[CONTRIBUTION FROM THE BIOCHEMICAL RESEARCH LABORATORY, THE DOW CHEMICAL CO.]

Phenylnitromethane. I. An Improved Synthesis of α-Nitrostilbenes

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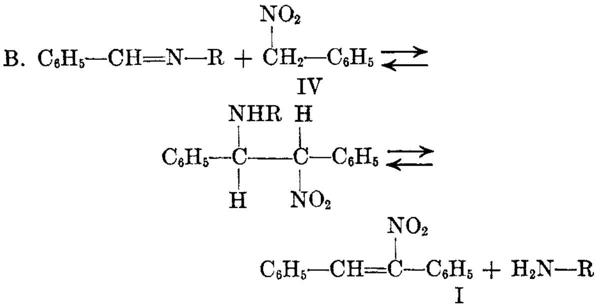
Received August 4, 1959

An improved synthesis of α-nitrostilbenes has been developed. High yields of pure products have been obtained by using Schiff's bases of aromatic aldehydes as intermediates and conducting the condensation with phenylnitromethane in acetic acid. The usual by-products, triphenylisoxazoline oxides and triphenylisoxazoles, are thus avoided. Comparative data with previous methods is included in tabular form. Nineteen new α-nitrostilbenes are reported.

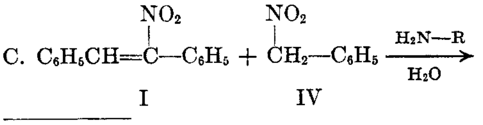
α-Nitrostilbenes have been prepared by the primary amine catalyzed condensation of aromatic aldehydes with phenylnitromethane[1] (α-nitrotoluene). Low yields are frequently encountered[1,2,3] and long reaction times (3–8 days) are usually required.[1,3] In addition, α-nitrostilbenes readily add phenylnitromethanes in the presence of ammonia[4] or aliphatic amines[5] to give, ultimately, triphenylisoxazoline oxide and triphenylisoxazole which are often troublesome by-products in the purification of α-nitrostilbenes.

α-Nitrostilbene (I) forms an isolatable addition product with piperidine and certain aromatic amines.[5] The adduct with piperidine is readily converted to triphenylisoxazoline oxide (II) and triphenylisoxazole (III). The reaction of other aliphatic amines with I leads directly to II and III, the adducts apparently being too unstable to isolate. Dornow and Boberg[5] have shown that the adduct of I with aniline can also be prepared in good yield by the reaction of phenylnitromethane (IV) with benzalaniline. I with IV in alcoholic ammonia gives II and III.[4] It seems clear, therefore, that the Knoevenagel reaction with aromatic aldehydes and phenylnitromethane, when catalyzed by primary amines, may be written as:

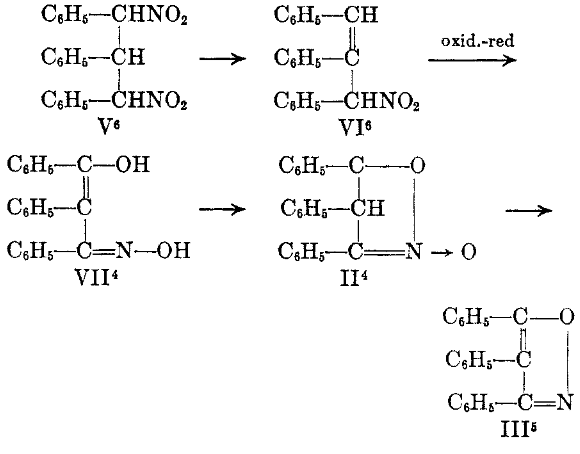
A. $C_6H_5{-}CHO + H_2N{-}R \rightleftarrows C_6H_5{-}CH{=}N{-}R + H_2O$



