p.s.i. in the presence of Raney nickel. After the solution was filtered, a yellow crystalline solid precipitated (approximately 1.5 g.) which was identified as 4,4′-di-(*p*-acetylphenylmercapto)-azoxybenzene dioxime, m.p. 222–223°.

Anal. Calcd. for $C_{28}H_{24}O_3N_4S_2$: C, 63.7; H, 4.54; N, 10.5. Found: C, 63.04; H, 4.46; N, 9.7.

An attempt to hydrolyze the compound to the corresponding diketone failed due to its insolubility in a mixture of acetic and hydrochloric acids.

The alcoholic solution from the hydrogenation after filtration of the azoxy compound was poured into water. The precipitated solid was filtered and recrystallized to yield the desired amino oxime, m.p. 169–169.5°; yield 1.5 g. (33.5%).

In another hydrogenation experiment using 3 g. of oxime in the presence of ammonia, there was again isolated the desired amino oxime, m.p. 169–169.5°; yield 1.5 g. (33.5%). In addition to this compound there was also obtained approximately 1.5 g. of an orange material, m.p. 246–247°. The analysis of this compound agrees closely with that expected for 4,4′-di-(*p*-acetylphenylmercapto)-azobenzene dioxime.

Anal. Calcd. for $C_{28}H_{26}O_2N_4S_2$: C, 65.74; H, 4.68; N, 10.9; S, 12.5. Found: C, 65.87; H, 5.00; N, 10.3; S, 12.12.

It was shown that short hydrogenation of the above azoxy compound, m.p. 223–224°, in alcoholic ammonia gave the azo compound, m.p. 246–247°.

This compound, unlike the azoxy compounds described above, showed a peculiar color change in the presence of strong acids. A solution of the material in concentrated hydrochloric acid gave an intense violet color which disappeared upon dilution.

Acknowledgment.—We acknowledge the financial support of a part of this project by the Sterling-Winthrop Research Institute.

PITTSBURGH 19, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF VANDERBILT UNIVERSITY]

Grignard Reagents of Sulfones. IV. Reactions with Nitriles, Esters and an Isocyanate[1]

BY LAMAR FIELD, JOHN E. LAWSON AND JOHN W. MCFARLAND

RECEIVED MARCH 30, 1956

Addition of *p*-tolylsulfonylmethylmagnesium bromide (I) to benzonitrile and to trimethylacetonitrile resulted, after hydrolysis, in the corresponding ketones, but addition to acetonitrile led to variable and generally much less satisfactory results. The course of reaction between the Grignard reagent I and methyl benzoate was delineated, α-(*p*-tolylsulfonyl)-acetophenone being formed in good yield. A similar reaction occurred with ethyl acetate. Ethyl chloroformate reacted as an acyl halide and gave diethyl *p*-tolylsulfonylmalonate. Phenyl isocyanate yielded *p*-tolylsulfonylmalonanilide with compound I, in contrast to its reaction with α-(*p*-tolylsulfonyl)-ethylmagnesium bromide, with which it gave α-(*p*-tolylsulfonyl)-propionanilide. Factors which determine the nature of the foregoing reactions are discussed.

Grignard reagents of sulfones, exemplified by *p*-tolylsulfonylmethylmagnesium bromide (I), undergo a variety of reactions in a manner which is generally rather typical of Grignard reagents as a class.[2] The characteristics of the reactions between a Grignard reagent of a sulfone and nitriles, esters and phenyl isocyanate are considered in the present paper.

Since the reactivity of Grignard reagents with benzophenone decreases with increasing electronegativity of the organic moiety,[3] compounds such as the reagent I should have a lower order of capability in such addition reactions than most Grignard reagents. Although no such diminution of activity was conspicuous in a reaction with benzaldehyde (in comparison with phenylmagnesium bromide),[4] it may well have failed to appear because of the high degree of reactivity and lack of selectivity of benzaldehyde. Nitriles, on the other hand, possess one of the least reactive of the common functional groups toward phenylmagnesium bromide,[5] and the nature of their reactions with Grignard reagents of sulfones therefore merited exploration.

A gum resulted when benzonitrile was added to the white solid reagent I, which had been prepared as shown by the equation. Heating at 70° and hydrolysis with aqueous ammonium chloride then resulted in 2-imino-2-phenylethyl *p*-tolyl sulfone (III) in 82% yield. One may reasonably conclude that the gum which appeared at the outset was a complex of the reagent I and the nitrile which rearranged[6] to the actual addition product fairly rapidly only upon being heated, because when the heating period was omitted the product was quite impure and was obtained in only 40% yield. The reaction of Grignard reagents such as I with nitriles is therefore less facile than with carbonyl compounds, which react readily at room temperature[4] and may indeed give less satisfactory results with heating.[7] Hydrolysis of the imine III resulted in the ketone IV in 95% yield, thus both confirming the structure of III and demonstrating a practical conversion of a nitrile to a ketosulfone.

Acetonitrile was next studied, as representing the class of lower aliphatic nitriles reasonably well. No extensive attempts were made to isolate an intermediate imine. Instead, the product was hydrolyzed directly to *p*-tolylsulfonylacetone (V), which was isolated in 46% yield. When attempts to improve this yield actually eventuated in much poorer ones, an effort was made to repeat the original experiment. This effort failed, however, and the ketone V was obtained in only 11% yield. Although no explanation for the original relatively

---

[1] Presented in part at the Southeastern Regional Meeting of the American Chemical Society at Birmingham, Ala., Oct. 21–23, 1954. Abstracted from a portion of the Ph.D. thesis of J. W. McF., June, 1953, and from the M.A. thesis of J. E. L., June, 1956.

