124. *The Synthesis of Some* p-*Arylsulphonylbenzaldehydes and Related Aldehydes and Ketones.*

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Representative *p*-arylsulphonylbenzaldehydes were obtained by the route, $Ar{\cdot}SO_2{\cdot}C_6H_4Me \longrightarrow Ar{\cdot}SO_2{\cdot}C_6H_4{\cdot}CH(OAc)_2 \longrightarrow Ar{\cdot}SO_2{\cdot}C_6H_4{\cdot}CHO$, provided that the group Ar was not susceptible to oxidation by chromic oxide. Related aldehydes and ketones were prepared by standard methods. Phenyl thiolacetate, PhSAc, did not undergo the Fries rearrangement or the Friedel–Crafts reaction, but the latter method was successful with thioanisole.

In connection with an investigation which we are carrying out on the synthesis of various diaryl sulphones of possible chemotherapeutic interest, we required various *p*-arylsulphonylbenzaldehydes as intermediates. An obvious route was by way of the *p*-arylsulphonylbenzonitriles, since Fuller, Tonkin, and Walker (*J.*, 1945, 633) have shown that *p*-methylsulphonylbenzaldehyde was readily obtained from *p*-methylsulphonylbenzonitrile by Stephen's method (*J.*, 1925, **127**, 1874). The preparation of *p*-arylsulphonylbenzonitriles was not readily accomplished by the methods we investigated. Thus, attempted condensation of various aryl iodides with sodium *p*-cyanobenzenesulphinate was not successful. A possible alternative route, as exemplified by the reaction between resorcinol dimethyl ether and *p*-cyanobenzenesulphonyl chloride in the presence of zinc chloride (Burton and Hoggarth, *J.*, 1945, 14), was studied, but the product was not homogeneous.

Since many *p*-tolyl aryl sulphones can be prepared simply and, according to the nature of the aryl group, in fairly good yield, we decided to investigate an alternative method, namely, the oxidation by chromic oxide in an acetic acid–acetic anhydride–sulphuric acid medium. This procedure is known (Liebermann and Connor, *Org. Synth.*, Coll. Vol., II, 1943, 441) to work well for substituted toluenes provided that these do not contain a group susceptible to oxidation. Application of this method to phenyl, p-*chlorophenyl*, p-*methoxyphenyl*, and 3 : 4-*dimethoxyphenyl* p-*tolyl sulphones* has given the corresponding p-*phenyl*-, 4-p-*chlorophenyl*-, and 4-p-*methoxyphenylbenzaldehydes* in yields of 60, 71, and 10%, respectively, but no 4-3′ : 4′-dimethoxyphenylbenzaldehyde. This aldehyde was not obtained nor was the yield of anisyl analogue improved by using chromyl chloride as the oxidising agent. The results with the methoxyl compounds were not unexpected, since the methoxylated aryl group must be more susceptible to oxidative rupture than either phenyl or *p*-chlorophenyl. *p*-Phenylsulphonylbenzaldehyde was also obtained from *p*-phenylsulphonyl-benzonitrile or -benzanilide by direct reduction or reduction of the corresponding imino-chloride by ethereal stannous chloride–hydrogen chloride.

A moderate yield of p-*sulphamylbenzaldehyde* can also be obtained by the above chromic oxide oxidation of *p*-toluenesulphonamide; a better procedure was to apply Stephen's method to *p*-cyanobenzenesulphonamide.

This investigation was in progress at the time of publication of the paper by Fuller, Tonkin, and Walker (*loc. cit.*), and we had prepared certain of the intermediates described therein. Although these authors failed to prepare *p*-methylsulphonylacetophenone by the Grignard method we had obtained a 17% yield using methylmagnesium iodide and *p*-methylsulphonylbenzonitrile in an ether–benzene medium. It is true that the reaction did not proceed smoothly, but the nature of the Grignard reagent as well as the methylsulphonyl group was apparently of some importance, since phenylmagnesium bromide with the same nitrile gave a good yield of p-*methylsulphonylbenzophenone*. As expected, we had no difficulty in preparing p-*phenylsulphonylacetophenone* from *p*-phenylsulphonylbenzonitrile and methylmagnesium iodide.

For the preparation of *p*-alkylthioacetophenones we first explored the possibility of obtaining the parent thiol by the Friedel–Crafts reaction or the Fries rearrangement using phenyl thiolacetate, PhSAc. No ketone was obtained by either method under a variety of experimental conditions. The Friedel–Crafts reaction was, however, successfully carried out on thioanisole, and proof that the product was p-*methylthioacetophenone* was obtained by oxidation of this to *p*-methylsulphonylacetophenone.

EXPERIMENTAL.

