Notes

Improved Preparations of Some Arenesulfonylhydrazones

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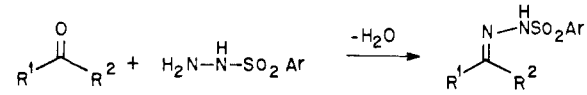
Arenesulfonylhydrazones are exceedingly important intermediates in organic synthesis, considering their triple role as precursors of diazo compounds and carbenes,[1,2] activating groups for regiospecific alkylations,[3] and synthons for vinyl carbanions and the derived olefins.[4] As a necessary part of our investigation of synthetically useful additions to the C–N double bond of arenesulfonylhydrazones,[5] we have prepared a number of these derivatives and made some observations of interest to other workers in this field. Included are the relative stabilities of aldehyde arenesulfonylhydrazones and the best strategies for their preparation, as well as the physical properties of a variety of ketone and aldehyde arenesulfonylhydrazone derivatives, most of them new compounds (see Tables I and II).

Results and Discussion

Although a small amount of pure *n*-heptanal tosylhydrazone[6] could be gleaned by the literature method (reaction in methanol followed by recrystallization from THF/petroleum ether),[7] we found that a good yield of analytically pure material could not be obtained in this way. Indeed, TLC and ^{1}H NMR showed that the product's purity decreased as it was manipulated at room temperature, under which conditions significant decomposition was observed during a period of several hours. Shechter and co-workers prepared aldehyde tosylhydrazones in methanol, crystallized them at −78 °C, and washed them with petroleum ether; they also reported that deterioration occurred upon attempted recrystallization from methanol.[2] When we attempted to prepare 3-methylpentanal tosylhydrazone by this method, the product was not analytically pure. Recrystallization from methanol produced analytically pure material, but the yield was only 16%. Pivaldehyde gave 67% of impure tosylhydrazone, which was recrystallized from methanol in 54% recovery (36% yield overall) to purify it. Similarly, preparing cyclohexanecarboxaldehyde tosylhydrazone in 60% aqueous methanol following a literature model[8a] yielded only 34% of oily solid, which was recrystallized from methanol in 46% recovery to achieve analytical purity. Rosini and Baccolini[8b] have prepared this compound in 95% (crude) yield in what is the only case we have found in which methanol was a satisfactory solvent for aldehyde tosylhydrazones.

Scheme I



While making the tosylhydrazones of *n*-heptanal, 3-methylpentanal and cyclohexanecarboxaldehyde, pressurization of the septum-sealed flasks containing the reaction mixtures was observed if they were left to crystallize at room temperature. Qualitatively, the stability of the 3-methylpentanal derivative in methanol fell between those of *n*-heptanal and cyclohexanecarboxaldehyde. With pivaldehyde only a small amount of gas evolution was detected. The thermal stability of aldehyde tosylhydrazones appears to increase with branching (i.e., steric hindrance) near the imino carbon.

After experimentation with many solvents and their combinations, it was discovered that dissolving the crude pivaldehyde tosylhydrazone in boiling diethyl ether (35 °C), filtering the warm solution, and cooling it in a freezer (−20 °C) gave an excellent recovery (95% in several crops) of analytically pure material. Noticeable decomposition did not occur during this recrystallization procedure. Fuchs has prepared α-epoxytosylhydrazones, which he reported to be unstable in "polar solvents", by stirring the starting materials in diethyl ether for 18 h at room temperature.[9] We prefer to use THF for the preparation of aldehyde tosylhydrazones because tosylhydrazine is more soluble in THF than in diethyl ether and the reactions are faster in it. Ketone trisylhydrazones[6] are best prepared in diethyl ether from which they crystallize directly in analytically pure form. The use of methanol or THF, as has been recommended,[4c,10] sometimes requires a second recrystallization step. Ironically, the material recrystallized from methanol in low recovery sometimes has a slightly higher melting point than that from ether, because the crystals from methanol are especially well formed. The use of ether represents the best compromise between quality and quantity.

It was not possible under any circumstances to isolate the *n*-heptanal trimyl-[6] or trisylhydrazones in pure form. Therefore, *n*-heptanal trisylhydrazone was prepared in ethereal solution, which was filtered through a short column of activated, powdered molecular sieves to remove the water produced by the reaction (Scheme I) as soon as TLC indicated that it was complete. Such solutions were used immediately;[5b] however, dilute solutions of *n*-aldehyde trisylhydrazones in diethyl ether could be stirred for several days at room temperature with little decomposition (as judged by TLC). The rate of decomposition in methanol was faster than in ether.