[2] For leading references, see paper III of this series, L. Field, THIS JOURNAL, **78**, 92 (1956).

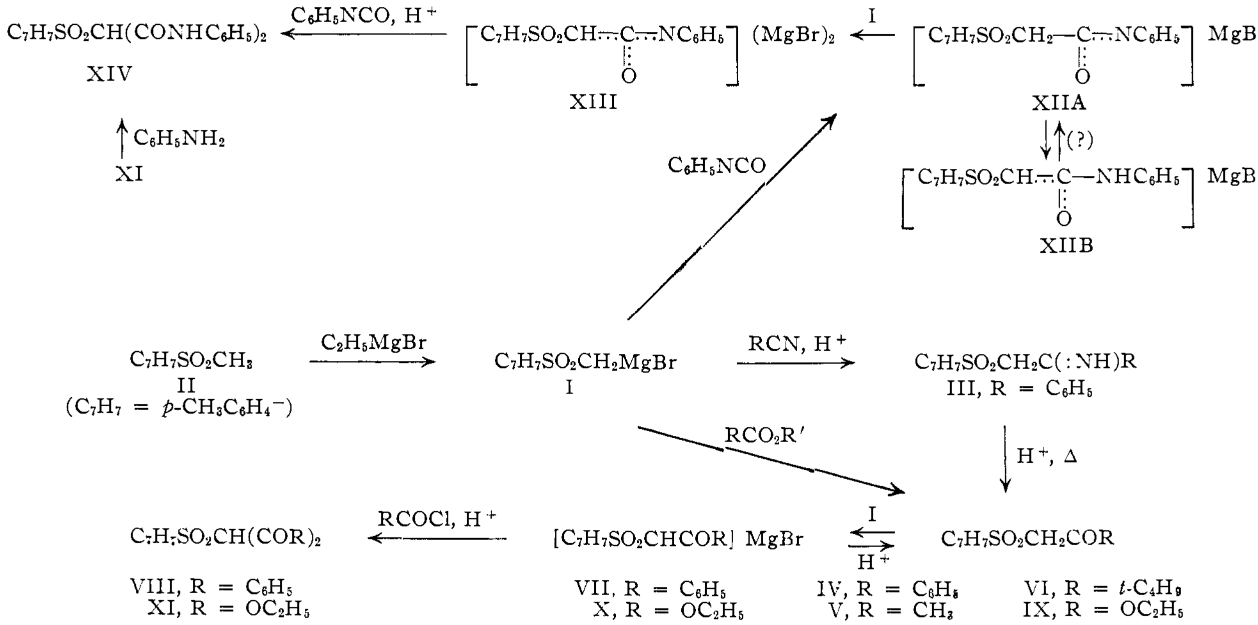
[3] M. S. Kharasch and S. Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).

[4] L. Field and J. W. McFarland, THIS JOURNAL, **75**, 5582 (1953).

[5] C. E. Entemann, Jr., and J. R. Johnson, *ibid.*, **55**, 2900 (1933).

[6] C. G. Swain, *ibid.*, **69**, 2306 (1947).

[7] L. Field, *ibid.*, **74**, 3919 (1952).



high yield is obvious, the poor subsequent results in all probability stem from the removal of an acidic hydrogen atom from the acetonitrile by the basic reagent I, followed by self-condensation of the resulting acetonitrile derivative.

Since self-condensation of a nitrile is particularly troublesome with large or complex Grignard reagents,[8] there seemed a good prospect that the polymeric character which has been suspected for reagents such as I[2] could be a significant factor in the reaction with acetonitrile. A report that a Grignard reagent similar to reagent I was more colloidal and more soluble in anisole[9] therefore suggested that improved results might be effected in anisole. The use of anisole resulted in a yield of about 26%, which did indeed represent a considerable improvement over all results except the original one, but still was not encouraging.

Assurance was sought that results of the kind obtained with acetonitrile would not be characteristic of the entire class of aliphatic nitriles but would be limited to members in which acidic hydrogen atoms could lead to side reactions. Trimethylacetonitrile, which is an aliphatic nitrile but lacks α-hydrogen atoms, upon reaction with the reagent I and subsequent hydrolysis, yielded p-tolylsulfonylmethyl t-butyl ketone (VI) in 82% yield; phenylmagnesium bromide adds to this nitrile to the extent of 71–84%.[10,11] This result thus affords a rather convincing argument for the culpability of the α-hydrogen atoms in the poor results with acetonitrile.

The result with trimethylacetonitrile also has other features of interest. Trimethylacetic acid and its derivatives show marked steric hindrance in a variety of reactions.[12] Trimethylacetonitrile would accordingly be expected to be among the least reactive members of the nitrile series, which itself is one of the least reactive toward Grignard reagents. The satisfactory formation of the ketone VI consequently provides a noteworthy commentary on the reactivity of Grignard reagents like I in addition reactions. Secondly, the reaction in which VI was formed resembles a reaction of I with a hindered carbonyl system,[4] in that there was no particularly notable tendency toward exertion of a blocking action by the sulfonyl group itself. This result, like that with the carbonyl system, therefore shows that the blocking action which the sulfonyl group manifests toward nucleophilic displacement on an adjacent atom[13] is not a characteristic of this group in other types of reaction; it probably arises in the special situation of nucleophilic displacement because of the electronic repulsion of the attacking anion by the sulfonyl group.[13]

In an examination of its reactions with esters, an excess of the reagent I was first used (with methyl benzoate) to simulate the situation in which one would wish to maximize the yield from a valuable ester. The ketosulfone IV was obtained in 71% yield. Since the sulfone II was recovered effectively from the excess Grignard reagent, operation in this way is not wasteful of the starting material II. The product IV was easily separated from neutral substances by extraction with alkali.

