Cyclocondensation of 3-Amino-1,2,4-triazole with Substituted Methyl Cinnamates

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The reaction of 3-amino-1,2,4-triazole (**1**) with substituted methyl cinnamates **2a-h** leads selectively to the formation of 7-aryl-6,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidin-5(4*H*)-ones **3a-h**. The structure elucidation of the products is based on ir, ^1H and ^{13}C nmr measurements and X-ray diffraction.

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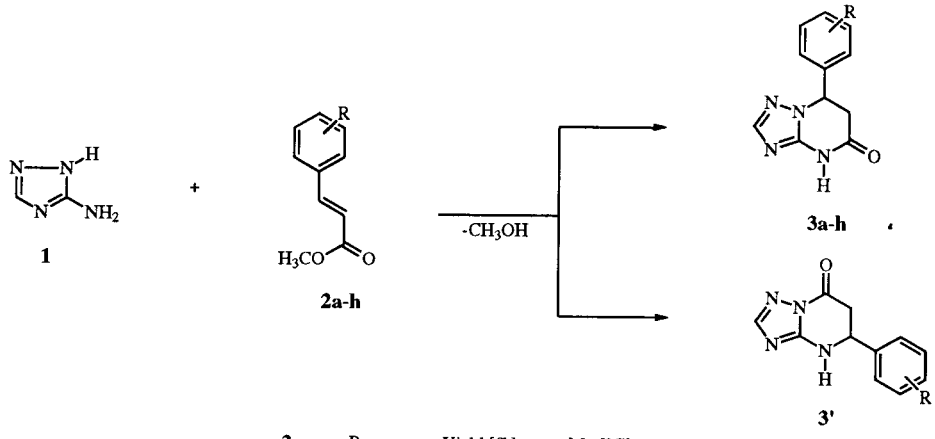
It is known [1] that the cyclocondensation of heterocyclic amines with aliphatic α,β-unsaturated esters can lead to isomeric bicyclic compounds with different positions of the oxo group in the generated pyrimidine rings. We studied now the reactions of 3-amino-1,2,4-triazole (**1**) with *m*- or *p*-substituted methyl cinnamates **2a-h**. Equimolar amounts of **1** and **2a-h** dissolved in dimethylformamide yielded selectively the 7-aryl-6,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidin-5(4*H*)-ones **3a-h**. The isomeric compounds **3'** cannot be detected. Thus the cyclocondensation resembles the reaction of 5-amino-3-methylthio-1*H*-1,2,4-triazole with crotonic acid [2]. Whether the initial attack of **2a-h** occurs on the NH group of the ring or on the exocyclic amino group remains an open question. Nucleophiles like acid chlorides leave both options [3].

1,2,4-Triazolo[1,5-*a*]pyrimidin-5(1*H*)-ones have attracted a lot of attention in various applications, *e.g.* as pharmacologically active compounds [4,5,6], as herbicides [7], in photographic techniques [8,9], and in corrosion protection [10].

Scheme 1



1 + **2a-h**

3	R	Yield [%]	Mp [°C]
a	H	52	215-217
b	*p*-CH_3	54	206-208
c	*p*-OCH_3	49	188-190
d	*p*-F	55	214-216
e	*p*-Cl	60	231-232
f	*m*-Cl	62	236-237
g	*m*-Br	68	243-245
h	*m*-NO_2	78	210-211

The structure of the obtained compounds **3a-h** was determined by spectroscopic methods. Characteristic ir absorptions (potassium bromide pellets) can be observed in the regions 1700-1708 cm^{-1}, 1544-1552 cm^{-1} and at ~3250 cm^{-1}, indicating stretching vibrations of the -CO-NH- group. The ^1H nmr spectra (Table 1) contain a broad singlet for NH ($11.5 < \delta < 11.8$), a sharp singlet for 2-H ($7.7 < \delta < 7.8$), signals for the aromatic protons ($6.9 < \delta < 8.2$) and signals of the $CH\text{-}CH_2$ fragment of the tetrahydropyrimidine ring ($2.8 < \delta < 5.9$; ABX spin pattern with J_{AB} = -16.5 ±0.1 Hz, J_{AX} = 4.6-6.5 Hz, J_{BX} = 6.9 ±0.1 Hz).

