523. *The Characterisation of Diazo-ketones.*

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ω-Diazo-4-nitroacetophenone and toluene-*p*-sulphonic acid monohydrate react more readily in acetonitrile, acetic anhydride, or acetic acid than in solvents previously employed. Diazo-ketones are satisfactorily characterised by treatment with toluene-*p*-sulphonic acid monohydrate in acetic anhydride, whereby high yields of toluene-*p*-sulphonates are obtained and nitrogen is quantitatively evolved.

According to Reichstein and Schindler,[1] α-toluene-*p*-sulphonyloxy-ketones are obtained by heating a benzene solution of anhydrous toluene-*p*-sulphonic acid and steroidal ω-diazo-ketones at 40—45° for 10 minutes, and Sumner, Ball, and Platner [2] reported the reaction of 4-bromo-ω-diazoacetophenone with various sulphonic acids. They stated that there was no appreciable reaction of the free sulphonic acid with the diazo-ketone in dioxan until a catalytic amount of cupric chloride was added and the mixture was heated at 60—70°. The conditions appeared to be unnecessarily drastic in both cases, since arenesulphonic acids are of the same acidic strength as hydrochloric acid [3] and the latter almost instantaneously decomposes diazo-ketones in the cold. The results of our study of the interaction of ω-diazo-4-nitroacetophenone and toluene-*p*-sulphonic acid in a variety of solvents at room temperature are listed in Table 1. The time intervals for evolution of 75% of the available nitrogen are also given.

Table 1.

Reactions of ω-diazo-4-nitroacetophenone.

	Solvent	Dielectric constant (*D*)	Time for 75% reaction (min.)	Toluene-*p*-sulphonate (%)	Other products (%)
1	H·CO$_2$H	47·9	1·5	—	72 (Formate)
2	MeCN	38·8	1·5	83	—
3	MeOH	33·7	3·5	3	67 (MeO-ketone)
4	COMe$_2$	21·4	9	82	—
5	Ac$_2$O	20·5	5·5	88	—
6	AcOH	7·1	1·5	65	—
7	Et$_2$O *	4·3	35	88	—
8	C$_6$H$_6$ *	2·3	18	70	—
9	Dioxan	2·3	35	89	—
10	Dioxan–CuCl$_2$ †	—	11	85	—
11	30% Aq. dioxan	—	16 hr.	—	56 (HO-ketone)

* Heterogeneous mixture. † Catalytic amount of CuCl$_2$.

Interaction with formation of toluene-*p*-sulphonate and nitrogen was faster in acetonitrile, acetic anhydride, and acetic acid (expts. 2, 5, and 6) than in benzene or dioxan (expts. 8 and 9). The results are consistent with the formulation: $\mathrm{R{\cdot}CO{\cdot}CH{:}N_2 + Ar{\cdot}SO_3H \rightleftharpoons R{\cdot}CO{\cdot}CH_2{\cdot}N_2^+ + Ar{\cdot}SO_3^- \longrightarrow R{\cdot}CO{\cdot}CH_2{\cdot}O{\cdot}SO_2{\cdot}Ar + N_2}$, since solvents of high dielectric constant should aid formation of the diazonium and sulphonate ions while basic solvents compete with the diazo-ketone for protonation. Further work is in hand to provide a more precise interpretation of these solvent effects.

In some instances, the toluene-*p*-sulphonate was not the major product, if indeed it was formed at all. The formation of ω-methoxy-4-nitroacetophenone exemplifies the interaction of a diazo-ketone and an alcohol under the catalytic influence of a protonic

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[1] Reichstein and Schindler, *Helv. Chim. Acta*, 1940, **23**, 669.

[2] Sumner, Ball, and Platner, *J. Org. Chem.*, 1959, **24**, 2017.

[3] Fieser and Fieser, "Organic Chemistry," George G. Harrap & Co. Ltd., London, 1953, p. 626.

acid. Previously, catalysts such as copper,[4] copper oxide,[5] and boron trifluoride[6] have been used under conditions much more drastic than ours. The methoxy-ketone was not formed *via* the toluene-*p*-sulphonate, since the latter was unchanged when heated with methanol for 3 hours. In 30% aqueous dioxan the product was the ω-hydroxy-ketone. In formic acid the reaction is almost instantaneous and the high yield of the corresponding ω-formyloxy-ketone is obtained without addition of toluenesulphonic acid. The catalytic influence of cupric chloride[2] was verified, as it decreased the time of reaction in dioxan from 50 to 15 minutes.

