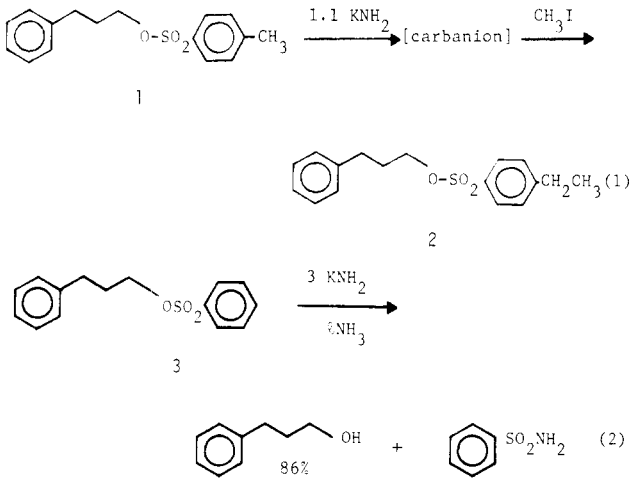
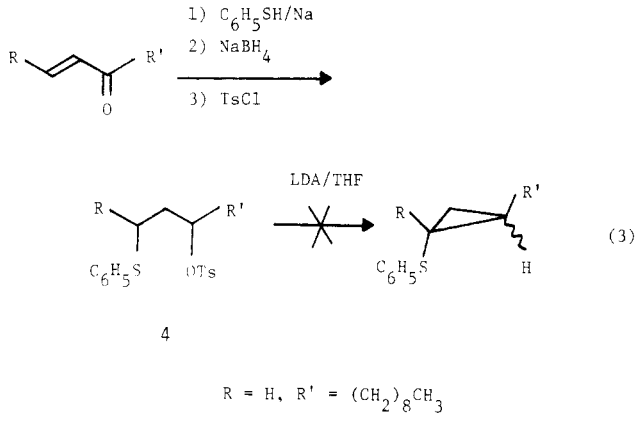


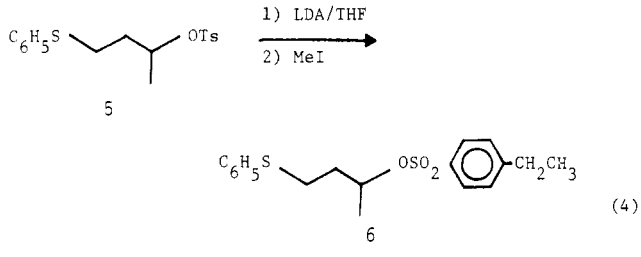
propanol and benzenesulfonamide, resulting from cleavage of the oxygen–sulfur bond, were obtained instead of products from β or γ elimination.

Realizing that deprotonation of the tosyl group affects reactivity under strongly basic reaction conditions, we reexamined a proposed general synthetic route to phenylthiocyclopropanes (eq 3) which was abandoned when

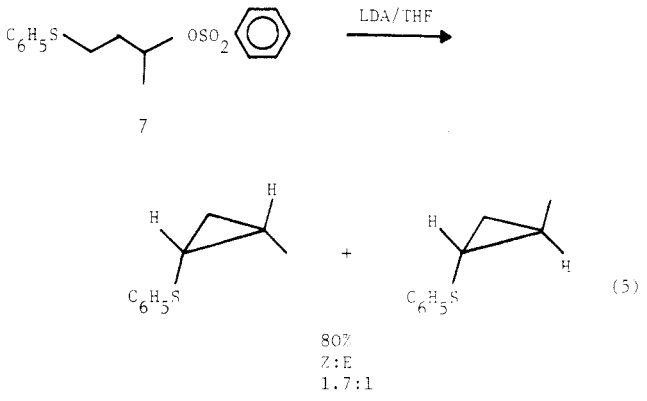


treatment of tosylate **4** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) did not result in cyclization.[4] Failure of the ring closure was attributed to inadequate carbanion stabilization by the phenylthio group since closure of the corresponding sulfone proceeded under the same conditions.

