SYNTHESIS OF SOME NEW 3,5,7-TRISUBSTITUTED PYRAZOLO[4,3-e]1,2,4-TRIAZINES

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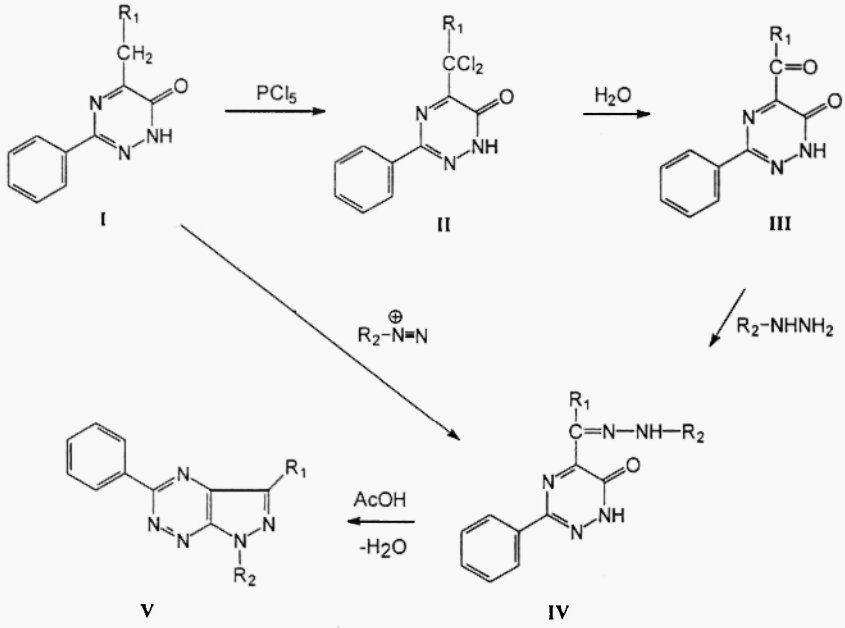
Abstract

This paper following the previous work[1] deals with the synthesis of new 3,5,7-trisubstituted pyrazolo[4,3-e]1,2,4-triazines. Easily prepared substituted phenylhydrazones of 3-phenyl-5-subst.benzoyl-6-oxo-1,6-dihydro-1,2,4-triazines **IVa-IVe** were cyclized to compounds **Va-Ve**.



Scheme 1.

I-III	**IV, V**	
a:R_1=Ph	a:R_1=Ph	R_2=4-Cl-Ph
b:R_1=3,4-$(CH_3O)_2$-Ph	b:R_1=3,4-$(CH_3O)_2$-Ph	R_2=Ph
c:R_1=4-Cl-Ph	c:R_1=4-Cl-Ph	R_2=4-Cl-Ph
	d:R_1=4-Cl-Ph	R_2=4-OH-Ph
	e:R_1=4-Cl-Ph	R_2=4-CH_3O-Ph

Introduction

Pyrazolo-[4,3-e]-1,2,4-triazines are interesting compounds found in microorganisms of the genus *Pseudomonas*[6] namely of *Pseudomonas fluorescens* strains and have antitumor and large antibiotic activities[7] . We now report the synthesis of similar compounds that are 3-phenyl-5,7-diaryl-pyrazolo-[4,3-e]-1,2,4-triazines. This work describes two methods of 3-phenyl-5-arylmethylene-6-oxo-1,6-dihydro-1,2,4-triazine skeleton[1,2,3] broadening to 3-phenyl-5,7-diaryl-pyrazolo-[4,3-e]-1,2,4-triazine. The first one used in case of synthesis **Ve** requires chloration of reactive methylene group of **Ie** and its further hydrolysis to carbonyl group **IIIe** as described in references[5,8]. Reaction of the formed carbonyl group with 4-methoxyphenylhydrazin and cyclization of reaction intermediate in boiling acetic acid to **Ve**

was performed in one reaction step. Compounds **IVa-IVd** were prepared in an easier way by coupling of reactive methylene group of **Ia-Id** with the corresponding diazonium salts in pyridine medium. For cyclization of these products, boiling acetic acid was also used.

Results and Discussion

Table 1 summarizes chemical and physical data of the herein described compounds. Table 2 shows selected IR frequencies of **IVa-IVe** and **Va-Ve,** stretching vibrations of (C=O), $(C-C)_{ar}$, (C=N), and out of plane deformation vibrations of $(C-H)_{ar}$. The absence of carbonyl frequencies of compounds **V** confirms the cyclization of pyrazolo-[4,3-e]-1,2,4-triazine ring accompanied by elimination of water. ^{1}H-NMR spectra proved the structures proposed for **Va, Vb, Vd** and **Ve.** Chemical shifts of these compounds are shown in Table 3. Spin-spin interaction constants between ortho C-H in the para disubstituted rings were 7,2 Hz.