Allowing *n*-butanal and trimylhydrazine to stir in methanol resulted in decomposition in 1 day. A number of minor products were present rather than one major decomposition product; therefore, the mechanism of de-

(1) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).
(2) G. M. Kaufman, J. A. Smith, G. G. Vander Stouw, and H. Shechter, *J. Am. Chem. Soc.*, **87**, 935 (1965).
(3) M. F. Lipton and R. H. Shapiro, *J. Org. Chem.*, **43**, 1409 (1978).
(4) (a) R. H. Shapiro, *Org. React.*, **23**, 405 (1976); (b) K. J. Kolonko and R. H. Shapiro, *J. Org. Chem.*, **43**, 1404 (1978); (c) A. R. Chamberlin, J. E. Stemke, and F. T. Bond, *ibid.*, **43**, 147 (1978); (d) A. R. Chamberlin and F. T. Bond, *Synthesis*, 44 (1979).
(5) (a) S. H. Bertz, *Tetrahedron Lett.*, **21**, 3151 (1980); (b) S. H. Bertz and G. Dabbagh, *J. Am. Chem. Soc.*, **103**, 5932 (1981).
(6) Tosyl = 4-methylbenzenesulfonyl, trimyl = 2,4,6-trimethylbenzenesulfonyl, and trisyl = 2,4,6-triisopropylbenzenesulfonyl.
(7) J. Jiricny, D. M. Orere, and C. B. Reese, *Synthesis*, 919 (1978).
(8) (a) Reference 4a, p 432; (b) G. Rosini and G. Baccolini, *J. Org. Chem.*, **39**, 826 (1974).
(9) P. L. Fuchs, *J. Org. Chem.*, **41**, 2935 (1976).
(10) N. J. Cusack, C. B. Reese, A. C. Risius, and B. Roozpeikar, *Tetrahedron*, **32**, 2157 (1976).

0022-3263/83/1948-0116$01.50/0

Table I. Compounds Prepared

product	aldehyde or ketone	hydrazone	% yield	mp, °C	lit. yield, %; mp, °C
1	isobutyraldehyde	tosyl	56[a]	98-100	65-75; not given[2]
2		trisyl	67[b]	106-108	
3	cyclohexanecarboxaldehyde	tosyl	91[c]	92-94	95[d]; 99-100[5b]
4		trimyl	57[b]	113-115	
5	3-methylpentanal	tosyl	72[b]	68-70	
6	2,4-dimethylhexanal	tosyl	62[e]	62-64	
7	pivaldehyde	tosyl	95[c]	111-113	85-95; not given[2]
8	*n*-heptanal	tosyl	52[b]	72-73	78; 70[7]
9	4-heptanone	tosyl	80[a]	79-81	84; 80-81[4b]
10		trimyl	83[a]	90-92	
11		trisyl	95[c]	92-94	64; 92-95[4c]
12	3-heptanone	trisyl	65[a]	96-97	
13	2-heptanone	trisyl	63[a]	77-79	
14	cyclohexyl methyl ketone	tosyl	86[b]	137-140	
15		trimyl	76[a]	156-158	
16		trisyl	87[a]	142-143	
17	cyclobutanone	tosyl	76[a]	108-111	
18		trimyl	86[a]	118-120	
19	cyclopentanone	trimyl	88[a]	148-150	
20	bicyclo[4.2.0]octan-7-one	tosyl	88[a]	141-143	

[a] One crop. [b] Two crops. [c] Three crops. [d] Repeating this procedure, we obtained 91% yield; mp 92-95 °C. [e] Purified by HPLC.