Our results concerning the interaction, in acetic anhydride, of toluene-*p*-sulphonic acid monohydrate with several diazo-ketones are summarised in Table 2. The high yields and melting points of most of the resulting toluene-*p*-sulphonates, the mild reaction conditions, and the short reaction time indicate that these compounds are satisfactory derivatives of diazo-ketones. Toluene-*p*-sulphonates may be characterised by reaction with pyridine, which provides yields of 1-phenacylpyridinium toluene-*p*-sulphonates considerably higher than those obtained by King and Miller.[7] Diazo-ketones are often characterised as the *p*-nitrobenzoates of the corresponding ω-hydroxy-ketones. This method, however, is not always satisfactory, as was shown by the reaction with ω-diazo-4-nitroacetophenone in acetone, when the yield of the ω-*p*-nitrobenzoate was only 35% after 47 hours' boiling, whereas toluene-*p*-sulphonic acid monohydrate in acetone gave an 88% yield of toluene-*p*-sulphonate in 13 min. at room temperature.

TABLE 2.

Formation of ω-toluene-*p*-sulphonyloxy-compounds from ω-diazo-ketones.

Product *	M. p.	Reaction time (min.)	Nitrogen evolved (%)	Yield (%)
Me·CO·CH$_2$·O·Tos	27—28°	10	Theor.	66
(·CH$_2$·CH$_2$·CO·CH$_2$·O·Tos)$_2$	121—122	1	Theor.	Theor.
Ph·CO·CH$_2$·O·Tos	99—100	2	Theor.	85
MeO·C$_6$H$_4$·CO·CH$_2$·O·Tos	118	1	Theor.	77
m-NO$_2$·C$_6$H$_4$·CO·CH$_2$·O·Tos	118	3	18	84
*p*NO$_2$·C$_6$H$_4$·CO·CH$_2$·O·Tos	142	8	Theor.	88
p-NO$_2$·C$_6$H$_4$·CO·CHMe·O·Tos......	139—141	5	82	53
Ph·CO·CHPh·O·Tos	105—106	1	Theor.	89

* Tos = *p*-C$_6$H$_4$Me·SO$_2$·.

The selectivity of the diazo-ketone reaction with sulphonic acids was demonstrated by competitive reaction of ω-diazo-4-nitroacetophenone with toluene-*p*-sulphonic acid and *p*-nitrobenzoic acid: 87% of the toluene-*p*-sulphonate was isolated and 70% of the *p*-nitrobenzoic acid was recovered as such.

Similar results were obtained when the sulphonic and carboxylic acid groups were in the same molecule. ω-Diazo-4-nitroacetophenone reacted selectively with the sulphonic acid group in both *o*- and *p*-sulphobenzoic acid, giving 80% and 76% yields, respectively. The conclusion that the sulphonic esters and not the carboxylic esters had been obtained in the reaction was based on the observation that the isomers were water-insoluble and with pyridine gave the corresponding pyridinium salts.

Hydrolysis of 4-nitro-ω-toluene-*p*-sulphonyloxyacetophenone by dilute mineral acid and the action of toluene-*p*-sulphonic acid in aqueous dioxan on ω-diazo-4-nitroacetophenone both provided high yields of ω-hydroxy-4-nitroacetophenone, m. p. 136°. According to Engler and Zielke[8] this compound has m. p. 121°. Examination of the

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[4] Yates, *J. Amer. Chem. Soc.*, 1952, **74**, 5376.

[5] Casanova and Reichstein, *Helv. Chim. Acta*, 1949, **32**, 647; 1950, **33**, 417.

[6] Newman and Beal, *J. Amer. Chem. Soc.*, 1950, **72**, 5161.

[7] King and Miller, *J. Amer. Chem. Soc.*, 1948, **70**, 4154.

[8] Engler and Zielke, *Ber.*, 1901, **22**, 204.

compound prepared by their procedure, kindly provided by Dr. A. R. Thompson and Dr. G. Whitehouse, of this Department, showed it to contain two strong infrared carbonyl bands (1748 and 1706 cm.$^{-1}$). It therefore appears that this product is *p*-nitrophenylglyoxal, resulting from oxidation of the hydroxy-ketone. The product of m. p. 136° showed only one carbonyl group, associated with one hydroxyl group. With acetyl chloride, it readily provided a material that did not depress the m. p. of authentic ω-acetoxy-4-nitroacetophenone, which on hydrolysis with 0·1% sulphuric acid also provided a product of m. p. 136°.

EXPERIMENTAL

Gaseous volumes below have been reduced to N.T.P.