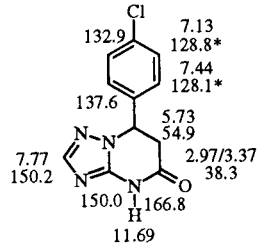
Table 1

^1H NMR Data of **3a-h** (δ Values, Dimethyl-d_6 Sulfoxide as the Solvent and Internal Standard, 400 MHz)

Compound	NH	2-H	6-H		7-H	^2J[Hz]	^3J[Hz]		Ar-H	CH_3
	s	s	AB		X					s
3a	11.58	7.75	2.92	3.42	5.73	-16.4	4.6	7.1	7.08/7.36	
3b	11.63	7.75	2.89	3.38	5.67	-16.5	4.6	7.0	6.94/7.16	2.23
3c	11.54	7.73	2.95	3.42	5.65	-16.5	4.7	6.9	6.92/7.04	3.70
3d	11.59	7.75	2.94	3.43	5.73	-16.5	5.4	6.9	7.16/7.23	
3e	11.69	7.77	2.97	3.37	5.73	-16.6	5.3	6.9	7.13/7.44	
3f	11.67	7.78	3.01	3.36	5.74	-16.6	5.7	6.9	7.03/7.22/7.41/7.41	
3g	11.67	7.78	3.02	3.36	5.73	-16.6	5.7	6.9	7.08/7.35/7.55/7.55	
3h	11.72	7.79	3.10	3.37	5.90	-16.6	6.5	6.8	7.61/7.70/8.05/8.20	

The NH proton is shifted by ~2 ppm to lower field in comparison to the 4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidines [2]. This effect is due to the neighborhood of the carbonyl group and favors the 5-oxo structure **3** versus the alternative 7-oxo structure **3'**. Another hint for structure **3** is given by the fact that the NH and the tertiary CH proton neither show a coupling nor a Nuclear Overhauser effect in the ^1H nmr spectroscopy.

A detailed correlation of the ^1H and ^{13}C chemical shifts is shown for **3e**:



3e

The FD ms spectrum of **3e** showed a peak for the molecular ions at m/z (%) = 248/250 (100, Cl isotope pattern).

Finally, the structure of **3a** was confirmed by an X-ray analysis. Figure 1 shows a perspective view of molecule **3a** with the bond lengths. (The used atomic numbers do not correspond to the nomenclature). Selected bond angles and torsion angles are listed in Table 2. The conformation of the tetrahydropyrimidine ring can be described as a distorted "sofa". (Puckering coordinates [11]: S = 0.48, θ = 49.3°, ϕ = 28.7°; the deviations of the atoms C(3) and C(4) from the plane of the remaining atoms of the tetrahydropyrimidine ring are 0.21(1) and 0.65(1) Å, respectively. The C(2)-N(4) and the C(3)-N(4) bond lengths (1.370(4) and 1.374(3) Å, respectively) indicate the conjugation between the carbonyl group and the triazole ring, in which the lone-pair of N(4) is involved; N(4) has a planar trigonal configuration. The phenyl group has a pseudoaxial position with torsion angles C(2)-N(2)-C(5)-C(6) of 89.3(3)° and C(2)-N(2)-C(5)-H(5) of -153.0(20)°.