B. $$C_6H_5{-}CH{=}N{-}R + \underset{IV}{\overset{NO_2}{C}H_2}{-}C_6H_5 \rightleftarrows C_6H_5{-}\underset{H}{\overset{NHR}{C}}{-}\underset{NO_2}{\overset{H}{C}}{-}C_6H_5 \rightleftarrows \underset{I}{C_6H_5{-}CH{=}\overset{NO_2}{C}{-}C_6H_5} + H_2N{-}R$$



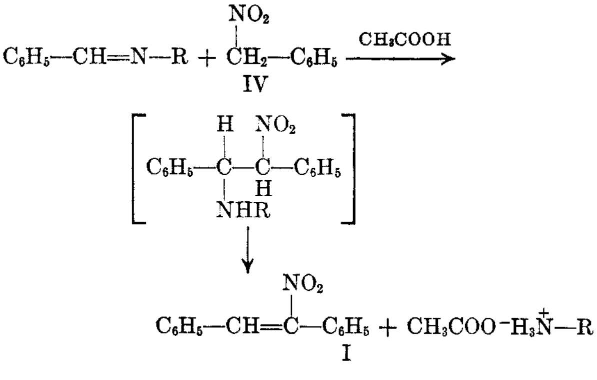
C. $$\underset{I}{C_6H_5CH{=}\overset{NO_2}{C}{-}C_6H_5} + \underset{IV}{\overset{NO_2}{C}H_2{-}C_6H_5} \xrightarrow[H_2O]{H_2N{-}R}$$



$$\underset{V^6}{\begin{matrix}C_6H_5{-}CHNO_2\\ C_6H_5{-}CH\\ C_6H_5{-}CHNO_2\end{matrix}} \longrightarrow \underset{VI^6}{\begin{matrix}C_6H_5{-}CH\\ C_6H_5{-}C\\ C_6H_5{-}CHNO_2\end{matrix}} \xrightarrow{\text{oxid.-red}}$$

$$\underset{VII^4}{\begin{matrix}C_6H_5{-}C{-}OH\\ C_6H_5{-}C\\ C_6H_5{-}C{=}N{-}OH\end{matrix}} \longrightarrow \underset{II^4}{\begin{matrix}C_6H_5{-}C{-}O\\ C_6H_5{-}CH\\ C_6H_5{-}C{=}N \rightarrow O\end{matrix}} \longrightarrow \underset{III^5}{\begin{matrix}C_6H_5{-}C{-}O\\ C_6H_5{-}C\\ C_6H_5{-}C{=}N\end{matrix}}$$

In considering this reaction, it was felt that a distinct improvement could be made by eliminating the water formed in reaction A and by tying up the basic amine formed in reaction B, thus excluding by-product formation according to reaction sequence C. This was readily accomplished by first forming the Schiff's base and contacting it with a solution of IV in an excess of glacial acetic acid at room temperature. The reaction may be represented by:



$$C_6H_5{-}CH{=}N{-}R + \underset{IV}{\overset{NO_2}{C}H_2{-}C_6H_5} \xrightarrow{CH_3COOH} \left[C_6H_5{-}\underset{NHR}{\overset{H}{C}}{-}\underset{H}{\overset{NO_2}{C}}{-}C_6H_5\right] \longrightarrow \underset{I}{C_6H_5{-}CH{=}\overset{NO_2}{C}{-}C_6H_5} + CH_3COO^-H_3\overset{+}{N}{-}R$$

Crowell and Peck[7] conducted a kinetic study of the Knoevenagel reaction between nitromethane (VIII) and piperonal (IX) using butylamine (X) as catalyst, concluding that the Schiff's base was an intermediate. The Schiff's base reacted rapidly with VIII when catalyzed by butylammonium acetate whereas IX did not.

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(1) E. Knoevenagel and L. Walter, *Ber.*, **37**, 4502 (1904).

(2) C. T. Bahner, H. E. Dickson and L. Moore, *J. Am. Chem. Soc.*, **70**, 1982 (1948).

