

A NEW SYNTHESIS OF PYRAZOLO[4,3-*e*][1,2,4]TRIAZINES VIA ACID PROMOTED RING CLOSURE OF THE PHENYLHYDRAZONES OF 5-ACYL-1,2,4-TRIAZINES¹

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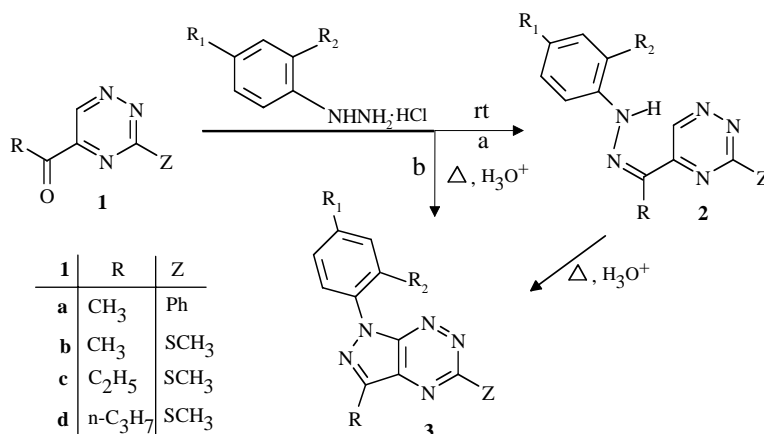
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Abstract - The reaction of various substituted phenylhydrazones of 5-acyl-1,2,4-triazines in the presence of 1.1 equivalent of HCl in boiling ethanol-dioxane mixture has been studied. In all reactions the formation of the corresponding pyrazolo[4,3-*e*][1,2,4]triazines (**3a-r**) takes place in good yield. The structures of **3a-r** were unequivocally established by spectroscopic methods as well as by X-Ray analysis of selected 5-methyl-3-phenyl-7-(*p*-tolyl)pyrazolo[4,3-*e*][1,2,4]triazine (**3a**).

In spite of the fact that pyrazolo[4,3-*e*][1,2,4]triazine skeleton is found in natural products such as pseudoiodinine² and nostocine A,³ possessing interesting pharmacological activity, only a few methods have been described for the synthesis of this heterocyclic ring system. The first one involves the construction of 1,2,4-triazine ring *via* reaction of 4-bromo-3-phenylpyrazol-5-yl hydrazonyl chloride with hydrazine or phenylhydrazine;⁴ the utility of this procedure is limited by the availability of not so simple starting materials. In the second method the annulated pyrazole ring has been prepared by condensation of either 5-arylidene- or 5-benzoyl-3-phenyl-1,2,4-triazin-6-ones with hydrazine and phenylhydrazine.^{5,6} This procedure can be effectively applied only in the synthesis of compounds containing phenyl or substituted phenyl groups and is inconvenient for preparing highly functionalized systems.

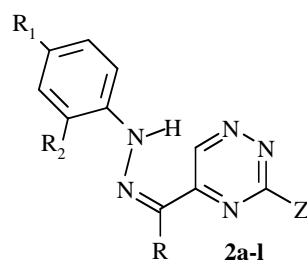
In connection with synthetic program designed to identify new therapeutic agents, a versatile synthesis of various substituted pyrazolo[4,3-*e*][1,2,4]triazines was required. We report here a new two-step synthesis of such compounds starting from easily available 5-acyl-1,2,4-triazines and various phenylhydrazines. This approach evolved from developments in direct nucleophilic acylation of 1,2,4-triazines and in 1,2,4-triazine annulation chemistry.⁷ The key elements of this synthesis are outlined in Scheme 1.