Although carbinols are usual products of reaction between Grignard reagents and esters, evidently none was formed in significant amount in this reaction. The interesting conclusion that the carbonyl group of the ketosulfone IV resists addition of a Grignard reagent apparently is valid not only for reagents like I but for Grignard reagents generally.

---

(8) C. R. Hauser and W. J. Humphlett, *J. Org. Chem.*, **15**, 359 (1950).

(9) W. E. Truce and K. R. Buser, THIS JOURNAL, **76**, 3577 (1954).

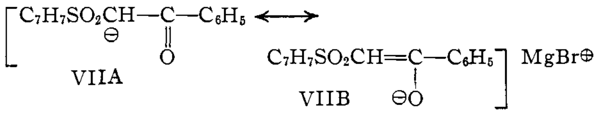
(10) P. Ramart-Lucas and F. Salmon-Legagneur, as cited by M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p. 802.

(11) J. H. Brewster, J. Patterson and D. A. Fidler, THIS JOURNAL, **76**, 6368 (1954).

(12) *Cf.* for example, C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 757–758, 776–778, 784.

(13) F. G. Bordwell and G. D. Cooper, THIS JOURNAL, **73**, 5184 (1951).

Thus after treatment of the ketosulfone IV with excess ethylmagnesium bromide, IV was recovered in 67% yield and hydroxylic compounds were not detected in the residue. Tröger and Beck also have noted the failure of phenylsulfonylacetophenone to undergo addition.[14] Since they reported that phenylsulfonylacetonitrile likewise undergoes no addition, resistance to addition is probably general, not only toward any Grignard reagent, but also for a variety of functional groups disposed in structures like that of IV. The resistance of IV to addition presumably originates in its rapid reaction as an acid to form the halomagnesium derivative VII, the hybrid structure of which can be represented by canonical forms VIIA and VIIB (and by other forms not shown which would involve the sulfonyl group). Both the charge of forms such as VIIA and the stability of forms such as VIIB no doubt militate against addition of a Grignard reagent.



$$\left[\underset{\text{VIIA}}{C_7H_7SO_2\underset{\ominus}{C}H-\underset{\underset{O}{\|}}{C}-C_6H_5} \longleftrightarrow \underset{\text{VIIB}}{C_7H_7SO_2CH=\underset{\underset{\ominus O}{|}}{C}-C_6H_5}\right] MgBr^{\oplus}$$

As the equation shows, two moles of reagent I is required for every mole of IV formed in the reaction with methyl benzoate, because IV reacts as an acid with I to liberate the sulfone II while being itself converted to VII. When approximately equimolar amounts of ester and reagent were used, the conversion of I to IV was 33%. The yield based on sulfone actually consumed, however, was 77%. Unconsumed sulfone being easily recoverable, this mode of operation should be practical when the sulfone is more valuable than the ester. A large excess of methyl benzoate and more vigorous conditions gave much the same result, thus confirming the supposition that the relatively low conversion is inherent in the reaction and is not simply a function of unsuitable conditions.

Direct evidence that the reaction involves the formation of IV and its subsequent conversion to VII seemed desirable. The reaction consequently was effected as before with approximately equimolar quantities of methyl benzoate and I. The intermediate enolate VII could then be converted with benzoyl chloride to dibenzoylmethyl *p*-tolyl sulfone (VIII), which was shown to be VIII and not an enol benzoate of IV both by chemical properties and comparison with presumably authentic VIII.

The fact that reagent I reacts with an ester to yield only a monoketosulfone, but with an acid chloride to yield a diketosulfone[15] owing to further reaction of the enolate VII, promises appreciable selectivity in reactions involving I. Assurance that the enolate VII cannot be easily acylated by methyl benzoate was provided by preparing VII from the ketosulfone IV with ethylmagnesium bromide and then treating it with methyl benzoate; the IV was recovered in 93% yield.

Selectivity such as shown by the ester, evidently most notable with less active and hence more selective functional groups, presents obvious synthetic possibilities. For example, acylation of a sulfone first by an ester and then by an acid halide should provide a practical method for introducing two different acyl groups onto the methyl group of a sulfone such as II in what would amount to only one operation.[16]

Ethyl chloroformate reacted only as an acyl halide with I, presumably with IX and X as intermediates, and yielded diethyl *p*-tolylsulfonylmalonate (XI, 22% conversion, 74% yield). This product could not be crystallized and was characterized by its neutral equivalent and as *p*-tolylsulfonylmalonanilide (XIV), the identity of which was confirmed by independent synthesis.

The reaction of ethyl acetate with an excess of reagent I was much like that of methyl benzoate, *p*-tolylsulfonylacetone (V) being isolated in 60% yield. Use of an aliphatic ester consequently does not lead to the difficulties encountered with an aliphatic nitrile. No clear-cut result was obtained, however, in the reaction of I and ethyl formate.

When approximately equimolar amounts of I and phenyl isocyanate were allowed to react, *p*-tolylsulfonylmalonanilide (XIV) was isolated (26% conversion, 40% yield). No *p*-tolylsulfonylacetanilide was isolated. Since two molecules of isocyanate reacted in the formation of XIV, this reaction resembles that of acid chlorides.