(3) P. Ruggli and B. Hegedus, *Helv. Chim. Acta*, **22**, 405 (1939).

(4) D. E. Worrall, *J. Am. Chem. Soc.*, **57**, 2299 (1935).

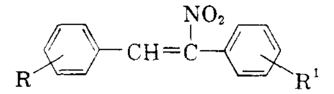
(5) A. Dornow and F. Boberg, *Ann.*, **578**, 94 (1952).

(6) F. Hein, *Ber.*, **44**, 2021 (1911).

(7) T. I. Crowell and D. W. Peck, *J. Am. Chem. Soc.*, **75**, 1075 (1953).

TABLE I

Substituted α-Nitrostilbenes[a]



	R	R¹	Reaction Time[b]	Yield, %[c]	M.P.[d]	Formula	Chlorine, %	
							Calcd.	Found
XI	2-Chloro	—	C C	87.3[e] 81.8	90–91	$C_{14}H_{10}ClNO_2$	13.65	13.37
XII	4-Chloro	—	B	74.7	113–114	$C_{14}H_{10}ClNO_2$	13.65	13.28
XIII	—	2-Chloro	C	54.6	92.8–93.5	$C_{14}H_{10}ClNO_2$	13.65	13.39
XIV	2,4-Dichloro	—	D	83.7	121–123	$C_{14}H_9Cl_2NO_2$	24.11	24.14
XV	3,4-Dichloro	—	C	65.3	110	$C_{14}H_9Cl_2NO_2$	24.11	23.84
XVI	2,6-Dichloro	—	D	83	136–136.5	$C_{14}H_9Cl_2NO_2$	24.11	24.00
XVII	2-Chloro	2-Fluoro	D	68.5	84.5–85.5	$C_{14}H_9ClFNO_2$	12.77	12.60
XVIII	2-Chloro	2-Chloro	A	63.3	120.5–121.5	$C_{14}H_9Cl_2NO_2$	24.11	24.66
XIX	2-Methoxy	2-Chloro	A	74.5	152–153	$C_{15}H_{12}ClNO_3$	12.24	12.14
XX	2-Ethoxy	2-Chloro	A	77	120–121	$C_{16}H_{14}ClNO_3$	11.67	11.41
XXI	2-Nitro	2-Chloro	E	80.8	155.8–156.6	$C_{14}H_9ClN_2O_4$	11.64	11.69
XXII	2,4-Dichloro	2-Chloro	B	78.3	90–91	$C_{14}H_8Cl_3NO_2$	32.37	32.12
XXIII	2,6-Dichloro-3-hydroxy	—	C	91 (crude)	170–171.3	$C_{14}H_9Cl_2NO_3$	22.86	22.48
							Bromine, %	
							Calcd.	Found
XXIV	2-Bromo	—	B	85.6	91.5–92.5	$C_{14}H_{10}BrNO_2$	26.28	26.79
							Nitrogen, %	
							Calcd.	Found
XXV	4-Carboethoxymethoxy	—	D	52	69.5–70.5	$C_{18}H_{17}NO_6$	4.28	4.43
XXVI	2-Ethoxy	—	A	67.1	108.7–109.4	$C_{16}H_{15}NO_3$	5.20	5.08
XXVII	2,4,6-Trimethyl	—	C	81.2	115–116	$C_{17}H_{17}NO_2$	5.24	5.32
							Carbon, %	
							Calcd.	Found
XXVIII	2-Fluoro	—	C	51.8	79–80	$C_{14}H_{10}FNO_2$	69.12	69.12
XXIX	4-Hydroxy	—	F	33.2	144.5–147	$C_{14}H_{11}NO_3$	69.94	69.71

[a] Recrystallized from ethanol or acetic acid. [b] A = 5–30 min.; B = 2–7 hours; C = overnight; D = over weekend; E = 1 min. at 125°; F = 1 week. [c] With one exception yields are of purified product. [d] Determined in a Townson and Mercer Mark 4 melting point apparatus. [e] Schiff's base made with *n*-propylamine.

