Tetrazole Compounds. 8 [1]. Synthesis of Tetrazolylpyrimidines from Tetrazolyl-substituted Enamino Ketones

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Tetrazolyl-substituted enamino ketones **1** react with various amidines **2** to give 5-(1-phenyl-1*H*-tetrazol-5-yl)pyrimidines **3**. In the case of the chloroacetyl enamine **4** 4-(*N,N*-dimethylaminomethyl)-substituted tetrazolylpyrimidines **5** were obtained. Subsequent hydrolysis of the 4-trifluoromethyl derivatives **3b**, **3d** and **3g** afforded the corresponding 5-(1-phenyl-1*H*-tetrazol-5-yl)pyrimidine-4-carboxylic acids **6**.

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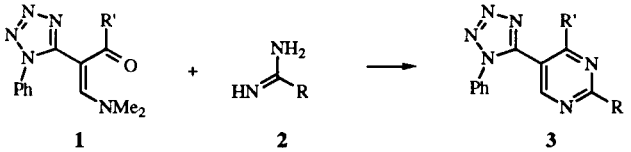
A series of tetrazolyl-substituted pyrimidines are of pharmacological interest because of their antiallergic [2-6], antiulcer [7], antiinflammatory and CNS depressant activity [8]. As a rule, these and other tetrazolylpyrimidines described in the literature [9-15] were synthesized starting from suitable pyrimidine derivatives, either through a tetrazole ring-closure reaction or by introducing a tetrazole moiety *via* displacement reactions [10,11].

In continuation of studies on tetrazole compounds bearing novel functionalities, this communication describes an alternative approach to tetrazolylpyrimidines using tetrazolyl-substituted enamino ketones of type **1** as precursors. The latter are accessible by acylation of 1-aryl-5-(2-dimethylaminovinyl)-1*H*-tetrazoles [16,17], the preparation of which is likewise very simple [18]. As reported in the previous paper [1], enaminones of type **1** proved to be useful building blocks for novel pyrazolyl- and isoxazolyltetrazoles and should function therefore also as promising starting compounds for tetrazolylpyrimidines [19].

Indeed, on reacting **1** in ethanolic solution with carboxylic acid amidines **2** (R = H, Me, Ph) in the presence of sodium ethoxide the 4- and 2,4-substituted 5-(1-phenyl-1*H*-tetrazol-5-yl)pyrimidines **3a-h** were obtained in good yields [20]. Under the same conditions, reaction of **1** with guanidine (**2**, R = NH_2) and *N*-methylguanidine (**2**, R = NHMe) gave the 2-amino derivatives **3i-p**. Analogously, *O*-methylisourea (**2**, R = OMe) and *S*-alkylisothioureas (**2**, R = SMe, SEt, SCH_2Ph) afforded the 2-methoxy and 2-alkylmercapto derivatives **3q-v**. In the case of **3q-s**, however, methanol/sodium methoxide should be used as the reaction medium, otherwise a partial transalkylation (formation of *O*- and *S*-ethyl products) takes place.

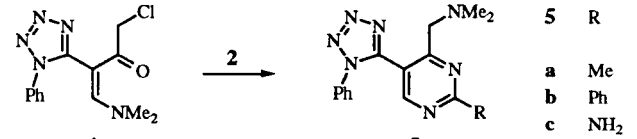


1 + **2** → **3**

3	R	R'	3	R	R'
a	H	Me	m	NH_2	Ph
b	H	CF_3	n	NHMe	Me
c	H	Ph	o	NHMe	CF_3
d	Me	CF_3	p	NHMe	Ph
e	Me	Ph	q	OMe	CF_3
f	Ph	Me	r	OMe	Ph
g	Ph	CF_3	s	SMe	Ph
h	Ph	Ph	t	SEt	CF_3
i	NH_2	Me	u	SEt	Ph
j	NH_2	CF_3	v	SCH_2Ph	Ph
k	NH_2	Et			
l	NH_2	Pr			

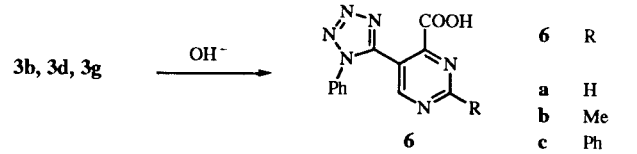
While a trifluoromethyl group in **1** under the conditions of the ring-closure reaction remains unaffected, the chloromethyl group of the enamino ketone **4** is transformed by released dimethylamine into a dimethylaminomethyl group, yielding tetrazolylpyrimidines of type **5**.

