Reactions with 3,5-Diaminopyrazoles: New Routes to Pyrazolo[1,5-*a*]pyrimidines

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Reactions of 3,5-diaminopyrazoles with chalcones and ethyl α-acetylcinnamates lead to new polyfunctional derivatives of pyrazolo[1,5-*a*]pyrimidine. The structures of the products and the mechanisms of their formation are reported.

Reaktion mit 3,5-Diaminopyrazol-Derivaten: neue Wege zu Pyrazolo [1,5-*a*]pyrimidinen

Reaktionen von 3,5-Diaminopyrazolen mit Chalconen und α-Acetylzimtsäure-Ethylestern führen zu polyfunktionellen Pyrazolo[1,5-*a*]pyrimidinen. Die Strukturen dieser Verbindungen und die Mechanismen ihrer Bildung werden dargestellt.

Pyrazolopyrimidines are purine analogues and as such they have useful properties as antimetabolites in purine biochemical reactions[1,2]. Moreover, these compounds have marked antitumor and antileukemic activity[3]. In previous work we have reported a variety of new procedures for the preparation of differently substituted pyrazolo[1,5-*a*]pyrimidine derivatives[4].

In this paper, the behaviour of 4-arylazo-3,5-pyrazolediamines **1** towards the action of a variety of α,β-unsaturated reagents was investigated: **1a-d** react with chalcones **2a-g** in ethanol containing catalytic amounts of piperidine to afford the 2-amino-3-arylazo-5,7-diaryl-pyrazolo[1,5-*a*]pyrimidines **5a-z** in good yield. The formation of **5** from the reaction of **1** with **2** is assumed to proceed by a *Michael* type addition of the most basic ring-N in **1** to the activated double bond in **2**. The intermediatly formed *Michael* adducts **3** cycliz by water elimination to give the dihydropyrazolopyrimidines **4** which aromatize to yield the end products **5**. - Although one may argue that the reaction of **1** with chalcones **2** may involve exocyclic or endocyclic pyrazole-N, involvement of endocyclic pyrazole-N leading to **5** was assumed based on the ability of pyrazoles to be alkylated at the ring-N[5] and in analogy to previous lit.[6].

The structure of **5** was established by elemental analysis, IR- and ^{1}H-NMR-spectra which reveal a broad singlet at δ = 5.82 ppm assignable to an amino group and a multiplet at δ 7.1-8.4 ppm assigned to pyrimidine-H and aromatic protones.

Table 1: List of compounds **5a-z, 10a-l,** and **11a-l**

Comp. no.	reflux h	yield %	m.p. °C	M.formula M.W.	Analysis	calcd. / found	
					C	H	N
5a	4	80	298	$C_{24}H_{17}BrN_6$	61.4	3.7	17.9
				469.3	61.9	4.0	17.6
5b	6	60	240	$C_{25}H_{20}N_6$	74.2	5.0	20.8
				404.4	74.7	5.4	20.4
5c	7	55	275	$C_{25}H_{20}N_6O$	71.5	4.8	19.5
				420.4	71.9	5.3	19.5
5d	7	52	260	$C_{24}H_{17}ClN_6$	67.8	4.0	19.8
				424.8	67.5	4.5	19.9
5e	9	48	272	$C_{25}H_{20}N_6$	74.2	5.0	20.8
				404.4	74.5	5.3	21.2
5f	8	35	270	$C_{24}H_{17}ClN_6$	67.8	4.0	19.8
				424.8	67.3	3.8	19.4
5g	5	75	225	$C_{24}H_{16}BrClN_6$	57.2	3.2	16.7
				503.7	56.7	3.5	16.2
5h	6	50	237	$C_{25}H_{19}ClN_6$	68.4	4.4	19.2
				438.9	68.5	3.8	18.8
5i	6	70	326	$C_{25}H_{19}ClN_6O$	66.0	4.2	18.5
				454.9	65.5	4.0	18.0