We observed that addition of methyl iodide to the reaction mixture prepared from a similar ester, **5**, and LDA in THF gives the ethyl derivative **6**[8] (eq 4) in 80% yield.



This suggested that a successful ring closure might be achieved if the benzenesulfonate were used instead of the tosylate. Indeed, with the benzenesulfonate **7** a mixture of *cis*- and *trans*-2-methylcyclopropyl phenyl sulfide is obtained in high yield (eq 5), demonstrating that LDA will in fact α-metalate alkyl aryl sulfides.[9] With the relatively



hindered base LDA, no complications arise from substitution at the sulfonyl moiety. Interestingly, the isomer distribution obtained (1.7:1 Z/E)[10] complements an alternate route[11] to the 2-methylcyclopropyl phenyl sulfides (1:5 Z/E).

Clearly these facile deprotonations by amide bases must be considered in the design of synthetic schemes and almost certainly may be extrapolated to include mesylates as well as tosylates.[4,12]

Acknowledgment. We are grateful to Professor J. F. Bunnett for stimulating discussions.

Registry No. **1**, 3742-75-4; **2**, 72444-53-2; **3**, 72444-54-3; **4**, 72444-55-4; **5**, 72444-56-5; **6**, 72444-57-6; **7**, 72444-58-7; 3-phenylpropyl iodide, 4119-41-9; 3-phenylpropyl bromide, 637-59-2; 3-phenylpropyl chloride, 104-52-9; 3-phenylpropyl fluoride, 2038-62-2; 3-phenyl-1-propanol, 122-97-4; benzenesulfonamide, 98-10-2; *cis*-2-methylcyclopropyl phenyl sulfide, 63365-89-9; *trans*-2-methylcyclopropyl phenyl sulfide, 63365-88-8; phenylcyclopropane, 873-49-4.

(9) If the alkyl group is not methyl, more forcing conditions have generally been required: Dolak, T. M.; Bryson, T. A. *Tetrahedron Lett.* **1977**, 1961.

(10) Determined by GLC (20% Carbowax 20M on Chromosorb W at 165 °C). Preparative GLC afforded pure samples of the *Z* and *E* isomers, each of which had spectral data in accord with literature values (see ref 11).

(11) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Rigby, J. H.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 3080.

(12) (a) Comparison of the pK_a data for $PhSO_2CH_3$ [pK_a = 29: Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006] to those for $PhSO_2PhCH_3$ [pK_a = 29.8: Bordwell, F. G.; Algrim, D.; Vanier, N. R. *J. Org. Chem.* **1977**, *42*, 1817] supports this extrapolation. (b) The α-lithio derivative of methyl methanesulfonate has been reported: Corey, E. J.; Durst, T. *J. Am. Chem. Soc.* **1966**, *88*, 5656.

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Oxidative Coupling Reactions Using Silica-Bound Ferric Chloride

Summary: Silica-bound ferric chloride serves as an oxidant for phenols and phenol ethers, leading to coupling of the aromatic rings.

Sir: It has recently been shown that ferric chloride supported on silica gel ($FeCl_3/SiO_2$) can be used for the dehydration and/or rearrangement of alcohols.[1] We re-

(1) Keinan, E.; Mazur, Y. *J. Org. Chem.* **1978**, *43*, 1020.

0022-3263/80/1945-0749$01.00/0

port here that certain aromatic ethers react readily with this reagent. These initial results demonstrate that solid-supported $FeCl_3$ can act as an electron-transfer oxidant, providing a very effective and convenient method for coupling aromatic rings. Two previously unreported coupling reactions have been accomplished with this reagent.