On subsequent treating with aqueous sodium hydroxide in ethanolic solution, however, the trifluoromethyl derivatives **3b**, **3d** and **3g** undergo hydrolysis to give the corresponding carboxylic acids **6a-c**. This fact is remarkable inasmuch as the alkaline hydrolysis of trifluoromethyl groups in aromatic systems requires certain structural suppositions [21]. In case of **3b**, **3d** and **3g** obviously the 1-aryl-1*H*-tetrazol-5-yl system supports the hydrolyzability of the trifluoromethyl group.



4 —(**2**)→ **5**

5	R
a	Me
b	Ph
c	NH_2
d	NHMe



3b, 3d, 3g —(OH^-)→ **6**

6	R
a	H
b	Me
c	Ph

The structure of the new compounds **3**, **5** and **6** is confirmed by spectroscopic and analytical data. In the ^1H nmr spectra of some 2-amino derivatives, **3j**, **3n-p** and **5d**, signal splitting is observed due to hindered rotation of the amino group [22].

Table 1

4- and 2,4-Substituted 5-(1-Phenyl-1*H*-tetrazol-5-yl)pyrimidines **3a-v** and **5a-d**

Compound	Yield %	Mp °C	^{1}H nmr δ, ppm	Molecular Formula	Analyses % Calcd./Found C	H	N
3a	76	114-115 [a]	2.36 (s, 3H, CH_3), 7.57 (s, 5H, C_6H_5), 8.73 (s, 1H, H-6), 9.19 (s, 1H, H-2)	$C_{12}H_{10}N_6$	60.50 60.37	4.23 4.11	35.27 34.95
3b	72	151-152 [b]	7.50-7.60 (m, 5H, C_6H_5), 9.46 (s, 1H, H-6), 9.70 (s, 1H, H-2)	$C_{12}H_7F_3N_6$	49.32 49.53	2.41 2.22	28.76 28.51
3c	75	121-122 [b]	6.85-7.44 (m, 10H, 2 x C_6H_5), 9.29 (s, 1H, H-6), 9.47 (s, 1H, H-2)	$C_{17}H_{12}N_6$	67.99 68.21	4.03 3.95	27.98 28.10
3d	97	140-141 [b]	2.83 (s, 3H, CH_3), 7.50-7.60 (m, 5H, C_6H_5), 9.32 (s, 1H, H-6)	$C_{13}H_9F_3N_6$	50.99 51.08	2.96 3.05	27.44 27.32
3e	89	130-131 [b]	2.77 (s, 3H, CH_3), 6.85-7.43 (m, 10H, 2 x C_6H_5), 9.15 (s, 1H, H-6)	$C_{18}H_{14}N_6$	68.78 68.59	4.49 4.35	26.73 26.60
3f	76	113-114 [b]	2.49 (s, 3H, CH_3), 7.53-8.47 (m, 10H, 2 x C_6H_5), 8.83 (s, 1H, H-6)	$C_{18}H_{14}N_6$	68.78 68.85	4.49 4.55	26.73 26.68
3g	95	134-135 [b]	7.60-8.47 (m, 10H, 2 x C_6H_5), 9.46 (s, 1H, H-6),	$C_{18}H_{11}F_3N_6$	58.70 58.87	3.01 2.93	22.82 22.68
3h	98	182-183 [c]	6.91-8.57 (m, 15H, 3 x C_6H_5), 9.37 (s, 1H, H-6)	$C_{23}H_{16}N_6$	73.39 73.21	4.28 4.19	22.32 22.15
3i	73	212-213 [c]	2.14 (s, 3H, CH_3), 7.21 (s, 2H, NH_2), 7.55-7.62 (m, 5H, C_6H_5), 8.08 (s, 1H, H-6)	$C_{12}H_{11}N_7$	56.91 57.10	4.38 4.45	38.72 38.51
3j	87	179-180 [c]	7.49-7.61 (m, 5H, C_6H_5), 8.01 (s, 1H, NH), 8.09 (s, 1H, NH), 8.69 (s, 1H, H-6)	$C_{12}H_8F_3N_7$	46.91 50.08	2.62 2.47	31.91 31.79
3k	90	170-171 [b]	1.00 (t, 3H, CH_3), 2.42 (q, 2H, CH_2), 7.24 (s, 2H, NH_2), 7.54-7.65 (m, 5H, C_6H_5), 8.12 (s, 1H, H-6)	$C_{13}H_{13}N_7$	58.42 58.60	4.90 4.95	36.68 36.47
