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Triazolines III. Synthesis of Polysubstituted 1,5-Diaryl-1,2,3-triazolines Bearing an *Ortho*- Substituent by the Cycloaddition of Diazomethane to Schiff Bases (1)

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The accelerating effect of small amounts of water on the 1,3-cycloaddition of diazomethane to Schiff bases has led to a versatile method for the synthesis in good yields, of the rarely encountered 1,2,3-triazolines, by carrying out the cycloaddition reaction in aqueous dioxane solutions (1-8). Thus, a number of hitherto difficultly available 1,5-diaryl-1,2,3-triazolines (II) bearing a single substituent on the *C*-phenyl and/or the *N*-phenyl have been obtained by the action of diazomethane on aromatic Schiff bases (anils) (I) (1). At the present time, the cycloaddition reaction appears to be the only general method for the synthesis of 1,5-diaryl-1,2,3-triazolines. In view of the potential importance of the 1,2,3-triazolines as a source of aziridines via photodecomposition reactions (2), it was of interest to investigate the utility of this addition reaction to the synthesis of polysubstituted 1,5-diaryl-1,2,3-triazolines.

During earlier work involving synthesis of the monosubstituted diaryltriazolines it has been observed that comparatively higher yields resulted when the substituent on the Schiff base was in the *o*-position on the *C*-phenyl (1,3). Since then a kinetic investigation has revealed that this *o*-substituent effect is predominantly steric in nature (4). The presence of an *o*-substituent on the *C*-phenyl results in a steric inhibition of resonance in the Schiff base which raises its ground state energy and thereby decreases its activation energy. It is now found that this favorable effect of *o*-substituents present on the *C*-phenyl can be used to advantage in the synthesis of many polysubstituted diaryltriazolines bearing an *o*-substituent in high yields. The addition of aryl azides to olefins (5) is impractical in the preparation of 1,5-diaryltriazolines due to the sluggish nature of the reaction (1). It is even more so

in the preparation of polysubstituted 1,5-diaryl-1,2,3-triazolines as the appropriately substituted phenyl azides and olefins are not readily available.

The presence of an *o*-substituent on the *N*-phenyl of the Schiff base does not contribute to increased yields; in fact, in all cases attempted it is found isolation of products is difficult and the yields are poor.

The majority of the triazolines reported here are polyhalo compounds; these were synthesized with a view to testing certain physiological properties, the results of which will be reported in due course.

EXPERIMENTAL (6)

Synthesis of Schiff Bases (Anils) (I).

The Schiff bases were prepared by refluxing a mixture of the appropriate aldehyde and amine in equimolar quantities in ethanol. In most cases, the Schiff base was formed with extreme ease, and separated out of the reaction mixture in pure form soon after admixture of the reactants. They were filtered, washed well with ethanol and recrystallized, as necessary, from suitable solvents.

Those Schiff bases with an *o*-substituent on the *N*-phenyl, offered difficulties. Anil formation did not go to completion and much of the aldehyde and amine was recovered unchanged. In the case of benzal-*o*-nitroaniline, the mixture of aniline (0.1 mole) and aldehyde (0.15 mole) was heated at 110-120° in an open flask for 2 hours. It was then cooled and shaken with petroleum ether to remove excess benzaldehyde. Further addition of acetone to the syrupy residue dissolved the unreacted aniline and yielded the Schiff base as an orange yellow crystalline powder, very sparingly soluble in acetone.

Similarly, benzal-2-methyl-4-nitroaniline was prepared by heating equimolar quantities of the aldehyde and aniline at 175-180° for 0.75 hour and removing the water formed in the reaction under reduced pressure. On cooling, a dark crystalline mass was formed from which the unreacted aniline was removed by solution in acetone, leaving behind the sparingly soluble Schiff base.

The *p*-aminobenzoic ester needed for the preparation of 2,4-dichlorobenzal-*p*-aminoethyl benzoate was prepared by refluxing *p*-aminobenzoic acid with ethanol saturated with hydrogen chloride (7). The various Schiff bases are listed in Table I along with other pertinent data.