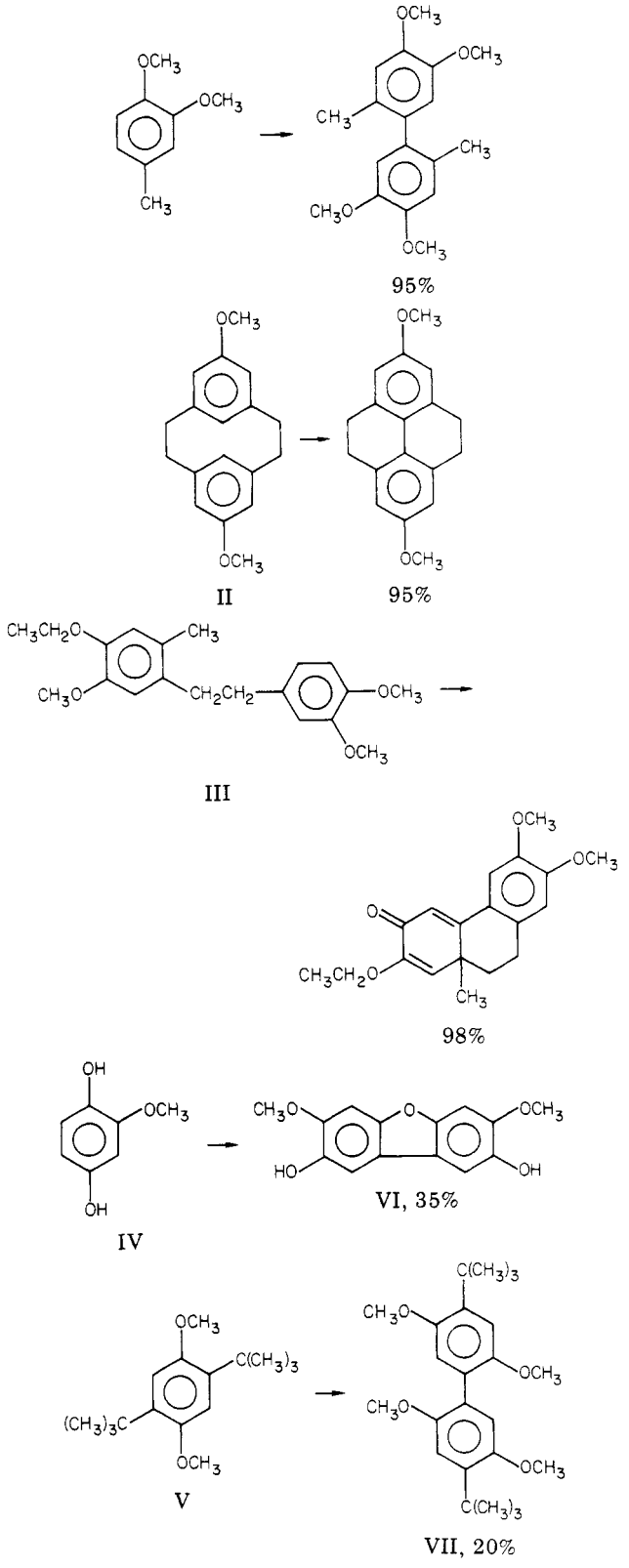
The oxidative coupling of phenols and phenol ethers has been previously accomplished by a wide variety of techniques.[2] These reactions, however, often lead to low yields of the desired products or suffer from disadvantages due to oxidant insolubility or to difficulties in separating the inorganic and organic products. It is, therefore, of interest to use a solid-supported[3] oxidant for these reactions. Initial experiments were performed by using $FeCl_3/SiO_2$ prepared by[1] dissolving an appropriate amount of $FeCl_3 \cdot 6H_2O$ in 95% absolute diethyl ether (5% absolute methanol). This is added to a weighed amount of oven-dried (150 °C) chromatographic-grade SiO_2 (60–200 mesh). The solvent is removed on a rotary evaporator, and the solid is then dried at 80 °C (0.5 torr) for 4 h. The reagent produced is a yellow powder which is moisture and light sensitive. The reactions were performed by adding the aromatic reactant (typically 100 mg) in 10 mL of CH_2Cl_2 to an appropriate amount of either 3 or 9% by weight $FeCl_3/SiO_2$. Usually, an immediate color change was seen. The solvent was removed under reduced pressure on a rotary evaporator, and the mixture was left rotating for 1 h. Water (1 mL) and CH_2Cl_2 (10 mL) were then added, the mixture was stirred, filtered, and washed with more CH_2Cl_2, and the organic products were isolated and identified spectroscopically.[4]