3l	94	132-133 [b]	0.78 (t, 3H, CH_3), 1.47 (m, 2H, CH_2), 2.36 (t, 2H, CH_2), 7.23 (s, 2H, NH_2), 7.53-7.63 (m, 5H, C_6H_5), 8.14 (s, 1H, H-6)	$C_{14}H_{15}N_7$	59.77 59.56	5.37 5.31	34.85 35.03
3m	90	267-268 [c]	6.78-7.40 (m, 10H, 2 x C_6H_5), 7.43 (s, 2H, NH_2), 8.63 (s, 1H, H-6)	$C_{17}H_{13}N_7$	64.75 64.82	4.16 4.09	31.09 30.95
3n	72	169-170 [d]	2.15/2.18 (2s, 3H, CH_3), 2.80/2.82 (2d, J = 4.0 Hz, 3H, NCH_3), 7.59 (s, 5H, C_6H_5), 7.65/7.71 (2br, 1H, NH), 8.07/8.15 (2s, 1H, H-6)	$C_{13}H_{13}N_7$	58.42 58.29	4.90 4.75	36.68 36.80
3o	96	168-169 [c]	2.87/2.89 (2d, J = 4.8 Hz, 3H, NCH_3), 7.51-7.65 (m, 5H, C_6H_5), 8.47/8.52 (2q, J = 4.8 Hz, 1H, NH), 8.70/8.79 (2s, 1H, H-6)	$C_{13}H_{10}F_3N_7$	48.60 48.76	3.14 3.20	30.52 30.38
3p	97	226-227 [c]	2.86/2.91 (2d, J = 4.5 Hz, 3H, NCH_3), 6.76-7.42 (m, 10H, 2 x C_6H_5), 7.91 (q, J = 4.5 Hz, 1H, NH), 8.61/8.71 (2s, 1H, H-6)	$C_{18}H_{15}N_7$	65.64 65.47	4.59 4.45	29.77 30.02
3q	78	97-98 [b]	4.07 (s, 3H, CH_3), 7.51-7.65 (m, 5H, C_6H_5), 9.20 (s, 1H, H-6)	$C_{13}H_9F_3N_6O$	48.45 48.61	2.82 2.77	26.08 25.95
3r	96	136-137 [b]	4.03 (s, 3H, NCH_3), 6.82-7.43 (m, 10H, 2 x C_6H_5), 9.04 (s, 1H, H-6)	$C_{18}H_{14}N_6O$	65.45 65.29	4.27 4.34	25.44 25.38
3s	76	178-179 [b]	2.60 (s, 1H, CH_3), 6.86-7.43 (m, 10H, 2 x C_6H_5), 9.04 (s, 1H, H-6)	$C_{18}H_{14}N_6S$	62.41 62.57	4.07 3.94	24.26 24.45
3t	51	105-106 [b]	1.35 (t, 3H, CH_3), 3.29 (q, 2H, CH_2), 7.57-7.63 (m, 5H, C_6H_5), 9.17 (s, 1H, H-6)	$C_{14}H_{11}F_3N_6S$	47.73 47.50	3.15 3.08	23.85 24.02
3u	79	128-129 [b]	1.34 (t, 3H, CH_3), 3.19 (q, 2H, CH_2), 6.83-7.40 (m, 10H, 2 x C_6H_5), 9.01 (s, 1H, H-6)	$C_{19}H_{16}N_6S$	63.31 63.45	4.47 4.51	23.32 23.18
3v	84	120-121 [b]	4.50 (s, 2H, CH_2), 6.83-7.45 (m, 15H, 3 x C_6H_5), 9.05 (s, 1H, H-6)	$C_{24}H_{18}N_6S$	68.23 68.37	4.29 4.15	19.89 20.05
5a	54	143-144 [d]	1.85 (s, 6H, CH_3NCH_3), 2.68 (s, 3H, CH_3), 3.35 (s, 2H, CH_2), 7.49-7.60 (m, 5H, C_6H_5), 8.83 (s, 1H, H-6)	$C_{15}H_{17}N_7$	61.00 59.84	5.80 5.67	33.20 33.11
5b	77	142-143 [d]	1.94 (s, 6H, CH_3NCH_3), 3.51 (s, 2H, NH_2), 7.54-8.50 (m, 10H, 2 x C_6H_5), 9.06 (s, 1H, H-6)	$C_{20}H_{19}N_7$	67.21 67.33	5.36 5.45	27.43 27.27
5c	52	194-195 [b]	1.86 (s, 6H, CH_3NCH_3), 3.15 (s, 2H, CH_2), 7.29 (s, 2H, NH_2), 7.48-7.62 (m, 5H, C_6H_5), 8.53 (s, 1H, H-6)	$C_{14}H_{16}N_8$	56.74 56.85	5.44 5.33	37.81 37.60
5d	61	197-198 [b]	1.86 (s, 6H, CH_3NCH_3), 2.81/2.83 (2s, 3H, NCH_3), 3.16/3.17 (2s, 2H, CH_2), 7.48-7.62 (m, 5H, C_6H_5), 7.80/7.82 (2s, 1H, NH), 8.23/8.31 (2s, 1H, H-6)	$C_{15}H_{18}N_8$	58.05 57.92	5.85 5.69	36.10 36.25