Table II

product	^{1}H NMR ($CDCl_3$/Me_4Si), δ	product	^{1}H NMR ($CDCl_3$/Me_4Si), δ
1	0.98 (d, J = 7 Hz, 6 H), 2.45 (m, 1 H), 2.45 (s, 3 H), 7.18 (d, J = 5 Hz, 1 H), 7.35 (d, J = 8 Hz, 2 H), 7.88 (d, J = 8 Hz, 2 H), 8.20 (br s, 1 H)	11	0.70 (t, J = 7 Hz, 3 H), 0.93 (t, J = 7 Hz, 3 H), 1.28 (d, J = 7 Hz, 18 H), 1.43 (m, 4 H), 2.15 (t, J = 7 Hz, 4 H), 2.92 (septet, J = 7 Hz, 1 H), 4.28 (septet, J = 7 Hz, 2 H), 7.17 (s, 2 H), 7.27 (br s, 1 H)
2	0.98 (d, J = 7 Hz, 6 H), 1.27 (d, J = 7 Hz, 18 H), 2.40 (m, 1 H), 2.93 (septet, J = 7 Hz, 1 H), 4.23 (septet, J = 7 Hz, 2 H), 7.10 (d, J = 5 Hz, 1 H), 7.18 (s, 2 H), 7.69 (br s, 1 H)	12[b]	0.68-1.12 (m, 6 H),[b] 1.27 (d, J = 7 Hz, 18 H), 1.3 (m, 4 H), 2.18 (m, 4 H), 2.92 (septet, J = 7 Hz, 1 H), 4.27 (septet, J = 7 Hz, 2 H), 7.17 (s, 2 H), 7.3 (br s, 1 H)
3	1.22 (m, 4 H), 1.62 (m, 6 H), 2.10 (m, 1 H), 2.42 (s, 3 H), 7.07 (d, J = 5 Hz, 1 H), 7.27 (d, J = 8 Hz, 2 H), 7.80 (d, J = 8 Hz, 2 H), 8.02 (br s, 1 H)	13[b]	0.75 (t, J = 7 Hz, 3 H), 1.27 (d, J = 7 Hz, 18 H), 1.3 (m, 6 H), 1.78 (s, 2.25 H),[b] 1.88 (s, 0.75 H),[b] 2.17 (m, 2 H), 2.92 (septet, J = 7 Hz, 1 H), 4.32 (septet, J = 7 Hz, 2 H), 7.0 (br s, 1 H), 7.18 (s, 2 H)
4	1.20 (m, 4 H), 1.60 (m, 6 H), 2.10 (m, 1 H), 2.30 (s, 3 H), 2.65 (s, 6 H), 6.95 (s, 2 H), 7.05 (d, J = 5 Hz, 1 H), 7.90 (br s, 1 H)		
5	0.75 (d, J = 6 Hz, 3 H), 0.80 (t, J = 6 Hz, 3 H), 1.13 (t, J = 6 Hz, 2 H), 1.35 (m, 1 H), 2.08 (m, 2 H), 2.42 (s, 3 H), 7.18 (t, J = 5.5 Hz, 1 H), 7.28 (d, J = 8 Hz, 2 H), 7.82 (d, J = 8 Hz, 2 H), 8.07 (br s, 1 H)	14	0.93-1.90 (m, 10 H), 1.73 (s, 3 H), 2.13 (m, 1 H), 2.43 (s, 3 H), 7.33 (d, J = 8 Hz, 2 H), 7.62 (br s, 1 H), 7.90 (d, J = 8 Hz, 2 H)
6[a]	0.50-1.57 (m, 11 H), 0.98 (d, J = 7 Hz, 3 H), 2.07 (m, 1 H), 2.43 (s, 3 H), 7.00 (d, J = 7 Hz, 0.6 H),[a] 7.07 (d, J = 6 Hz, 0.4 H),[a] 7.30 (d, J = 8 Hz, 2 H), 7.83 (d, J = 8 Hz, 2 H), 8.13 (br s, 1 H)	15	0.90-1.93 (m, 10 H), 1.73 (s, 3 H), 2.13 (m, 1 H), 2.30 (s, 3 H), 2.67 (s, 6 H), 6.93 (s, 2 H), 7.40 (br s, 1 H)
7	0.97 (s, 9 H), 2.40 (s, 3 H), 7.13 (s, 1 H), 7.28 (d, J = 8 Hz, 2 H), 7.82 (d, J = 8 Hz, 2 H), 8.17 (br s, 1 H)	16	0.87-1.87 (m, 10 H), 1.27 (d, J = 7 Hz, 18 H), 1.75 (s, 3 H), 2.13 (m, 1 H), 2.93 (septet, J = 7 Hz, 1 H), 4.28 (septet, J = 7 Hz, 2 H), 7.18 (s, 2 H), 7.2 (br s, 1 H)
8	0.85 (m, 3 H), 1.22 (m, 8 H), 2.13 (m, 2 H), 2.40 (s, 3 H), 6.8 (br s, 1 H), 7.25 (t, J = 6 Hz, 1 H), 7.28 (d, J = 8 Hz, 2 H), 7.82 (d, J = 8 Hz, 2 H)	17	2.00 (m, 2 H), 2.47 (s, 3 H), 2.87 (m, 4 H), 7.35 (d, J = 8 Hz, 2 H), 7.80 (br s, 1 H), 7.90 (d, J = 8 Hz, 2 H)
9	0.77 (t, J = 7 Hz, 3 H), 0.87 (t, J = 7 Hz, 3 H), 1.47 (m, 4 H), 2.17 (m, 4 H), 2.43 (s, 3 H), 7.10 (br s, 1 H), 7.30 (d, J = 8 Hz, 2 H), 7.87 (d, J = 8 Hz, 2 H)	18	1.93 (m, 2 H), 2.30 (s, 3 H), 2.67 (s, 6 H), 2.83 (m, 4 H), 6.95 (s, 2 H), 7.55 (br s, 1 H)
10	0.73 (t, J = 7 Hz, 3 H), 0.93 (t, J = 6 Hz, 3 H), 1.43 (sextet, J = 7 Hz, 2 H), 1.48 (sextet, J = 6 Hz, 2 H), 2.08 (d, J = 7 Hz, 2 H), 2.18 (d, J = 6 Hz, 2 H), 2.30 (s, 3 H), 2.68 (s, 6 H), 6.95 (s, 2 H), 7.72 (br s, 1 H)	19	1.77 (m, 4 H), 2.17 (m, 4 H), 2.25 (s, 3 H), 2.63 (s, 6 H), 6.95 (s, 2 H), 7.70 (br s, 1 H)
		20	0.50-2.03 (m, 8 H), 2.22 (m, 1 H), 2.40 (s, 3 H), 2.58 (m, 2 H), 3.08 (m, 1 H), 7.28 (d, J = 8 Hz, 2 H), 7.83 (d, J = 8 Hz, 2 H), 7.9 (br s, 1 H)