As shown in the reactions of compounds I–V (Scheme I) both intermolecular and intramolecular coupling reactions have been accomplished. The yields, which are indicated, refer to isolated products and are based on added starting material. Compound V reacted incompletely even with excess $FeCl_3/SiO_2$.

Reactions of I–III have been previously reported to proceed by using electrochemical and/or chemical oxidations.[5] The oxidation of III proceeds by coupling and rearrangement. The electrochemical mechanism has in this case been carefully studied,[6] and it is clear that the initial step is electron transfer from the substrate to the anode. The specificity of coupling suggests that the $FeCl_3/SiO_2$ mechanism is similar. As expected from this kind of mechanism, we have shown that for the reactions of I–III, 2 mol of $FeCl_3$ is necessary to give 1 mol of organic product. Equimolar amounts of $FeCl_3$ and organic reactant give product yields of 35–45%. It is found that $FeCl_3/SiO_2$ is not a sufficiently strong oxidant to attack anisole or other substrates which are known to have more positive oxidation potentials. These observations place the effective oxidation potential of the reagent at about 1 V with reference to a saturated calomel electrode.

The reaction product from compound IV has not been previously reported.[7] The mechanism of its formation can be rationalized in terms of electron-transfer oxidation and C–C coupling para to the methoxy group, followed by closure of the furan ring. The observed reaction of V is also new. The product, whose structure proof assumes that the remaining substituents retain their initial arrangement, comes from ipso substitution for the *tert*-butyl groups.

Scheme I



(2) See, for example, references cited in: Miller, L. L.; Stewart, R. F.; Gillespie, J. P.; Ramachandran, V.; So, Y. H.; Stermitz, F. R. *J. Org. Chem.* **1978**, *43*, 1580.

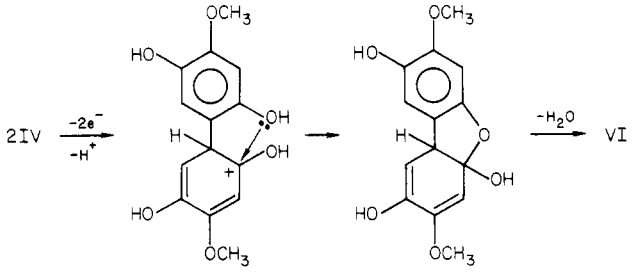
(3) For reviews, see: Posner, G. H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 487. McKillop, A.; Young, D. W. *Synthesis* **1979**, 401.

(4) All products were identified by comparison of their NMR, IR, and mass spectra with those from authentic samples. New compounds VI and VII had proper high-resolution mass spectra. Details will be reported.

(5) These reactions have been previously reported. Reaction of I: McKillop, A.; Turrell, A. G.; Taylor, E. C. *J. Org. Chem.* **1977**, *42*, 164. Reaction of II: Becker, J. Y.; Miller, L. L.; Boekelheide, V.; Morgan, T. *Tetrahedron Lett.* **1976**, 2939. Reaction of III: Falck, J. R.; Miller, L. L.; Stermitz, F. R. *J. Am. Chem. Soc.* **1974**, *96*, 2981.

(6) Kerr, J. B.; Miller, L. L. *J. Am. Chem. Soc.*, in press.

(7) A similar reaction producing VI has been accomplished by R. F. Stewart by anodic oxidation: unpublished results, University of Minnesota.



