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SYNTHESIS WITH MANGANIC SALTS; Part IV[1]: FREE RADICAL TROST ALLYLATION

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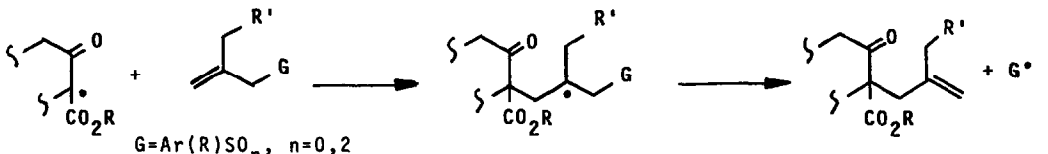
Summary: SH_2, allylations of various keto compounds with 2-substituted allylic sulfones or sulfides have been efficiently performed using a ternary oxidizing mixture -i.e. manganic acetate, cupric acetate and lead dioxide- in acetic acid.

As part of an ongoing programme dealing with the synthesis of steroidal compounds[1], we needed to perform the allylation of an acidic keto-ester with a sulfur derivative. Though such a problem could be solved using palladium catalysis (Trost allylation[2a]), or any related transition metal catalysis[2], it seemed to us that the addition of an α-keto free radical, eventually formed by oxidation by manganic salts of the starting ketone, to the double bond of the allylic system, followed by the displacement of a sulfur centered free radical as depicted in scheme 1, would provide a valuable alternative to the Trost process, avoiding for instance both the use of expensive catalysts and the need to operate under basic conditions.

Scheme 1

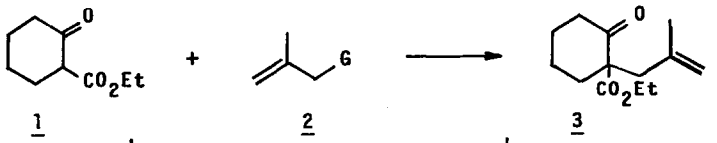


G=Ar(R)SO_n, n=0,2

The free radical chemistry of allylic sulfones or sulfides is well documented[3]. The planned substitution was, however, challenging since both the entering α-keto and the leaving sulfonyl or sulfenyl radicals are electrophilic. Previous attempts by other workers to displace the sulfonyl group by such an electrophilic species has met with failure[3e], hence it seems likely that it is the so-called polar effect that is the major underlying factor in determining the success of these free radical substitutions.

Using ethyl cyclohexanone-2-carboxylate, 1[4], and the sulfone 2a as model substrates, we systematically studied the influence of factors such as the nature of the oxidant (Mn^{3+}, Cu^{2+}, PbO_2[5], alone or combined), the ratio of the reagents, or the order of their admixture, in the hope that the lowering of the α-keto free radical/allylic substrate ratio through the whole process would be beneficial. As expected, we have developed an acceptable protocol which involves the slow addition of the α-keto-ester to a well deoxygenated mixture of the sulfone (three fold excess) with the ternary Mn(III)acetate-Lead dioxide-cupric acetate oxidizing system (molar ratio: 0.1/2/2) and one equivalent of pyridine in acetic acid, then stirring the thus produced heterogeneous mixture under argon for two days (table 1, entry 1). The yield was improved using the parent t-butylsulfone 2b (entry 2) but much more consistantly with the sulfides 2c and 2d (entries 3 and 4).

Table 1:



1 + 2 → 3

G	Conversion (%)		3, Yield (%)	
	1	2	relative to 1	relative to 2
2a, $PhSO_2$	100	17.5	36	68
2b, t-$ButSO_2$	"	33	41	48.5
2c, PhS	"	30.5	65	71.5
2d, t-ButS	"	28	73	87
2e, PhSO	"	16	--	90

Standard conditions: The keto-ester (10 mmol) was added dropwise to a well deoxygenated (three freeze and thaw cycles) mixture of anhydrous manganic acetate (231 mg, 1 mmol), cupric acetate (3.64 g, 20 mmol), lead dioxide (4.78 g, 20 mmol), the allylic reagent (30 mmol), and pyridine (0.8 ml), in acetic acid (100 ml). After two days of stirring at room temperature, under argon, the clear solution was poured into brine and the resulting suspension extracted thoroughly with methylene chloride. Filtration on silica gel was followed by fractional distillation of the resulting 2+3 mixture.

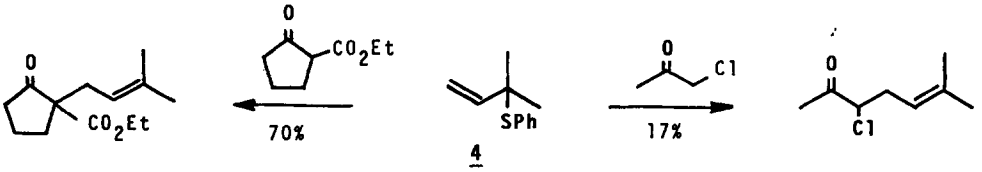
We have been unable, so far, to identify any product which could result from the evolution of the incipient sulfur centered radical[6].