[a] Hydrazone is a mixture of diasteriomers. [b] Hydrazone is a mixture of *E* and *Z* isomers.

composition was not pursued. Two specific possibilities were ruled out, however, by GLC with authentic samples; no *cis*- or *trans*-4-octene was detected, and only a trace of methyl butyl ether was present. The absence of 4-octene rules out a polar mechanism in which one tosylhydrazone molecule acting as an enamine (i.e., a nucleophile at the imino carbon atom) attacks a second one at the imino carbon in a manner analogous to the nucleophilic attack of an enamine on a ketone. Methyl ethers have been reported from the decomposition of conjugated tosylhydrazones in alkaline methanol,[11] which observation prompted us to check for methyl butyl ether. No 1-heptene was observed from preparations of *n*-heptanal

(11) R. Grandi, A. Marchesini, U. M. Pagnoni, and R. Trave, *J. Org. Chem.*, **41**, 1755 (1976).

Table III. Percent Arenesulfonylhydrazone Remaining[a]

solvent	(concn)	time, h	tosyl	trimyl	trisyl	av trisyl
THF-d_8	(1 M)	2	88[b] (86)[c]	(70)[b] 78[c]	(65)[b,d] (100)[c,d]	82
THF-d_8	(1 M)	24	73 (68)	(32) 36	(58) (90)	74
THF-d_8	(2 M)	2	83 (76)	(60) 70	(70) (100)	85
THF-d_8	(2 M)	24	38 (37)	(14) 16	(36) (67)	51
MeOH-d_4	(2 M)[e]	2	20 (22)	(30) 12	(64)[e] (f)	64
MeOH-d_4	(2 M)[e]	24	11 (0)	(0) 0	(0)[e] (f)	0

[a] Best values for comparison are those without parentheses, see footnote d. [b] This column based on intensity of imino C (tosyl, δ 151.4; trimyl, δ 149.4; trisyl, δ 148.9, all in THF). [c] This column based on intensity of α-C (δ 34.8-35.1). [d] Intensity of imino C < $^1/_{19}$ of total intensity due to trisylhydrazone (25% error); intensity of α-C > $^1/_{19}$ of total intensity (20% error). Average is within 5% of correct value; see last column. For tosylhydrazone, imino C is slightly more accurate (<3% error); for trimylhydrazone, α-C is more accurate (<10% error). [e] Trisyl 1 M, due to solubility problems at 2 M. [f] Peak not resolved.