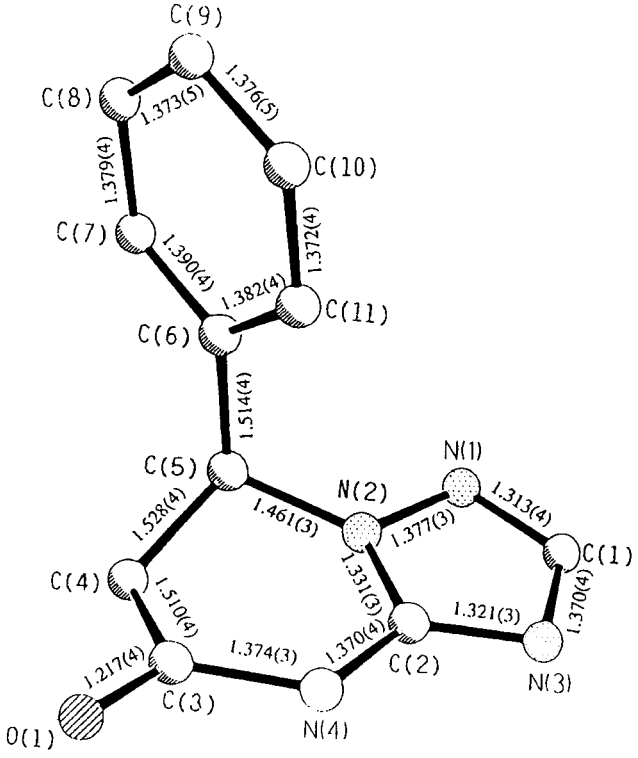


Figure 1. Molecular structure of **3a** in the crystal.

Table 2

Selected Bond Angles and Torsion Angles [°] of **3a**

Bond Angles		Torsion Angles	
N(2)-N(1)-C(1)	101.4(2)	N(2)-C(2)-N(4)-C(3)	3.5(4)
N(1)-N(2)-C(2)	109.5(2)	C(2)-N(4)-C(3)-C(4)	9.4(4)
C(2)-N(2)-C(5)	124.3(2)	N(4)-C(3)-C(4)-C(5)	-35.4(4)
C(1)-N(3)-C(2)	101.4(2)	C(3)-C(4)-C(5)-N(2)	44.8(3)
C(2)-N(4)-C(3)	121.6(2)	C(4)-C(5)-N(2)-C(2)	-34.6(3)
N(1)-C(1)-N(3)	116.1(3)	C(5)-N(2)-C(2)-N(4)	11.6(4)
N(2)-C(2)-N(3)	111.5(2)	C(3)-C(4)-C(5)-H(5)	162.0(18)
N(2)-C(2)-N(4)	121.4(2)	C(3)-C(4)-C(5)-C(6)	-77.8(3)
N(4)-C(3)-C(4)	115.6(3)	C(2)-N(2)-C(5)-C(6)	89.3(3)
C(3)-C(4)-C(5)	115.5(2)	C(2)-N(2)-C(5)-H(5)	-153.0(20)
N(2)-C(5)-C(4)	105.9(2)		

Due to intermolecular hydrogen bonds, molecules **3a** form centrosymmetric dimers in the crystal. The distance between the hydrogen atom on N(4) and the atom N(3) of the neighbor molecule amounts to 1.971(1) Å; the angle N(4)-H(4)···N(3)' is 170.4 (5)°.

Table 3

Elementary Analyses of the 7-Aryl-6,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidin-5(4*H*)-ones **3a-h**

Compound			Calculated [%]			Found [%]		
3	7-Aryl	Formula	C	H	N	C	H	N
a	Phenyl	$C_{11}H_{10}N_4O$	61.66	4.71	26.16	61.52	4.81	26.29
b	4-Methylphenyl	$C_{12}H_{12}N_4O$	63.13	5.30	24.56	62.91	5.25	24.69
c	4-Methoxyphenyl	$C_{12}H_{12}N_4O_2$	58.99	4.95	22.95	59.07	5.01	22.86
d	4-Fluorophenyl	$C_{11}H_9FN_4O$	56.88	3.91	24.14	57.06	3.90	24.20
e	4-Chlorophenyl	$C_{11}H_9ClN_4O$	53.13	3.65	22.53	53.42	3.60	22.70
f	3-Chlorophenyl	$C_{11}H_9ClN_4O$	53.13	3.65	22.53	53.02	3.61	22.48
g	3-Bromophenyl	$C_{11}H_9BrN_4O$	45.21	3.11	19.18	45.30	3.15	19.08
h	3-Nitrophenyl	$C_{11}H_9N_5O_3$	50.95	3.50	27.03	51.12	3.56	27.23

Table 4

Atomic Coordinates[10^4 Å] and Equivalent Anisotropic Thermal Parameters for C, N, O Atoms/Isotropic Thermal Parameters for H Atoms for 6,7-Dihydro-7-phenyl[1,2,4]-triazolo[1,5-*a*]pyrimidin-5(4*H*)-one (**3a**)