Scheme 1



The starting 5-acyl-1,2,4-triazines (**1a-d**) differing in the type of an alkyl group at the carbonyl carbon and in substituents at C-3, were readily prepared according to our previously established method from the corresponding 1,2,4-triazines and the nitronate ions.⁸⁻¹⁰ Treatment of 5-acetyl-3-phenyl-1,2,4-triazine (**1a**) with *p*-tolylhydrazine hydrochloride in ethanol in the presence of 1.1 equivalent of 10% HCl at room temperature afforded *p*-tolylhydrazone (**2a**) in good yield (Table 1). When the same reaction was carried out in refluxing ethanol for 14 h, 5-methyl-3-phenyl-7-(*p*-tolyl)pyrazolo[4,3-*e*][1,2,4]triazine (**3a**) was obtained. The product was evidently formed in a tandem reaction in which the first formed (**2a**) cyclised to pyrazolotriazine derivative (**3a**). It was confirmed by employing alternative procedure: the reaction of **2a** in refluxing ethanol containing 1.1 equivalent of 10% HCl for 14 h gave **3a** in 69% yield. When instead of ethanol, dioxane-ethanol mixture 3:1 is used and the same reaction conditions were applied as mentioned above, the conversion of **2a** into **3a** was completed within 2 h (Table 2). Utilizing the same reaction sequence a number of phenylhydrazones (**2b-l**) were obtained which could be converted readily into required pyrazolo[4,3-*e*][1,2,4]triazines (**3b-l**) (Scheme 1, route a) (Tables 1 and 2). Alternatively, reactions of **1a** and **1b** with some phenylhydrazine hydrochlorides in refluxing dioxane-ethanol mixture 3:1 containing 1.1 equivalent of 10% HCl gave directly the expected products (**3m-r**) in moderate yields (Scheme 1, route b) (Table 3).

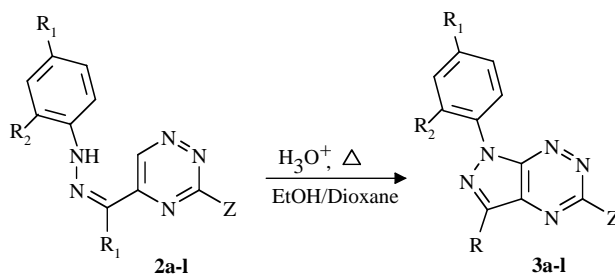
Table 1. Yields, melting points, IR, ¹H NMR spectra and elemental analyses of compounds (**2a-l**)



2	Z	R	R ₁	R ₂	Yield %	Mp °C	IR N-H cm ⁻¹	¹ H NMR δ (CDCl ₃) H-6; N-H		Analyses %		
										Calcd	Found	Formula
a	Ph	CH ₃	CH ₃	H	83	262	3231	9.87	7.92	71.28	5.61	23.10
										71.29	5.65	23.08
										C ₁₈ H ₁₇ N ₅		
b	Ph	CH ₃	Cl	H	80	254	3332	9.86	8.47	63.06	4.33	21.64
										63.13	4.22	21.64
										C ₁₇ H ₁₄ N ₅ Cl		
c	Ph	CH ₃	OCH ₃	H	77	228	3234	9.86	8.20	67.71	5.32	21.94
										67.56	5.19	21.87
										C ₁₈ H ₁₇ N ₅ O		
d	Ph	CH ₃	Cl	Cl	82	233	3300	9.9	8.5	57.14	3.64	19.60
										56.86	3.37	19.55
										C ₁₇ H ₁₃ N ₅ Cl ₂		
e	SCH ₃	CH ₃	H	H	56	224	3225	9.63	8.05	55.60	5.02	27.03
										55.53	5.09	26.99
										C ₁₂ H ₁₃ N ₅ S		

f	SCH ₃	CH ₃	CH ₃	H	55	219	3226	9.62	8.01	57.14 57.15	5.49 5.49	25.64 25.64
g	SCH ₃	CH ₃	Cl	H	61	233	3236	9.60	8.00	49.15 49.20	4.09 3.85	23.89 24.10
h	SCH ₃	C ₂ H ₅	H	H	87	192	3236	9.60	8.18	57.14 56.89	5.49 5.53	25.64 25.44
i	SCH ₃	C ₂ H ₅	CH ₃	H	82	205	3230	9.59	8.114	58.54 58.34	5.92 6.03	24.39 24.27
j	SCH ₃	n-C ₃ H ₇	H	H	63	189	3240	9.61	8.18	58.54 58.30	5.92 5.86	24.39 24.57
k	SCH ₃	n-C ₃ H ₇	CH ₃	H	66	191	3230	9.60	8.14	59.80 59.70	6.31 6.34	23.25 23.28
l	SCH ₃	n-C ₃ H ₇	Cl	H	70	212	3228	9.58	8.14	52.34 52.17	4.99 4.93	21.81 21.74

