JOC Article

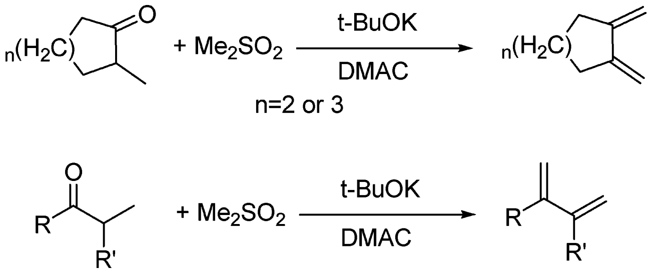
Studies of the Condensation of Sulfones with Ketones and Aldehydes

Michael E. Garst,[†] Lloyd J. Dolby,* Shervin Esfandiari, Rachel A. Okrent, and Alfred A. Avey

Organic Consultants, Inc., 132 East Broadway, Suite 107, Eugene, Oregon 97401

Orgcon2@Mindspring.com

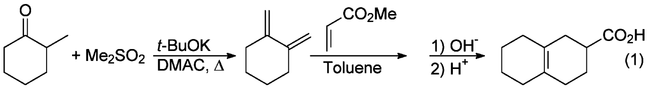
Received September 16, 2005



The condensation of ketones or aldehydes with sulfones was shown to give a variety of products. Condensation of 2-methylcyclohexanone with dimethyl sulfone using potassium *t*-butoxide as base gave useful yields of 1,2-dimethylenecyclohexane. Under the same conditions, cycloheptanone, 3-methyl-2-butanone, and 2-butanone were converted to dienes. Remarkably, these reaction conditions converted acetophenone into *p*-terphenyl (10%) and (*E*)-1,4-diphenyl-3-penten-1-one (44%). Propiophenone was converted to 2′-methyl-*p*-terphenyl (61%). Using α-tetralone produced 1-methynaphthalene and naphthalene. No reaction took place with *β*-tetralone. Using diethyl sulfone with α-tetralone lead to pure naphthalene. Condensation of isobutyraldehyde and dimethyl sulfone using potassium *t*-butoxide gave isoprene in low yield. Using benzaldehyde and benzyl phenyl sulfone in *N*,*N*-dimethylacetamide gave 1,2-diphenyl-1-phenylsulfonylethylene, *N*,*N*-dimethylcinnamide, and a complex condensation product. Only 1,2-diphenyl-1-phenylsulfonylethylene was obtained when the solvent was THF.

Introduction

The critical step of a recent synthesis required 1,2-dimethylenecyclohexane (**1a**). The Diels−Alder condensation of **1a** with methyl acrylate gives the required octalin intermediate **2a** with the double bond in the desired position. Most reported preparations of 1,2-dimethylenecyclohexane are several steps and are not readily adapted to large-scale synthesis.[1,2] One report claims good yields of **1a** from condensation of dimethyl sulfoxide with 2-methylcyclohexanone.[1b] However, the published yields from this synthesis were higher than we were able to achieve. In our hands, the reaction gave very poor yields and a noteworthy stench. On consideration of the proposed mechanism, it appeared to us that the reaction might go better by substituting dimethyl sulfone for dimethyl sulfoxide. We were pleased to find that the condensation of 2-methylcyclohexanone with dimethyl sulfone using potassium *t*-butoxide in *N*,*N*-dimethylacetamide (DMAC) gave useful yields of 1,2-dimethylenecyclohexane (eq 1). The crude 1,2-dimethylenecyclohexane is contaminated with impurities which are difficult to separate. However, the toluene solution of the crude diene **1a** was used directly in the Diels−Alder reaction with methyl acrylate and the desired adduct was readily purified. This sequence gave 1,2,3,4,5,6,7,8-octahydro-2-naphthoic acid[1a] (**2a**) in 49% yield based on 2-methylcyclohexanone.



1a **2a**

[†] Allergan Inc., 2525 DuPont Drive, Mail Code RD3D, Irvine, California 92612.

