished or not existent.

The structure of product **4**, resulting from reaction of "guanylhydrazone" **1a** with benzoyl chloride, was found to be similar to structure **2a** (C_6H_5CO instead of

Table 1. ^{1}H NMR data of aromatic carbaldehyde (diaminomethylene)hydrazones **1a–1i** (δ, *DMSO*-d_6)

	N=CH	Aromatic Protons	NH_2	Other Protons
1a[a]	7.98	7.72–7.60(2,6), 7.44–7.21(3,4,5)	5.89, 5.53	–
1b[a]	7.95	7.65–7.50(2,6), 6.94–6.83(3,5)	5.79, 5.40	3.75(OCH_3)
1c[a]	7.92	6.98(2,6)	5.94, 5.50	3.80(3,5-OCH_3), 3.65(4-OCH_3)
1d	8.22	7.52(6), 6.63(3)	5.88, 5.46	3.80(4-OCH_3), 3.78(2-OCH_3), 3.74(5-OCH_3)
1e	7.92	7.99(2), 7.54(6), 7.03(5)	6.60–4.40	3.82(OCH_3)
1f	8.26	8.10(6), 7.53(3), 7.30(5), 7.16(4)	6.06, 5.78	–
1g·HCl	9.04	8.45(8), 8.18(2), 8.00(4), 7.96(5), 7.62(7), 7.56(3), 7.55(6)	7.92	12.34(NH)
1h	8.16	7.34(5), 7.13(3), 7.01(4)	5.70, 5.55	–
1i[a]	7.92	8.49–8.41(2,6), 7.62–7.54(3,5)	6.10, 5.76	–

[a] See Ref. [2]

CH_2CO) considering the similarities with compounds **2a–2h** with respect to the chemical shifts of the triazoline C-atoms as well as the carbonyl-C resonances.

In contrast, the NMR spectra of compound **3** (cf. Experimental), obtained upon treatment of **1i** with acetic anhydride, exhibit some deviations compared to those of the series **2a–2h**, indicating **3** not to be the expected corresponding triazoline derivative. Again, applications of different NMR techniques (NOE difference spectra, determination of direct and long-range ^{13}C-^1H correlations by 1D HETCOR and long-range INEPT experiments with selective excitation) finally enabled us to verify structure **3** and to perform complete and unambiguous assignments of all carbon and proton resonances. All these data are in full accordance with the 1,2,4-triazole structure of this compound following from the X-ray analysis.

Table 2. ^1H NMR data of 1,2,4-triazolines **2a–2h** (δ, *DMSO*-d_6)

	N–CH–N	Aromatic Protons	NH	Acetyl-H			OCH_3
				1-Ac	4-Ac	NH–Ac	
2a	7.03	7.56(2,6), 3.37(3,4,5)	10.62	2.06	2.09	2.14	–
2b	6.98	7.46(2,6), 6.92(3,5)	10.56	2.05	2.07	2.13	3.74
2c	7.02	6.96(2,6)	10.70	2.07	2.11	2.13	3.77(3,5), 3.67(4)
2d	7.09	7.01(6), 6.69(3)	10.30	2.04	2.02	2.15	3.80(2), 3.79(4), 3.69(5)
2e	6.97	7.74(2), 7.52(6), 7.10(5)	10.60	2.06	2.11	2.13	3.84
2f	7.19	7.58(6), 7.57(3), 7.40(5), 7.25(4)	10.52	2.05	2.08	2.15	–
2g	7.78	8.53(8), 7.94(4,5), 7.81(2), 7.61(7), 7.54(3,6)	10.60	2.07	2.03	2.19	–
2h	7.29	7.52(5), 7.29(3), 6.99(4)	10.52	2.08	2.15	2.13	–

Table 3. ^{13}C NMR data of aromatic carbaldehyde (diaminomethylene)hydrazones **1a–1i** (δ, *DMSO*-d_6)

