clave temperatures of 120° (15 p.s.i.) is shown in Fig. 2. Only 23% loss occurred in 30 minutes at *p*H 7. This result indicates the feasibility of using CoA in studies involving the necessity of sterilization.

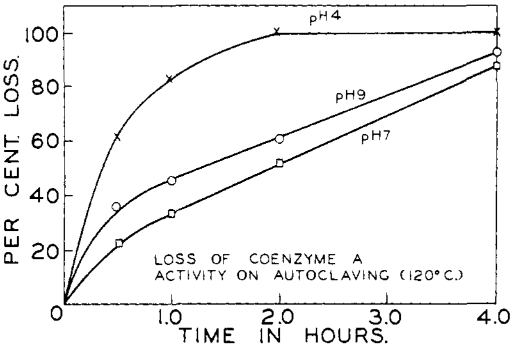

Fig. 2.—Stability of CoA to autoclaving (120°) in aqueous solutions of various *p*H values.

Acid and Alkali Treatments.—Table III shows the loss of CoA activity at alkaline *p*H values. The results show the inadvisability of keeping CoA solutions at room temperature for long periods of time, particularly if alkaline. Pyridine appeared to have a specific destructive effect, since solutions of CoA in aqueous pyridine lost up to 90% of their activity after 24 hours even though the *p*H was only slightly alkaline.

TABLE III

LOSS OF COENZYME A ACTIVITY AT ALKALINE *p*H VALUES

*p*H	Temp., °C.	Time in hours 1.5	3.0	24
		% of original activity lost		
7	0	0	0	6.1
	25	0	5.0	..
	40	0	11.5	..
8	0	0	0	6.0
	25	0	10.4	31.0
	40	0	11.3	42.0
9	0	0	0	7.7
	25	0	17.4	..
	40	0	24.4	..
10	0	0	0	21.7
	25	4.3	23.4	..
	40	13.0	28.6	..

One of the steps in the preparation of CoA by the method of Beinert, *et al.*,[3] involves precipitation from 0.5 *N* sulfuric acid solution at 40°. This precipitation requires from 10 to 20 minutes. It was found in the present study that this exposure to acid causes a 20 to 30% loss in activity.

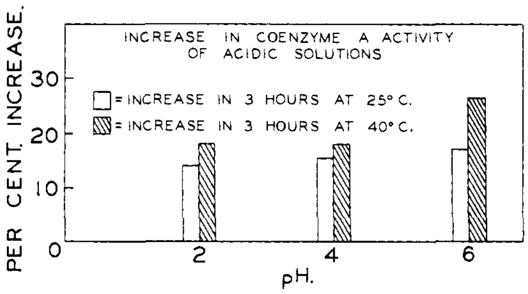

Fig. 3.—Increase in CoA activity of acidic solutions.

Figure 3 shows an interesting phenomenon that was observed when studying the stability of coenzyme A in aqueous solution at acid *p*H values. At *p*H 2 to 6 under the conditions shown in Fig. 3 there was no destruction, but actually an increase in activity. This increase was time and temperature dependent and reached a maximum of 20–25% in three hours at 40°. After four hours at 40° the activity began to decrease and had returned to its original level after 24 hours. Previously published work has suggested the possible existence of two active forms of CoA.[3] The main evidence for a second active component was a minor transacetylase-active peak beside the major peak in the electrophoretic pattern of CoA. Whether or not this minor peak and the transitory existence of a more active form are related has not yet been determined.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

The Metalation of Dialkyl Sulfones

BY WILLIAM E. TRUCE AND KENNETH R. BUSER

RECEIVED FEBRUARY 15, 1954

Dimethyl sulfone (I) was monometalated by ethylmagnesium bromide, methylmagnesium iodide and *n*-butyllithium; the resulting organometallic compounds were added to benzaldehyde and benzophenone. With the intermediate methanesulfonylmethylmagnesium bromide (II), superior yields were obtained using anisole rather than benzene as the solvent. Tetrahydrothiophene-1,1-dioxide was metalated in poor yield by ethylmagnesium bromide.

The recent report of mono- and dimetalation of dimethyl sulfone (I) by ethylmagnesium bromide[1] has prompted the presentation of the following related work. The only earlier reference to the action of organometallic compounds on dialkyl sulfones is the report[2] that Grignard reagents have no effect on diisoamyl sulfone; however, this work was not properly designed to detect metalation. Several workers[1,3] have investigated the action of organometallic reagents on alkyl aryl sulfones.

The present investigation concerns the metalation of I by methylmagnesium iodide, ethylmagnesium bromide and *n*-butyllithium. The metalated derivatives were added successfully to benzophenone

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(1) L. Field and J. W. McFarland, THIS JOURNAL, **75**, 5583 (1953).

(2) H. Hepworth and H. W. Clapham, *J. Chem. Soc.*, 1192 (1921).