The parent sulfoxide, 2e, was also tried (table 1,entry 5). The allylated product 3 was obtained in good yield. In this experiment, we isolated, apart from the unreacted sulfoxide 2e, a small amount of S-phenyl phenylthiosulfonate, and, surprisingly, some sulfone 2a (31 % relative to 2e). The sulfoxide 2e remained unchanged when submitted separately -i.e. without added keto-ester 1- to the oxidizing mixture. Taken together with the formation of a small amount of thiosulfonate, this fact suggests the following free radical chain pathway:

$$PhSO^{\cdot} \longrightarrow PhSO_2^{\cdot}$$

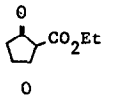
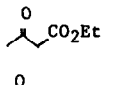
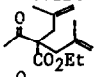
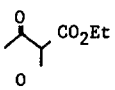
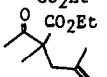
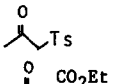
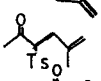
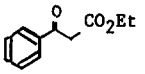
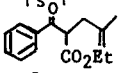
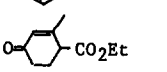
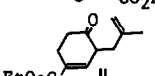
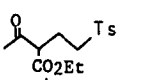
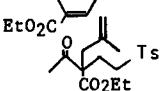
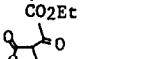
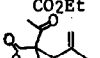
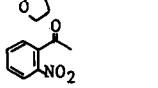
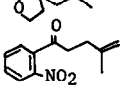
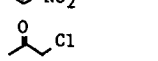
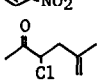
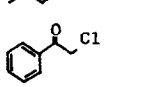
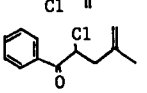
$$PhSO_2^{\cdot} + \underset{\textbf{2e}}{CH_2=C(CH_3)-CH_2-SOPh} \rightleftharpoons PhSO_2-CH_2-\dot{C}(CH_3)-CH_2-SOPh \rightleftharpoons \underset{\textbf{2a}}{PhSO_2-CH_2-C(CH_3)=CH_2} + PhSO^{\cdot}$$

Using strictly similar conditions, various keto compounds were reacted with sulfide 2d (table 2), and in most cases the allylated product was isolated in good yields. Noteworthy is the fact that α-chloroketones could be used. Using the isoprenic sulfide 4[7], some useful prenylations could be achieved:



The potential synthetic importance of this reaction was definitively established using the sulfide 5, easily prepared from pulegone[9].

Table 2: Reaction of various α-substituted ketones with sulfide **2d**.

Starting ketone	Product	Yield, % §	Yield, % §§
		86	91
		35	25.5
		88	63.5
		68.5	21.5
		20	18*
		5	4
		96	22
		77.5	45.5
		85	12
		43	26.5**
		84	39

§ based on the unrecovered sulfide **2d**

§§ based on the ketone

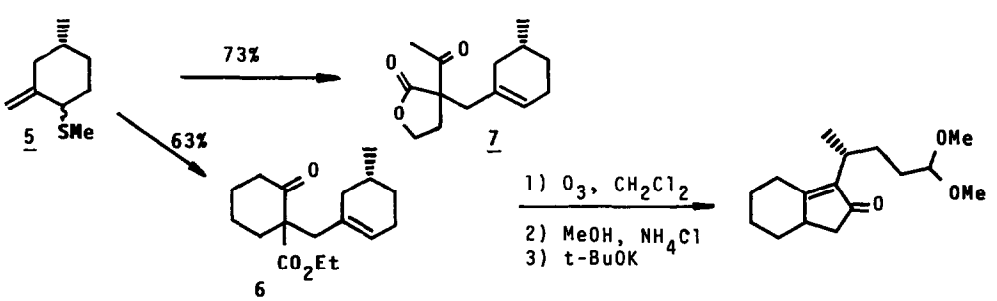
* some dialkylated product also formed

** unstable

(Ts=Tosyl)

Both the ketoester **1** and acetobutyrolactone gave with **5** the homologated products, respectively **6** and **7**, in fair yields[10] (scheme 2). As it is shown, the hydrindenone framework was reached, from **6**, using simple reactions. Hence, the method could be used to prepare steroidal compounds bearing C-20 substituent with the correct chirality. Further work using keto-esters *en route* to such targets is now in progress.

Scheme 2



In conclusion, the SH_2, free radical displacement of an allylic alkylthio (or sulfonyl) group by acidic ketones can be considered as a valuable alternative to procedures using transition metal catalysis, especially when the use of basic conditions has to be avoided.

Acknowledgments: We thank Mr. Perrot (Elf Aquitaine) for a generous gift of t-Butylmercaptan an Dr. Howard Williams for helpfull comments.

References and Notes

1- Part III: P. breuilles and D. Uguen, Bull.Soc.Chim.Fr., 1988, 705.