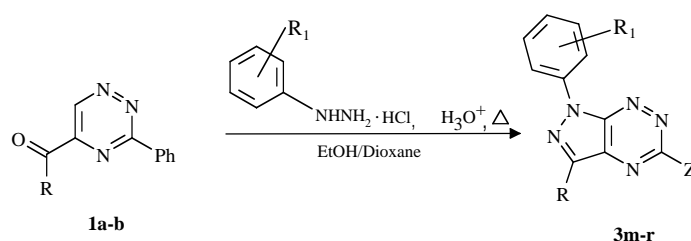
Table 2. Yields, reaction times, melting points and elemental analyses of compounds (**3a-l**)



3	Z	R	R ₁	R ₂	Yield %	Time (h)	Mp °C	Analyses %		
								Calcd	Found	Formula
								C	H	N
a	Ph	CH ₃	CH ₃	H	79	2	225	71.76 71.54	4.98 4.86	23.25 23.28
b	Ph	CH ₃	Cl	H	75	7	200	63.45 63.37	3.73 3.49	21.77 21.64
c	Ph	CH ₃	OCH ₃	H	77	2	162	68.18 68.17	4.73 4.48	22.08 22.20

d	Ph	CH ₃	Cl	Cl	82	66	180	57.46	3.10	19.72
								57.60	2.92	19.73
										C ₁₇ H ₁₁ N ₅ Cl ₂
e	SCH ₃	CH ₃	H	H	52	7.5	105	56.03	4.28	27.23
								55.67	4.13	27.05
										C ₁₂ H ₁₁ N ₅ S
f	SCH ₃	CH ₃	CH ₃	H	52	7.5	149	57.56	4.80	25.83
								57.68	4.71	25.76
										C ₁₃ H ₁₃ N ₅ S
g	SCH ₃	CH ₃	Cl	H	23	7.5	184	49.48	3.44	24.05
								49.24	3.34	23.88
										C ₁₂ H ₁₀ N ₅ SCl
h	SCH ₃	C ₂ H ₅	H	H	54	4	87	57.56	4.79	25.83
								57.53	4.93	25.75
										C ₁₃ H ₁₃ N ₅ S
i	SCH ₃	C ₂ H ₅	CH ₃	H	57	4	127	58.95	5.26	24.56
								59.14	5.34	23.82
										C ₁₄ H ₁₅ N ₅ S
j	SCH ₃	n-C ₃ H ₇	H	H	52	3	71	58.95	5.26	24.56
								58.94	5.40	24.38
										C ₁₄ H ₁₅ N ₅ S
k	SCH ₃	n-C ₃ H ₇	CH ₃	H	49	3	114	60,20	5.68	23.41
								60.18	5.81	23.68
										C ₁₅ H ₁₇ N ₅ S
l	SCH ₃	n-C ₃ H ₇	Cl	H	47	2	80	52.66	4.39	21.94
								52.84	4.32	21.79
										C ₁₄ H ₁₄ N ₅ SCl

Table 3. Yields, reaction times and elemental analyses of compounds (**3m-r**)