tosylhydrazone or trimylhydrazone in methanol, thus ruling out a third possibility.[1]

The course of the reactions was monitored by ^{13}C NMR in order to obtain a more quantitative comparison of the stabilities of the three arenesulfonylhydrazone derivatives in THF and methanol. Table III lists the amount of arenesulfonylhydrazone present as a function of time, solvent, and concentration. In dilute solution (≤1 M) the order of stability appears to be trisyl ~ tosyl > trimyl. In more concentrated solution (2 M), all the arenesulfonylhydrazones are less stable, and the order is trisyl > tosyl ≫ trimyl. This explains the difficulty encounted in the isolation of aldehyde arenesulfonylhydrazones, as concentration is a necessary prelude to crystallization. While the *n*-heptanal tosylhydrazone could be induced to crystallize in modest yield, the trisylhydrazone derivative is more soluble and could not be induced to crystallize. It was concentrated to a viscous oil that decomposed with gas evolution even at −20 °C in a freezer. Since the electron effect (+*I*) that causes the trimyl derivative to be less stable than the tosyl one can be predicted to make the trisyl derivative even less stable, we believe that a steric effect is responsible for the relative stability of the trisyl derivative. Models show that the NH group of trisylhydrazones is shielded by the *o*-isopropyl groups of the trisyl moiety, and in some conformations even the C–N double bond is shielded.

By employing ethereal solvents, we were able to isolate pure isobutyraldehyde trisylhydrazone and cyclohexanecarboxaldehyde trimylhydrazone, confirming in a dramatic way the importance of steric effects in stabilizing aldehyde arenesulfonylhydrazones.

The ^1H NMR spectra of the compounds in Table I are listed in Table II. Those cases in which a mixture of isomers was present are noted, and in some cases peaks due to each isomer were resolved well enough to allow individual integration. These are listed as fractional protons. The stereochemistry of arenesulfonylhydrazones is important because, under the appropriate conditions, it can control the regiochemical outcome of a reaction, for example, the reaction with alkyllithium bases.[4,12]

In conclusion, aldehyde tosylhydrazones are best prepared in THF with as short a reaction time as possible and recrystallized from diethyl ether. The corresponding trimyl and trisyl derivatives of primary aldehydes must be prepared in situ. Branching near the aldehyde group stabilizes the corresponding arenesulfonyl derivative.

Experimental Section

The aldehydes and ketones used as starting materials were reagent grade (>95% pure) and were used as received unless otherwise specified. THF and diethyl ether were distilled from sodium benzophenone ketyl. Melting points were measured with a Mettler FP-5 or a Mel-Temp apparatus and are uncorrected. ^1H NMR spectra were obtained with a Varian T-60 and ^{13}C NMR spectra with a JEOL FX-90Q at 22.49 MHz. All the compounds in Table I had good microanalyses: C within 0.25, H within 0.26, N within 0.30, and S within 0.18 except for one which was within 0.33. Galbraith Laboratories (Knoxville, TN) or Schwarzkopf Microanalytical Laboratory (Woodside, NY) performed all the elemental analyses.

***n*-Heptanal Tosylhydrazone (8). General Procedure for Aldehyde Tosylhydrazones.** A 9.3 g quantity of tosylhydrazine (Aldrich) was added to 100 mL of THF. The mixture was swirled vigorously and then filtered to remove 0.4 g of insoluble material. The resulting solution of tosylhydrazine[13] (8.9 g, 48 mmol) was treated with 5.4 g (48 mmol) of distilled *n*-heptanal in a 250-mL recovery flask sealed with a rubber septum. The reaction mixture was stirred magnetically for 30 min, after which time TLC (developed with 25% EtOAc/hexane) indicated that the reaction was complete. The THF was evaporated under reduced pressure at room temperature, and the last traces of it were removed by an oil pump, whereupon the residual oil solidified. The cream-colored solid (mp 55–60 °C)[14] was taken up in 40 mL of diethyl ether with gentle boiling. The warm solution was filtered to remove 0.2 g of insoluble material and placed in the freezer (−20 °C) for 4 h. Filtration gave 0.9 g of 8, mp 72–73 °C. The volume was reduced to 20 mL under a stream of nitrogen, and the solution was placed in the freezer for 24 h to obtain 6.1 g of 8 (52% total), mp 72–73 °C. Reducing the volume to 5 mL and storage in the freezer for 2 days did not produce additional product, nor did cooling to −70 °C.