Phenyl *p*-tolyl sulphone was obtained in 90% yield by Newell's procedure (*Amer. Chem. J.*, 1898, **20**, 303).

p-*Chlorophenyl* p-*Tolyl Sulphone* (4-*Chloro*-4'-*methyldiphenyl Sulphone*).—Powdered aluminium chloride (30 g.) was added in small portions to a solution of *p*-toluenesulphonyl chloride (40 g.) in chlorobenzene (55 g.) kept at 90°. The mixture was then heated at 95° for 1 hour and the cooled product added to warm dilute hydrochloric acid. Excess of chlorobenzene was removed by steam distillation. The *sulphone* (45 g.) crystallised from alcohol in colourless prisms, m. p. 124° (Found : C, 58·4; H, 4·5. $C_{13}H_{11}O_2ClS$ requires C, 58·5; H, 4·1%).

p-*Methoxyphenyl* p-*Tolyl Sulphone* (4-*Methoxy*-4'-*methyldiphenyl Sulphone*).—Aluminium chloride (30 g.) was added in small portions to a solution of *p*-toluenesulphonyl chloride (40 g.) in anisole (40 g.) at 75°. Further heating at 80—90° for 1 hour, followed by decomposition with dilute hydrochloric acid and steam distillation, gave the crude sulphone which was shaken vigorously with hot 2N-sodium hydroxide (100 c.c.). Acidification of the alkaline filtrate gave a small amount of a phenolic substance, presumably 4-hydroxy-4'-methyldiphenyl sulphone, m. p. 125°. The insoluble 4-*methoxy*-4'-*methyldiphenyl sulphone* (40 g.) recrystallised from alcohol in colourless needles, m. p. 104—105° (Found : C, 64·1; H, 5·5. $C_{14}H_{14}O_3S$ requires C, 64·1; H, 5·3%).

3 : 4-*Dimethoxyphenyl* p-*Tolyl Sulphone* (3 : 4-*Dimethoxy*-4'-*methyldiphenyl Sulphone*).—Aluminium chloride (30 g.) was added in small portions, with frequent shaking, to *p*-toluenesulphonyl chloride (40 g.) in veratrole (50 c.c.) at 100°. After ½ hour at 130° (bath temp.), the resulting dark green viscous liquid was decomposed and purified as for the *p*-methoxyphenyl analogue. The *sulphone* (25 g.) separated from 95% alcohol in colourless needles, m. p. 128° (Found : C, 61·7; H, 5·6. $C_{15}H_{16}O_4S$ requires C, 61·6; H, 5·4%).

p-*Phenylsulphonylbenzaldehyde*.—(*a*) To a cold, well-stirred solution of phenyl *p*-tolyl sulphone (16 g.) in a mixture of glacial acetic acid (150 c.c.), acetic anhydride (115 c.c.), and concentrated sulphuric acid (17 c.c.), small amounts of chromic oxide (20 g.) were added so that the temperature was kept below 10°. Stirring was then continued in the cold until all the oxide had dissolved (4—5 hours). The crude *diacetate*, obtained when the mixture was poured into ice-water (1000 c.c.), had m. p. 153—154° after crystallisation from alcohol (Found : C, 58·4; H, 4·8; S, 9·7. $C_7H_{16}O_6S$ requires C, 58·5; H, 4·6; S, 9·2%), and was hydrolysed without further purification by boiling for 1½ hours with alcohol (50 c.c.), water (30 c.c.), and concentrated sulphuric acid (2 c.c.). The hot hydrolysis mixture was filtered from a little insoluble matter and cooled. The *aldehyde* (10 g.) which separated crystallised from benzene in colourless needles, m. p. 128°, raised to 130° by further crystallisation from 50% alcohol (Found : C, 63·5; H, 4·2. $C_{13}H_{10}O_3S$ requires C, 63·4; H, 4·1%). The aldehyde formed a solid sodium hydrogen sulphite compound which could be used conveniently for purification.

(*b*) A solution of *p*-phenylsulphonylbenzonitrile (24 g.) (Fuller, Tonkin, and Walker, *loc. cit.*) in chloroform (160 c.c.) was added to a Stephen's reagent prepared from anhydrous stannous chloride (36 g.), and the mixture shaken for 7 hours. After being kept overnight the solid stannichloride was decomposed by water, and the aldehyde (20 g.) isolated from a chloroform solution through its sodium hydrogen sulphite compound. Recrystallised from 50% alcohol it had m. p. and mixed m. p. 130°.

