[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

The Effect of Nuclear Substituents on the Ionic Reactions of Substituted Styrenes. I. The Reaction of Active Methylene Compounds with *o*-, *m*- and *p*-Nitrostyrene[1,2]

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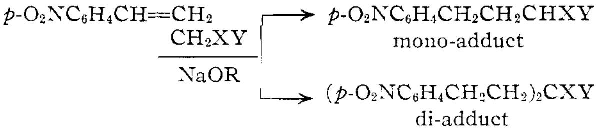
Various sodio enolates have been found to react readily in alcohol solution with *o*- and *p*-nitrostyrene to give the expected Michael-type adducts. *Under the same experimental conditions, no addition of enolates could be effected to m-nitrostyrene* or to styrene itself.

Very few data have appeared in the literature which attempt to correlate the electronic effects of ring substituents with the ionic reactions of substituted styrenes. The ionic behavior of styrene is characteristically nucleophilic and styrene does not therefore unite under ordinary conditions with such reagents as amines or metal enolates. However, when a negative group such as the nitro group is conjugated with the double bond, the unsaturated linkage assumes an electrophilic character. Thus, Hass and Bender[3] treated 2-nitropropane with *p*-nitrostyrene in methanolic sodium methoxide solution and obtained the expected adduct, 3-methyl-3-nitro-1-(*p*-nitrophenyl)-butane in 72% yield. Also, Bjork and co-workers[4] have observed that 2,4,6-trinitrostyrene is unreactive toward bromine in carbon tetrachloride solution but combines readily with ammonia in anhydrous ether to form bis-(2,4,6-trinitro-β-phenylethyl)-amine. Furthermore, Eliel, Goldkamp and Carosino[5] have found that *p*-nitrostyrene unites with hydrogen bromide only with difficulty, requiring aluminum bromide as catalyst.

The *m*- and *p*-nitrostyrenes used in this study were prepared by methods already described in the literature. A procedure was developed to obtain the *ortho* isomer as a by-product from the preparation of the *para* isomer.

In this research, various active methylene compounds have been added to *o*- and *p*-nitrostyrene at reflux temperatures using sodium alkoxide as catalyst and a mole ratio of addendum to acceptor of 1.5. Under these conditions, no addition of enolates could be effected to *m*-nitrostyrene or to styrene itself.

The reactions provided two types of products, which incorporate either one or two equivalents of nitrostyrene.



$$p\text{-}O_2NC_6H_4CH{=}CH_2 \xrightarrow[\text{NaOR}]{CH_2XY} \begin{cases} p\text{-}O_2NC_6H_4CH_2CH_2CHXY & \text{mono-adduct} \\ (p\text{-}O_2NC_6H_4CH_2CH_2)_2CXY & \text{di-adduct} \end{cases}$$

The yields and physical characteristics of the products are given in Tables I and II.

Both mono and di-addition products were obtained from reactions of *p*-nitrostyrene with the malonic and acetoacetic esters. However, with methyl and ethyl cyanoacetate and also with cyanoacetamide, high yields of di-addition adducts were obtained, but no mono products were isolated.

In the case of *o*-nitrostyrene, only the mono type of addition product was obtained, with one exception; cyanoacetamide gave a 42% yield of the di adduct but no mono product was isolated from the reaction mixture. A careful analysis of the product from the reaction of *o*-nitrostyrene with methyl malonate yielded only 2% of the di adduct.

Concentration experiments were performed to test the effect of varying amounts of addenda with a given amount of acceptor. With *p*-nitrostyrene, when the ratio of ethyl malonate to acceptor was varied from 0.5 to 3.0, the yield of mono addition product was increased from 19 to 42% and the yield of di addition product was decreased from 31 to 15%. In the case of *o*-nitrostyrene, the same variation in the ratio of ethyl malonate to acceptor increased the yield from 21 to 70% of the mono addition product, but no di addition product could be isolated at either extreme of the addendum concentration. However, when equimolar amounts of ethyl β-(*o*-nitrophenyl)-ethylmalonate and *o*-nitrostyrene were refluxed in ethanol for 13 hours with sodium ethoxide as catalyst, 39% of the expected di adduct was obtained.