(1) (a) Bailey, W. J.; Golden, H. R. *J. Am. Chem. Soc.* **1953**, *75*, 4780. (b) Arenz, T.; Vostell, M.; Frauenerath, H. *Synlett* **1991**, 23. (c) Bloomquist, A. T.; Longone, D. T. *J. Am. Chem. Soc.* **1957**, *79*, 3916. (d) Bartlett, P. D.; Wingrove, A. S.; Owyang, R. *J. Am. Chem. Soc.* **1968**, *90*, 6067. (e) Van Straten, J. W.; van Norden, J. J.; van Schaik, T. A. M.; Franke, G. T.; de Wolf, W. H.; Bickelhaupt, F. *Recl.: J. R. Neth. Chem. Soc.* **1978**, 105. (f) Quin, L. D.; Leimert, J.; Miller, R. W.; McPhail, A. T. *J. Org. Chem.* **1979**, *44*, 6. (g) Block, E.; Aslam, M. *Org. Synth. Coll. Vol. VIII*, **1993**, 212.

(2) Bailey, W. J.; Golden, H. R. *J. Am. Chem. Soc.* **1957**, *79*, 6516.

10.1021/jo051947s CCC: $33.50

TABLE 1. Summary of Diene Synthesis and Diels−Alder Reactions

ketone/aldehyde	diene	yield (%)/method	dienophile	product	yield (%)
2-methylcyclohexanone	**1a**	A	methyl acrylate	**2a**	49
3-methyl-2-butanone	**3**	ca. 40/A	methyl acrylate	**4**	36
2-butanone	**5**	26/A			
isobutyraldehyde	**11**	7.5/B			
2-methylcycloheptanone	**1b**	42/A	maleic anhydride	**2b**	30

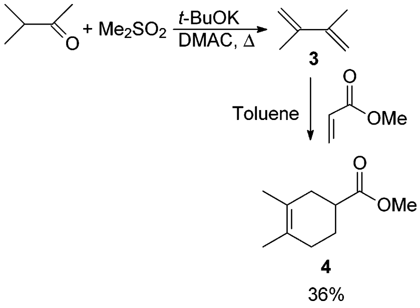
We have made a preliminary study of the scope of this reaction by using various ketones and aldehydes with three sulfones.

Results and Discussion

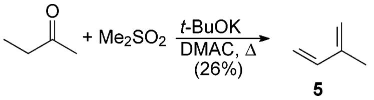
Reaction of Ketones with Dimethyl Sulfone. A study of reaction conditions was carried out for the synthesis of diene **1a**. First, a variety of solvents were explored. *N*-methylpyrrolidone, DMSO, DMAC, DMF, glyme, and diglyme gave similar results. However, a poor yield (<10%) was obtained in refluxing THF: this is most likely due to the lower reaction temperature. To test this hypothesis, two identical reactions in DMAC were run at 100 and 90 °C giving the diene **1a** in yields of 60% and 40%, respectively. DMAC was chosen as the solvent simply because it is easily removed by aqueous extraction.