[a] Cyclohexane. [b] Methanol. [c] Acetonitrile. [d] Ethanol.

EXPERIMENTAL

Melting points were determined on a "Boetius" hot-stage apparatus and are uncorrected. The ^{1}H nmr spectra were recorded with a Bruker AM 250 instrument (250 MHz) at ambient temperature using DMSO-d_6 as the deuterated solvent and TMS as the internal reference. The preparation of the enamino ketones **1** and **4** is described [17,18]. The amidines **2** were used in the form of the following salts: Formamidine as the acetate, acetamidine, benzamidine, *N*-methylguanidine and *S*-benzylthiopseudourea as the hydrochlorides, *S*-ethylthiopseudourea as the hydrobromide, guanidine and *S*-methylthiopseudourea as the sulfates, and *O*-methylisourea as the hydrogen sulfate.

General Procedure for the Preparation of Tetrazolylpyrimidines **3a-v** and **5a-d**.

To a hot solution of 5 mmoles of enamino ketones **1** or **4**, respectively, and 10 mmoles of amidines **2** (used in form of the salts mentioned above) in ethanol (30 ml) a 1*M* ethanolic solution of sodium ethoxide (10 ml, 10 mmoles) was added; in the case of **2**, R = OMe and SMe methanol/sodium methoxide was used as reaction medium. After refluxing for 2 hours with magnetic stirring, the solvent was partially distilled off (*ca.* 30 ml). On cooling or if necessary by dropwise addition of water the products **3** and **5** precipitated as colorless crystals. Yields and physical properties as well as the solvents used for recrystallization are reported in Table 1.

General Procedure for the Preparation of Tetrazolylpyrimidine-4-carboxylic Acids **6a-c**.

Under refluxing and magnetic stirring 5*N* aqueous sodium hydroxide (20 ml) was added dropwise to a solution of 5 mmoles of **3b**, **3d** and **3g**, respectively, in ethanol (20 ml). After refluxing for 4 hours, part of ethanol (*ca.* 15 ml) was removed by distillation an the cold concentrate neutralized with concentrated hydrochloric acid to give acids **6a-c**.

5-(1-Phenyl-1*H*-tetrazol-5-yl)pyrimidine-4-carboxylic Acid (**6a**).

This compound was obtained in 55% yield as colorless needles (ethanol/water), mp 160-161°; ^{1}H nmr: δ 7.56 (s, 5H, C_6H_5), 8.43 (s, 1H, H-6), 8.46 (s, 1H, H-2), 13.16 (br, 1H, COOH).

Anal. Calcd. for $C_{12}H_8N_6O_2$: C, 53.73; H, 3.01; N, 31.33. Found: C, 54.02; H, 2.83; N, 31.18.

2-Methyl-5-(1-phenyl-1*H*-tetrazol-5-yl)pyrimidine-4-carboxylic Acid (**6b**).

This compound was obtained in 76% yield as colorless crystals (ethanol), mp 237-238°; ^{1}H nmr: δ 2.36 (s, 3H, CH_3), 7.77 (s, 5H, C_6H_5), 8.35 (s, 1H, H-6), 13.01 (br, 1H, COOH).

Anal. Calcd. for $C_{13}H_{10}N_6O_2$: C, 55.32; H, 3.57; N, 29.78. Found: C, 55.44; H, 3.49; N, 29.52.

2-Phenyl-5-(1-phenyl-1*H*-tetrazol-5-yl)pyrimidine-4-carboxylic Acid (**6c**).

This compound was obtained in 84% yield as colorless needles (acetic acid), mp 284-285° dec; ^{1}H nmr: δ 7.54-8.18 (m, 10H, 2 x C_6H_5), 8.61 (s, 1H, H-6), 13.35 (br, 1H, COOH).

Anal. Calcd. for $C_{18}H_{12}N_6O_2$: C, 62.79; H, 3.51; N, 24.41. Found: C, 62.59; H, 3.38; N, 24.64.

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[22] The split signals coalesce at temperature up to 50°.