Similar anodic de-*tert*-butylation processes have been previously observed.[8]

Further applications of $FeCl_3/SiO_2$ as an oxidant will be reported at a later date.

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Registry No. I, 494-99-5; II, 19254-82-1; III, 52711-85-0; IV, 824-46-4; V, 7323-63-9; VI, 72442-70-7; VII, 72428-45-6; ferric chloride, 7705-08-0; 2,2'-dimethyl-4,4',5,5'-tetramethoxydiphenyl, 62012-51-5; 2,7-dimethoxy-4,5,9,10-tetrahydropyrene, 19254-83-2; 9,10-dihydro-10a-methyl-2-ethoxy-6,7-dimethoxy-3(10a*H*)-phenanthrone, 52711-88-3.

(8) Suttie, A. B. *Tetrahedron Lett.* **1969**, 953. Cauquis, G.; Fauvelot, G.; Rigaudy, J. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1967**, *264*, 1758, 1958. Popp, G. *J. Org. Chem.* **1972**, *37*, 3058, 3646. Ronlan, A.; Parker, V. D. *J. Chem. Soc. C* **1971**, 3241.

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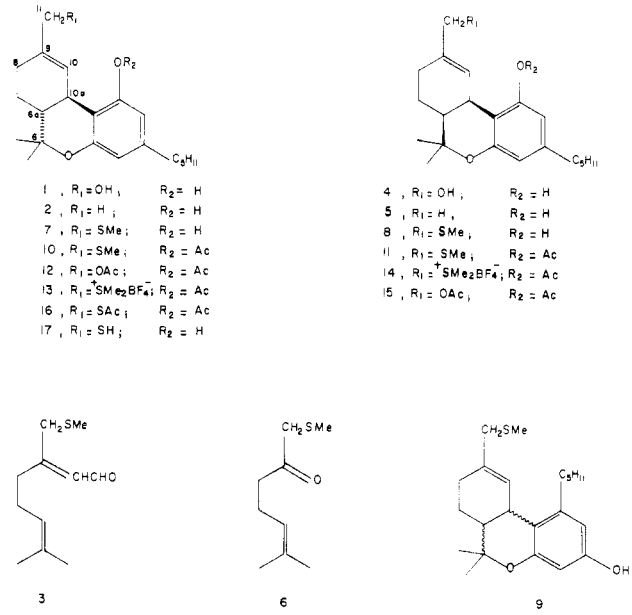
Synthesis of (±)-11-Hydroxy-Δ⁹-6a,10a-*trans*-tetrahydrocannabinol and Other 11-Substituted Δ⁹-Tetrahydrocannabinoids

Summary: 11-Substituted Δ⁹-tetrahydrocannabinoids, including the racemate of the biologically important 11-hydroxy-Δ⁹-6a,10a-*trans*-tetrahydrocannabinol (1) and the corresponding 11-mercapto analogue, are synthesized via condensation of olivetol with the terpenoid synthon 3 prepared from 6-methylhept-5-en-2-one.

Sir: The 11-hydroxy derivative (1) of (−)-Δ⁹-6a,10a-*trans*-tetrahydrocannabinol [(−)-Δ⁹-THC] is a major, pharmacologically important metabolite of (−)-Δ⁹-THC (2), the principal psychoactive component of *Cannabis sativa*.[1] Its formation is significant in man,[1] animals,[1] and certain fungi.[2] Previous preparations of this key metabolite (1)



in racemic or chiral form have involved the introduction of oxygen into an intact tetrahydrocannabinoid skeleton or condensation of olivetol with a functionalized monoterpenoid synthon. The former approach requires either Δ⁹- or Δ⁸-THC and is relatively inefficient whether it is carried out chemically[3] or biologically.[2,4] Cyclic monoterpenoid synthons for the second type of approach have been prepared in several steps from acyclic precursors[5] or from *p*-mentha-1,8-dien-7-al.[6] We present here an alternative route to racemic 11-OH-Δ⁹-THC (1), in which an acyclic terpenoid synthon (3) is prepared from readily available 6-methylhept-5-en-2-one and then condensed with olivetol. The synthesis also yields the corresponding racemic 6a,10a-cis isomer of 11-hydroxy-Δ⁹-tetrahydrocannabinol (4). This isomer (in chiral form) is of interest as a potential mammalian metabolite of Δ⁹-6a,10a-*cis*-tetrahydrocannabinol (5) which has recently been recognized[7] in certain phenotypes of *Cannabis sativa*.