(*c*) *p*-Phenylsulphonylbenzanilide (16·8 g.) (Newell, *loc. cit.*), phosphorus pentachloride (10·5 g.), and tetrachloroethane (60 c.c.) were heated under reflux at 140° for 1 hour. After removal of phosphoryl chloride under reduced pressure the residual imino-chloride, redissolved in the minimum volume of tetrachloroethane, was added to Stephen's reagent (from 40 g. of anhydrous stannous chloride). The mixture was shaken for 2 hours and then kept overnight. The resulting crystalline stannichloride was decomposed by warm 2N-hydrochloric acid, and the aldehyde (7 g.) crystallised from benzene, m. p. 128—130°.

4-p-*Chlorophenylsulphonylbenzaldehyde*.—*p*-Chlorophenyl *p*-tolyl sulphone (20 g.) was oxidised with chromic oxide (20 g.) in acetic acid (150 c.c.), acetic anhydride (150 c.c.), and concentrated sulphuric acid (17 c.c.) as described for the phenylsulphonyl analogue. The intermediate 4-p-*chlorophenylsulphonylbenzylidene diacetate* crystallised from alcohol in colourless prisms, m. p. 152° (Found : C, 53·5; H, 4·1; S, 8·3. $C_{17}H_{15}O_6ClS$ requires C, 53·6; H, 3·9; S, 8·3%). Hydrolysis of the crude diacetate gave the free *aldehyde* (15 g.) which when recrystallised from benzene—light petroleum had m. p. 154° (Found : C, 55·4; H, 3·4. $C_{13}H_9O_3ClS$ requires C, 55·6; H, 3·2%), depressed to 130° by admixture with the diacetate.

4-p-*Methoxyphenylsulphonylbenzaldehyde*.—(*a*) The crude intermediate diacetate, which contained an appreciable amount of unchanged starting material, obtained as above from *p*-methoxyphenyl *p*-tolyl sulphone (19 g.), was hydrolysed, and the *aldehyde* (2 g.) purified from a solution in chloroform through its sodium hydrogen sulphite compound and then by crystallisation from benzene–light petroleum; m. p. 133—134° (Found: C, 60·7; H, 4·4. $C_{14}H_{12}O_4S$ requires C, 60·9; H, 4·4%).

(*b*) A solution of *p*-methoxyphenyl *p*-tolyl sulphone (8 g.) in chloroform (10 c.c.) was added slowly to chromyl chloride (7 g.) in chloroform (10 c.c.); there was no immediate reaction, but slow separation of a precipitate, accompanied by evolution of heat, occurred. The mixture was shaken frequently for 2 hours and then refluxed on the steam-bath for 1 hour; the colour changed to deep brown and more solid separated. After standing overnight the product was treated with excess of aqueous sulphur dioxide and the chloroform evaporated. The aldehyde (1 g.), purified as in (*a*), had m. p. and mixed m. p. 133°.

Application of either of these procedures to 3 : 4-dimethoxyphenyl *p*-tolyl sulphone gave unchanged material as the only solid product. When this sulphone (5 g.) was oxidised with boiling aqueous potassium permanganate (6 g.), unchanged material (3·5 g.) was extracted from the manganese dioxide cake left on filtration. Acidification of the filtrate gave carbon dioxide and a little 4-3′ : 4′-*dimethoxyphenylsulphonylbenzoic acid* (0·5 g.), which separated from dilute acetic acid as an amorphous powder, m. p. 273° (Found: C, 55·5; H, 4·6. $C_{15}H_{14}O_6S$ requires C, 55·9; H, 4·3%).

p-*Sulphamylbenzaldehyde*.—(*a*) *p*-Toluenesulphonamide (12 g.) was oxidised with chromic oxide (15 g.) in a mixture of acetic acid (100 c.c.), acetic anhydride (100 c.c.), and concentrated sulphuric acid (17 c.c.); after all the oxide had dissolved, benzene (100 c.c.) and light petroleum (50 c.c.) were added. The precipitated dark green sticky solid was suspended in water, and adhering acid neutralised by a little solid sodium hydrogen carbonate. The product was hydrolysed by refluxing with alcohol (10 c.c.), water (10 c.c.), and concentrated sulphuric acid (2 c.c.). The *aldehyde* (4 g.) separated from water in transparent prisms, m. p. 118—120° (Found: C, 45·5; H, 4·1. $C_7H_7O_3NS$ requires C, 45·4; H, 3·9%).