The reaction of *p*-nitrostyrene with acetylacetone proceeded in an unexpected manner. Instead of the usual mono or di adduct, there resulted a 34% yield of 5-(*p*-nitrophenyl)-2-pentanone. No other products were isolated. This monoketone presumably resulted from addition of the enolate to *p*-nitrostyrene followed by cleavage of the diketone.

Similar results were obtained with active methylene compounds containing the benzoyl grouping. When ethyl benzoylacetate reacted with *p*-nitrostyrene under conditions similar to those of the other Michael reactions, there was obtained an unidentified oil and 19% of a white solid which proved to be 4-(*p*-nitrophenyl)-1-phenyl-1-butanone. With benzoylacetone, an unidentified oil of a similar boiling range was obtained together with 21% of the same ketone which resulted from the above reaction. With dibenzoylmethane the identical ketone was again isolated in 21% yield but in this experiment an amount of acetophenone was obtained which represented 75% of the theoretical.

The white solid obtained from the above three experiments was the same product which would have resulted from the successful Michael-type

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[1] Based on a thesis submitted by C. W. S. to the Graduate School of the University of Missouri in partial fulfillment of the requirements for the M.A. degree.

[2] Presented in part before the Division of Organic Chemistry at the Chicago, Illinois, Meeting of the American Chemical Society, September, 1953.

[3] H. B. Hass and M. L. Bender, THIS JOURNAL, **71**, 3482 (1949).

[4] C. F. Bjork, W. A. Gey, J. H. Robson and R. W. VanDolah, *ibid.*, **75**, 1988 (1953).

[5] E. L. Eliel, A. H. Goldkamp and L. E. Carosino, Abstracts of papers presented to the Division of Organic Chemistry at the Buffalo, New York, Meeting of the American Chemical Society, March, 1952.

TABLE I

PRODUCTS OF THE CONDENSATION OF ACTIVE METHYLENE COMPOUNDS WITH *o*-NITROSTYRENE

Addendum	Type of adduct	M.p. or b.p., °C.	$n^{20}\mathrm{D}$	Yield, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Ethyl malonate	Mono[a]	205–210 (1 mm.)	1.5053	72	58.24	58.14	6.16	6.29
Methyl malonate	Mono	200–205 (1 mm.)	1.5200	49	55.51	55.45	5.38	5.56
	Di	117–118		2	58.60	58.30	5.15	5.37
Ethyl acetoacetate	Mono[a]	195–200 (1 mm.)	1.5221	42	60.20	60.41	6.14	6.35
Methyl acetoacetate	Mono[a]	200–205 (1 mm.)	1.5325	32	58.86	59.19	5.70	5.97
Ethyl cyanoacetate	Mono[a]	(Hickman still)	....	78	59.53	58.96	5.38	5.53
Methyl cyanoacetate	Mono[a]	(Hickman still)	....	69	58.06	59.12	4.87	5.18
Cyanoacetamide	Di[b]	157–158		42	59.68	59.40	4.75	4.74
Ethyl ethylmalonate	Mono	190–194 (1 mm.)	1.5020	44	60.52	60.66	6.87	7.07
Ethyl *n*-butylacetoacetate	Mono	190–195 (1 mm.)	1.5108	61	64.46	64.50	7.51	7.70

[a] No di product could be isolated. [b] No mono product could be isolated.