	CH=N	N=C–N	Aromatic C						OCH_3[b]	$^1J_{CH=N}$ (Hz)
			C-1	C-2	C-3	C-4	C-5	C-6		
1a[a]	143.4	160.7	136.9	126.2	128.4	127.8	128.4	126.2	–	159.6
1b[a]	143.5	160.2	129.6	127.6	113.9	159.3	113.9	127.6	55.1	159.3
1c[a]	143.5	160.4	132.5	103.6	153.0	137.7	153.0	103.6	60.0(4), 55.8(3,5)	160.6
1d	139.1	159.9	116.8	151.8	98.2	150.1	143.2	109.0	56.5(2), 56.1(5), 55.7(4)	162.4
1e	141.8	160.2	131.1	129.9	111.2	155.0	112.4	127.3	56.3	161.1
1f	141.1	161.4	135.3	122.2	132.7	129.2	127.5	127.1	–	164.2
1g HCl	145.8	155.5	c						–	163.2
1h	138.3	159.9	–	142.2	126.2	127.2	125.2	–	–	163.8
1i[a]	140.3	161.9	–	149.6	120.4	144.3	120.4	149.6	–	163.0

[a] See Ref. [2]; [b] ^1J = 144.1–144.4 Hz; [c] 133.2(4a), 130.7(4), 130.2(8a), 128.6(5), 128.5(1), 127.2(7), 126.6(2), 126.0(6), 125.2(3), 123.1(8)

Table 4. ^{13}C NMR data of 1,2,4-triazolines **2a**–**2h** (δ, *DMSO*-d_6)

	Triazoline-C		Aromatic C						C=O[b]			$COCH_3$[c]				$^1J_{N-CH-N}$ (Hz)
	N–C–N	N=C–N[a]	C-1	C-2	C-3	C-4	C-5	C-6	1-Ac	4-Ac	NHAc	N-1	N-4	NH	OCH_3	
2a	74.9	140.8	137.3	126.6	128.3	128.8	128.3	126.6	165.7	166.6	170.2	20.3	23.0	23.0	–	162.4
2b	74.6	140.7	129.6	128.1	113.7	159.6	113.7	128.1	165.5	166.6	170.1	20.4	23.1	23.0	d	162.2
2c	74.8	140.9	132.7	104.4	152.9	138.1	152.9	104.4	165.8	166.1	170.9	20.3	22.9	22.8	e	162.6
2d	71.6	140.5	116.8	151.7	99.0	150.7	142.9	113.2	165.0	167.0	169.3	20.5	23.2	23.2	f	163.2
2e	74.0	140.6	131.0	131.1	110.4	155.7	112.4	127.4	165.7	166.2	170.4	20.3	22.9	22.8	g	162.9
2f	75.6	140.2	136.3	122.3	132.6	130.5	128.1	129.1	165.4	166.4	170.1	20.4	23.0	23.0	–	164.4
2g	72.4	140.7	h						165.9	166.7	170.2	20.4	23.1	23.0	–	162.3
2h	70.4	140.5	–	139.6	126.5	126.4	127.0	–	165.4	166.6	169.8	20.1	22.9	23.0	–	165.1

[a] $^3J_{N-C-N,N-CH-N} = 2.4–3.7$ Hz; [b] $^2J_{COCH3} = 5.8–6.8$ Hz; [c] $^1J_{COCH3} = 128.9–129.9$ Hz; [d] 55.1 (4-OCH_3), $^1J = 144.3$ Hz; [e] 59.8 (4-OCH_3), $^1J = 144.2$ Hz; 55.9 (3,5-OCH_3), $^1J = 144.7$ Hz; [f] 56.9 (2-OCH_3), $^1J = 144.5$ Hz; 56.3 (5-OCH_3), $^1J = 144.0$ Hz; 55.7 (4-OCH_3), $^1J = 144.7$ Hz; [g] 56.2 (4-OCH_3), $^1J = 145.5$ Hz; [h] 134.1 (1), 132.8 (4a), 129.9 (8a), 129.6 (4), 128.2 (5), 126.2 (7), 125.6 (6), 125.5 (2), 125.3 (3), 123.3 (8)

Experimental

General and preparation of **1a–c** and **1i** see Ref. [2]. NMR: Varian Uniplus 300 (300 MHz for ^1H, 75 MHz for ^{13}C), Bruker AC-80 (80 MHz for ^1H, 20 MHz for ^{13}C), standard pulse sequences. The center of the solvent peak was used as in internal standard which was related to *TMS* with $\delta = 7.26$ ppm (^1H, $CDCl_3$), $\delta = 2.49$ ppm (^1H, *DMSO*-d_6), $\delta = 77.00$ ppm (^{13}C, $CDCl_3$), and $\delta = 39.50$ ppm (^{13}C, *DMSO*-d_6). For the complete assignment of proton and carbon resonances in the course of the present study, the following experimental techniques were applied: NOE difference, *J*-modulated spin-echo, COSY, TOCS, HMQC [21], and 1D HETCOR [21]. Furthermore, coupling information obtained from fully ^1H coupled ^{13}C NMR spectra (gated decoupling) as well as comparison with literature data [15, 22, 23] was used for this purpose.