The scope of this reaction was explored by studying variations in ring size and substituents for cyclic ketones. The reaction was further examined with several aromatic and acyclic ketones. The reaction of cyclohexanone and dimethyl sulfone with potassium *t*-butoxide in DMAC was expected to give 3-methylenecyclohexene. The reaction gave a mixture of four compounds by GC analysis. Analysis of the mixture by UV, NMR, and GC/MS showed all four of the compounds to be isomers of the molecular formula C_7H_{10}.[3] It appears that the expected product is formed and suffers double-bond isomerization under the strongly basic reaction conditions. Unfortunately, no reaction occurred when potassium carbonate was used as the base. However, the diene products obtained from dimethyl sulfone and cyclohexanone are markedly different from the product obtained with dimethyl sulfoxide and cyclohexanone which was identified as 2-methylenecyclohexyl methanesulfenate.[1b] This result shows that the products obtained with dimethyl sulfoxide are not derived from contaminating dimethyl sulfone. The reaction of 2,6-dimethylcyclohexanone with dimethyl sulfone and potassium *t*-butoxide in DMAC gave a mixture of seven unidentified compounds. Similarly, the reaction of 2-methylcyclopentanone gave no useful products. However, under the same conditions, 2-methylcycloheptanone gave 1,2-dimethylenecycloheptane[1e,g] (**1b**), isolated as the Diels−Alder adduct of maleic anhydride (5-oxatricyclo[7.5.0.0⟨3,7⟩]tetradec-1(9)-ene-4,6-dione, **2b**) in 30% overall yield (Table 1). These conditions, when applied to 3-methyl-2-butanone, gave 2,3-dimethyl-1,3-butadiene (**3**, Scheme 1). To get an estimate of the yield, a portion of the crude product was treated with methyl acrylate to give 3,4-dimethylcyclohex-3-ene carboxylate (**4**)[4] in 36% yield. This reaction is thus quite convenient for producing a solution of 2,3-dimethyl-1,3-butadiene (**3**) to use in Diels−Alder condensations if an alternative to the pinacol procedure is needed.[5]

SCHEME 1



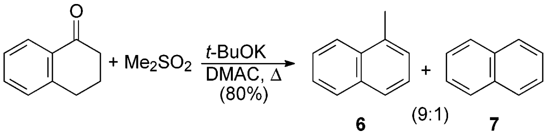
Treatment of 2-butanone under identical conditions gave isoprene (**5**) in 26% yield after distillation (eq 2).



5

(2)

When a solution of α-tetralone and dimethyl sulfone in DMAC was treated with potassium *t*-butoxide, a 9:1 mixture of 1-methylnaphthalene (**6**) and naphthalene (**7**) was obtained in 85% combined yield (eq 3). The origin of the naphthalene was explored in connection with the study of the condensation of α-tetralone with diethyl sulfone, a reaction which gives naphthalene (**7**) exclusively (vide infra).

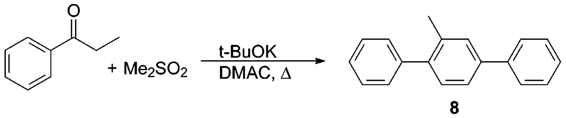


6 **7**

(3)

However, when *β*-tetralone was used instead of α-tetralone, no reaction took place. It appears that *β*-tetralone is converted to the enolate under the reaction conditions, and there is not a high enough concentration of dimethyl sulfone anions and free *β*-tetralone to give a reaction.

Surprisingly, when propiophenone was treated with dimethyl sulfone and potassium *t*-butoxide in DMAC, 2′-methyl-*p*-terphenyl (**8**)[6] was formed in 61% yield (eq 4). That **8** is indeed the product was confirmed by X-ray crystallography. Formation of **8** requires two molecules of propiophenone and one carbon from dimethyl sulfone as well as a two-electron oxidation.



8
(61%)

(4)

---

[3] Spangler, C. W.; Hartford, T. W. *J. Chem. Soc., Perkin Trans. I* **1976**, *16*, 1792.

[4] Inukai, T.; Kasai, M. *J. Org. Chem.* **1965**, *30*, 3567.

[5] Allen, C. F. H.; Bell, A. *Org. Synth. Coll. Vol III*, 312.

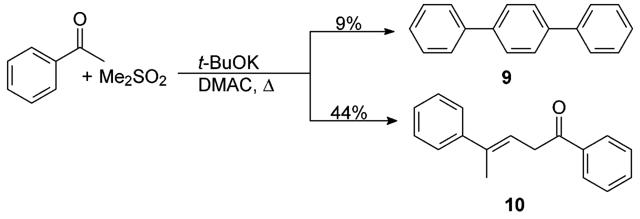
[6] Sidorova, N. G.; Nikonovich, S. D. *Zh. Obshch. Khim.* **1960**, *30*, 921; *Chem. Abstr.* **1960**, *55*, 6451f.