Atom	X/a	Y/b	Z/c	10^3U_{eq}
O(1)	-615(2)	-1005(4)	-1910(1)	47(1)
N(1)	-2637(3)	5764(5)	-226(1)	42(1)
N(2)	-2192(2)	4266(4)	-737(1)	33(1)
N(3)	-1062(2)	2811(4)	161(1)	35(1)
N(4)	-731(2)	749(5)	-890(1)	34(1)
C(1)	-1916(3)	4816(6)	290(2)	39(1)
C(2)	-1290(3)	2547(5)	-490(1)	30(1)
C(3)	-1013(3)	718(6)	-1569(1)	35(1)
C(4)	-1770(3)	2988(6)	-1853(2)	40(1)
C(5)	-2875(3)	4176(6)	-1405(1)	35(1)
C(6)	-4296(3)	2798(5)	-1405(1)	33(1)

Table 4 (continued)

Atom	X/a	Y/b	Z/c	10^3U_{eq}
C(7)	-5423(3)	3517(6)	-1838(1)	41(1)
C(8)	-6701(3)	2215(7)	-1865(2)	46(1)
C(9)	-6886(3)	193(7)	-1459(2)	48(1)
C(10)	-5778(3)	-526(7)	-1026(2)	49(1)
C(11)	-4502(3)	760(6)	-1000(2)	43(1)
H(4N)	-119(30)	-473(60)	-701(14)	50
H(1)	-1930(27)	5487(54)	738(14)	50
H(4A)	-1006(32)	4007(60)	-1938(13)	50
H(4B)	-2270(29)	2502(57)	-2280(14)	50
H(5)	-3083(29)	5813(58)	-1543(14)	50
H(7)	-5264(30)	4887(57)	-2121(14)	50
H(8)	-7409(30)	2738(58)	-2154(14)	50
H(9)	-7810(31)	-683(56)	-1483(14)	50
H(10)	-5912(31)	-1847(57)	-763(14)	50
H(11)	-3759(31)	210(56)	-721(14)	50

EXPERIMENTAL

The melting points were measured with a Kofler apparatus and were not corrected. The ^1H and ^{13}C nmr spectra were recorded on a Bruker AM 400 or on a Bruker WP 200 spectrometer in CD_3SOCD_3. The ir spectra were obtained as potassium bromide pellets with a Specord M 80 spectrograph. The FD mass spectrum was recorded on a Finnigan M 95 spectrometer.

General Procedure for the Preparation of the 7-Aryl-6,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidin-5(4*H*)-ones **3a-h**.

A solution of 0.84 g (10.0 mmoles) of 3-amino-1,2,4-triazole (**1**) and 10.0 mmoles of methyl cinnamate **2a-h** in 3.0 ml of dimethylformamide was refluxed for 3 hours. After cooling to ambient temperature the reaction mixture was diluted with 30 ml of benzene and the precipitate formed was filtered. Recrystallization from ethanol led to analytically pure products. The yields and the melting points are summarized in Scheme 1.

Crystal Structure Analysis of **3a**.

The analysis is based on the following data: $C_{11}H_{10}N_4O$, FW 214.2, monoclinic, space group $P2_1/c$, Z = 4, T = 293 K, a = 9.291(2), b = 5.380(1), c = 20.024 Å, β = 92.12 (3)°, V = 1000.2(3) Å^3, crystal size 0.4 x 0.2 x 0.1 mm, D_c = 1.423 g • cm^{-3}, F(000) = 448, graphite monochromated radiation Mo(K_α) with λ = 0.71073 Å, μ = 0.091 mm^{-1}. The intensities of 1084 reflections (926 independent, R_{int} = 29.7%), 852 observed with F > 6.0 σ(F) were measured on a Siemens P3/PC automatic four-cycle diffractometer (θ/2θ, scan 2° < 2 θ < 50°). The structure was solved by direct methods and refined in anisotropic (H atoms isotropic) approximation by full-matrix least squares versus F_o to R = 0.032 (ωR = 0.066, S = 1.41). All calculations were carried out by using SHELXTL PLUS package [12]. The final atomic parameters are listed in Table 4.

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