General Method for the Preparation of **1d–1h**

1.36 g (10 mmol) aminoguanidine hydrogen carbonate was acidified with a 2 *N* aqueous solution of the corresponding mineral acid (see Table 5). This leads to vigorous evolution of CO_2 and results in a clear solution and cooling. A methanolic solution of 10 mmol aldehyde was added and the reaction mixture boiled under reflux for the time given in Table 5. The precipitated salts were dissolved in hot water from which the free bases were obtained upon addition of equivalent amounts of aqueous KOH. The reaction mixture was processed as usual; for physical data of the recovered salts and free bases see Table 5.

Preparation of 1,4-Diacyl-3-acylamino-5-aryl-4,5-dihydro-1,2,4-triazoles (**2a–2h**), *Method A*

1 mmol **1a–1h** in 0.55 ml acetic anhydride was placed in an oil bath at 100 °C and stirred for the time given in Table 6 at this temperature. The yellow to light brown reaction mixture was concentrated *in vacuo*. Repeated codistillation with tolune left a semicrystalline residue which was recrystallized from the solvent given in Table 6. In the case of **2b**, the resulting mixture was chromatographed on Kieselgel 40 (70–230 mesh) with $CHCl_3/CH_3OH$ (95:5) as eluent.

Preparation of 1,4-Diacyl-3-acylamino-5-aryl-4,5-dihydro-1,2,4-triazoles (**2a–2h**), *Method B*

A suspension of 10 mmol of **1a** in 12 ml of pyridine was cooled to 0 °C and 3 mmol of the corresponding acid chloride were added dropwise over 10 min with constant stirring. After 30 min, the cooling bath was removed and the mixture poured into an ice-cold $KHSO_4$ solution and extracted several times with methylene chloride. The combined extracts were successively washed with water and a saturated $KHSO_4$ solution, dried with anhydrous $MgSO_4$, and concentrated to give a slightly yellow-colored product. For recrystallization, see Table 6.

2b: ^1H NMR ($CDCl_3$): $\delta = 10.40$ (s, 1H, NH), 7.46–7.30 (m, 5H, phenyl-H), 6.83 (s, 1H, triazoline-H), 2.31 (s, 3H, NH–$COCH_3$), 2.17 (s, 3H, N1–$COCH_3$), 1.97 (s, 3H, N4–$COCH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 169.8$ (N4–CO), 167.6 (NH–CO), 166.9 (N1–CO), 141.7 (triazoline N–C=N), 136.3 (phenyl C-1), 129.8 (phenyl C-4), 129.1 (phenyl C-3,5), 126.8 (phenyl C-2,6), 74.4 (d, $^1J = 159.9$ Hz, triazoline N–C–N), 24.6 (NH–$COCH_3$), 24.5 (N4–$COCH_3$), 20.7 (N1–$COCH_3$) ppm.

2a (C_6H_5CO instead of CH_3CO): ^1H NMR ($CDCl_3$): $\delta = 10.99$ (s, 1H, NH), 7.91–7.18 (m, 20H, phenyl-H), 7.35 (s, 1H, triazoline-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 170.6$, 163.7, 163.1 (C=O), 142.0 (d, $^3J = 3.8$ Hz, triazoline N–C=N), 136.8, 134.2, 133.0, 132.6, 132.2, 132.1, 131.6, 130.3, 129.4, 129.0, 128.9, 128.6, 127.9, 127.5, 126.8, 126.6 (phenyl-C), 76.6 (d, $^1J = 164.0$ Hz, triazoline N–C–N) ppm.