In view of the above, an attempt was made to condense IV with benzalbutylamine in methanol using butylammonium acetate as catalyst. No crystalline product could be isolated.

The reaction between benzaldehyde, IV and one equivalent of butylammonium acetate in acetic acid was very slow. Crystallization could not be induced (seeding) after 3 hr. and 20 hr. were required to obtain a 53.7% yield. Benzalbutylamine and IV in acetic acid began to deposit crystals (on seeding) after 30 min. and a yield of 60.8% was obtained in only 2 hr. A commercial grade of IV was used in these two reactions which probably accounts for the lower yields (compare XXX in Table II).

Raiford and Fox[8] used the system ammonium-acetate–acetic acid for the condensation of aromatic aldehydes with nitroalkanes to form β-nitrostyrenes, a method which bears some resemblance to the Schiff's base method of the present report. As commonly carried out, however, the method of Raiford and Fox often gives tars and low yields and seems to work best for hydroxy and alkoxy benzaldehydes. It was not satisfactory for the preparation of α-nitrostilbenes.

The method of Heinzelmann[9] for nitrostyrenes, wherein the condensation of a primary nitroparaffin with an aromatic aldehyde is carried out in an inert solvent and the water of reaction is removed azeotropically, likewise was not satisfactory for α-nitrostilbenes.

Adaptation of the Schiff's base method to the preparation of β-nitrostyrenes was not extensively investigated, although it has given good results in some cases[10] where the usual alkali hydroxide or amine catalyzed condensations were unsatisfactory and spectroscopic evidence (infrared) suggests that it may be widely applicable.

The Schiff's bases are conveniently formed by reaction of equimolar amounts of the appropriate aldehyde and amine in benzene solution, (200–500 ml. per mole of reactants) the water of reaction being removed by azeotropic distillation. In practice, it has been found best to remove the sol-

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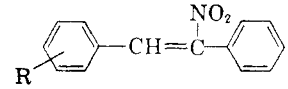
(8) L. C. Raiford and D. E. Fox, *J. Org. Chem.*, 9, 170 (1944).

(9) R. V. Heinzelmann, U. S. Patent 2,601,282 (June 24, 1952).

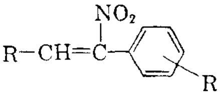
(10) D. N. Robertson, U. S. Patent 2,855,429 (October 7, 1958).

TABLE II

COMPARATIVE YIELDS: LITERATURE VS. SCHIFF'S BASE METHOD



		Literature			Via Schiff's Base		
	R[a]	Yield, %	Time, Hr.	M.P.	Yield,[b] %	Time, Hr.	M.P., °C.[c]
XXX	H[d]	60–70	8 days	75	88	88	73–74
					80.4	2	73–74
XXXI	2-Methoxy[e]	85	15	117.5–119	74	0.5	117.5–118
XXXII	4-Methoxy[d]	85	8 days	151	74.5	0.5	153
XXXIII	3,4-Dimethoxy[f]	Quant.	7 days	109	58.2	20	107–108
XXXIV	3,4-Methylenedioxy[d]	82	8 days	124	63.2	2	129–129.5
XXXV	3-Methoxy-4-hydroxy[g]	24	2–4 days	124.8–125.5	24.3	14 days	124–125
XXXVI	2-Methyl[h]	Not given	Not given	99	56.3	20	98.5–99.5
XXXVII	4-Methyl[h]	85	3–5 days	79	83.7	0.5	73–75.5
XXXVIII	2-Nitro[i]	21.5	72	106	45.2	0.5	101.5–102.5
XXXIX	3-Nitro[j]	7.5	96	112	71.8	20	112.8–113.8
XL	4-Nitro[k]	Not given	24	155	64.8	2.5	159.3–159.8