Reaction of the first molecule of isocyanate with I would yield an intermediate XII. Whether XII is best represented as XIIA or XIIB, or as a mixture of both, would depend upon the relative acidity of the amidic and methylenic hydrogen atoms of *p*-tolylsulfonylacetanilide. For conversion of XIIA to XIV, metalation to XIII seemed a prerequisite. With the thought that XIIB might preponderate, however, and react directly to give XIV without the loss of I entailed in further metalation, more isocyanate was used. The conversion increased to 38% and the yield to 50%; a little triphenyl isocyanurate also formed.

Phenyl isocyanate condenses with the sodium salt of nitromethane but not with that of nitroethane.[17] This marked difference aroused our interest as to whether an α-methyl substituent could effect a similar retardation in the reaction of the reagent I with phenyl isocyanate. The reaction of phenyl isocyanate with α-(*p*-tolylsulfonyl)-ethylmagnesium bromide (XV) was therefore effected in essentially the same way as with reagent I.

The reaction yielded a mixture of products from which fractional crystallization separated only α-(*p*-tolylsulfonyl)-propionanilide (XVI) in 14% yield.

$$\underset{\text{XV}}{C_7H_7SO_2CH(CH_3)MgBr} + C_6H_5NCO \longrightarrow \underset{\text{XVI}}{C_7H_7SO_2CH(CH_3)CONHC_6H_5}$$

Use of anisole as a solvent for the reaction and chromatographic separation of the products still resulted only in the anilide XVI (15%). Accordingly, there seems a good probability that the

---

[14] J. Tröger and O. Beck, *J. prakt. Chem.*, [2] **87**, 289 (1913); *C.A.*, **7**, 2543 (1913).

[15] (a) E. P. Kohler and H. Potter, THIS JOURNAL, **57**, 1316 (1935); (b) **58**, 2166 (1936).

[16] Monoketosulfones have been acylated with a second and different group *via* their magnesium enolates.[15b]

[17] R. N. Boyd and R. Leshin, THIS JOURNAL, **75**, 2762 (1953).

methyl group has an effect on the reaction which favors the formation of the monoanilide rather than the dianilide, but whether this effect is achieved *via* steric or electronic means or a combination of the two is not clear.

The foregoing evidence seems to justify the generalization that only one group is introduced onto the methyl group of a sulfone such as II by reaction of its Grignard reagent with esters and nitriles and only two groups by reaction with isocyanates and acid chlorides. Thus far at least, nothing has been observed which would suggest that three groups can be introduced on the same carbon atom under any circumstances.[18] Although the factors which control the number of groups which can be introduced are difficult to disentangle, they probably include at least: (1) the extent to which the reaction product with the first mole of acylating agent is stabilized by resonance and thereby rendered less prone toward subsequent reaction; (2) the extent to which steric and inductive contributions from groups already present on the carbon atom undergoing acylation affect subsequent reaction; (3) the extent to which the functional group of the acylating agent has sufficient activity to transcend passivity induced in the intermediates by the factors outlined in (1) and (2).

Acknowledgment.—This work was supported by the Office of Ordnance Research, U. S. Army, and in the beginning phases by Research Corporation of New York.

Experimental[19]

Starting Materials.—Esters, nitriles and phenyl isocyanate were redistilled (ethyl acetate was washed beforehand with aqueous sodium carbonate) and usually stored over anhydrous calcium sulfate or sodium sulfate (acetonitrile over phosphorus pentoxide). Unless otherwise specified, *p*-tolylsulfonylmethylmagnesium bromide (I) was prepared by adding ethylmagnesium bromide to the indicated amount of the sulfone II (0.0071–0.0078 mole/g. of II) in benzene (10–16 ml./g. of II) during 10 minutes, stirring for 10 minutes and heating at the reflux temperature for 3 minutes (occasionally the benzene was used in 2 portions[21] and usually a little was reserved for washing in the ethylmagnesium bromide).

Reactions of Nitriles. (a) **Benzonitrile.**—A solution of 12.82 g. of benzonitrile in 25 ml. of benzene was added during 1 hr. with stirring to I prepared from 16.17 g. of II. The white solid I disappeared and a yellow gum appeared. The mixture was then stirred for 1 hr., heated to the reflux temperature (70°) during 2 hr. and thereat for 1 hr. A chilled saturated solution of ammonium chloride (50 ml.) was added and a chloroform extract was then washed with water, 2% aqueous sodium hydroxide (acidification gave no α-(*p*-tolylsulfonyl)-acetophenone (IV)) and again with water until neutral. Solid obtained from the chloroform was recrystallized from carbon tetrachloride; yield of **2-imino-2-phenylethyl *p*-tolyl sulfone** (III), 21.2 g. (82%), m.p. 112–113.5°; constant m.p. after further recrystallization, 113–114°.

Anal. Calcd. for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12; S, 11.73; mol. wt., 273. Found: C, 66.11; H, 5.66; N, 5.01; S, 11.77; mol. wt. (Rast), 329.

Omission of heating resulted in a mixture having m.p. 78–105° (yield calcd. as III, 40%). Omission only of the actual reflux period (and less cautious acidification using 1 *N* hydrochloric acid) resulted in III in 45% yield (m.p. 107–110°) and the ketone IV in 15% yield (m.p. 106–107.5°); IV could be separated easily owing to its solubility in dilute alkali.

