[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ALMA COLLEGE]

The Reaction of Grignard Reagents with α,β-Unsaturated Sulfones. I.

BY HOWARD POTTER

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The behavior of α,β-unsaturated sulfones is variable according to the degree of substitution at the β-carbon, being similar to the behavior of comparable unsaturated ketones in yielding products of conjugate addition or of alternative reactions, but different in that the reaction with phenyllithium is influenced the same as is the reaction with phenylmagnesium bromide.

The reaction of Grignard reagents with α,β-unsaturated ketones is well known and may be summarized as yielding either unsaturated alcohols by 1,2-addition to the carbonyl group or saturated ketones by 1,4-addition to the conjugated system followed by ketonization. The course of the reaction, the Grignard reagent being the same, is determined by the relative degree of substitution around the carbonyl carbon compared to the β-carbon.

The α,β-unsaturated sulfones are of interest because they are similar in that the ethylenic bond behaves as if conjugated,[1] yet the sulfone group cannot participate in 1,4-addition without more than eight electrons in the valence shell of the sulfur atom. Addition of phenylmagnesium bromide to styryl *p*-tolyl sulfone (I) was reported earlier[1] to be analogous to the addition to benzalacetophenone. This type of reaction, yielding a saturated sulfone, may be described as "conjugate addition," using the term to imply that the reaction does not go in the absence of an influential group such as carbonyl or sulfonyl but without commitment concerning the mechanism. β-Phenylbenzalacetophenone contrasts with benzalacetophenone, giving 1,2-addition instead of 1,4-addition. Likewise β,β-diphenylvinyl *p*-tolyl sulfone (II) contrasts with I, giving reduction and cleavage instead of conjugate addition[2]

$$(C_6H_5)_2C{=}CH{-}SO_2{-}C_7H_7 + C_6H_5MgBr \longrightarrow$$

$$\text{II} \qquad C_6H_5{-}S{-}C_7H_7 \text{ and } (C_6H_5)_2C{=}CH{-}S{-}C_7H_7$$

The present work is an exploration of the degree to which the series of variously substituted vinyl aryl sulfones is analogous to the corresponding series of ketones.

In the series of carbonyl compounds, the alternative to conjugate addition is a well-known and exceedingly general reaction and is precisely what would happen if the double bond were not present, whereas in the sulfone series, the cleavage and reduction in the manner observed with II is not known to occur in general. Diaryl sulfones are not attacked by the Grignard reagent under like conditions, alkyl sulfones not highly hindered have active α-hydrogen atoms which are replaced by the metal, and the less substituted unsaturated sulfone I gives conjugate addition. Therefore reduction and cleavage may be peculiar to structures of the type of II.

Since phenyl *p*-tolyl sulfone is recovered unchanged when treated with phenylmagnesium bromide, cleavage of II to phenyl *p*-tolyl sulfone is unlikely as a first step. The products obtained from II are identical with those from β,β-diphenylvinyl *p*-tolyl sulfoxide[2] (III) and analogous to the products from styryl *p*-tolyl sulfoxide[1] (IV). The unsaturated sulfides are stable to phenylmagnesium bromide. Therefore the alternative to conjugate addition is reduction of the sulfone to the sulfoxide group, and the products isolated are due to the subsequent reaction of the unsaturated sulfoxide thus formed. The reduction of sulfoxides to sulfides by Grignard reagent is in accord with the easy reduction of sulfoxides in general. Preliminary work in this Laboratory indicates that the concurrent cleavage is not general to alkyl aryl sulfoxides.

In the carbonyl series, increased substitution at the β-carbon may hinder 1,4-addition, thereby allowing the 1,2-reaction to compete successfully. In the sulfone series, steric hindrance at the β-carbon could account for the failure of conjugate addition, but the susceptibility of the sulfone group to reduction indicates that substituents have an activating influence on the conjugating group. Hydrogen iodide (another reducing agent that characteristically reduces sulfoxides but not sulfones) is readily oxidized by II but not by I, but the product is the saturated sulfone instead of the unsaturated sulfide.[2]

We have failed to identify any compound containing the unsaturated group cleaved from the sulfur in II and III. Presumably it is lost in the red-brown tarry residue that is left from each of these experiments. By analogy to IV, 1,1,4,4-tetraphenylbutadiene was expected.