	R	R[l]	Yield, %	Time, Hr.	M.P.	Yield,[b] %	Time, Hr.	M.P., °C.[c]
XLI	2-Furfuryl[l]	—	93 (crude)	72	87–87.5	81.3	0.25	87.5–88
XLII	2-Thienyl[j]	—	32.3	3	123	81.4	2	126.5–127
XLIII	2-Furfuryl[j]	2-Chloro	34.9	72	101.1	82.4	0.2	103–104

[a] Recrystallized from ethanol or acetic acid. [b] Yields are of purified product. [c] Determined in Townson and Mercer Mark 4 melting point apparatus. [d] E. Knoevenagel and L. Walter, *Ber.*, **37**, 4508 (1904). [e] W. D. McPhee, E. S. Erickson, Jr., U. J. Salvador, *J. Am. Chem. Soc.*, **68**, 1866 (1946). [f] H. Kaufmann, *Ber.*, **52**, 1431 (1919). [g] R. Stewart and R. H. Clark, *Can. J. Res.*, **26B**, 7 (1948). [h] J. Meisenheimer, *et al.*, *Ann.*, **468**, 222 (1929). [i] P. Ruggli and B. Hegedus, *Helv. Chim. Acta*, **22**, 405 (1939). [j] C. T. Bahner, H. E. Dickson and L. Moore, *J. Am. Chem. Soc.*, **70**, 1982 (1948). [k] J. W. Baker and I. S. Wilson, *J. Chem. Soc.*, 844 (1927). [l] B. Reichert and W. Kuhn, *Ber.*, **74B**, 328 (1941).

vent prior to the next step in order to facilitate the work-up. It is not necessary to purify the Schiff's base, which may be poured directly into a solution of IV in glacial acetic acid (250 ml. per mol of IV is a convenient quantity). Although 0.5 to 2 hr. is usually sufficient reaction time (see Tables I and II), allowing the reaction to proceed overnight or even longer may give slightly higher yields (see Example XXX). Low yields and long reaction times were encountered only with the hydroxybenzaldehydes (XXIX and XXXV).

Room temperature is usually preferred. Lower yields were encountered in two experiments in which the reactants were brought to the boiling point and immediately quenched by pouring over crushed ice. In one instance, however, good results were obtained by a one minute reaction time at 125° (XXI).

Because of its availability, *n*-butylamine was used almost exclusively. A Schiff's base with *n*-propylamine was used once as a check and gave slightly better results under the same conditions (XI).

The presence of ethanol in the reaction mixture is definitely detrimental. In one preparation of XI a little alcohol was added to the reaction mixture and the yield was reduced (26.5%). A lower than average yield of XXXVIII was obtained and here again ethanol had been added during the reaction. The products, however, are stable in both ethanol and acetic acid, the preferred solvents for recrystallization.

EXPERIMENTAL

Schiff's bases. General procedure. A solution of 0.1 mol. each of an aromatic aldehyde and *n*-butylamine in 20–50 ml. of benzene in a 100 ml. round bottom flask is attached to a water separator (a modified Dean and Stark moisture trap) and refluxed until the theoretical amount of water has been collected (15 to 30 min.). The solvent is then removed by distillation, finally under aspirator pressure. The crude Schiff's base may be used directly in the next step.

α-Nitrostilbenes. General procedure. To a solution of 0.1 mol. of phenylnitromethane in 25 ml. of glacial acetic acid is added 0.1 mol. of the appropriate Schiff's base. The clear homogeneous mixture is allowed to stand at room temperature. If crystallization has not begun within 0.5 hr., a drop of the mixture is added to a little water in a watch crystal and scratched with a glass rod to obtain seed crystals. If this procedure fails, the mixture is allowed to stand overnight and another attempt is then made. When crystallization is complete, the solid is filtered, washed with water and recrystallized from ethanol or acetic acid. Alternatively, the reaction mixture may be poured into ice water to obtain the product.

In only two cases (XXIX and XXXV) are reaction times longer than overnight necessary.

MIDLAND, MICH.