The imine III was hydrolyzed to the ketone IV by heating 4.00 g. in 80 ml. of 6 *N* hydrochloric acid with stirring under reflux for 21 hr.; III did not seem to dissolve completely until the reflux temperature was reached. After neutralization, 3.81 g. (95%) of IV was isolated, m.p. and mixture m.p. with authentic[14] material, 106–108.5°.

(b) **Acetonitrile.**—A solution of 2.90 g. of acetonitrile in 15 ml. of benzene was added during 15 minutes to I prepared from 10.00 g. of II. The mixture was stirred for 1 hr., heated slowly to the reflux temperature during 1.25 hr. and thereat for 0.75 hr. Extraction of the slightly acidified mixture yielded 11.97 g. of dark oil which was heated under reflux with 135 ml. of methanol and 45 ml. of 12 *N* hydrochloric acid for 7 hr. The mixture was neutralized and 150 ml. of 5% aqueous sodium hydroxide added. After extraction with benzene, salt was added and the mixture acidified. Oily solid was extracted which after recrystallization from methanol–water amounted to 5.76 g. (46%) of *p*-tolylsulfonylacetone (V), m.p. and mixture m.p. with authentic[4] V, 45–50°.

Attempts to improve upon this result with larger proportions of I or of acetonitrile were unavailing. An effort to repeat the original reaction resulted only in 2.31 g. (19%) of V, m.p. 43–47°, which after further recrystallization amounted to 1.32 g. (11%), m.p. and mixture m.p. 46–51° (a recovery of the sulfone II in 46% yield, m.p. 83–86°, was disregarded in calculating the yield, for consistency with the other reactions with nitriles).

When the original reaction was repeated with anisole as a solvent instead of benzene, V was isolated in 41% yield, m.p. 42–49°. Two recrystallizations reduced the yield to 26%, m.p. and mixture m.p. 49.5–52°.

(c) **Trimethylacetonitrile.**—Trimethylacetonitrile (5.06 g.) in 10 ml. of benzene was added at 25–27° during 25 minutes to I prepared from 8.00 g. of II. The mixture was heated to the reflux temperature during 1.5 hr. and thereat for 2.5 hr. It was then acidified and a benzene extract was washed with water. Solid (11.9 g.) isolated from the benzene was heated under reflux with 230 ml. of 6 *N* hydrochloric acid for 26 hr. An ether extract was then washed with water and extracted with 150 ml. of 10% aqueous sodium hydroxide in 5 portions. The alkaline extract was washed with ether and, after addition of salt, acidified with 12 *N* hydrochloric acid. A chloroform extract yielded ***p*-tolylsulfonylmethyl *t*-butyl ketone** (VI, 9.75 g., 82%, m.p. 107–113.5°). Recrystallization from aqueous methanol yielded 9.11 g. (76%) with m.p. 114.5–115°, unchanged by further recrystallization.

Anal. Calcd. for $C_{13}H_{18}O_3S$: C, 61.39; H, 7.13. Found: C, 61.13; H, 7.16.

Reactions of Methyl Benzoate. (a) **With Excess I.**—Methyl benzoate (4.98 g., 0.037 mole) in 15 ml. of benzene was added with stirring during 35 minutes to I prepared in 160 ml. of benzene using 21.80 g. (0.128 mole) of II and 0.109 mole of ethylmagnesium bromide. The mixture was stirred for 2 hr. and then for 2 hr. more at the reflux temperature. A benzene extract of the acidified mixture was then washed with water followed by 250 ml. of cold 2% aqueous sodium hydroxide in 6 portions (an emulsion which formed initially was broken by filtration). The alkaline extract was washed with ether, acidified and extracted with chloroform, yield 7.90 g. (79%) of IV, m.p. 93–106°, which after recrystallization from methanol amounted to 7.10 g.

---

(18) Reaction of the Grignard derivative of the diketosulfone VIII with benzoyl chloride resulted in an excellent yield of the enol benzoate and not in C-acylation.[15b]

(19) Melting points are corrected and boiling points are uncorrected. In Grignard reactions, apparatus was dried at 110° overnight, assembled while hot and protected with calcium chloride. Solvents were dried over sodium; anisole was previously heated at 120° with sodium, separated and distilled. Sulfones were dried to constant weight at 0.1 mm. and stored over phosphorus pentoxide. "Ethylmagnesium bromide" refers to a solution in diethyl ether (*ca.* 3.5 *N*) obtained from Arapahoe Chemicals, Inc. (Boulder, Colo.), which was centrifuged, stored under nitrogen and titrated[20] at intervals. Products were isolated from moist extracts by drying over anhydrous magnesium sulfate or sodium sulfate and removing solvent from the filtered extract by distillation under reduced pressures.

We are indebted to Dr. Ernest Jones of Vanderbilt University and Dr. Nelson Fuson of Fisk University and their associates for the infrared spectra. Analyses were by Micro-Tech Laboratories, Skokie, Ill., or Clark Microanalytical Laboratory, Urbana, Ill.

(20) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1955, p. 269.

(21) W. M. Ziegler and R. Connor, THIS JOURNAL, **62**, 2596 (1940).

(71%), m.p. and mixture m.p. with authentic[14] IV, 106–109°.

The benzene raffinate was washed with water and yielded II which after being triturated with cold petroleum ether amounted to 16.6 g. (76% recovery), m.p. 78–83°.