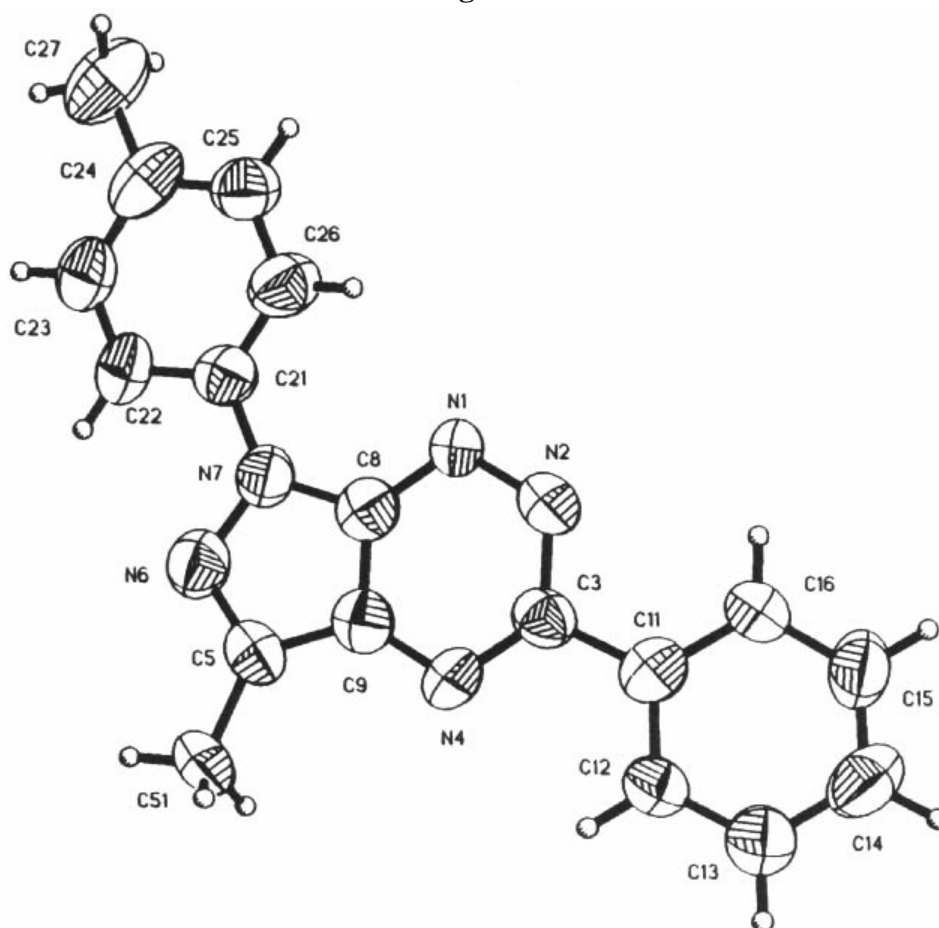


3	Z	R	R ₁	Yield %	Time (h)	Mp °C	Analysis %		
							Calcd	Found	Formula
							C	H	N
m	Ph	CH ₃	<i>m</i> -Cl	86	7.5	156	63.46	3.76	21.77
							63.47	3.61	21.82
									C ₁₇ H ₁₂ N ₅ Cl
n	Ph	CH ₃	<i>p</i> -NO ₂	52	31	237	61.44	3.61	25.30
							61.35	3.34	25.19
									C ₁₇ H ₁₂ N ₆ O ₂

o	Ph	CH ₃	<i>o</i> -CH ₃	60	3	162	71.74	5.02	23.24
							71.77	4.78	22.94
							C ₁₈ H ₁₅ N ₅		
p	Ph	CH ₃	<i>m</i> -CH ₃	78	2	169	71.74	5.02	23.24
							71.87	4.98	23.11
							C ₁₈ H ₁₅ N ₅		
r	SCH ₃	C ₂ H ₅	H	67	3	87	57.56	4.79	25.83
							57.53	4.93	25.75
							C ₁₃ H ₁₃ N ₅ S		

The structures of **3a-r** were unequivocally established by their elemental analysis and ¹H NMR spectra clearly showing the absence of the N-H and H-6 proton in 1,2,4-triazine ring. Finally, the structure of selected pyrazolotriazine (**3a**) was confirmed by X-Ray analysis. ORTEP drawing of **3a** is shown in Figure 1.

Figure 1



The bond lengths and angles in pyrazolo[4,3-*e*][1,2,4]triazine ring (Table 4) are in good agreement with those found in *nostocine A*.³ Two N - N, five N - C and two C - C bonds have the intermediate values between expected single- and double-bond lengths characteristic for π -electron system. The least-squares planes of phenyl rings are inclined by 11.4(2)^o with respect to each other and by 5.6(2)^o for C11 - C16 and 6.9(2)^o for C21 - C26 rings with respect to the plane of pyrazolotriazine moiety. These dihedral angles show that the molecule of **3a** as a whole is almost planar.

Table 4. Selected bond distances (Å) and angles (°) for **3a**.

N(1)-C(8)	1.327(8)	C(8)-N(1)-N(2)	113.3(5)
N(1)-N(2)	1.351(6)	N(1)-N(2)-C(3)	120.5(5)
N(2)-C(3)	1.390(7)	C(3)-N(4)-C(9)	114.3(6)
N(4)-C(3)	1.321(7)	C(5)-N(6)-N(7)	109.2(5)
N(4)-C(9)	1.322(7)	N(6)-N(7)-C(8)	108.1(5)
N(6)-C(5)	1.335(8)	N(4)-C(3)-N(2)	125.1(6)
N(6)-N(7)	1.365(7)	N(6)-C(5)-C(9)	108.7(6)
N(7)-C(8)	1.397(8)	N(1)-C(8)-C(9)	125.6(6)
N(7)-C(21)	1.409(7)	N(1)-C(8)-N(7)	126.9(6)
		C(9)-C(8)-N(7)	107.5(6)
		N(4)-C(9)-C(8)	121.2(7)
		N(4)-C(9)-C(5)	132.4(7)
		C(8)-C(9)-C(5)	106.5(6)

EXPERIMENTAL

Melting points are uncorrected. IR spectra were measured with a Magna IR-760 spectrophotometer. The ¹H NMR spectra were recorded in deuteriochloroform on a Varian-Gemini 200 MHz spectrometer.