(3) E. P. Kohler and H. Potter, THIS JOURNAL, **57**, 1316 (1935); W. M. Ziegler and R. Conner, *ibid.*, **62**, 2596 (1940); F. J. Webb, *Iowa State Coll. J. Sci.*, **17**, 152 (1942); H. A. Potter, paper presented to the Spring Meeting of the Midland Section of the A.C.S. in 1951; L. Field, THIS JOURNAL, **74**, 3920 (1952).

and benzaldehyde to give the corresponding β-hydroxysulfones. Field and McFarland[1] reported only a 33% yield (based on I) of adduct *via* methanesulfonylmethylmagnesium bromide (II) and benzaldehyde. The low yield was attributed to dimetalation of I. However, when II is prepared in anisole and added to benzaldehyde, a 65% yield of β-hydroxy-β-phenylethyl methyl sulfone (III) is obtained. This product is of comparatively high purity even without recrystallization and there is little evidence of side products such as would be formed by dimetalation. The latter yield is based on benzaldehyde, which makes it difficult to make a close comparison with Field and McFarland's work as regards the effect of solvent on the reaction. However, the results do establish that there is a solvent effect in this reaction. The superiority of anisole as a solvent may be related to its intermediate basicity as compared to ether and benzene. Although a basic solvent retards the formation of the ketone-Grignard coördination complex which is a suggested intermediate in both normal and abnormal Grignard reactions, anisole and phenetole have been found to be superior to less basic solvents such as benzene as well as to more basic solvents such as ether, tetrahydrofuran and tertiary amines.[4] The abnormal behavior obtained in benzene is apparently due to the insolubility of the metalated derivative in this solvent. Although a precipitate of II is observed in anisole as well as in benzene, this precipitate appears to be much more colloidal and more soluble in anisole than it is in benzene. Furthermore, a higher reaction temperature may be realized with anisole than with benzene.

The most active metalating agent was found to be *n*-butyllithium, which metalates I in benzene to give excellent yields of methanesulfonylmethyllithium (IV). Addition of IV to benzaldehyde gave an 85% yield of III.

$$\underset{\text{I}}{CH_3SO_2CH_3} \xrightarrow[C_6H_6]{n\text{-}C_4H_9Li} \underset{\text{IV}}{CH_3SO_2CH_2Li} \xrightarrow{C_6H_5CHO} \xrightarrow{H^+,\ H_2O} \underset{\text{III (85\%)}}{CH_3SO_2CH_2CH(OH)C_6H_5}$$

The structure of III was established by comparison with a sample prepared from the corresponding Grignard reagent,[1] and by dehydration to the known β-phenylvinyl methyl sulfone (V).[5]

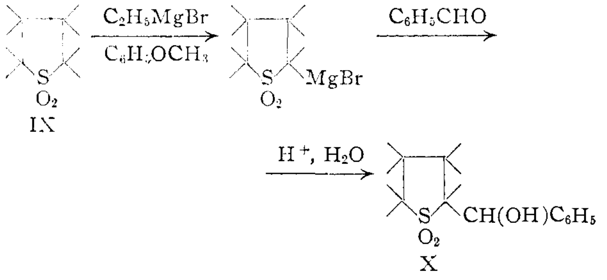
Methanesulfonylmethylmagnesium iodide (VI) was prepared by metalation of I with methylmagnesium iodide. When VI was prepared in benzene and treated with benzophenone, β,β-diphenyl-β-hydroxyethyl methyl sulfone (VII) was obtained in 19% yield.

$$\underset{\text{VI}}{CH_3SO_2CH_2MgI} \xrightarrow{(C_6H_5)_2CO} \xrightarrow{H^+,\ H_2O} \underset{\text{VII}}{CH_3SO_2CH_2C(OH)(C_6H_5)_2}$$

However, when diethyl ether was used as the solvent, no product could be isolated. The superiority of anisole in this reaction was also demonstrated since the preparation of VII in this solvent using II as the addendum was accomplished in 48% yield.

When IV was treated with benzophenone in benzene, VII was isolated in 46% yield and in this case IV appears to have little advantage over II when the latter agent is used in anisole. Dehydration of VII yielded β,β-diphenylvinyl methyl sulfone (VIII).

Tetrahydrothiophene-1,1-dioxide (IX) was metalated in anisole by ethylmagnesium bromide and the metalated derivative was treated with benzaldehyde to give a very poor yield (4%) of 2-(phenylhydroxymethyl)-tetrahydrothiophene-1,1-dioxide (X).



Variations in reaction conditions applied to the metalation of I are summarized in Table I. This compilation indicates that superior yields are obtained when the metalating agent is refluxed approximately three hours with the sulfone. When the subsequent reactant is benzophenone, best yields are obtained by heating the reaction mixture for 1.5 to 2 hours followed by stirring overnight at room temperature, whereas with benzaldehyde, heating seems to be unnecessary.