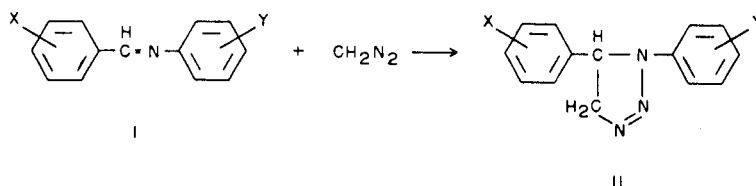
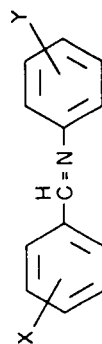


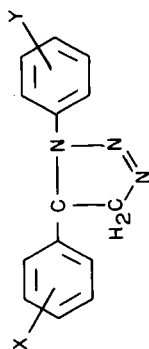
TABLE I
Synthesis of Schiff Bases (Anils)



Compound No.	Substituent		Color and Crystallization Solvent (a)	M. P.	Yield, % (b)	Calcd.		Analysis Found		Notes
	C-Phenyl (X)	N-Phenyl (Y)				C	H	C	H	
1	2,4-Di-Cl	H	Pale yellow, E	89.5°	(85.6)	62.40	3.60	62.55	3.78	
2	2,4-Di-Cl	<i>m</i> -NO ₂	Colorless, E	140-141°	65.0	52.88	2.71	52.99	2.88	
3	2,4-Di-Cl	<i>m</i> -Cl	Cream yellow, E	77-80°	(85.0)	54.83	2.81	55.10	3.01	
4	2,4-Di-Cl	<i>p</i> -Br	Cream yellow, E-A	134-135.5°	72.0	47.43	2.43	47.66	2.52	
5	2,4-Di-Cl	<i>p</i> -COOEt	Yellow, E	91-93°	(84.5)	59.63	4.04	59.81	4.24	
6	2,4-Di-Cl	<i>p</i> -CH ₃	Yellow, E	84-85.5°	75.5	63.64	4.17	63.74	4.25	
7	<i>o</i> -NO ₂	3,4-Di-Cl	Yellow, E	126-127°	(81.0)	52.88	2.71	52.98	2.80	
8	<i>o</i> -Cl	3,4-Di-Cl	Tan, A	87-90°	65.4	54.83	2.81	54.99	2.98	
9	<i>o</i> -CH ₃	3,4-Di-Cl	Light yellowish buff, E	65-67.5°	66.3	63.64	4.17	63.70	4.20	
10	2,4-Di-Cl	3,4-Di-Cl	Cream yellow, E	130-133°	(87.5)	48.90	2.19	49.10	2.29	
11	H	<i>o</i> -NO ₂	Yellow, A	124.5-127°	28.0	69.03	4.42	69.32	4.55	
12	H	2-CH ₃ -4-NO ₂	Brown needles, IP	115-118°	20.0	70.00	5.00	70.22	4.98	

(a) A, acetone; E-A, ethanol-acetone mixture; E, Ethanol; IP, isopropyl alcohol. (b) The figures in parenthesis refer to yields of Schiff bases obtained directly from the reaction mixture in pure form. They had melting points the same as the analytical samples obtained by crystallization from the appropriate solvents.

TABLE II
 Synthesis of Polysubstituted 1,5-Diaryl-1,2,3-triazolines



Compound No.	Substituent		Reaction Time (hr.)	Color and Crystallization Solvent (a)	Yield, % (b)	M.P.	Calcd.		Analyses		Found	
	C-Phenyl (X)	N-Phenyl (Y)					H	C	N	C	H	N
1	2,4-Di-Cl	H	96	Colorless (c), E	64	77-78° (d)	3.77	57.53	14.38	57.63	3.84	14.48
2	2,4-Di-Cl	m-NO ₂	120	Yellow Crystals (e)	20	106.5-110°	2.99	49.87	16.62	50.13	3.15	16.94
3	2,4-Di-Cl	m-Cl	72	Colorless, E	(91.7)	104-106°	3.09	51.48	---	51.35	3.13	---
4	2,4-Di-Cl	p-Br	96	Colorless, E	(61)	118-120°	2.69	45.29	11.32	45.23	2.88	11.41
5	2,4-Di-Cl	p-COOEt	96	Cream white, ET	(68) (f)	89-89.5°	4.12	56.04	11.54	55.85	4.28	11.64
6	2,4-Di-Cl	p-CH ₃	120	Colorless (g)	35	81.5-82.5°	4.25	58.82	13.73	58.99	4.27	13.82
7	o-NO ₂	3,4-Di-Cl	96	Buff yellow, A-P	(80) (h)	115-117° (i)	2.99	49.87	16.62	49.97	3.03	16.78
8	o-Cl	3,4-Di-Cl	96	Buff coloured needles, A	(98)	104.5° (j)	3.09	51.48	12.86	51.43	3.21	13.04
						106.5°						
9	o-CH ₃	3,4-Di-Cl	122	Pale Buff (k)	50	114-116.5°	4.25	58.82	13.73	58.95	4.39	13.81
10	2,4-Di-Cl	3,4-Di-Cl (l)	72	Colorless, E-A	(87.3)	124.5-125°	2.50	46.59	---	46.47	2.63	---
11	H	o-NO ₂	96	Yellow (m)	(m)	170-176°	---	---	20.89	---	---	20.66
12	H	2-CH ₃ -4-NO ₂	143	Yellow (n)	(n)	98-102°	4.96	63.83	19.86	63.94	4.98	19.99