Phenyllithium adds to benzalacetophenone in the 1,2-manner (69%) rather than 1,4- (13%),[3] which is the opposite of the behavior of phenylmagnesium bromide. Therefore the sulfur analog I was treated with phenyllithium to determine whether the non-conjugate reaction would be observed here also. Such was not the case. The reaction is similar in all details to the reaction with phenylmagnesium bromide to give the same saturated sulfone. This demonstration of conjugate addition, together with the general immunity of phenyllithium to steric hindrance,[4] gave the hope that with it conjugate addition to II would occur, leading to the compound β,β,β-triphenylethyl *p*-tolyl sulfone, obtained by oxidation as an anomalous by-product of the reaction of the Grignard reagent with sulfoxide IV.[1] This also was not realized, the reaction again being identical with that of the magnesium compound, namely, cleavage and reduction. Phenyllithium also cleaves and reduces sulfoxide III.

Acknowledgment.—The investigation of the mode of reaction of these organometallic com-

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[1] E. P. Kohler and H. Potter, THIS JOURNAL, **57**, 1316 (1935).

[2] H. Potter, Thesis, Harvard University, 1936.

[3] H. Gilman and R. Kirby, THIS JOURNAL, **63**, 2046 (1941).

[4] G. Wittig and H. Petri, *Ber.*, **68B**, 924 (1935); W. Young and J. Roberts, THIS JOURNAL, **66**, 1444 (1944).

pounds with various α,β-unsaturated sulfones is being continued, facilitated by a grant from Research Corporation of New York.

Experimental[5]

Preparation of Unsaturated Sulfur Compounds. (a) **Styryl *p*-Tolyl Sulfone (I).**—The formation of *cis* and *trans* sulfide by the addition of *p*-toluenethiol to phenylacetylene, and oxidation of these yields all members of the monophenyl series.[1] The sulfone I (m.p. 121°) can be prepared more conveniently by the addition of *p*-toluenesulfonylmethylmagnesium bromide to benzaldehyde, and dehydration of the alcohol as described by Field.[6]

(b) **β,β-Diphenylvinyl *p*-Tolyl Sulfide, Sulfoxide (III) and Sulfone (II).**[7]—A methanol solution of 172 g. (1.11 moles) of phenacyl chloride and one equivalent of sodium *p*-thiocresolate was heated under reflux until precipitation of sodium chloride was complete. The mixture was concentrated to small volume by distillation and the residue shaken with water and ether. The residue from evaporation of the ether layer was distilled under reduced pressure. Acetophenone (0.42 mole) was obtained in the forerun, then phenacyl *p*-tolyl sulfide distilled, b.p. 182–184° (5 mm.) and m.p. 46°. The yield was 168 g. (0.69 mole). Analysis gave low and variable values for carbon, but the material was oxidized by peroxide quantitatively to phenacyl *p*-tolyl sulfone, m.p. and m.m.p. 107°.

Anal. Calcd. for $C_{15}H_{14}SO$: C, 74.4; H, 5.79. Found: C, 69.3 (max.); H, 5.82.

Phenacyl *p*-tolyl sulfide is subject to cleavage by phenylmagnesium bromide. Therefore a cold ether solution of phenylmagnesium bromide (0.5 mole approx.) was added to an ice-cold ether solution of the sulfide (0.4 mole, 100 g.) rapidly with vigorous stirring and cooling by an ice-bath. After ten minutes at 0° the mixture was shaken with iced hydrochloric acid. The ether layer was extracted with sodium hydroxide solution, from which 24 g. of *p*-toluenethiol was recovered by acidification. The ether layer was steam distilled to remove biphenyl, then the dried residue distilled at 3–4 mm. pressure. Phenyl *p*-tolyl sulfide, b.p. 131–132° (5 mm.) (32 g.), was removed at bath temperatures below 200°. At bath temperatures of 280–300° an oil distilled that reacted with sodium metal and acetic anhydride and had the composition of β,β-diphenyl-β-hydroxyethyl *p*-tolyl sulfide.