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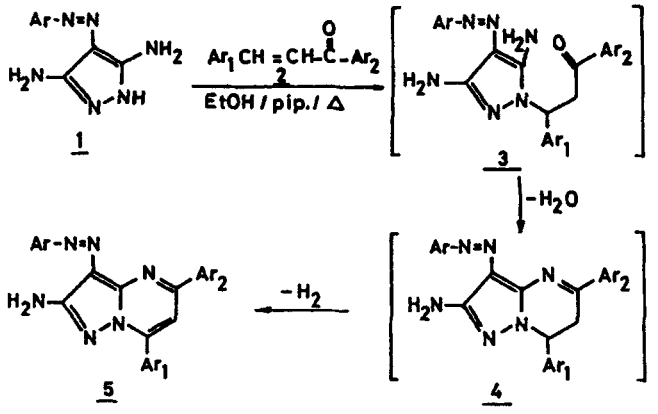
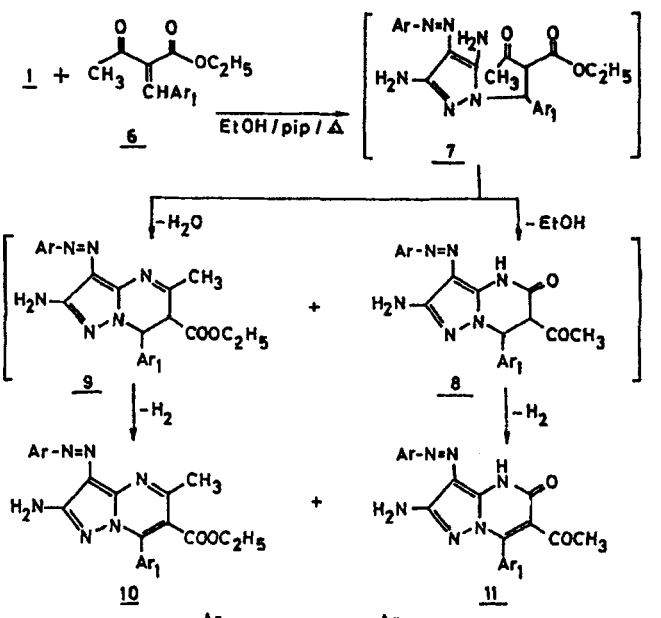


	Ar	Ar_1	Ar_2
a	C_6H_5	C_6H_5	4-Br-C_6H_4
b	C_6H_5	C_6H_5	4-H_3C-C_6H_4
c	C_6H_5	C_6H_5	4-H_3CO-C_6H_4
d	C_6H_5	4-Cl-C_6H_4	C_6H_5
e	C_6H_5	4-H_3C-C_6H_4	C_6H_5
f	4-Cl-C_6H_4	C_6H_5	C_6H_5
g	4-Cl-C_6H_4	C_6H_5	4-Br-C_6H_4
h	4-Cl-C_6H_4	C_6H_5	4-H_3C-C_6H_4
i	4-Cl-C_6H_4	C_6H_5	4-H_3CO-C_6H_4
j	4-Cl-C_6H_4	4-Cl-C_6H_4	C_6H_5
k	4-Cl-C_6H_4	4-H_3C-C_6H_4	C_6H_5
l	4-Cl-C_6H_4	4-H_3CO-C_6H_4	C_6H_5
m	4-H_3C-C_6H_4	C_6H_5	C_6H_5
n	4-H_3C-C_6H_4	C_6H_5	4-Br-C_6H_4
o	4-H_3C-C_6H_4	C_6H_5	4-H_3C-C_6H_4
p	4-H_3C-C_6H_4	C_6H_5	4-H_3CO-C_6H_4
q	4-H_3C-C_6H_4	4-Cl-C_6H_4	C_6H_5
r	4-H_3C-C_6H_4	4-H_3C-C_6H_4	C_6H_5
s	4-H_3C-C_6H_4	4-H_3CO-C_6H_4	C_6H_5
t	4-H_3CO-C_6H_4	C_6H_5	C_6H_5
u	4-H_3CO-C_6H_4	C_6H_5	4-Br-C_6H_4
v	4-H_3CO-C_6H_4	C_6H_5	4-H_3C-C_6H_4
w	4-H_3CO-C_6H_4	C_6H_5	4-H_3CO-C_6H_4
x	4-H_3CO-C_6H_4	4-Cl-C_6H_4	C_6H_5
y	4-H_3CO-C_6H_4	4-H_3C-C_6H_4	C_6H_5
z	4-H_3C-C_6H_4	Naphthyl	4-Cl-C_6H_4