TABLE II

PRODUCTS OF THE CONDENSATION OF ACTIVE METHYLENE COMPOUNDS WITH *p*-NITROSTYRENE

Addendum	Type of adduct	M.p. or b.p., °C.	$n^{20}\mathrm{D}$	Yield, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Ethyl malonate	Mono	180–184 (1 mm.)	1.5092	45	58.24	57.95	6.16	6.21
	Di	135–135.5		34	60.25	60.09	5.72	6.03
Methyl malonate	Mono	200–204 (1 mm.)	1.5244	43	55.51	55.33	5.38	5.57
	Di	136.5–137		32	58.60	58.62	5.15	5.36
Ethyl acetoacetate	Mono	190–195 (1 mm.)	1.5244	47	60.20	60.29	6.14	6.29
	Di	107–108		19	61.67	61.69	5.65	5.63
Methyl acetoacetate	Mono	195–199 (1 mm.)	1.5333	38	58.86	58.69	5.70	5.98
	Di	142–143		24	60.86	60.60	5.35	5.13
Ethyl cyanoacetate	Di[a]	101.5–102		80	61.37	61.37	5.15	5.28
Methyl cyanoacetate	Di[a]	146–147		79	60.45	60.80	4.82	5.08
Cyanoacetamide	Di[a]	160–160.5		73	59.68	59.45	4.75	4.56
Ethyl ethylmalonate	Mono	168–169		56	60.52	60.78	6.87	7.03
Ethyl *n*-butylacetoacetate	Mono	195–200 (1 mm.)	1.5082	57	64.46	64.91	7.51	7.67
Malononitrile	Di[a]	173–174		36	62.63	63.02	4.43	4.82

[a] No mono product could be isolated.

condensation of acetophenone with *p*-nitrostyrene. Since the attempted reaction of acetophenone with *p*-nitrostyrene under the conditions of these Michael reactions gave no definite products, it was concluded that the 4-(*p*-nitrophenyl)-1-phenyl-1-butanone resulted from a Michael addition of the parent addendum to the *p*-nitrostyrene, followed by favorable cleavages of the primary adducts to give the monoketone.

Other studies are in process on the effect of nuclear substituents on the course of the ionic reactions of a variety of substituted styrenes, using reagents of both electrophilic and nucleophilic character.

Experimental

All melting points and boiling points are uncorrected.

Preparation of β-(*p*-Nitrophenyl)-ethyl Bromide and β-(*o*-Nitrophenyl)-ethyl Bromide.—β-(*p*-Nitrophenyl)-ethyl bromide was obtained in 56% yield by the method of Foreman and McElvain.[6] After separation of the crystalline *para* isomer, the mother liquors yielded 35% of β-(*o*-nitrophenyl)-ethyl bromide, b.p. 138–142° (2 mm.). These isomeric nitrobromides were used without further purification for the preparation of *o*- and *p*-nitrostyrene. It was found that the reaction time for the nitration of β-phenylethyl bromide could be reduced to 45 minutes by the addition of small pieces of Dry Ice to the reaction mixture during the addition of both nitric acid and β-phenylethyl bromide. The yields of the nitration products and of the related nitrostyrenes were comparable to those obtained with the slower method of nitration.

Great care was observed in the distillation of these nitrophenylethyl bromides and the nitrostyrenes derived from them. On several occasions, prolonged heating during slow fractionation, localized heating with a hot coil, or distillation to small residues resulted in explosions.

Preparation of *p*-Nitrostyrene.—*p*-Nitrostyrene was prepared in 81% yield by the method of Strassburg, Gregg and Walling[7] and was used without further purification for the reactions of *p*-nitrostyrene described below.

Preparation of *o*-Nitrostyrene.—Using a method similar to the above preparation of *p*-nitrostyrene, *o*-nitrostyrene was prepared in 65% yield from β-(*o*-nitrophenyl)-ethyl bromide, b.p. 90–93° (1 mm.). Since the crude product was contaminated only with *p*-nitrostyrene, the composition of the mixture was calculated from ultraviolet absorption spectra at the peak of the *para* curve, 290 mμ. The crude *o*-nitrostyrene proved to contain 8.8% of the *para* isomer. *o*-Nitrostyrene of this purity was used generally for the experiments described below. Attempts to purify the *ortho* isomer further by careful fractionation resulted in explosive decomposition.

Preparation of *m*-Nitrostyrene.—The procedure of Wiley and Smith[8] was used with modification. Into a 500-ml., three-necked, round-bottomed flask, equipped with a reflux condenser and stirrer, were placed 150 ml. of quinoline, 40 g. (0.235 mole) of *m*-nitrocinnamic acid and 1 g. of hydroquinone. The mixture was heated until solution of the acid was complete. Six grams of copper powder was then added and the solution was heated for five hours at 215–220° with vigorous stirring. The reaction solution was

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[6] E. L. Foreman and S. M. McElvain, THIS JOURNAL, **62**, 1435 (1940).