Anal. Calcd. for $C_{21}H_{20}SO$: C, 78.7; H, 6.25. Found: C, 77.6; H, 6.05.

At bath temperatures of 200–220° (3–5 mm.) the distillate which was obtained slowly and with some decomposition was β,β-diphenylvinyl *p*-tolyl sulfide, m.p. 84° after recrystallization from acetone–pet. ether or from glacial acetic acid–methanol.

Anal. Calcd. for $C_{21}H_{18}S$: C, 83.4; H, 5.96. Found: C, 83.3; H, 6.18.

The unsaturated sulfide was treated with one equivalent of hydrogen peroxide (30%) in glacial acetic acid solution at 10° for two hours, then left at room temperature overnight. The reaction mixture was poured into a large volume of water, the product taken into an ether layer, washed free from acid and dried. After evaporation of the ether, the sulfoxide crystallized from acetone by addition of petroleum ether. The yield of recrystallized solid, m.p. 124–125°, was 50%. Oxidation of the crystallization residues gave sulfone to account for the remainder of the material.

Anal. Calcd. for $C_{21}H_{18}SO$: C, 79.2; H, 5.66. Found: C, 79.0; H, 5.93.

By the same procedure, the sulfide with two equivalents or the sulfoxide with one equivalent of hydrogen peroxide were converted to the sulfone in quantitative yield, m.p. 103–103.5° after recrystallization from methanol. Permanganate in acetone was rapidly reduced by the sulfone and benzophenone was identified by mixed m.p. as a product of the oxidation. Subsequently the unsaturated sulfone was found to be identical by m.p. and m.m.p. with the product of the Field[6] procedure in which *p*-toluenesulfonylmethylmagnesium bromide was added to benzophenone and the resulting carbinol dehydrated.

Anal. Calcd. for $C_{21}H_{18}SO_2$: C, 75.45; H, 5.39. Found: C, 75.4; H, 5.54.

Reactions with Phenylmagnesium Bromide and with Phenyllithium. (a) **The Standardized Procedure.**—The reagent was prepared in the usual manner by addition of bromobenzene to the metal in ether, in amount calculated to yield five moles of reagent for one mole of sulfur compound to be added, assuming 90% yield from the bromobenzene. The sulfur compound was added in ether or benzene at a rate limited by refluxing of the solvent. The mixture was left at room temperature for a day or longer, or benzene added and the ether distilled and the benzene solution refluxed for one or more hours. The higher reaction temperature produced no different result, with the exception noted below. The scale of the operation was in the range of 0.02 to 0.1 mole of sulfur compound in each run. Yields were approximately reproducible and figures given here are representative of typical favorable cases.

(b) **β,β-Diphenylvinyl *p*-Tolyl Sulfone II and Sulfoxide III.**—These two compounds, each treated with the phenyl derivatives of the two metals either at room temperature or in boiling benzene gave in each case reduction and cleavage. The reaction mixture was treated with ice acid, the solvent layer washed with water and subjected to steam distillation. after solvent, biphenyl, etc., phenyl *p*-tolyl sulfide steam distilled slowly. The sulfide may be obtained as a pale yellow liquid by distilling the steam-volatile material under reduced pressure, but the extent of the cleavage reaction was best determined by collecting all steam-volatile material with the aid of an ether layer, which was dried and evaporated and the residue oxidized with excess 30% hydrogen peroxide in glacial acetic acid. The acetic acid solution was diluted with water and the insoluble material again steam distilled, whereby biphenyl, etc., was removed from the non-volatile phenyl *p*-tolyl sulfone. From reactions with the magnesium reagent the sulfone thus obtained was pure, m.p. 123–125° after a single recrystallization from methanol and undepressed when mixed with a sample obtained by the action of *p*-toluenesulfonyl chloride on benzene in presence of aluminum chloride. From reactions with phenyllithium, the sulfone was not made pure by one recrystallization. From such material a solid was separated by repeated recrystallization, m.p. 114–117°; m.m.p. with phenyl *p*-tolyl sulfone, below 105°; m.m.p. with diphenyl sulfone (m.p. 125°), 115–119°. In each case the sulfone from the volatile sulfide was obtained in amounts indicating approximately one third of the reaction was cleavage.