	Ar	Ar_1
a	C_6H_5	C_6H_5
b	C_6H_5	4-H_3C-C_6H_4
c	C_6H_5	4-H_3CO-C_6H_4
d	4-Cl-C_6H_4	C_6H_5
e	4-Cl-C_6H_4	4-H_3C-C_6H_4
f	4-Cl-C_6H_4	4-H_3CO-C_6H_4
g	4-H_3C-C_6H_4	C_6H_5
h	4-H_3C-C_6H_4	4-H_3C-C_6H_4
i	4-H_3C-C_6H_4	4-H_3CO-C_6H_4
j	4-H_3CO-C_6H_4	C_6H_5
k	4-H_3CO-C_6H_4	4-H_3C-C_6H_4
l	4-H_3CO-C_6H_4	4-H_3CO-C_6H_4

The behaviour of the 5-aminopyrazoles **1** towards ethyl α-acetylcinnamates **6** was also investigated: **1** reacted with **6** in ethanol containing catalytic amounts of piperidine to give a mixture of ethyl 2-amino-3-arylazo-7-aryl-5-methyl-pyrazolo[1,5-*a*]pyrimidin-6-carboxylates **10a-l** and 2- amino-6-acetyl-3-arylazo-7-aryl-4,5-dihydropyrazolo[1,5-*a*]-pyrimidin-5- ones **11a-l**. These two types of compounds are separated by fractional crystallization. The formation of **10** and **11** from **1** and **6** is assumed to proceed via addition of the most basic N in **1** to the α,β-unsaturated double bond in **6** to give the intermediate **7**. This *Michael* adduct then cyclizes by ethanol or water elimination to give the intermediate dihydropyrazolopyrimidines **8** and **9**, respectively, which are dehydrogenated under the reaction conditions to yield the pyrazolo[1,5-*a*] pyrimidine derivatives **10** and **11**.

The structure of **10** could be established for these products on the basis of their elemental analysis and spectral data

Table (1): Cont.

Comp. no.	reflux h	yield %	m.p.°C	M.formula M.W.	Analysis	calcd. / found %	
					C	H	N
5j	8	60	245	$C_{24}H_{16}Cl_2N_6$	62.8	3.5	18.3
				459.3	62.6	3.4	17.9
5k	8	70	285	$C_{25}H_{19}ClN_6$	68.4	4.4	19.2
				438.9	67.9	4.2	18.6
5l	5	35	300	$C_{25}H_{19}ClN_6O$	66.0	4.2	18.5
				454.9	65.5	3.7	17.9
5m	7	60	260	$C_{25}H_{20}N_6$	74.2	5.0	20.8
				404.4	74.5	4.5	20.9
5n	7	70	288	$C_{25}H_{19}Br\ N_6$	62.1	4.0	17.4
				483.3	62.6	4.4	17.9
5o	8	60	240	$C_{26}H_{22}N_6$	74.6	5.3	20.1
				448.4	74.3	5.7	19.6
5p	12	60	265	$C_{26}H_{22}N_6O$	71.9	5.1	19.3
				434.4	72.3	5.6	18.9
5q	10	65	275	$C_{25}H_{19}ClN_6$	68.4	4.4	19.2
				438.9	68.8	4.7	18.7
5r	12	58	260	$C_{26}H_{22}N_6$	74.6	5.3.	20.1
				418.4	74.1	5.7	19.7

Table (1): Cont.

Comp. no.	reflux h	yield %	m.p.°C	M.formula M.W.	Analysis calcd. / found % C	H	N
5s	11	68	280	$C_{26}H_{22}N_6O$	71.9	5.1	19.3
				434.4	72.3	5.5	19.8
5t	12	45	272	$C_{25}H_{20}N_6O$	71.4	4.8	20.0
				420.4	71.8	5.0	19.5
5u	5	70	235	$C_{25}H_{19}BrN_6O$	60.1	3.8	16.8
				499.6	60.5	4.3	16.4
5v	7	50	275	$C_{26}H_{22}N_6O$	71.9	5.1	19.3
				434.4	71.5	5.6	19.2
5w	8	70	230	$C_{26}H_{22}N_6O_2$	69.3	4.9	18.7
				450.4	68.9	5.2	19.0
5x	7	75	230	$C_{25}H_{19}ClN_6O$	66.0	4.0	18.5
				454.9	65.8	3.9	18.9
5y	11	48	270	$C_{26}H_{22}N_6O$	71.9	5.1	19.3
				434.4	71.9	5.4	18.9
5z	4	60	280	$C_{29}H_{21}ClN_6$	71.2	4.3	17.2
				488.9	71.3	4.8	16.8

Table (1): Cont.