In determining whether ethylmagnesium bromide would add to IV, a mixture of 0.109 mole with 10.00 g. (0.036 mole) of IV in 150 ml. of benzene was stirred for 7.5 hr. and then heated at the reflux temperature for 0.5 hr. Hydrolysis yielded 6.65 g. (67%) of the IV, m.p. and mixture m.p. 106–108.5°. Residual oily product (2.06 g.) left after isolation of the IV gave no response which would indicate the presence of significant amounts of hydroxylic components (infrared spectrum, ceric nitrate test[4]).

(b) **With a Limiting Amount of I.**—Methyl benzoate (5.72 g., 0.042 mole) in 40 ml. of benzene was added during 0.5 hr. to I from 10.00 g. (0.059 mole) of II. As in (a), the mixture was stirred and heated, acidified and IV isolated with alkali (225 ml.), yield 5.36 g. (33% conversion), m.p. 103.5–106.5°. Recrystallization gave 4.70 g. (29%), m.p. and mixture[14] m.p. 106–109°. The benzene raffinate from the alkali extraction yielded greasy solid which after treatment with petroleum ether and recrystallization from aqueous ethanol amounted to 5.66 g. of II, m.p. 81.5–89.5°, undepressed by the original II. Based on this recovery, the yield of unrecrystallized IV was 77%.

Reaction of 0.0840 mole of methyl benzoate with I from 0.0583 mole of II, with stirring for 1 hr. and then at the reflux temperature for 6 hr., resulted (after recrystallization) in 4.71 g. (29% conversion) of IV, m.p. and mixture[14] m.p. 107–109°. Based on recovery of 0.0359 mole of II, the actual yield of IV was 77%.

(c) **With Subsequent Addition of Benzoyl Chloride.**—The preparation of I from 10.00 g. of II and its reaction with 6.13 g. of methyl benzoate was effected essentially as described under (b). Instead of hydrolysis as in (b), however, 4.11 g. of benzoyl chloride in 10 ml. of benzene was added during 5 minutes and the mixture then stirred under reflux for 0.5 hr. The mixture was cooled and acidified.

Solid insoluble in both phases was combined with a benzene extract and shaken with 125 ml. of cold 2% aqueous sodium hydroxide. Solid which then separated was mixed with water and acidified. Chloroform extraction yielded 4.30 g. of dibenzoylmethyl *p*-tolyl sulfone (VIII), m.p. 177–188°; since 5.05 g. (51%) of crude II was isolated from the benzene raffinate, the yield of VIII based on II consumed was 39%. Recrystallization from methanol left 3.46 g. (31%) of VIII, m.p. and mixture m.p. with authentic material,[22] 197–198°. Only small amounts of poorly defined material were obtained by acidifying the alkaline extract.

Further evidence that the product had structure VIII was provided by extraction of 0.456 g. from chloroform into 50 ml. of 0.25% aqueous sodium hydroxide; extraction of the alkali with chloroform, acidification and recrystallization then yielded 0.443 g. (97% recovery) of VIII, m.p. and mixture m.p. 194–196°. Furthermore, the product showed no indication of olefinic character in a permanganate test but gave the rapid response expected of a ketone with 2,4-dinitrophenylhydrazine.

In demonstrating the failure of the enolate VII to react with methyl benzoate, the VII was prepared from 10.00 g. of the ketosulfone IV and 0.046 mole of ethylmagnesium bromide in the same way that I was prepared from II. Methyl benzoate (6.48 g. in 35 ml. of benzene) was then added and the mixture stirred for 2 hr. both at 25° and at 79°. After hydrolysis 9.33 g. (93%) of IV was recovered, m.p. 101–108°. Recrystallization left 7.83 g. (78%), m.p. and mixture m.p. 107.5–109.5°.

Reactions of Other Esters. (a) **Ethyl Chloroformate.**—Ethyl chloroformate (7.65 g.) was added with stirring during 10 minutes to I from 15.00 g. of II and 0.081 mole of ethylmagnesium bromide. Stirring was continued for 2 hr. at 25° and for 1 hr. under reflux. The mixture was cooled and acidified. A benzene extract (sodium chloride facilitated separation of the layers) was washed with 150 ml. of cold 2% aqueous sodium hydroxide in 6 portions and then with water; it yielded crude II which, after being rubbed with cold petroleum ether, amounted to 10.53 g. (70% recovery) of II, m.p. 78–86°.

The alkaline extract was washed with ether and acidified. The resulting oil was extracted into ether; yield 6.14 g. (22% conversion, 74% yield) of diethyl *p*-tolylsulfonylmalonate (XI) as nearly colorless oil which resisted crystallization; neutral equivalent (0.1 *N* alkali and phenolphthalein), 348 (calcd. for XI, 314). This oil (3.06 g.) was heated with freshly distilled aniline (1.81 g.) for 6 hr. at 116–123°. The cooled mixture was triturated with hydrochloric acid and then with chilled absolute ethanol. White *p*-tolylsulfonylmalonanilide (XIV) resulted, which after recrystallization from 3:2 ethanol–acetone amounted to 2.28 g. (57%, based on the oil as pure XI), small colorless needles, m.p. and mixture[23] m.p. 247–252.5° dec.

(b) **Ethyl Acetate.**—The procedure was essentially that used with methyl benzoate (reaction a). After addition of ethyl acetate (2.20 g. in 15 ml. of benzene) during 5 minutes to I from 15.00 g. of II, stirring and acidification, the benzene extract was washed with aqueous salt solution and alkali. After acidification (12 *N* acid), extraction yielded solid which was rubbed with petroleum ether containing a trace of benzene; yield of *p*-tolylsulfonylacetone (V), 4.06 g. (77%), m.p. 40–49°. Recrystallization proved difficult but was achieved by slowly cooling a solution in *ca.* 10 volumes of 3:1 methanol–water; yield of V, 60%, m.p. and mixture[4] m.p. 50–51°.