Experimental

Eastman Kodak Co. anisole for this work was purified by distillation and then dried with calcium hydride. All melting points are uncorrected.

Methanesulfonylmethylmagnesium Bromide (II).—To a solution of 6.59 g. (0.07 mole) of dimethyl sulfone (I)[6] in 300 cc. of dry anisole under nitrogen was added dropwise 46.6 cc. of 1.5 *N* ethylmagnesium bromide in ether. The reaction mixture was heated for 3 hours at 90–100°, and was then allowed to stir at room temperature for 2 hours.

Methanesulfonylmethylmagnesium Iodide (VI).—This procedure was modified in a number of respects as subsequent investigations were carried out. Details may be obtained from Table I. A typical procedure is given below.

A mixture of 6.59 g. (0.07 mole) of I and 100 cc. of dry benzene was metalated with a methylmagnesium iodide-ether solution prepared from 1.71 g. (0.07 mole) of magnesium turnings and 9.94 g. (4.36 cc., 0.07 mole) of methyl iodide. The reaction mixture was refluxed gently for 2 hours.

Methanesulfonylmethyllithium (IV).—A solution of I in 300 cc. of dry benzene was metalated with *n*-butyllithium. The number of moles of I was determined by the normality of the *n*-butyllithium solution. A mole-per-mole ratio of *n*-butyllithium to sulfone was used. The reaction mixture in each case was refluxed for 2.5 to 3 hours under nitrogen.

β-Hydroxy-β-phenylethyl Methyl Sulfone (III). Procedure A.—A solution of 5.3 g. (0.05 mole) of freshly distilled benzaldehyde in 20 cc. of dry anisole was added rapidly to a mixture of II in anisole. This reaction mixture was stirred at room temperature for 17 hours. Hydrolysis with 2.5 *N* hydrochloric acid was followed by extraction with benzene and the organic layer was washed with a saturated solution of sodium chloride. After drying with anhydrous sodium sulfate, low boiling solvents were removed by atmospheric pressure distillation and then anisole was removed at reduced pressure. The crystalline residue left in the flask

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[4] R. N. Lewis and J. R. Wright, THIS JOURNAL, **74**, 1255 (1952).

[5] W. E. Truce, J. A. Simms and H. E. Hill, *ibid.*, **75**, 5412 (1953).

[6] H. Gilman and H. S. Broadbent, *ibid.*, **69**, 2053 (1947).

TABLE I

EFFECT OF REACTION CONDITIONS ON THE YIELD OF ADDUCT OBTAINED WITH $CH_3SO_2CH_2M$[a]

Metalating agent	Moles metal- ating agent	Solvent	Moles of sulfone	Reflux temp. of metalation reactn., °C.	Reflux time of sulfone with metalating agent, hr.	Type of reactant added	Moles of reactant added	Reflux temp. of CH_3SO_2-CH_2M with reactant, °C.	Reflux time of CH_3SO_2-CH_2M with reactant, hr.	Yield of adduct, %
CH_3MgI	0.07[b]	C_6H_6	0.07	80	0.5	$(C_6H_5)_2CO$	0.04	80 25	1 16.5	10
CH_3MgI	.07[b]	C_6H_6	.07	80	2	$(C_6H_5)_2CO$	.05	80 25	2 16.5	19
CH_3MgI	.07[b]	C_6H_6	.07	80	2	$(C_6H_5)_2CO$	.05	80 25	7 12	16
CH_3MgI	.07[b]	$(C_2H_5)_2O$	.07	36	2	$(C_6H_5)_2CO$	.05	36 25	2 16.5	0
C_2H_5MgBr	.07[c]	$C_6H_5OCH_3$	.07	90	3	$(C_6H_5)_2CO$	.05	90 25	1.5 16.5	48
n-C_4H_9Li	.07[c]	C_6H_6	.07	80	2.5	$(C_6H_5)_2CO$	.06	25	18	46
C_2H_5MgBr	.07[c]	$C_6H_5OCH_3$	.07	100 25	3 2	C_6H_5CHO	.05	25	17	65
n-C_4H_9Li	.046[c]	C_6H_6	.046	80	3	C_6H_5CHO	.04	25	14	85

[a] In the formula $CH_3SO_2CH_2M$, M refers to –MgI, –MgBr, or –Li. [b] Calculated to be the theoretical possible yield. [c] Yield as determined by actual titration of an aliquot sample.

after the anisole had been removed was recrystallized twice from benzene–carbon tetrachloride, yielding 6.50 g. (65%) of III, m.p. 104–105°. Two more recrystallizations from benzene–carbon tetrachloride raised the melting point to 106.0–106.5°, lit. 102–104°.[1]

Anal. Calcd. for $C_9H_{12}O_3S$: C, 53.95; H, 6.04; S, 16.00. Found: C, 53.83; H, 6.03; S, 15.82.