Influence of Solvent on the Interaction of ω*-Diazo-4-nitroacetophenone and Toluene-*p*-sulphonic Acid Monohydrate.*—The following general procedure was used. To a stirred solution or suspension of the diazo-ketone (1·0 g., 0·0052 mole) in the selected solvent (25 ml.) at 20° was rapidly added a solution or suspension of toluene-*p*-sulphonic acid monohydrate (1·1 g., 0·0058 mole) in the same solvent (15 ml.). The volume of nitrogen evolved was measured at suitable time intervals and the time for complete reaction was noted. (Vapours of low-boiling organic solvents were removed by a trap cooled in solid carbon dioxide and methanol.) The solvent was removed under reduced pressure and the yellow residue was stirred with water (25 ml.) for about an hour. The fine yellow precipitate of the crude *4-nitro-ω-toluene-*p*-sulphonylacetophenone* (*4-nitrophenacyl toluene-*p*-sulphonate*) (Found: C, 53·6; H, 3·6; N, 4·1; S, 9·7. $C_{15}H_{13}NO_6S$ requires C, 53·7; H, 3·9; N, 4·2; S, 9·6%) was filtered off and recrystallised from methanol as cream plates, m. p. 142°. In some cases the bulk of the crude toluene-*p*-sulphonate separated from the reaction mixture and this material was filtered off before evaporation of the solvent. The results obtained are in Table 1.

In some instances, solvent intervened with the following results:

(1) *Methanol.* The reaction mixture was left at 0° overnight, and the yellow needles (A), m. p. 116—118°, were filtered off. The filtrate was concentrated to about half volume under reduced pressure, and the solid (B), m. p. 109—113°, was filtered off. The filtrate was then evaporated to dryness, under reduced pressure, and the solid residue was stirred with water (25 ml.) for 1 hr. and filtered off [solid (C); m. p. 98—112°]; 70% of the original toluene-*p*-sulphonic acid was present in this aqueous filtrate. Solid B, on crystallisation from ethanol, provided 4-nitro-ω-toluene-*p*-sulphonyloxyacetophenone (3%), m. p. and mixed m. p. 142°. Solids A and C, on recrystallisation from ethanol, provided light yellow needles (total yield 67%) of *ω-methoxy-4-nitroacetophenone*, m. p. 118—119° (Found: C, 55·7; H, 4·5; N, 7·2. $C_9H_9NO_4$ requires C, 55·4; H, 4·6; N, 7·2%) [*2,4-dinitrophenylhydrazone* (80%), orange needles (from ethyl acetate), m. p. 255—256° (decomp.) (Found: N, 18·7. $C_{15}H_{13}N_5O_7$ requires N, 18·7%)]. When the experiment was repeated with the diazo-ketone (1·03 g., 0·0054 mole) and only a catalytic amount of toluene-*p*-sulphonic acid monohydrate (0·23 g.), the reaction time increased to 45 min. The yield of ω-methoxy-4-nitroacetophenone increased to 78%, but 3% of the toluene-*p*-sulphonate was still obtained and the aqueous filtrate contained 59% of the initial amount of toluene-*p*-sulphonic acid.

(2) *Aqueous dioxan.* After 24 hr. at room temperature, the reaction mixture was boiled for 1 hr. and concentrated to 5 ml. The residue was stirred with water (25 ml.), and the solid product was separated and crystallised from ethanol, to provide *ω-hydroxy-4-nitroacetophenone* as brownish needles (56%), m. p. 136° (Found: C, 53·1; H, 3·9; N, 7·8. $C_8H_7NO_4$ requires C, 53·0; H, 3·9; N, 7·7%). 87% of the toluene-*p*-sulphonic acid was present in the aqueous filtrate.

(3) *Formic acid.* When 98—100% formic acid was added to ω-diazo-4-nitroacetophenone, the latter was completely decomposed in 2 min., without the addition of toluene-*p*-sulphonic acid. Removal of the excess of formic acid under reduced pressure, and crystallisation of the residue from ethanol, provided *ω-formyloxy-4-nitroacetophenone* (76%) as straw-coloured needles, m. p. 99·5—100·5° (Found: C, 51·5; H, 3·5; N, 6·7. $C_9H_7NO_5$ requires C, 51·7; H, 3·4; N, 6·7%).