Comp. no.	reflux h	yield %	M.P.°C	M.formula M.W.	Analysis C	Calc. / found % H	N
10a	6	50	210	$C_{22}H_{20}N_6O_2$	66.0	5.0	21.0
				400.4	65.5	5.4	20.5
10b	3	55	220	$C_{23}H_{22}N_6O_2$	66.6	5.4	20.3
				414.4	66.8	5.8	19.9
10c	4	60	180	$C_{23}H_{22}N_6O_3$	64.2	5.2	19.5
				430.4	63.8	5.2	19.2
10d	5	58	140	$C_{22}H_{19}ClN_6O_2$	60.8	4.4	19.3
				434.8	60.6	5.0	19.2
10e	4	52	240	$C_{23}H_{21}ClN_6O_2$	61.5	4.7	18.7
				448.9	62.0	5.2	18.8
10f	4	60	232	$C_{23}H_{21}ClN_6O_3$	59.4	4.6	18.1
				464.9	59.2	4.0	18.3
10g	5	55	230	$C_{23}H_{22}N_6O_2$	66.6	5.4	20.3
				414.4	67.1	5.1	19.9
10h	6	50	202	$C_{24}H_{24}N_6O_2$	67.3	5.7	19.6
				428.4	67.8	5.2	19.2
10i	6	56	155	$C_{24}H_{24}N_6O_3$	64.9	5.4	18.9
				444.4	64.5	5.0	18.4
10j	4	53	230	$C_{23}H_{22}N_6O_3$	64.2	5.2	19.5
				430.4	64.5	5.7	18.9

(IR, ^{1}H-NMR). Structure **10** seems to be logic according to the ^{1}H-NMR-spectra which reveal a triplet at δ = 1.1 ppm assigned to a methyl ester group, a singlet at δ = 2.5 ppm assignable to a methyl group and a quarted at δ = 4.0 ppm assigned to CH_2-CH_3. - Structure **11** was established based on ^{1}H-NMR-spectra which reveal a methyl group at δ = 2.6 ppm and a NH group at δ = 11.6 ppm.

These results, when combined with our previous results indicate that the reaction of 5-aminopyrazole **1** with suitable α,β-unsaturated keto compounds can be used as a convenient route for the synthesis of several, otherwise difficultly accessible pyrazolo[1,5-*a*]pyrimidine derivatives.

Table (1): Cont.

Comp. no.	reflux h	yield %	M.P.°C	M.formula M.W.	Analysis C	calcd/ found% H	N
10k	6	48	160	$C_{24}H_{24}N_6O_3$	64.8	5.4	18.9
				444.4	64.9	5.3	18.8
10l	5	65	155	$C_{24}H_{24}N_6O_4$	62.6	5.3	18.3
				460.4	62.9	5.1	18.6
11a	6	25	330	$C_{20}H_{16}N_6O_2$	64.5	4.3	22.6
				372.3	64.1	3.9	23.0
11b	3	30	320	$C_{21}H_{18}N_6O_2$	65.3	4.7	21.8
				386.4	65.6	4.2	21.3
11c	4	18	340	$C_{21}H_{18}N_6O_3$	62.7	4.5	20.9
				402.4	62.2	4.1	20.5
11d	5	19	283	$C_{20}H_{15}ClN_6O_2$	59.0	3.7	20.7
				406.8	59.5	4.1	20.3
11e	4	23	332	$C_{21}H_{17}ClN_6O_2$	59.9	4.1	20.0
				420.8	60.0	4.6	19.6
11f	4	15	335	$C_{21}H_{17}ClN_6O_2$	57.7	3.9	19.2
				436.8	58.2	4.0	18.9
11g	5	19	340	$C_{21}H_{18}N_6O_2$	65.3	4.7	21.8
				386.4	64.9	5.2	21.3
11h	6	22	320	$C_{22}H_{20}N_6O_2$	66.0	5.0	21.0
				400.4	66.6	5.7	20.5
11i	6	20	327	$C_{22}H_{20}N_6O_3$	63.4	4.8	20.2
				416.4	63.8	5.1	20.5
11j	4	17	330	$C_{21}H_{18}N_6O_3$	62.7	4.5	20.9
				402.4	62.2	4.0	20.4
11k	6	20	310	$C_{22}H_{20}N_6O_3$	63.4	4.8	20.2
				416.4	62.9	5.1	19.8
11l	5	22	318	$C_{22}H_{20}N_6O_4$	61.1	4.7	19.4
				432.4	61.4	5.0	19.8