(a) A, acetone; A-P, acetone-petroleum ether mixture; E, ethanol; E-A, ethanol-acetone mixture; ET, diethyl ether. (b) The yields in parentheses refer to triazolines obtained pure, directly from reaction mixture. They had melting points the same as the analytical samples obtained by crystallization from the respective solvents. (c) The low melting triazoline often separated out as an oil; it solidified when the mixture was shaken with 25-30 ml. of petroleum ether and allowed to stand in the cold for 2 days. (d) Decomposes with evolution of nitrogen only around 110°. (e) The product (4.6 g.), m.p. 92-105°, was obtained from the reaction mixture. This recrystallized from isopropyl alcohol to give 3.4 g. of material, m.p. 102-107. Further recrystallization from ethanol yielded 2.8 g. (56%) of triazoline, m.p. 105-109°. Final crystallization from acetone-hexane mixture gave the pure compound. (f) On adding water to the reaction mixture, the triazoline separated out as an oil, and failed to solidify even after standing in the refrigerator for more than two months. At the end of this period, the water was decanted off and the oil dissolved in diethyl ether, followed by addition of petroleum ether until cloudiness appeared. The latter, on standing in the cold for 2-3 days, deposited pure crystals of the triazoline. (g) The crude product, m.p. 60-80°, was recrystallized from ethanol to give 60% of triazoline, m.p. 79.5-82.5°. Further recrystallization from diethyl ether yielded a purer product. (h) The deep yellow tan product, obtained by diluting the reaction mixture with water, was dried, ground well with ether and filtered, leaving behind a buff crystalline material, m.p. 115-117°. (i) Recrystallization from acetone-petroleum ether mixture gave a sample, m.p. 118-119°. The product appeared to be very sensitive to light and on standing turned yellow on the surface in 3-4 hours. (j) Recrystallization from acetone gave a sample, m.p. 105-107°. (k) The crude product obtained from the reaction mixture had m.p. 50-110°. This was ground well with a mixture of petroleum ether and diethyl ether, leaving behind a crystalline material, m.p. 109.5-115.5°. The latter recrystallized from ethanol to give the pure triazoline. (l) The triazoline was strikingly more stable than the others, and did not decompose during a period of 8-10 months at room temperature. (m) A third of the anil remained insoluble during the course of the reaction and did not react; this was filtered off. From the filtrate, upon dilution with water, an orange yellow precipitate was obtained, which after two crystallizations from acetone gave a very small amount of the product. (n) On diluting the reaction mixture with water, a brown oil separated, and solidified into a sticky precipitate (estimated yield, 12%) after standing in the cold for a few days. The latter, after two crystallizations from acetone-diethyl ether mixture and one from diethyl ether yielded a few crystals of the pure triazoline.

Synthesis of 1,2,3-triazolines (II).

The triazolines were prepared by the cycloaddition reaction of diazomethane (0.05 mole) to Schiff bases (0.015 mole) in aqueous dioxane solutions (75 ml.), described earlier (1). Unlike in previous experiments, no additional dioxane was added to dissolve the sparingly soluble anils; it was found they gradually went into solution during the course of the reaction.

In many cases, the polysubstituted triazolines were obtained pure directly from the reaction mixture and needed no further purification. They exhibited stabilities comparable to the monosubstituted compounds; they underwent slow decomposition on standing for 2-3 months and many of them decomposed with evolution of nitrogen at or above their melting points.

The synthesis of triazolines bearing an *o*-substituent on the *N*-phenyl could not be achieved with any degree of success; out of several cases attempted, only in two was it possible to obtain any product at all.

The data on the synthesis of the various triazolines are presented in Table II.

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Neil F. Fannin. The undergraduate participation of Petroleum Research Scholar, Thomas F. Colturi is acknowledged. Address all inquiries to P. K. Kadaba, Christian Brothers College, Memphis, Tennessee 38104.

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