Table 1. Chemical and analytical data of **IVa – IVe** and **Va - Ve.**

Compd.	Formula	M. w.	M. p. /°C	Yield/%	%C	%H calcd./ found	%N
IV a	$C_{22}H_{16}ON_5Cl$	401.9	239-241	85.9	65.75/66.0	4.01/3.7	17.43/17.4
IV b	$C_{24}H_{21}O_3N_5$	427.5	230-232	32.2	67.45/67.6	4.92/4.6	16.39/16.2
IV c	$C_{22}H_{15}ON_5Cl_2$	436.3	255-257	86.8	60.55/60.6	3.44/3.4	16.06/15.9
IV d	$C_{22}H_{16}O_2N_5Cl$	417.8	238-240	80.0	63.39/63.1	3.60/3.4	16.81/16.8
IV e	$C_{23}H_{18}O_2N_5Cl$	431.9	242-244	21.1	63.96/64.2	4.20/4.0	16.21/15.9
V a	$C_{22}H_{14}N_5Cl$	383.8	215-217	87.7	68.82/68.8	3.68/3.4	18.25/18.0
V b	$C_{24}H_{19}O_2N_5$	409.4	197-199	52.1	70.39/70.0	4.68/4.4	17.11/16.8
V c	$C_{22}H_{13}N_5Cl_2$	418.3	277-279	96.7	63.17/63.4	3.14/3.3	16.74/16.6
V d	$C_{22}H_{14}ON_5Cl$	399.8	291-293	28.9	66.07/66.3	3.50/3.2	17.52/17.3
V e	$C_{23}H_{16}ON_5Cl$	413.9	203-205	A)84.2 B)24.7	66.75/66.7	3.87/3.9	16.93/17.0

Table 2. Selected IR data (cm^{-1}) of **IVa-IVe** and **Va-Ve.**

	ν(C=O)	ν(C=N)	$\nu(C-C)_{ar}$	$\gamma(C-H)_{ar}$
IVa	1658	1598	1492	696
IVb	1655	1601	1456	696
IVc	1644	1610	1492	696
IVd	1648	1596	1447	670
IVe	1658	1585	1443	693
Va	-	1497	1432	694
Vb	-	1599	1422	696
Vc	-	1494	1424	696
Vd	-	1640	1424	660
Ve	-	1511	1452	693

Table 3. Chemical shifts (ppm) of ^{1}H-NMR spectra of **Va, Vb, Vd** and **Ve.**

Compound	Aromatic	p-disubstitution			CH_3O	OH
		p-ClPh	p-OHPh	p-MeOPh		
Va	7.62-8.71	7.81, 8.54	-	-	-	-
Vb	7.30-8.69	-	-	-	3.93, 4.01	-
Vd	7.09-8.66	7.75, 8.59	7.10, 8.14	-	-	10.04
Ve	7.30-8.71	7.80, 8.66	-	7.31, 8.32	3.93	-

In addition, results of mass spectrometry corroborated structure of described pyrazolo-[4,3-e]-1,2,4-triazines. In all cases the molecular peak was observed and isolated in the ionic trap. It was fragmented by a collision dissociation. All synthetised compounds are crystallic, well soluble in common organic solvents and poorly in water.

Apparatus and methods

Melting points were determined on a Boetius block and are uncorrected. The IR spectra were recorded by ATI Unicam Genesis FTIR using KBr pellets. Elemental analyses were made by means of EA 1108 Elemental Analyser (Fisons Instrument). The mass spectra were measured on an LCQ Finnigam MAT Instrument. ^{1}H-NMR spectra were recorded on a Bruker AMX 360 NMR spectrometer.

Experimental

4-chlorophenylhydrazone of 3-phenyl-5-benzoyl-6-oxo-1,6-dihydro-1,2,4-triazine IVa

To a stirred solution of **1a** (1.3, 4.9 mmol) in pyridine (15 mL) kept at 0°C, a solution of 4-chlorobenzendiazonium chloride (0.86g, 4.9mmol) in water (10mL) was added dropwise. After 2 days keeping in dark at 0°C, the solution had turned dark red and **IVa** (1.69g, 85.9%) precipitated as a deep red solid was filtered off and crystallized (EtOH/C_6H_6 1:1).