(*b*) Finely powdered *p*-cyanobenzenesulphonamide (15 g.) suspended in dry ether (200 c.c.) was saturated with dry hydrogen chloride and then added to Stephen's reagent from anhydrous stannous chloride (30 g.) in ether (300 c.c.). The mixture was shaken for 6 hours, and after being kept overnight the colourless stannichloride was decomposed with warm, dilute hydrochloric acid (50 c.c.). The aldehyde separated when the solution was cooled, and was recrystallised from water; m. p. and mixed m. p. 118—120°.

p-*Methylthioacetophenone*.—Acetic anhydride (8 g.) was added gradually with stirring to a gently boiling mixture of thioanisole (12·4 g.), carbon disulphide (40 c.c.), and anhydrous aluminium chloride (26·7 g.). The resulting green solution was boiled for 1 hour, the carbon disulphide distilled off, and the viscous residue poured while still warm into vigorously stirred ice-cold dilute hydrochloric acid. The resulting mixture was heated on the steam-bath for ½ hour, cooled, and the p-*methylthioacetophenone* crystallised from alcohol. It separated in colourless prisms, m. p. 80° (yield 14 g.) (Found: C, 65·0; H, 6·0. $C_9H_{10}OS$ requires C, 65·1; H, 6·0%).

p-*Methylsulphonylacetophenone*.—(*a*) *p*-Methylthioacetophenone (4 g.) in acetic acid (10 c.c.) was oxidised with 30% hydrogen peroxide (15 c.c.) at 100° for ½ hour. Evaporation to a small volume gave, on cooling, colourless prisms, m. p. 126°, unchanged by recrystallisation from alcohol.

(*b*) *p*-Methylsulphonylbenzonitrile (5·5 g.) in warm benzene (130 c.c.) was added gradually with, stirring to methylmagnesium iodide from magnesium (2·8 g.), methyl iodide (16·5 g.), and ether (60 c.c.) A yellow gelatinous precipitate formed immediately. The mixture was stirred for 1 hour, refluxed for a further 18 hours, and after being kept overnight was poured slowly on ice (200 g.) and concentrated sulphuric acid (60 c.c.). After 2 hours' heating at 100° under reflux, the benzene and aqueous layers were filtered from some insoluble, tarry solid (*A*). The benzene layer was combined with the benzene extract of the aqueous solution, then washed successively with dilute sodium hydroxide and water. The dried (Na_2SO_4) benzene solution was concentrated and ligroin then added; crystals contaminated with a little tar separated. Recrystallisation from alcohol (charcoal) gave the ketone (1 g.), m. p. 126°, unchanged by admixture with that prepared under (*a*) (Fuller, Tonkin, and Walker, *loc. cit.*, give m. p. 128—129°) (Found: C, 54·4; H, 5·0. Calc. for $C_9H_{10}O_3S$: C, 54·5; H, 5·0%).

The tarry solid (*A*), which had m. p. *ca.* 100°, was obviously largely unchanged nitrile since it was hydrolysed by sodium hydroxide to *p*-methylsulphonylbenzoic acid, m. p. 265—267°, after crystallisation from alcohol.

p-*Phenylsulphonylacetophenone*.—*p*-Phenylsulphonylbenzonitrile (12 g.) in benzene (100 c.c.) was added with stirring to the Grignard reagent from magnesium (4·8 g.), methyl iodide (28·4 g.), and ether (50 c.c.). After 3 hours' stirring, benzene (100 c.c.) was added, and the mixture refluxed for 20 hours. Decomposition as above (filtration not being necessary) gave the *ketone* (8 g.) which crystallised from benzene in almost colourless prisms, m. p. 136—137° (Found: C, 64·4; H, 4·6. $C_{14}H_{12}O_3S$ requires C, 64·6; H, 4·6%).

p-*Methylsulphonylbenzophenone*.—*p*-Methylsulphonylbenzonitrile (9 g.) in benzene (200 c.c.) with the Grignard reagent from magnesium (4·8 g.), bromobenzene (31·4 g.), and ether (100 c.c.) gave, after being refluxed for 16 hours and then decomposed as above, the *ketone* (10 g.) which separated from benzene–ligroin in nearly colourless plates, m. p. 134—136° (Found: C, 65·0; H, 4·6. $C_{14}H_{12}O_3S$ requires C, 64·6; H, 4·6%).

p-*Phenylsulphonylbenzophenone*.—Finely powdered, anhydrous aluminium chloride (5 g.) was added gradually to *p*-phenylsulphonylbenzoyl chloride (10 g.) in benzene (30 c.c.) at 75°. The mixture was then heated, with frequent shaking, at 85—90° for 2 hours, and, after cooling, decomposed with dilute hydrochloric acid. The excess of benzene was evaporated and the resulting solid product washed with dilute hydrochloric acid and then heated with dilute sodium hydroxide at 100 for 1 hour. The *ketone* (8 g.) crystallised from alcohol in colourless prisms, m. p. 144° (Found: C, 70·3; H, 4·5. $C_{19}H_{14}O_3S$ requires C, 70·8; H, 4·4%).

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