TABLE 2. Summary of Reactions with Aromatic Ketones and Aldehydes with Various Sulfones

compound	sulfone	product	method	yield (%)
propiophenone	Me_2SO_2	**8**	A	61
acetophenone	Me_2SO_2	**9**	A	9
		10		44
α-tetralone	Me_2SO_2	9:1 ratio of **6**/**7**	A	85
α-tetralone	Et_2SO_2	**7**	A	87
α-tetralone	benzyl phenyl sulfone	NR	A	
β-tetralone	Me_2SO_2	NR	A	
2-methylcyclohexanone	Et_2SO_2	no useful product	A	
benzaldehyde	benzyl phenyl sulfone	**12**	B	7.8
		13		57
		14		25
benzaldehyde	benzyl phenyl sulfone	**12**	B[a]	78

[a] THF solvent.

SCHEME 2

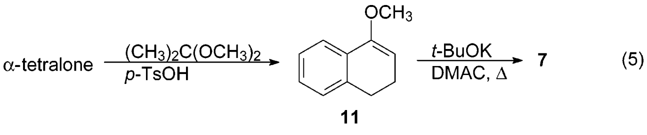


Under the same reaction conditions, acetophenone and dimethyl sulfone gave *p*-terphenyl (**9**)[7] and *E*-1,4-diphenyl-3-penten-1-one (**10**)[8] (Scheme 2).

Formation of *p*-terphenyl must involve two molecules of acetophenone and requires two carbons from dimethyl sulfone. A plausible mechanism involves ketone **10** as an intermediate. Ketone **10** would be expected to lead to a mixture of the 2,5-diphenyl-1,3,5-hexatrienes, which in turn would give terphenyl upon cyclization and oxidation.

Reaction of Ketones with Diethyl Sulfone and Benzyl Phenyl Sulfone. Reaction of 2-methylcyclohexanone and diethyl sulfone with potassium *t*-butoxide in DMAC did not give any useful products. As noted before, when α-tetralone was treated with dimethyl sulfone, 1-methylnaphthalene (**6**) and naphthalene (**7**) were formed in the ratio of 9:1 (eq 3, Table 2). However, when α-tetralone was treated with diethyl sulfone, only naphthalene was formed in 87% yield.

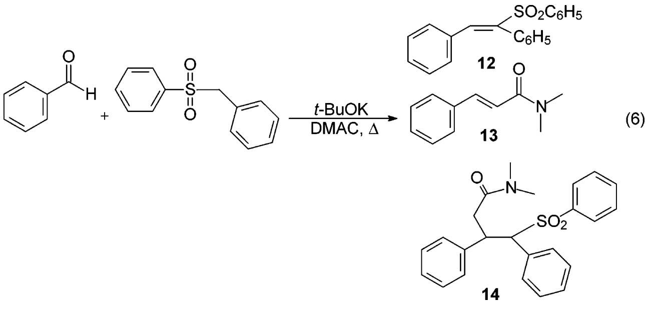
In an attempt to determine the intermediate in this reaction, α-tetralone was converted to 1-methoxy-3,4-dihydronaphthalene (**11**)[9] with 1,2-dimethoxypropane in the presence of *p*-TsOH. When **11** was treated with potassium *t*-butoxide in DMAC, naphthalene was formed in nearly quantitative yield (eq 5).



From this result, it appears that the enolate of α-tetralone is alkylated on oxygen by diethyl sulfone to give 1-ethoxyl-3,4-dihydronaphthalene which would lead to naphthalene. Using dimethyl sulfone, which is more acidic than diethyl sulfone, causes more condensation and less alkylation of the enolate to take place.

Only starting materials were recovered from the attempted condensation of α-tetralone with benzyl phenyl sulfone using potassium *t*-butoxide in DMAC. We conclude that the anion derived from benzyl phenyl sulfone is too stable to react with a sluggish ketone. However, benzyl phenyl sulfone does condense with the more reactive benzaldehyde (vide infra).