2c: ^1H NMR ($CDCl_3$): $\delta = 10.33$ (s, 1H, NH), 6.75 (s, 1H, triazoline-H), 6.64 (s, 2H, phenyl H-2,6), 3.81 (s, 6H, 3,5-OCH_3), 3.79 (s, 3H, 4-OCH_3), 2.29 (s, 3H, NH–$COCH_3$), 2.17 (s, 3H, N1–$COCH_3$), 2.00 (s,

Table 5. Preparative details, elementary analyses, and physical data of aromatic carbaldehyde (diaminomethylene)hydrazones **1d–1h**

	M p. (°C) Recryst. solvent	Yield (%)	React. temp. React. time	Molecular formula Molecular mass	Analysis Calcd. Found				MS (m/z, %)
					C	H	N	other	
1d	214–216	89		$C_{11}H_{16}N_4O_3$	52.37	6.39	22.39		252(11.4), 179(100)
	Water			252.3	52.11	6.42	21.85		
1d·HCl	249–251	91	100 °C	$C_{11}H_{17}ClN_4O_3$	45.75	5.93	19.47		
	Water/ethanol		10 min	288.7	45.43	5.79	19.26		
1e	183–185	84		$C_9H_{11}BrN_4O$			20.66	29.47 (Br)	271(12.7), 43(100)
	Ethanol			271.1			20.39	29.37 (Br)	
1e·HCl	264–266	96	100 °C	$C_9H_{12}BrClN_4O$			18.22	11.52(Cl)	
	DMF/EtOAc		10 min	307.6			18.51	11.67 (Cl)	
1f	166–168			$C_8H_{10}BrN_4$			23.24	33.15 (Br)	241(4.7), 43(100)
	Water			241.1			23.14	33.45 (Br)	
1f·HNO_3	220–222 (dec.)	80	100 °C	$C_8H_{10}BrN_5O_3$	31.56	3.31	23.03	26.27 (Br)	
	Water		25 min	304.1	31.29	3.20	22.98	25.89 (Br)	
1g	183–185	93		$C_{12}H_{12}N_4$	67.90	5.70	26.40		212(29.7), 36(100)
	Ethanol/water			212.2	67.54	5.48	26.61		
1g·HCl	151–154	96	20 °C	$C_{12}H_{13}ClN_4$	57.95	5.27	22.53	14.26 (Cl)	
	Ethanol/ether		3 h	248.7	57.97	5.03	22.58	14.69 (Cl)	
1h	148–152	76	20 °C	$C_6H_8N_4S$	42.84	4.78	33.31	19.06 (S)	168(61), 43(100)
	Water		1 h	168.2	43.12	4.56	33.61	19.16(S)	

Table 6. Preparative details, elementary analyses, and physical data of 4,5-dihydro-1,2,4-triazoles **2a**–**2h**

	M.p. (°C) Recryst. solvent	Yield (%)	Method Time	Molecular formula Molecular mass	Analysis Calcd. Found			IR (cm^{-1})	MS (*m/z*, %)
					C	H	N		
2a	162–165	81	A	$C_{14}H_{16}N_4O_3$	58.32	5.59	19.44	3250, 3178, 1732,	288(3.3),
	Ethanol		2 h	288.3	58.57	5.50	19.23	1700, 1654, 1546	246(100)
2b	162–163	65	A	$C_{15}H_{18}N_4O_4$	56.60	5.70	17.60	3430, 3256, 1692,	318(11.6),
	Benzene		2 h	318.3	56.81	5.69	17.53	1656, 1595	43(100)
2c	178–180	65	A	$C_{17}H_{22}N_4O_6$	53.96	5.86	14.81	3430, 3256, 1692,	378(16.7),
	Ethanol		1 h	378.4	54.17	5.65	14.93	1656, 1596	43(100)
2d	–	71	A	$C_{17}H_{22}N_4O_6$	53.96	5.86	14.81	3428, 3262, 1730,	378(14),
	–		2 h	378.4	54.22	5.91	14.85	1688, 1660, 1520	43(100)
2e	170–174	57	A	$C_{15}H_{17}BrN_4O_4$	45.35	4.31	14.10	3246, 3178, 1728,	396(0.4),
	Ethanol		1 h	397.2	44.39	3.86	14.50	1698, 1654, 1540	43(100)
2f	133–135	62	A	$C_{14}H_{15}BrN_4O_3$	45.79	4.12	15.25	3274, 3210, 1728	366(0.9),
	Toluene		1 h	367.2	46.04	3.90	15.32	1694, 1656, 1532	43(100)
2g	206–208	75	A	$C_{18}H_{18}N_4O_3$	63.89	5.36	16.56	3444, 3258, 1686,	338(1.3),
	Ethanol		1 h	338.4	63.98	5.29	16.57	1662, 1526	43(100)
2h	115–118	75	A	$C_{12}H_{14}N_4O_3S$	48.96	4.79	19.04	3274, 3108, 1726,	294(0.4),
	Ethanol		2 h	294.3	49.23	4.49	19.32	1692, 1660, 1528	43(100)
3	158–160	45	A	$C_{13}H_{15}N_5O_3$	53.97	5.23	24.21	3432, 3198, 3036,	289(1.3),
	EtOAc		0.5 h	289.3	54.21	5.02	24.49	1712, 1654, 1534	43(100)
4	211–213	57	B	$C_{29}H_{22}N_4O_3$	73.40	4.67	11.81	3250, 3034, 2942,	475(4.2),
	Ethanol		16 h	474.5	73.59	5.03	11.90	1730, 1688, 1530	105(100)