The benzene raffinate from the alkali extraction gave 11.77 g. (79% recovery) of II, m.p. and mixture m.p. 79–86°.

Reactions of Phenyl Isocyanate. (a) **With I.**—Phenyl isocyanate (21.44 g., 0.180 mole) in 40 ml. of benzene was added at 25–30° during 1 hr. to I from 10.21 g. (0.060 mole) of II. A clear solution resulted after 3 hr. of stirring. Acidification resulted in insoluble white solid, which was separated and digested briefly with 50 ml. of absolute ethanol. Filtration of the chilled mixture then gave 9.40 g. of the anilide XIV (38% conversion, 50% yield based on unrecovered II), m.p. 243–248° dec. Similarly prepared XIV recrystallized from absolute ethanol (150 ml./g.) had constant m.p. 253.5–255° dec. The mixture m.p. with authentic XIV[23] was 253.5–256° dec., and the infrared spectra of the two samples were identical.

Anal. Calcd. for $C_{22}H_{20}N_2O_4S$: C, 64.69; H, 4.93; N, 6.86; S, 7.85. Found: C, 64.89; H, 4.68; N, 7.02; S, 7.63.

The organic layer from the original reaction mixture was combined with benzene extracts of the aqueous layer. Oil was isolated which after standing in carbon tetrachloride at −5° yielded solid. Digestion of this solid with boiling alcohol, chilling, filtration and recrystallization yielded 2.40 g. of presumed triphenyl isocyanurate, containing nitrogen but not sulfur, m.p. 280–281.5°, m.p. reported[24] 281°.

Anal. Calcd. for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23. Found: C, 70.82; H, 4.28.

The ethanol filtrate from the isocyanurate yielded 2.31 g. (23% recovery) of crude II, m.p. and mixture m.p. 75–85°.

A reaction identical with the foregoing, save for the use of only 9.53 g. (0.080 mole) of phenyl isocyanate in 20 ml. of benzene, after digestion yielded 6.30 g. (40% yield, 26% conversion) of XIV, m.p. 241–247° dec., undepressed by authentic XIV. The II was recovered in 36% yield, m.p. and mixture m.p. 84–86.5°.

(b) **With α-(*p*-Tolylsulfonyl)-ethylmagnesium Bromide (XV).**—The reagent XV was prepared from 9.21 g. of ethyl *p*-tolyl sulfone[4] in 100 ml. of benzene by adding 0.067 mole of ethylmagnesium bromide in 20 ml. of benzene and heating as described previously.[4] Phenyl isocyanate (17.9 g.) in benzene (40 ml.) was added to the mixture at 25° during 1 hr. The mixture was then stirred for 3 hr. and acidified. Insoluble carbanilide was removed which after recrystallization amounted to 0.7 g., m.p. and mixture[25] m.p. 241.5–244°.

---

(22) Prepared by modifying the procedure of Kohler and Potter[15a] and recrystallizing to constant m.p. 196–197°. *Anal.* Calcd. for $C_{22}H_{18}O_4S$: C, 69.82; H, 4.79. Found: C, 69.96; H, 5.12. The C, H% and m.p. given in reference 15a for VIII are evidently mistakes, since they actually are suitable for its enol benzoate. Presumably correct data for both compounds are given in reference 15b.

(23) Authentic XI was prepared according to the procedure of L. Field for diethyl phenylsulfonylmalonate [THIS JOURNAL, **74**, 394 (1952)] and converted to the anilide XIV as described above; constant m.p. after recrystallization from ethanol, 254–256° dec.

(24) J. R. Bailey and A. T. McPherson, *ibid.*, **39**, 1338 (1917).

(25) T. L. Davis and K. C. Blanchard, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 453.

One-half of the benzene solution yielded 10.6 g. of semisolid which was warmed with carbon tetrachloride. Chilling and filtration separated 1.76 g. of material, m.p. 139–166°, which after recrystallization from 85–95% methanol gave 1.03 g. (14%) of α-(*p*-tolylsulfonyl)-propionanilide (XVI), m.p. 171–173°, constant m.p. 172.5–173.5°.

Anal. Calcd. for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65. Found: C, 63.66; H, 5.70.

Residual material in the carbon tetrachloride resisted purification. Solid obtained from the other half of the benzene solution was washed with petroleum ether–benzene and subjected to systematic fractional crystallization from methanol, but the yield of XVI was not improved.

In a similar experiment with the same quantities of reagents, but with anisole rather than benzene as the solvent, the ethylmagnesium bromide was mixed with 10 ml. of anisole and added to ethyl *p*-tolyl sulfone in 150 ml. of anisole. The seemingly homogeneous mixture was stirred and then heated during 1.7 hr. to 100°. The mixture was cooled and phenyl isocyanate in 5 ml. of anisole added. After 3 hr., hydrolysis followed by concentration of the anisole phase gave semisolid which was washed with ether–petroleum ether and chromatographed on alumina. Recrystallization of the fraction eluted using benzene–ethanol gave 2.24 g. (15%) of XVI, m.p. 172–173.5°.