Cyclohexyl Methyl Ketone Trisylhydrazone (16). General Procedure for Stable Trisylhydrazones.[6] Cyclohexyl methyl ketone (2.52 g, 0.02 mol) was added to 5.97 g (0.02 mol) of trisylhydrazine[10] suspended in 70 mL of diethyl ether in a 100-mL recovery flask sealed with a rubber septum. The reaction mixture became homogeneous, and TLC on silica gel developed with 65:30:5 hexane/ethyl acetate/methanol showed trisylhydrazine at R_f 0.50 and product at R_f 0.67. After the mixture had been stirred magnetically for 18 h, TLC indicated that the reaction was complete. The ether was evaporated with a stream of nitrogen until crystallization commenced, whereupon the mixture was placed in the freezer (−20 °C) for 1 h. The white solid was isolated by suction filtration on a sintered-glass frit and washed with a little cold ether. It was dried under a nitrogen cone and then under vacuum to yield 7.08 g (87%) of product, mp 142–143 °C. Two further crops, totaling 4%, could be gleaned from the mother liquors by repeating the cycle of reducing the volume and cooling.

Cyclobutanone Trimylhydrazone (18). General Procedure for Ketone Tosyl- and Trimylhydrazones.[6] Commercial (Aldrich Chemical Co.) [(2,4,6-trimethylphenyl)sulfonyl]hydrazine was spread out on a piece of white paper, and the occasional small, hard, yellow chunks were removed from the white crystalline material, which was then of suitable purity for further use. A

(12) W. G. Dauben, G. T. Rivers, and W. T. Zimmerman, *J. Am. Chem. Soc.*, **99**, 3414 (1977).

(13) This solution gave the same results as a solution of recrystallized tosylhydrazine and is much easier to prepare.

(14) Although its melting point was low, this crude material (obtained in quantitative yield) had a good ^1H NMR spectrum and might be suitable for some purposes.

4.3-g (0.02 mol) quantity of this material dissolved in 20 mL of warm (<50 °C) methanol was treated with 1.4 g (0.02 mol) of cyclobutanone, added by syringe to the septum-covered 50-mL recovery flask. The reaction mixture which soon deposited crystals was allowed to stand at room temperature for several hours and then refrigerated for 1 h to give 4.6 g (86%) of product, mp 118–120 °C. Recrystallization from methanol (83% recovery) gave the analytical sample, mp 122–124 °C.

^{13}C NMR Study. Arenesulfonylhydrazines were dissolved or suspended in methanol-d_4 or tetrahydrofuran-d_8 (tosyl and trimyl, 4.00 mmol/2.0 mL of solvent; trisyl, 2.00 mmol/2.0 mL of solvent) in septum-sealed 10-mm NMR tubes. The trisylhydrazine was recrystallized from ether immediately before use. Tetramethylsilane (0.1 mL) was added as an internal reference. Distilled *n*-butanal (1.00 mol equiv) was injected into each tube, which was then placed in a shaker at ambient temperature. Proton-decoupled spectra were accumulated after 2, 24, and 168 h. The accumulation parameters were as follows: pulse width, 29 μs; pulse delay, 58.8 s; number of scans, 60. Increasing the pulse delay to 300 s or decreasing the pulse width to 14 μs did not significantly affect the results. For the other THF data in Table III, the tosyl and trimyl experiments were run at 1.0 M and the trisyl at 2.0 M.

Registry No. 1, 20208-71-3; 2, 83477-63-8; 3, 34266-29-0; 4, 83477-64-9; 5, 75938-54-4; 6, 75938-55-5; 7, 5362-74-3; 8, 52718-79-3; 9, 36432-88-9; 10, 83477-65-0; 11, 63883-82-9; (*Z*)-12, 83486-40-2; (*E*)-12, 83477-72-9; (*Z*)-13, 83477-66-1; (*E*)-13, 83477-73-0; 14, 83477-67-2; 15, 83477-68-3; 16, 83477-69-4; 17, 2524-51-8; 18, 83477-70-7; 19, 83477-71-8; 20, 54211-17-5; isobutyraldehyde, 78-84-2; cyclohexanecarboxaldehyde, 2043-61-0; 3-methylpentanal, 15877-57-3; 2,4-dimethylhexanal, 20514-48-1; pivaldehyde, 630-19-3; *n*-heptanal, 111-71-7; 4-heptanone, 123-19-3; 3-heptanone, 106-35-4; 2-heptanone, 110-43-0; cyclohexyl methyl ketone, 823-76-7; cyclobutanone, 1191-95-3; cyclopentanone, 120-92-3; bicyclo[4.2.0]octan-7-one, 54211-18-6; tosylhydrazine, 1576-35-8; trisylhydrazine, 39085-59-1; trimylhydrazine, 16182-15-3.