3H, N4–$COCH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 169.8$ (N4–CO), 167.7 (NH–CO), 167.2 (N1–CO), 153.8 (phenyl C-2,6), 74.4 (d, $^1J = 160.2$ Hz, triazoline N–C–N), 60.6 (4-OCH_3), 56.4 (3,4-OCH_3), 24.6 (NH–$COCH_3$), 24.5 (N4–$COCH_3$), 20.7 (N1–$COCH_3$) ppm.

1-(1-Acetoxy-1-(4-pyridylmethyl))-3-acetamido-5-methyl-1,2,4-triazole (**3**)

Method of preparation: A; for physical data, see Table 6. ^{1}H NMR (*DMSO*-d_6): $\delta = 10.18$ (s, 1H, NH), 8.62 (m, 2H, pyridine H-2,6), 7.73 (s, 1H, O–CH–N), 7.44 (m, 2H, pyridine H-4,5), 2.57 (s, 3H, triazole-CH_3), 2.20 (s, 3H, O–$COCH_3$), 1.98 (s, 3H, NH–$COCH_3$) ppm; ^{1}H NMR ($CDCl_3$): $\delta = 8.68$ (m, 2H, pyridine H-2,6), 8.45 (broad s, 1H, NH), 7.57 (s, 1H, O–CH–N), 7.28 (m, 2H, pyridine H-3,5), 2.56 (s, 3H, triazole-CH_3), 2.26 (s, 3H, NH–$COCH_3$), 2.24 (s, 3H, O–$COCH_3$) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 169.0$ (dq, $^2J_{CO,Me} = 6.8$ Hz, $^3J_{CO,O-CH-N} = 3.1$ Hz, O–C=O), 168.0 (m, NH–CO), 155.9 (s, triazole C-3), 153.9 (dq, $^2J_{C-5,Me} = 7.1$ Hz, $^3J_{C-5,O-CH-N} = 1.5$ Hz, triazole C-5), 149.7 (m containing ^1J, pyridine C-2,6), 143.4 (m, pyridine C-4), 121.3 (m containing ^1J, pyridine C-3,5), 77.0 (td, $^1J = 128.2$ Hz, NH–$COCH_3$), 20.2 (q, $^1J = 130.3$ Hz, O–$COCH_3$), 11.5 (q, $^1J = 130.2$ Hz, triazole-CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 170.0$ (broad, NH–CO), 168.9 (dq, $^2J_{CO,Me} = 7.0$ Hz, $^3J_{CO,O-CH-N} = 3.5$ Hz, O–CO), 156.4 (s, triazole-C-3), 150.1 (dq, $^2J_{C-5,Me} = 7.3$ Hz, $^3J_{C-5,O-CH-N} = 2.0$ Hz, triazole-C-5). 150.1 (m containing ^1J, pyridine C-3,5), 77.2 (td, $^1J = 158.2$ Hz, $^3J_{O-CH-N,pyr\,H-3,5} = 4.0$ Hz,