NASHVILLE 5, TENN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Rearrangement of α,β-Epoxy Ketones. IV. The Synthesis of Cyclic β-Diketones

BY HERBERT O. HOUSE AND RICHARD L. WASSON[1]

RECEIVED MARCH 19, 1956

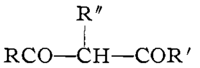
2-Benzalcyclopentanone oxide, 2-benzalcyclohexanone oxide and 2-benzalcycloheptanone oxide have been isomerized to 2-phenyl-1,3-cyclohexanedione, 2-phenyl-1,3-cycloheptanedione and 2-phenyl-1,3-cyclooöctanedione, respectively, by treatment with boron trifluoride etherate in benzene solution. When the same cyclohexanone and cycloheptanone derivatives were treated with boron trifluoride in ether solution, the products were fluorohydrins. The thermal rearrangement of 2-cyclohexylidenecyclohexanone oxide produced spiro[5.6]dodecane-7,12-dione. Rearrangement of 3,4-epoxy-4-methyl-2-pentanone with boron trifluoride etherate in benzene solution formed 2,2-dimethyl-3-oxobutyraldehyde; the same oxide, when passed over alumina at 250°, yielded methyl isopropyl ketone.

The general preparative methods for β-dicarbonyl compounds,[2] the base-catalyzed acylation of ketones with esters (the Claisen condensation) and the acid-catalyzed acylation of ketones with acid anhydrides, are limited to compounds of the types I and II which can form stable enolates. Satisfactory synthetic procedures for compounds of type III have involved the alkylation of β-dicarbonyl compounds[2,3] and the acylation of the sodium enolates of mono-carbonyl compounds with acid chlorides.[2] The first of these synthetic methods is often complicated by O-alkylation of the β-diketone.[4] Similarly, the acylation of metallic enolates of carbonyl compounds with acid chlorides may lead to the formation of O-acyl derivatives (enol esters).[2] Our previous[5] and present studies have indicated that isomerization of the appropriate α,β-epoxy ketones can serve as a useful preparative method for dicarbonyl compounds of the types II and III.[6]

It was of interest to learn whether the same type of isomerization could be employed to prepare cyclic β-diketones of type IV. Five- and six-membered cyclic β-diketones (IV, n = 2 and 3) are readily accessible *via* intramolecular Claisen acylations[2]; the six-membered cyclic diketones (IV, n = 3) have also been prepared by the alkylation of dihydroresorcinol.[4] However, consideration of the difficulty with which seven-membered and larger carbocycles are formed and the reversible nature of the base-catalyzed acylations leads to the expectation that the Claisen reaction will be of little value for compounds of type IV in which n has values greater than three.[7] To explore the possibility that compounds of type IV could be prepared by isomerization of α-keto epoxides, a study of the 2-benzalcycloalkanone oxides (V) was undertaken.

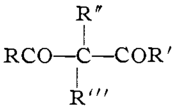
$RCO—CH_2—COR'$

I



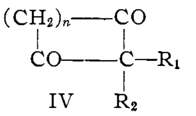
$RCO—\overset{R''}{\overset{|}{C}}H—COR'$

II



$RCO—\overset{R''}{\overset{|}{\underset{R'''}{\underset{|}{C}}}}—COR'$

III



IV

R_1 and R_2 = H, alkyl or aryl

2-Benzalcycloheptanone oxide (Va) and 2-benzalcyclohexanone oxide (Vb) were prepared by treatment of the corresponding unsaturated ketones VIa and VIb with alkaline hydrogen peroxide.[8] Repeated attempts to prepare 2-benzalcy-

---

(1) Alfred P. Sloan Foundation Research Assistant, 1956.

(2) C. R. Hauser, F. W. Swamer and J. T. Adams, *Org. Reactions*, **8**, 59 (1954).

(3) H. Adkins, W. Kutz and D. D. Coffman, THIS JOURNAL, **52**, 3212 (1930); J. M. Sprague, L. J. Beckham and H. Adkins, *ibid.*, **56**, 2665 (1934).

(4) For example see H. Stetter and W. Dierichs, *Chem. Ber.*, **85**, 61 (1952).

(5) (a) H. O. House, THIS JOURNAL, **76**, 1235 (1954); (b) H. O. House and D. J. Reif, *ibid.*, **77**, 6525 (1955); (c) H. O. House, *ibid.*, **78**, 2298 (1956).

(6) Our investigations related to the preparation of compounds of the type I will be reported in a subsequent paper of this series.

(7) Cyclization of the appropriate keto esters for the preparation of diketones of type IV in which n = 4 or 5 yields instead of the α-acyl derivatives of cyclopentanone and cyclohexanone (reference 2). The related Dieckmann reaction has not been satisfactory for the preparation of carbocyclic ketones with more than six ring members [W. Dieckmann, *Ann.*, **317**, 27 (1901)]. Since such acylations are reversible, the use of high-dilution conditions would not be expected to favor medium- and large-ring formation unless the cyclic product could be removed from the reaction mixture as it was formed (*e.g.*, by means of the insolubility of the metal enolate of the product in the reaction solvent). The use of the Dieckmann reaction to prepare a heterocyclic ketone of medium ring size, reported by N. J. Leonard and R. C. Sentz [THIS JOURNAL, **74**, 1704 (1952)], appears to represent a case of this type.

(8) The positions of maximum absorption (284–298 mμ) in the ultraviolet spectra of the 2-benzylcycloalkanones (VI) employed suggest that all of the unsaturated ketones have the *trans* configuration (see reference 9). However, the stereochemistry of the oxides V is