The residue from the first steam distillation was an intractable dark red or brown tar, from which β,β-diphenylvinyl *p*-tolyl sulfide could not be separated by crystallization or vacuum distillation. Treatment of the whole residue with hydrogen peroxide in glacial acetic acid converted the sulfide to the sulfone which could be separated from the tar by crystallization from methanol and identified by m.p. and m.m.p. 103°. The yield accounted for another third of the starting material.

(c) **Styryl *p*-Tolyl Sulfone and Phenyllithium.**—The reaction was in every way similar to the reaction of the same sulfone with phenylmagnesium bromide.[1] The saturated sulfone from conjugate addition was obtained in as high as 85% yield before recrystallization. One recrystallization from methanol gave pure product, m.p. 150–151°, undepressed by mixture with an authentic sample.

Exceptions to the Standard Procedure. (a) **Sulfone II with One Molecular Equivalent of Phenylmagnesium Bromide.**—To 16.7 g. (0.05 mole) of II in hot, vigorously stirred benzene, an ether solution of 0.05 mole of Grignard reagent was added drop by drop, the vaporized ether being removed through a short fractionating column. After one hour at the boiling point, the mixture was left at room temperature 24 hours, then worked up as described in (b) above. After 2 l. of steam distillate was collected no more volatile material was observed and the residue crystallized on addition of a small volume of ether. Solid (14.5 g.) melting from 90 to 95° was thus obtained. This melting point was raised by addition of starting material (103°) and pure starting material was obtained by a single recrystallization from methanol. No sulfoxide (m.p. 125°) could be isolated.

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[5] Robert Hudson, Harry Hill, James Fookes, Carl Dibert and Roland Gohlke have contributed to the work described here, as part of the requirements for the B.S. Degree.

[6] L. Field, THIS JOURNAL, **74**, 3919 (1952).

[7] These compounds were first prepared under the direction of E. P. Kohler and the data given here are recorded in ref. 2.

(b) Isolation of an Unidentified Hydrocarbon.—To an ether solution of 0.25 mole of phenyl Grignard reagent, 0.05 mole of sulfone II in benzene was added. After standing overnight at room temperature, the ether was removed by distillation and the benzene solution refluxed for three hours. After treating the reaction mixture as in (b) above, the biphenyl fraction was distilled under reduced pressure. After biphenyl, a white solid distilled, b.p. 165° (24 mm.), which weighed 3.5 g. and crystallized from methanol as gleaming plates, m.p. 58–60°. By mixed melting points it was found not to be biphenyl, triphenylethylene[8] (m.p. 68–69°) or 1-*o*-biphenyl-1-phenylethylene[9] (m.p. 59–61°). Analysis gave C 94.5% and H 6.2%. Production of this hydrocarbon could be repeated under the same conditions, but it could not be found among the products after six days at room temperature only. Therefore it was presumed to be the result of the higher temperature reaction of excess Grignard reagent with the primary products and was not further investigated. It was not found in any reaction with phenyllithium.

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[8] A. H. Blatt, "Organic Syntheses," Coll. Vol. II, J. Wiley and Sons, Inc., New York, N. Y., 1943, p. 606.