Procedure B.—A solution of 4.25 g. (4.05 cc., 0.04 mole) of freshly distilled benzaldehyde in 20 cc. of dry benzene was added rapidly to IV prepared from 4.33 g. (0.046 mole) of I and 0.046 mole of n-butyllithium. This mixture was stirred at room temperature for 14 hours. Hydrolysis and purification were carried out as in procedure A giving 6.8 g. (85%) of III, m.p. 103.0–104.5°. A mixed melting point with material prepared by procedure A was not depressed.

β,β-Diphenyl-β-hydroxyethyl Methyl Sulfone (VII).—Several different procedures were followed in preparing this compound and the variations in reaction conditions are summarized in Table I. Below are typical procedures describing the preparation of VII by use of each type of the three organometallic derivatives.

Procedure C.—A solution of 9.1 g. (0.05 mole) of benzophenone in 10 cc. of dry benzene was added dropwise to VI in benzene. The reaction mixture was refluxed gently for 2 hours followed by stirring at room temperature for 16.5 hours. Hydrolysis and purification were carried out as in the preparation of III yielding 2.65 g. (19%) of VII, m.p. 139.0–139.5°.

Anal. Calcd. for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.84; S, 11.60. Found: C, 65.19; H, 5.85; S, 11.50.

Procedure D.—A solution of 9.1 g. (0.05 mole) of benzophenone in 20 cc. of dry anisole was added slowly to II in anisole. The reaction mixture was heated for 2 hours between 90–100° and was then stirred 16.5 hours at room temperature. Hydrolysis was executed as usual and extraction, washing and drying were performed as given in the above procedures in benzene. Anisole was removed under reduced pressure. A crystalline residue remained which after recrystallization from benzene–carbon tetrachloride twice amounted to 6.56 g. (48%) of VII, m.p. 139.0–139.5°.

Procedure E.—A solution of 10.93 g. (0.06 mole) of benzophenone in 20 cc. of dry benzene was added rapidly to IV prepared from 0.07 mole of I and 0.07 mole of n-butyllithium. The reaction mixture was stirred 18 hours at room temperature under nitrogen. Hydrolysis and purification were carried out as usual yielding after recrystallization from benzene–carbon tetrachloride, 7.63 g. (46%) of VII, m.p. 139.5–140.0°.

Metalation of Tetrahydrothiophene-1,1-dioxide (IX).—A solution of 8.41 g. (0.07 mole) of IX in 300 cc. of dry anisole was treated with 0.07 mole of 1.5 N ethylmagnesium bromide in ether. The mixture was refluxed for 3 hours.

2-(Phenylhydroxymethyl)-tetrahydrothiophene-1,1-dioxide (X).—A solution of 5.30 g. (5.05 cc., 0.05 mole) of freshly distilled benzaldehyde in 20 cc. of dry anisole was added rapidly to cooled IX and this reaction mixture was stirred at room temperature for 18 hours. Hydrolysis, extraction, washing, drying and solvent removal were carried out as for the above metalations in anisole. The black oily residue was dissolved in benzene, decolorized with Norite and then the benzene was evaporated. A brown oil remained which crystallized on trituration with benzene–carbon tetrachloride. Recrystallization three times from benzene–carbon tetrachloride gave 0.49 g. (4%) of X, m.p. 159.0–159.5°.

Anal. Calcd. for $C_{11}H_{14}O_3S$: C, 58.38; H, 6.24; S, 14.17. Found: C, 58.47; H, 6.43; S, 14.11.

β-Phenylvinyl Methyl Sulfone (V).—Seventeen cubic centimeters of 85% orthophosphoric acid and 2.54 g. (0.013 mole) of III were stirred 15 minutes at reflux temperature. The solution was cooled and 40 g. of ice was added while stirring. The solution was extracted with benzene and the benzene solution was washed with a saturated solution of sodium chloride. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed leaving a crystalline residue. Recrystallization from aqueous ethanol once and aqueous methanol twice gave 0.81 g. (35%) of V, m.p. 79–80°, lit. 79–80°.[5]

A mixed melting point of this compound with an authentic sample prepared by Mr. J. A. Simms[5] was not depressed.

β,β-Diphenylvinyl Methyl Sulfone (VIII).—This procedure was identical with the preparation of V except for the fact that 3.00 g. (0.011 mole) of VII was dehydrated using 20 cc. of 85% orthophosphoric acid; yield of VIII, 1.89 g. (68%), m.p. 113–115°.

Anal. Calcd. for $C_{15}H_{14}O_2S$; C, 69.74; H, 5.42; S, 12.41. Found: C, 69.77; H, 5.54; S, 12.61.

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