[7] R. W. Strassburg, R. A. Gregg and C. Walling, *ibid.*, **69**, 2141 (1947).

[8] R. H. Wiley and N. R. Smith, *ibid.*, **70**, 2295 (1948).

acidified with 580 ml. of 3 *N* hydrochloric acid and the *m*-nitrostyrene was removed by steam distillation. A total of 15.5 g. (51%) of *m*-nitrostyrene was obtained, b.p., 85–90° (1 mm.).

Reaction of Enolates with Nitrostyrenes.—The reactions of the active methylene compounds with the nitrostyrenes were all performed in a similar manner. The following example is typical of the whole series.

Reaction of *p*-Nitrostyrene with Ethyl Malonate.—To 100 ml. of absolute ethanol, 0.75 g. (0.033 mole) of clean sodium metal was added. When solution was complete, 25.0 g. (0.15 mole) of ethyl malonate was added, followed by 14.9 g. (0.10 mole) of *p*-nitrostyrene, containing 0.5% hydroquinone. The resulting solution was refluxed for six hours and then allowed to remain overnight at room temperature. The solution was poured into a beaker containing 4 ml. of concentrated hydrochloric acid in 1-l. of water. The product was extracted with ether and the ether extract was washed with water. The extracts were dried over anhydrous sodium sulfate and the solvent removed by distillation. The last traces were removed under vacuum, which caused a small amount of crystalline solid to separate. With the addition of ethanol (50 ml.) and cooling, more of the solid separated. A total of 7.8 g. (34%) of solid (di-addition product) was obtained, m.p., 135–135.5°.

The oil obtained from the above filtrate was distilled. There was obtained 14.1 g. (45%) of a light yellow oil (mono-addition product); b.p. 180–184° (1 mm.).

Reaction of β-(*p*-Nitrophenyl)-ethyl Bromide with Ethyl Malonate.—Ethyl malonate was alkylated with β-(*p*-nitrophenyl)-ethyl bromide using equivalent amounts of reactants and sodium ethoxide in ethanol. A white solid was obtained in 13% yield which was identical with the di addition product obtained from the above reaction of *p*-nitrostyrene with ethyl malonate.

Reaction of *o*-Nitrostyrene with Ethyl β-(*o*-Nitrophenyl)-ethylmalonate.—To 38 ml. of absolute ethanol was added 0.25 g. (0.011 mole) of sodium metal. After reaction was complete, 15.5 g. (0.05 mole) of ethyl β-(*o*-nitrophenyl)-ethylmalonate and 7.5 g. (0.05 mole) of *p*-nitrostyrene were added. The resulting solution was refluxed for 13 hours. The reaction yielded 9.0 g. (39%) of the di-addition product, m.p. 100–101°.

Anal. Calcd. for $C_{23}H_{26}O_8N$: C, 60.25; H, 5.72. Found: C, 59.96; H, 5.86.

Reaction of *p*-Nitrostyrene with Acetylacetone.—To 75 ml. of ethanol was added 0.75 g. (0.033 mole) of sodium. After the reaction was complete 15.0 g. (0.15 mole) of acetylacetone and 14.9 g. (0.10 mole) of *p*-nitrostyrene were added. The resulting solution was refluxed for 12 hours and then allowed to remain overnight at room temperature. The reaction product, isolated as described above, was fractionated under reduced pressure. Five grams of the original *p*-nitrostyrene was recovered together with 7.0 g. (34%) of an orange oil, 5-(*p*-nitrophenyl)-2-pentanone, b.p. 180–184° (1 mm.), $n^{20}\text{D}$ 1.5391.

Anal. Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32. Found: C, 63.49; H, 6.31.

The semicarbazone of the above compound was prepared and recrystallized from ethanol, m.p. 175–176°.

Anal. Calcd. for $C_{12}H_{16}O_3N_4$: C, 54.55; H, 6.10. Found: C, 54.31; H, 6.27.