Preparation of phenylhydrazones of 5-acyl-1,2,4-triazines (**2a-l**): general procedure.

To a solution of **1** (1 mmol) and phenylhydrazine hydrochloride (1.5 mmol) in 20 mL of ethanol was added 10% hydrochloric acid (0.4 mL) and the resulting reaction mixture was stirred for 5 min at rt. After that time the precipitated solid was filtered off. The crude product was recrystallized from ethanol-water mixture to give **2a-l**. For analytical data see Table 1.

Preparation of pyrazolo[4,3-*e*][1,2,4]triazines (**3a-l**) from phenylhydrazones of 5-acyl-1,2,4-triazines (**2a-l**): general procedure.

A solution of **3a-l** (0.2 mmol) and 10% hydrochloric acid (0.08 mL) in dioxane-ethanol mixture 3:1 (20 mL) was refluxed for several hours. After that time the solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (silica gel, chloroform) and was recrystallized from ethanol-water mixture. For analytical data see Table 2.

Preparation of pyrazolo[4,3-*e*][1,2,4]triazines (**3m-r**) from 5-acyl-1,2,4-triazines (**1**) and phenylhydrazine hydrochlorides.

To a solution of 5-acyl-1,2,4-triazine (**1a**) or (**1b**) (0.25 mmol) and the corresponding phenylhydrazine hydrochloride (0.37 mmol) in dioxane-ethanol 3:1 (20 mL) was added 10% hydrochloric acid (0.1 mL). The reaction mixture was refluxed for several hours. The solvent was evaporated to dryness and the residue was purified by column chromatography (silica gel, chloroform). After evaporation of the solvent the products (**3m-r**) were recrystallized from ethanol-water mixture. For analytical data see Table 3.

X-Ray structure determination

Crystal data for 3a: C₁₈H₁₅N₅, M = 301.35, monoclinic, space group C2/c, a = 21.960(3), b = 8.953(3),

$c = 16.812(5)$ Å, $\beta = 112.55(1)^\circ$, $V = 3052(1)$ Å³, $Z = 8$, $D_x = 1.311$ g cm⁻³, $F(000) = 1264$, $\mu(\text{CuK}\alpha) = 0.653$ mm⁻¹, crystal size 0.10 x 0.30 x 0.70 mm. Yellow plate crystals were obtained by slow evaporation of an acetone solution. X-ray data were collected on a Nonius MACH-3 four-circle diffractometer at room temperatures. Lattice parameters were obtained from least-squares refinement of setting angles of 15 reflections (θ range 18.6 - 22.6°). Intensity data were collected using CuK α radiation ($\lambda = 1.54178$ Å) and applying $\omega - 2\theta$ scan technique; no. of measured reflection 1341 (θ range 4.36 - 64.7°, index ranges $0 \leq h \leq 25$, $-10 \leq k \leq 0$, $-19 \leq l \leq 16$), no. of independent reflection 1309 ($R_{\text{int}} = 0.10$). The structure was solved by direct methods using SHELXS86¹¹ and refined by full-matrix least squares with anisotropic temperature factors for non-hydrogen atoms using SHELXL93.¹² All hydrogen atoms were placed in calculated positions and their coordinates were refined using a riding model with isotropic displacement parameters taken as 1.5 times those of respective parent atoms. Fifteen strong reflections affected by secondary extinction were suppressed during the last few cycles of refinement. The final $R = 0.0741$, $wR = 0.1695$ for 1294 reflections [$I > 2\sigma(I)$] and 208 parameters, $S = 1.050$, $(\Delta/\sigma)_{\text{max}} = 0.000$, $(\Delta\rho)_{\text{max}} = 0.278$ and $(\Delta\rho)_{\text{min}} = -0.200$ eÅ⁻³.

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