Table 7. Crystallographic data for **1a**, **1b**, and **3**

	1a	**1b**	**3**
Empirical formula	$C_{14}H_{16}N_4O_3$	$C_{15}H_{18}N_4O_4$	$C_{13}H_{15}N_2O_3$
Formula weight	288.31	318.33	289.29
Crystal colour, habit	colourless, prism	colourless, prism	colourless, prism
Crystal dimensions [mm]	0.12 × 0.22 × 0.40	0.20 × 0.35 × 0.45	0.25 × 0.25 × 0.41
Temperature [K]	173(1)	173(1)	173(1)
Crystal system	monoclinic	monoclinic	orthorhombic
Space group	$P2_1/c$	$P2_1/c$	$P2_12_12$
Z	4	4	4
a [Å]	7.312(2)	10.029(3)	14.919(3)
b [Å]	22.990(3)	8.175(2)	17.888(2)
c [Å]	8.591(1)	19.140(2)	5.238(3)
β [°]	106.50(2)	96.55(2)	90
V [Å^3]	1384.8(5)	1559.0(5)	1397.9(8)
d_{calcd} [g cm^{-3}]	1.383	1.356	1.374
μ(MoK$_\alpha$) [mm^{-1}]	0.094	0.094	0.095
$2\theta_{max}$ [°]	55	55	60
Total reflections measured	3525	4034	2972
Symmetry independent reflections	3194	3572	2840
Observed reflections [$I > 3\sigma(I)$]	1868	2470	2314
Parameters refined	254	280	250
Final R	0.0494	0.0458	0.0354
R_w	0.0467	0.0484	0.0326
Weights $w = [\sigma^2(F_o) + (pF_o)^2]^{-1} \cdot p$	0.005	0.0075	0.005
Goodness of fit	1.991	2.275	1.653
Final Δ_{max}/σ	0.005	0.007	0.001
$\Delta\rho$ (max; min) [e·Å^{-3}]	0.23; −0.37	0.26; −0.20	0.22; −0.17

O–CH–N), 23.6 (q, ^1J = 129.2 Hz, ^3J = 2.0 Hz, NH–$COCH_3$). 20.5 (q, ^1J = 130.6 Hz, O–$COCH_3$), 11.9 (q, ^1J = 130.6 Hz, triazole-CH_3).

Acetylation of **1a** *in pyridine*

To a cooled solution of **1a** (1.62 g, 10 mmol) in pyridine (23 ml), 8 ml of acetic anhydride was added. After 16 h, the volatile components were removed *in vacuo* and the mixture was coevaporated with 40 ml of toluene. The resulting yellow oil (3.3 g) was chromatographed on Kieselgel 40 with chloroform/methanol (97:3) as eluent. Yield, 0.30 g (14.5%) of **4** and 0.33 g (11.4%) of **2a**; m.p. of **4**: 132–136 °C (Ref. [2]: 132–136 °C.)

Crystal Structure Determinations [24]

The X-ray data for **1a**, **1b**, and **3** were collected at low temperature on a Rigaku AFC5R diffractometer using graphite-monochromated Mo-K_α radiation (λ = 0.71069 Å), $\omega - 2\theta$ scans and a 12 kW rotating anode generator. Scan speed: 16° min^{-1} with up to 4 scans per reflection; structure solution by direct methods with SHELXS-86; full-matrix least-squares on F; non-hydrogen atoms refined anisotropically, hydrogen atoms refined isotropically; all calculations performed with TEXSAN. Compound **3** was enantiomerically pure, but the enantiomorph used in the structure refinement was chosen arbitrarily. For other crystal data, see Table 7.

References

[1] (a) Thiele J (1892) Liebigs Ann Chem **270**: 1; (b) Lieber E, Smith GBL (1939) Chem Rev **25**: 213

[2] Holzer W, Györgydeák Z (1992) Monatsh Chem **123**: 1163

[3] Andreani A, Rambaldi M, Locatelli A, Bossa R, Fraccari A, Galatulas I (1992) J Med Chem **35**: 4634

[4] (a) Richter PH, Wunderlich I, Schleuder M, Keckeis A (1993) Pharmazie **48**: 83; (b) Richter PH, Wunderlich I, Schleuder H, Keckeis A (1993) Pharmazie **48**: 163

[5] Thiele J, Bihan R (1898) Liebigs Ann Chem **302**: 299

[6] Grammaticakis P (1952) Bull Soc Chim France: 446

[7] (a) Staab HA, Seel G (1959) Chem Ber **92**: 1302; (b) Pólya JB (1984) In: Katritzky AR, Rees CW (eds) Comprehensive Heterocyclic Chemistry, vol 5, part 4.12. Pergamon Press, Oxford New York Toronto Sydney Paris Frankfurt, p 739

[8] Tsujikawa T, Tatsuta M (1977) Heterocycles **6**: 423

[9] (a) Zelenin KN, Sergutina VP, Solod OV, Pinson VV (1987) Khim Geterotsikl Soed: 1071; (b) Khrustalev VA, Solod OV, Zelenin KN (1986) Zhur Org Khim **22**: 500