The general procedure for the interaction of ω-diazo-ketones and toluene-*p*-sulphonic acid monohydrate was similar to that described above for ω-diazo-4-nitroacetophenone, but in all instances acetic anhydride was used as solvent. The following products are new: *ω-toluene-*p-*sulphonyloxyacetone* (Found: S, 14·2. $C_{10}H_{12}O_4S$ requires S, 14·05%); *1,8-ditoluene-*p-*sulphonyloxyoctane-2,7-dione* (Found: S, 13·2. $C_{22}H_{26}O_8S_2$ requires S, 13·3%); *phenacyl* (Found: S, 11·2. $C_{10}H_{14}O_4S$ requires S, 11·05%), *4-methoxyphenacyl* (Found: S, 9·9. $C_{16}H_{16}O_5S$ requires S, 10·0%), and *3-nitrophenacyl toluene-*p-*sulphonate* (Found: S, 9·6. $C_{15}H_{13}O_6NS$ requires S, 9·6%); *4-nitro-ω-toluene-*p-*sulphonyloxypropiophenone* (Found: S, 9·2. $C_{16}H_{15}O_6NS$ requires S, 9·2%); *benzoin toluene-*p-*sulphonate* (Found: S, 8·9. $C_{21}H_{18}O_4S$ requires 8·75%). Other details are in Table 2.

*4-Nitro-ω-*p-*nitrobenzoyloxyacetophenone.*—The reaction between ω-diazo-4-nitroacetophenone and *p*-nitrobenzoic acid in boiling acetone, according to the procedure of Bradley and Schwarzenbach,[9] took 47 hr. to complete and yielded *4-nitro-ω-*p-*nitrobenzoyloxyacetophenone* (35%) as yellow plates, m. p. 177—178° (from ethanol) (Found: C, 54·6; H, 3·4; N, 9·0. $C_{15}H_{10}N_2O_7$ requires C, 54·6; H, 3·1; N, 8·5%).

*Interaction of ω-Diazo-4-nitroacetophenone and Toluene-*p-*sulphonic Acid Monohydrate in the Presence of* p-*Nitrobenzoic Acid.*—To a stirred solution of *p*-nitrobenzoic acid (1·05 g.) and the diazo-ketone (0·83 g.) in acetic anhydride (50 ml.), was added a solution of toluene-*p*-sulphonic acid monohydrate (0·93 g.) in acetic anhydride (10 ml.), at such a rate that a continuous gas evolution was obtained. After 35 min., nitrogen (90 ml., 94%) had been evolved. Removal of the acetic anhydride under reduced pressure and treatment of the residue with sodium carbonate solution provided *p*-nitrobenzoic acid (0·73 g., m. p. and mixed m. p. 239°) and 4-nitro-ω-toluene-*p*-sulphonyloxyacetophenone (1·27 g.), m. p. and mixed m. p. 142°.

Interaction of ω-Diazo-4-nitroacetophenone and p- *and* o-*Sulphobenzoic Acid.*—*p*-Sulphobenzoic acid (1·25 g.) in acetonitrile (50 ml.) was added to the diazo-ketone (1·14 g.) in acetonitrile (25 ml.). The theoretical volume of nitrogen was evolved in 3 min. and there resulted *ω-*p-*carboxybenzenesulphonyloxy-4-nitroacetophenone* (*4-nitrophenacyl-*p-*carboxybenzenesulphonate*) (70%), m. p. 231—232° (from aqueous acetone) (Found: S, 8·8. $C_{15}H_{11}NO_8S$ requires S, 8·8%). The latter, with an excess of pyridine at 60°, rapidly provided a quantitative yield of *1-4′-nitrophenacylpyridinium* p-*carboxybenzenesulphonate*, m. p. 243—244°, white needles from aqueous ethanol (Found: N, 6·3. $C_{20}H_{16}N_2O_8S$ requires N, 6·3%). When *o*-sulphobenzoic acid was used reaction was very slow (85% of the theoretical volume of nitrogen in 30 hr.). The expected sulphonate could not be obtained crystalline but with pyridine provided *1-4′-nitrophenacylpyridinium* o-*carboxybenzenesulphonate*, m. p. 214—215° (from aqueous ethanol) (Found: N, 6·3%).

ω-Hydroxy-4-nitroacetophenone.—When 4-nitro-ω-toluene-*p*-sulphonyloxyacetophenone (2·0 g.) was heated under reflux with 33% aqueous dioxan (120 ml.) for 17½ hr., there resulted ω-hydroxy-4-nitroacetophenone (47%), m. p. 136° (from carbon tetrachloride). This material proved identical with that obtained by the hydrolysis[10] of ω-acetoxy-4-nitroacetophenone with 0·1% sulphuric acid. Further, the hydroxy-ketone, with acetyl chloride, provided an acetate, yellow needles, m. p. 122—123°, which did not depress the m. p. of the authentic acetate.

Microanalyses were carried out by Mr. V. Manohin.

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[9] Bradley and Schwarzenbach, *J.*, 1928, 2904.

[10] Thompson and Whitehouse, private communication.