6-Methyl-1-methylthiohept-5-en-2-one [6, bp 71 °C (0.1 mm)] was prepared (72%) from the *N,N*-dimethylhydrazone of 6-methylhept-5-en-2-one by reaction[8] of the regiospecifically generated anion (1 equiv of *n*-BuLi, THF, −78 °C, 40 min) with dimethyl disulfide (−78 °C, 1 h, then warmed to 25 °C) and hydrolysis[9] of the hydrazone on wet (10% H_2O) silica gel (CH_2Cl_2, room temperature 24 h). Formylmethylenation of the ketone 6 by reaction with the lithium salt of diethyl 2-(cyclohexylamino)vinylphosphonate[10] (10 equiv, THF, reflux 24 h) and hydrolysis [two phase, 20% aqueous HOAC–petroleum ether (40–60 °C), 15 min] gave the required synthon (3, 78%) as a

(1) Reviews: (a) Mechoulam, R., Ed.; "Marijuana. Chemistry, Pharmacology, Metabolism and Clinical Effects"; Academic Press: New York, 1973. (b) Wall, M. E. *Recent Adv. Phytochem.* **1975**, *9*, 29. (c) Mechoulam, R.; McCallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 75. (d) Nahas, G. G., Ed.; "Marihuana: Chemistry, Biochemistry and Cellular Effects"; Springer-Verlag: New York, 1976. (e) Burstein, S. *ACS Symp. Ser.* **1979**, *No. 98*, 1.

(2) Christie, R. M.; Rickards, R. W.; Watson, W. P. *Aust. J. Chem.* **1978**, *31*, 1799.

(3) (a) Ben-Zvi, Z.; Mechoulam, R.; Burstein, S. H. *Tetrahedron Lett.* **1970**, 4495. (b) Pitt, C. G.; Hauser, F.; Hawks, R. L.; Sathe, S.; Wall, M. E. *J. Am. Chem. Soc.* **1972**, *94*, 8578. (c) Razdan, R. K.; Uliss, D. B.; Dalzell, H. C. *Ibid.* **1973**, *95*, 2361. (d) Pitt, C. G.; Fowler, M. S.; Sathe, S.; Srivastava, S. C.; Williams, D. L. *Ibid.* **1975**, *97*, 3798.

(4) Wall, M. E.; Brine, D. R.; Brine, G. A.; Pitt, C. G.; Freudenthal, R. I.; Christensen, H. D. *J. Am. Chem. Soc.* **1970**, *92*, 3466.

(5) Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. *J. Am. Chem. Soc.* **1978**, *100*, 2929.

(6) Lander, N.; Ben-Zvi, Z.; Mechoulam, R.; Martin, B.; Nordqvist, M.; Agurell, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 8.

(7) Smith, R. M.; Kempfert, K. D. *Phytochemistry* **1977**, *16*, 1088.

(8) (a) Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, 4687. (b) Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337.

(9) Several literature methods failed to remove the *N,N*-dimethylhydrazone: (a) Avaro, M.; Levisalles, J.; Rudler, H. *Chem. Commun.* **1969**, 445. (b) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3. (c) Corey, E. J.; Knapp, S. *Ibid.* **1976**, 3667.

(10) (a) Nagata, W.; Hayase, Y. *J. Chem. Soc. C* **1969**, 460. (b) Nagata, W.; Wakabayashi, T.; Hayase, Y. *Org. Synth.* **1973**, *53*, 44.

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