Experimental Part

Melting points: uncorrected. - IR spectra (KBr): Pye Unicam Sp-1000 spectrophotometer. - ^{1}H-NMR spectra: Varian EM-390 90 MHz spectrometer, DMSO as solvent, TMS as int. reference. Chemical shifts in δ units (ppm). - Analytical data: Microanalytical Centre at Cairo University, Egypt

2-Amino-3-arylazo-5,7-diarylpyrazolo[1,5-a]pyrimidines **5a-z**

A suspension of **1** (0.01 mol) in absol. ethanol (30 ml) was refluxed with chalcones **2** (0.01 mol) and two drops of piperidine for 4-12 h, the mixture was left to cool to room temp. The crystals separating on cooling, were filtered off and crystallized from benzene/petroleum ether (cf. table 1).

Ethyl 2-amino-7-aryl-3-arylazo-5-methylpyrazolo[1,5-a]-pyrimidine-6-carboxylates **10a-l** *and 2-amino-6-acetyl-7-aryl-3-arylazo-4,5-dihydropyrazolo[1,5-a]pyrimidine-5-ones* **11a-l**

A solution of 5-aminopyrazole **1** (0.01 mol) and ethyl α-acetylcinnamate **6** (0.01 mol) in absol. ethanol (30 ml) and a few drops of piperidine was refluxed for 3-8 h, cooled, the precipitate was filtered off and crystallized from aqueous dioxane. The first fraction comprises compounds **10a-l** (cf.

Table 2: Spectroscopic data for compounds listed in Table 1

Compound	IR (cm^{-1})(KBr)	^1H-NMR (δ ppm)
5a	3400-3300 (NH_2)	7.2-8.44 (m, 15H, $2C_6H_5$, C_6H_4 and pyrimidine-H)
5n	3450-3320 (NH_2)	2.4 (s, 3H, CH_3); 7.2-8.4 (m, 14H, C_6H_5, $2C_6H_4$ and pyrimidine-H)
5y	3400-3330 (NH_2)	2.6 (s, 3H, CH_3); 3.90 (s, 3H, OCH_3); 7.1-8.4 (m, 14H, C_6H_5, $2C_6H_4$ and pyrimidine-H)
5z	3450-3300 (NH_2)	2.4 (s, 3H, CH_3); 7.2-8.6 (m, 16H, $2C_6H_4$, naphthyl protons and pyrimidine-H)
10b	3500-3200 (NH_2); 1700 (CO)	1.1 (t, 3H, ester CH_3); 2.28 (s, 3H, CH_3); 2.48 (s, 3H, CH_3); 4.0 (q, 2H, CH_2); 5.9 (d, br, 2H, NH_2); 7.02-7.80 (m, 9H, C_6H_5 and C_6H_4)
10d	3450-3200 (NH_2); 1720 (CO)	1.8 (t, 3H, CH_3); 2.5 (s, 3H, CH_3); 4.0 (q, 2H, CH_2); 6.04 (d, br, 2H, NH_2); 7.18-7.92 (m, 9H, C_6H_5 and C_6H_4)
10f	3500-3200 (NH_2); 1700 (CO)	1.12 (t, 3H, CH_3); 2.55 (s, 3H, CH_3); 3.82 (s, 3H, OCH_3); 4.0 (q, 2H, CH_2); 5.88 (s, br, 2H, NH_2); 6.9-7.8 (m, 8H, $2C_6H_4$)
11g	3300-3000 (NH_2, NH); 1700 (CO)	2.32 (s, 3H, CH_3); 2.48 (s, 3H, CH_3); 6.06 (s, 2H, NH_2); 7.04-7.88 (m, 9H, C_6H_5 and C_6H_4)
11h	3500-3400 (NH_2; NH); 1700 (CO)	2.3 (s, 3H, CH_3); 2.34 (s, 3H, CH_3); 2.48 (s, 3H, CH_3); 5.92 (s, br, 2H, NH_2); 6.82-7.77 (m, 8H, $2C_6H_4$); 11.6 (s, br, 1H, NH)
11i	3500-3300 (NH_2; NH); 1680 (CO)	2.42 (s, 3H, CH_3); 2.57 (s, 3H, CH_3); 3.78 (s, 3H, OCH_3); 6.0 (s, br, 2H, NH_2); 6.88-7.85 (m, 8H, $2C_6H_4$); 11.42 (s, br, 1H, NH)

10). Two ml of water were then added to the filtrate, the formed solid was filtered off and crystallized from dioxane to yield compounds **11a-l** (table 1).

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