Reaction of Aldehydes with Sulfones. The reaction of isobutyraldehyde and dimethyl sulfone with potassium *t*-butoxide in DMAC gave 2-methyl-1,3-butadiene (**5**) in 7.5% yield after distillation. The reaction of *n*-heptanal and dimethyl sulfone under these conditions did not afford 1,3-octadiene. However, benzaldehyde and benzyl phenyl sulfone in the presence of potassium *t*-butoxide in DMAC gave a mixture of 1,2-diphenyl-1-phenylsulfonylethylene (**12**),[10] *N*,*N*-dimethylcinnamide (**13**),[11] and a condensation product (**14**) derived from one molecule of each of the three organic materials in the reaction mixture (eq 6). The structure of compound **14** was obtained by X-ray crystallography.



When this reaction was carried out in THF instead of DMAC, only **12** was formed in 78% yield.

Experimental Section

General. Gas chromatography was performed on a capillary column (HP-1 30 m × 0.32 mm and 0.25 μm film) with flame ionization detection or on a megabore column (HP-5 10 m × 0.53 mm and 2.53 μm film) with thermal conductivity detection. NMR spectra were obtained on a 300 MHz or on a 60 MHz, in $CDCl_3$ with 1% TMS, instrument. All reactions were performed under nitrogen. Column chromatography was performed on flash silica

---

[7] Carnelley, T. *J. Chem. Soc.* **1880**, *37*, 701.

[8] Koppes, M. J. C. M.; Crabbendam, A. M.; Cerfontain, H. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 676.

[9] (a) Motohashi, S.; Satomi, M.; Fujimoto, Y.; Tatsuno, T. *Synthesis* **1982**, *12*, 1021. (b) Ortholand, J.-Y.; Vicart, N.; Greiner, A. *J. Org. Chem.* **1995**, *60*, 1880.

[10] Hellman, H.; Erbele, D. *Ann.* **1963**, *662*, 188.

[11] Staudinger, H.; Kon, N. *Liebigs Ann. Chem.* **1911**, *384*, 38.

gel (60 Å, 32−63 μ). All reagents and solvents were purchased from commercial suppliers and used as received without further purification.

Method A. General Procedure for Condensations of Ketones with Dimethyl Sulfone as Exemplified by Preparation of 1,2-Dimethylenecyclohexane. A mechanically stirred solution of 2-methylcyclohexanone (208 g, 1.86 mol) and dimethyl sulfone (419.5 g, 4.28 mol) in DMAC (2750 mL) was heated on a steam bath to 75 °C. Powdered potassium *t*-butoxide (500 g, 4.46 mol) was added all at once. The inside temperature rose to 98 °C upon addition, and heating continued for 2 h. The GC analysis of the reaction showed the reaction to be complete. The reaction was cooled to room temperature in an ice bath, diluted with water (2 L), and extracted with toluene (3 × 1 L). The toluene solution could be processed to isolate the primary condensation products or used directly in a Diels−Alder reaction.

Method B as Exemplified by Preparation of 2-Methyl-1,3-butadiene. A 500 mL three-necked flask fitted with a distillation head with an efficient condenser, mechanical stirrer, and thermometer was charged with dimethyl sulfone (43.2 g, 0.46 mol), potassium *t*-butoxide (53.76 g, 0.48 mol), and DMAC (200 mL). The solution was then heated on a steam bath. When the internal temperature reached 90 °C, a solution of isobutyraldehyde (14.4 g, 0.2 mol) in DMAC (50 mL) was added dropwise over a period of 30 min. Volatile product began to collect in the receiving flask, which was cooled in an ice−methanol bath. Distillation was complete after 1 h. The distillate (8 g) was washed with ice cold water (1 × 5 mL) and 1 M HCl (1 × 5 mL) and filtered through 1 PS paper to give 1.0 g of 2-methyl-1,3-butadiene (**5**) (7.5%).

Acknowledgment. We thank Prof. Marilyn Olmstead of the Chemistry Department of the University of California, Davis, for the crystal structure determinations.

Supporting Information Available: Text giving experimental details, characterization of new compounds, and X-ray crystallographic files for **8** and **14** in CIF format is presented. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051947S