2- a) B.M. Trost, N.R. Schmuff and J.J. Miller, J.Am.Chem.Soc., 1980, 102, 5979; b) J. Tsuji, I Shimizu, I. Minami, Y. Ohashi, T. Sugura and K. Takahashi, J.Org.Chem., 1985, 50, 1523; c) Y Masuyama, K. Yamada and Y. Kurusu, Tetrahedron Lett., 1985, 28, 443; d) T. Cuvigny and M. julia, J. of Organomet.Chem., 1986, 317, 383; e) B.M. Trost, Bull.Chem.Soc.Jpn., 1988, 61, 107.

3- For leading references on the free radical reactions of allylic sulfones and sulfides, see: a) B. Geese, Radicals in Organic Synthesis, Pergamon Press, Oxford, New-York, Beijing, Frankfurt, Sao-Paolo, Sydney, Tokyo, Toronto, 1986, page 129; b) M. Newcomb and J. Kaplan, Tetrahedron Lett., 1987, 28, 1615; c) D.H.R. Barton and D. Crick, J.Chem.Soc.,Perkin Trans. I, 1986, 1613; d) E.S. Huyser and R.M. Kellog, J.Am.Chem.Soc., 1965, 87, 2867; e) T.A.K. Smith and G.H. Whitam, J.Chem.Soc., Chem.Commun., 1985, 897; f) S.N. Lewis, J.J. Miller and S. Winstein, J.Org.Chem., 1972, 37, 1478; g) A.N. Abeywickrema, A.L.J. Beckwith and S. Gerba, J. Org. Chem., 1987, 52, 4072; h) G.E. Keck and J.M. Byers, J.Org.Chem., 1985, 50, 5442; i) M. Hannaby and S. Warren, Tetrahedron Lett., 1986, 27, 765.

4- Cyclohexanone did not react at an appreciable rate at room temperature.

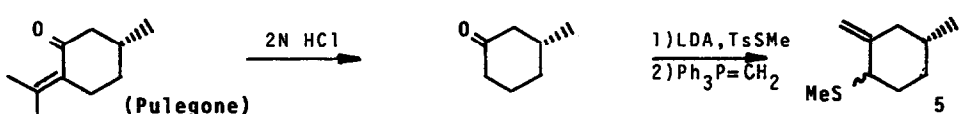
5- For a preliminary experiment using PbO_2 and MnO_2, see: P. Breuilles and D. Uguen, in Progress in Terpene Chemistry, D. Joulain Editor, Editions Frontières, Gif-sur-Yvette, 1986, page 129.

6- All the compounds described in this letter have been characterized by ^1H NMR, mass, elemental analysis. The allylated product 3 has been further identified by conversion into hydrindenone by ozonolysis, then treatment with refluxing 1N KOH (R.A. Raphael and A.M. Islam, J.Chem.Soc., 1952, 4086).

7- Easily prepared by H_2SO_4 catalyzed addition of thiophenol to isoprene according to reference 3f. The chloroketone resulting from the prenylation of chloroacetone was further converted into the known[8] 6-methyl-3,5-heptadiene-2-one (7% overall yield from chloroacetone; UV(EtOH): λmax 285 nm) by sequential treatment with parathiocresol and anhydrous K_2CO_3 in DMF (overnight at room temperature), m-chloroperbenzoic acid in CH_2Cl_2 at -20°, then thermal elimination of the sulfinic acid in the resulting sulfoxide (toluene,$CaCO_3$,reflux)

8- G. Saucy and R. Marbet, Helv.Chim.Acta, 1967, 50, 1158.

9- 3-Methyl-6-methylthio-cyclohexanone was prepared from R(+)Pulegone following a procedure described by Oppolzer (W. Oppolzer and M.Petrzilka, Helv.Chim.Acta, 1978, 61, 2758) for the parent phenylthio derivative, but using S-Methyl phenylthiosulfonate instead of diphenyldisulfide. Reaction with Wittig reagent, in the dark to avoid extensive isomerisation of the thus formed allylic sulfide 5[3i], was then performed according to T. Cohen and B.B. Guo, Tetrahedron, 1986, 42, 2803:



(Pulegone) 5

10- 6, ^1H NMR(250MHz): 0.76-0.9(m,3H), 0.9-2.68(m,20H), 4.04-4.19(m,2H), 5.2 and 5.33(two bs,1H); 7, ^1H NMR(250MHz): 0.94(d,J=6,5Hz,3H), 1.4-2.3(m in which s at 2.1,7H), 2.38(d,J=3Hz,2H), 2.5-3.06(m,3H), 3.4-3.72(m,2H), 4.1-4.4(m,2H), 5.34 and 5.47(two s,1H)-^{13}C NMR: 21.3, 21.55, 24.89, 25.19, 25.48, 26.76, 28.81, 29.71, 29.99, 30.21, 37.13, 37.31, 41.55, 42.55, 42.82, 66.35, 125.65, 126.04, 156, 175.7, 202.41, 202.63.

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