Phenylhydrazone of 3-phenyl-5-(3,4-dimethoxybenzoyl)-6-oxo-1,6-dihydro-1,2,4-triazine IVb

To a stirred solution of **1b** (0.7, 2.17mmol) in pyridine (20 mL) kept at 0°C, a solution of 4-chlorobenzendiazonium chloride (0.31g, 2.17mmol) in water (5mL) was added dropwise. After 2 days keeping in dark at 0°C the solution was treated with water (15mL) and precipitated dark yellow powder **IVb** (0.29g, 32.2%) was filtered off and crystallized (C_6H_6).

4-chlorophenylhydrazone of 3-phenyl-5-(4-chlorbenzoyl)-6-oxo-1,6-dihydro-1,2,4-triazine IVc

To a stirred solution of **1a** (1.0 g, 3.4 mmol) in pyridine (15 mL) kept at 0°C, a solution of 4-chlorobenzendiazonium chloride (0.60g, 3.4mmol) in water (7.5mL) was added dropwise. After 2 days keeping in dark at 0°C the solution had turned dark red and **IVc** (1.27g, 86.6%) precipitated as a deep red solid was filtered off and crystallized (C_6H_6).

4-hydroxyphenylhydrazone of 3-phenyl-5-(4-chlorbenzoyl)-6-oxo-1,6-dihydro-1,2,4-triazine IVd

To a stirred solution of **1a** (1.0, 3.4 mmol) in pyridine (15 mL) kept at 0°C, a solution of 4-hydroxybenzendiazonium chloride (0.54g, 3.4mmol) in water (7.5mL) was added dropwise. After 2 days keeping in dark at 0°C the solution had turned dark red and **IVd** (1.42g, 80.0%) precipitated as a violet solid was filtered off and crystallized (EtOH/C_6H_6 1:1).

4-methoxyphenylhydrazone of 3-phenyl-5-(4-chlorobenzoyl)-6-oxo-1,6-dihydro-1,2,4-triazine IVe

A solution of 4-methoxyphenylhydrazine (0.2g, 1.4mmol) in 50% acetic acid (5mL) was added to a stirred solution of 0,4g (1,3 mmol) of **IIIc** in mixture of water and ethanol (40mL/80mL). The mixture was refluxed for one hour. After cooling a violet solid occured (0.13g, 21.2%) and crystallized (C_6H_6).

3,5-diphenyl-7-(4-chlorophenyl)-pyrazolo[4,3-e]1,2,4-triazine Va

The compound **IVa** (0.6g, 1.5mmol) was refluxed in glacial acetic acid (100mL) for 16 hours. After cooling the solution a yelow powder was obtained (0.50, 87.7%) and crystallized ($EtOH/C_6H_6$ 1:1).

3,7-diphenyl-5-(3,4-dimethoxyphenyl)-pyrazolo[4,3-c]1,2,4-triazine Vb
The compound **IVb** (1.0g, 2.0mmol) was refluxed in glacial acetic acid (200mL) for 75 hours. After cooling the solution an orange solid was obtained (0.40g, 52.2%) and crystallized (EtOH).

3-phenyl-5,7-bis-(4-chlorophenyl)-pyrazolo[4,3-e]1,2,4-triazine Vc
The compound **IVc** (1.3g, 3.0mmol) was refluxed in glacial acetic acid (300mL) for 14 hours. After cooling the solution an orange solid was obtained (1.21g, 96.8%) and crystallized (C_6H_6).

3-phenyl-5-(4-chlorophenyl)-7-(4-hydroxyphenyl)-pyrazolo[4,3-e]1,2,4-triazine Vd
The compound **IVd** (0.4g, 1.0mmol) was refluxed in glacial acetic acid (50mL) for 6 hours. After cooling the solution a red powder occured (0.12g, 28.9%) and after crystallization (EtOH) red needles were obtained.

3-phenyl-5-(4-chlorophenyl)-7-(4-methoxyphenyl)-pyrazolo[4,3-e]1,2,4-triazine Ve
Method A) The compound **IVe** (0.4g, 1.0mmol) was refluxed in glacial acetic acid (80mL) for 5 hours. After thickening and cooling the solution an orange solid was obtained (0.35g, 84.2%) and crystallized ($EtOH/C_6H_6$ 1:1).
Method B) The compound **IIIc** (1.3g, 4.2mmol) and 4-methoxyphenylhydrazine (0.6g, 4.3mmol) was refluxed in glacial acetic acid (210mL) for one hour. After thickening and cooling the solution an orange solid was obtained (0.43g, 24.8%) and crystallized ($EtOH/C_6H_6$ 1:1).

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