[10] (a) Miyamoto Y, Kobana R, Yamazaki C (1988) Chem Pharm Bull **36**: 1963; (b) Miyamoto Y (1985) Chem Pharm Bull **33**: 2678; (c) Miyamoto Y, Yamazaki C, Matzui M (1990) J Heterocycl Chem **27**: 1553

[11] Younes MI, Abdel-Lim A-A, Abbas HH, Metwally SA (1987) Arch Pharm **320**: 1196

[12] Abdulla RF, Jones ND, Swartzendruber JK (1985) Chem Ber **118**: 5009

[13] (a) Fusco R, Dalla-Croce P (1969) Gazz Chim Ital **99**: 69; (b) Khrustalev VA, Sergutina VP, Zelenin KH, Pinson VV (1982) Khim Geterotsikl Soed: 1071; (c) Takahashi M, Tan H, Fukushima K, Yamazaki H (1977) Bull Chem Soc Jpn **50**: 953; (d) Neunhoeffer H, Karafiat U, Köhler G, Sowa B (1992) Liebigs Ann Chem 115

[14] (a) Uda M, Kubota S (1979) J Heterocycl Chem **16**: 1273; (b) Kubota S, Toyooka K, Ikeda J, Yamamoto N, Shibuya H (1983) J Chem Soc Perkin Trans 1: 967; (c) Andreae S, Schmitz E (1983) Z Chem **23**: 450; (d) Andreae S, Schmitz E, Seeboth H (1986) J Prakt Chem **328**: 205; (e) Toyooka K, Kubota S (1988) Chem Pharm Bull **36**: 96; (f) Usova EV, Krapivin GD, Zavodnik VE, Kul'nevich VG (1988) Khim Geterotsikl Soed: 1570; (g) Usova EV, Krapivin GD, Zavodnik

VE, Kul'nevich VG (1990) Khim Geterotsikl Soed 931; (h) Zelenin KN, Kuznetsova OB, Alekseev VV, Sergutina VP, Terentyev PB, Ovchatenko VV (1991) Khim Geterotsikl Soed: 1515; (i) Somogyi L (1993) Liebigs Ann Chem: 931

[15] Kadaba PK (1989) Adv Heterocycl Chem **46**: 169

[16] Atkinson MR, Komzak AA, Parkes EA, Pólya JB (1954) J Chem Soc: 4508

[17] (a) Tennant G (1979) In: Barton D, Ollis WD (eds) Comprehensive Organic Chemistry, vol 2. Pergamon Press, Oxford New York Toronto Sydney Paris Frankfurt, p 407; (b) Zaugg HE (1982) Synthesis: 85 and 181; (c) Fisher MJ, Overman LE (1990) J Org Chem **55**: 1447; (d) Hiemstra H, Speckamp WN (1991) In: Trost BM, Fleming I (eds) Comprehensive Organic Synthesis, vol 2, chapter 4.5. Pergamon Press, Oxford New York Toronto Sydney Paris Frankfurt; (e) Arai Y, Fujii A, Ohno T, Koizumi T (1982) Chem Pharm Bull **40**: 1670; (f) Esch PM, Hiemstra H, Speckamp WN (1992) Tetrahedron **48**: 3445

[18] Barta-Szalai G, Getter J, Lempert K, Møller J, Párkányi L (1983) J Chem Soc Perkin Trans 1: 2003

[19] (a) Dumas DJ (1993) Heterocycles **35**: 659; (b) Cooper MJ, Hull R, Wardleworth M (1975) J Chem Soc Perkin Trans **1**: 1433

[20] Kalinowski H-O, Berger S, Braun S (1984) ^{13}C-NMR Spektroskopie. G Thieme, Stuttgart New York, p 194

[21] Kessler H, Gehrke M, Griesinger C (1988) Angew Chem **100**: 507; (1988) Angew Chem Int Ed Engl **27**: 490; and references cited therein

[22] (a) Kalchhauser H, Robien W (1985) J Chem Inform Comput Sci **25**: 103; (b) SADTLER Collection, SADTLER Research Laboratories, Philadelphia, PA, U.S.A.

[23] Pretsch E, Seibl J, Simon W (1981) Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Methoden, 2nd ed. Springer, Berlin Heidelberg New York

[24] Further details of the crystal structure investigations are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, on quoting the depository numbers CSD-401046 (for **1a**), -401045 (for **1b**), -401044 (for **3**), the names of the authors and the journal citation

Received January 2, 1995. Accepted January 13, 1995