[9] C. K. Bradsher, This Journal, 66, 45 (1944). A sample of this compound was available by courtesy of Dr. Bradsher.

Alma, Michigan

[Contribution from the Noyes Chemical Laboratory, University of Illinois]

Restricted Rotation in Aryl Amines. XVII. Effect of Varying the 4-Substituent on the Stability of Optically Active N-Benzenesulfonyl-N-carboxymethyl-1-amino-2-methylnaphthalene

By Roger Adams and K. V. Y. Sundstrom[1]

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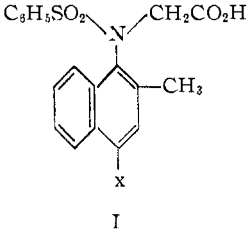
The influence of sterically non-interfering substituents on the stability of various optically active N-benzenesulfonyl-N-carboxymethyl-1-amino-2-methylnaphthalenes is described. Nine 4-substituted derivatives of this compound have been synthesized and resolved. Electron-withdrawing substituents increase, electron-supplying substituents decrease the racemization rate of these optically active compounds.

In previous work reported on aromatic amines which exhibit restricted rotation, only a few have been synthesized in which the substituents on the nitrogen and in the positions *ortho* to it have been the same from compound to compound. The variation in these molecules has consisted merely of the modification of the substituent in the position *para* to the site of restricted rotation. The comparison of the rates of racemization of the optically active forms of such molecules affords a means of determining the presence and character of factors other than strictly steric which may influence stability.

In the previous paper[2] in this series, compounds of this type have been discussed and the effect of certain electron-attracting groups in the 4-position of N-benzenesulfonyl-N-carboxymethyl-1-amino-2-methylnaphthalene has been described. The presence of such groups causes a decrease in the stability of the molecules.

This study has now been extended to include ten compounds of type I in which x represents the variable substituent. Racemizations were carried out in dimethylformamide solution at 118° (boiling point of *n*-butyl alcohol). The following half-lives of optical activity were found, where the experimental error, with the exception of the nitro compound, was probably 0.2 to 0.3 hour.

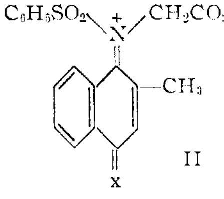


I

Substituent x	Half-life, hours
NO_2	0.42
Cl	3.7; 4.0[2]
Br	3.8; 3.7[2]
I	4.4
H	4.9
$NHSO_2C_6H_5$	3.8
$NHCOCH_3$	5.0
$NHCOC_6H_5$	5.9
OH	8.7
NH_2	9.7

Since the groups which interfere sterically with free rotation about the carbon–nitrogen bond are the same in all of these compounds, the variation in half-life of the optically active forms must be due to the electronic effect of the *para* substituent, x.

Racemization of restricted-rotation isomers probably involves the deformation of atoms and the distortion of bonds since no bonds are broken. The process is usually accepted as proceeding through a planar transition state, and factors which might tend to induce such a state must be considered. Among these factors are resonance forms, such as II, which involve the aromatic nucleus and the lone pair of electrons on the nitrogen. The presence of such forms would lower the energy barrier to racemization by resonance stabilization of the transition state and this would be reflected in an increased rate of racemization. The prevalence of such forms is influenced profoundly by the nature of the substituent, x, in the *para* position relative to the nitrogen. It follows, therefore, that those substituents which favor the formation of such structures should promote racemization; conversely, those which do not should impede racemization.



II

The experimental data agree with this postulation, since resonance according to structure II requires that the substituent x be electron withdrawing. In such compounds (best illustrated by the

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[1] An abstract of a thesis submitted by K. V. Y. Sundstrom to the Graduate College of the University of Illinois, 1953, in partial fulfillment of the requirements for the degree of Doctor of Philosophy; Cincinnati Chemical Co. Fellow, 1951–1952, 1952–1953.

[2] R. Adams and R. H. Mattson, This Journal, 76, 4925 (1954).