Reaction of *p*-Nitrostyrene with Ethyl Benzoylacetate, Benzoylacetone and Dibenzoylmethane.—To 75 ml. of absolute ethanol was added 0.75 g. (0.033 mole) of sodium. When the reaction was complete 28.8 g. (0.15 mole) of ethyl benzoylacetate and 14.9 g. (0.10 mole) of *p*-nitrostyrene were added and the resulting solution was refluxed for nine hours. The reaction product yielded 8.0 g. of an unidentified oil, b.p. 150–160° (1 mm.), and 5.0 g. (19%) of a white solid, 4-(*p*-nitrophenyl)-1-phenyl-1-butanone, m.p. 109–110°.

Anal. Calcd. for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61. Found: C, 71.48; H, 5.70.

The semicarbazone of the 4-(*p*-nitrophenyl)-1-phenyl-1-butanone was prepared and recrystallized from ethanol, m.p. 205–205.5°.

Anal. Calcd. for $C_{16}H_{16}O_3N_4$: C, 62.56; H, 5.56. Found: C, 62.44; H, 5.66.

When the above reaction was performed using 24.3 g. (0.15 mole) of benzoylacetone instead of ethyl benzoylacetate, there was obtained 5.5 g. (21%) of 4-(*p*-nitrophenyl)-1-phenyl-1-butanone, 6.0 g. of the original *p*-nitrostyrene and 3.5 g. of an unidentified oil, b.p. 155–160° (1 mm.). However, when dibenzoylmethane (33.6 g., 0.15 mole) was used under the same reaction conditions, 5.6 g. (21%) of 4-(*p*-nitrophenyl)-1-phenyl-1-butanone was isolated together with 6.0 g. of unchanged *p*-nitrostyrene and 13.5 g. (75%) of acetophenone (b.p. 65–70° (1 mm.); semicarbazone, m.p. 197–198°; phenylhydrazone, m.p. 104–105°).

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Disproportionative Condensations. II. The N-Alkylation of Anilines with Primary Alcohols

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Benzyl alcohol has been found to condense readily with aniline in the presence of potassium benzylate and U.O.P. nickel[2] to give N-benzylaniline. With *para*-substituted benzyl alcohols the reaction rate decreased with decreasing ability of the substituent to release electrons in the order $(CH_3)_2N$, CH_3O, CH_3, H, Cl. The reverse order was obtained when *para*-substituted anilines were condensed with benzyl alcohol. The products were isolated as the pure hydrochlorides in 80 to 90% yields. *p*-Nitroaniline with benzyl alcohol gave *p,p'*-dibenzalaminoazobenzene in 50% yield while cyclohexylamine gave a 49% yield of N-benzalcyclohexylamine. Primary aliphatic alcohols react satisfactorily as exemplified by the 70 to 80% yields of N-*n*-alkylanilines obtained from *n*-hexyl and *n*-decyl alcohols. A reaction course is proposed and evaluated.

Exploratory experiments on the attempted extension of the Guerbet condensation, the subject of the first paper of this series,[3] to the condensation of an alcohol with an amine showed that benzyl alcohol readily condensed with aniline in the presence of potassium benzylate and U.O.P. nickel[2] to give high yields of N-benzylaniline.

$$C_6H_5CH_2OH + C_6H_5NH_2 \longrightarrow C_6H_5CH_2NHC_6H_5 + H_2O \quad (1)$$

In Table I are shown the effects of varying the amount of benzyl alcohol. A xylene solution of the specified amount of benzyl alcohol was treated with 0.04 mole of potassium; 0.125 mole of aniline and 1.0 g. of U.O.P. nickel were then added and the mixture was heated under reflux in an apparatus equipped with a Dean–Stark trap until water evolution was complete. Extraction of an ether solu-

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[1] From the Ph.D. thesis of E. J. Frazza, Feb., 1954.

[2] National Institutes of Health Fellow, 1952–1954.

[3] E. F. Pratt and D. G. Kubler, THIS JOURNAL, **76**, 52 (1954).