Preparative and Stereochemical Features of the Sulfoxide–Sulfenate [2,3] Sigmatropic Rearrangement in 17-Vinyl-17-hydroxy Steroids

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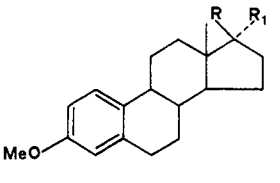
Attempts to achieve configurational inversion of tertiary allylic alcohols by the "classical" approach comprising S_N2-type displacement of suitable derivatives are invariably thwarted by the almost exclusive formation of allylic rearrangement and/or elimination products,[1] nor does the diethyl azodicarboxylate–triphenylphosphine system work with tertiary substrates.[2]

Sparse reports suggest that the allyl sulfoxide–sulfenate rearrangement could be advantageously exploited to this end, although in one direction only. Illustrations on this concern are provided by the conversion of prostaglandin (13*Z*,15*R*)-PGE$_1$ into the 13*E*,15*S* analogue[4] and a new route to the dihydroxyacetone side chain from a 17α-ethynyl-17β-hydroxy steroid.[5]

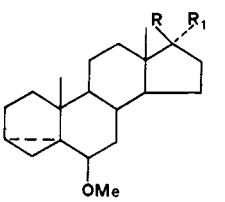
In this paper we report (a) that an effective "one-pot" epimerization procedure of 17α-vinyl-17β-hydroxy steroids to the rather inaccessible 17-epimers[6] can be assembled by the use of the above rearrangement and (b) some stereochemical observations on this process.

Results and Discussion

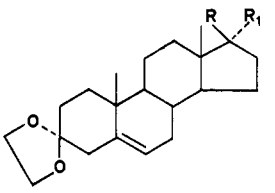
Treatment of **1a** with phenylsulfenyl chloride according to the procedure of Mislow[7] afforded the sulfoxide **4a** as a single isomer. The stereohomogeneity of **4a** was indicated by the sharp singlet for the angular methyl group in both $CDCl_3$ and C_6D_6.



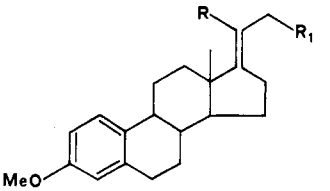
1a, R = OH; R1 = CH=CH2
b, R = CH=CH2; R1 = OH
c, R = OSPh; R1 = CH=CH2
d, R = CH=CH2; R1 = OSPh



2a, R = OH; R1 = CH=CH2
b, R = CH=CH2; R1 = OH



3a, R = OH; R1 = CH=CH2
b, R = CH=CH2; R1 = OH



4a, R = H; R1 = (S)-S(=O)Ph
b, R = H; R1 = (R)-S(=O)Ph
c, R = H; R1 = SO2Ph

The 17,20 double bond was assigned the *E* geometry on comparison of the chemical shift of the 13-Me group to other related compounds of known stereochemistry.[5,8]

Consideration of the relative energies of model transition states (see below) led to allocation of configuration at sulfur as depicted.

Exposure of **4a** to the highly efficient thiophile trimethyl phosphite[9] in refluxing methanol provided a mixture of **1b** and **1a** in a 73:27 ratio (88% overall yield). An analogous result was obtained when the two-step sequence was performed without isolating **4a**. Reaction of **1b** with phenylsulfenyl chloride gave the sulfoxide **4b**, again as a single isomer.

A 1:1 mixture of **4a** and **4b** was oxidized with *m*-chloroperbenzoic acid to the sulfone **4c**, confirming that these compounds differ only with respect to chirality at sulfur. Furthermore, each isomer was equilibrated to a 1:1 mixture by heating in C_6D_6 at 65 °C for 4 h. At 80 °C the equilibration was complete within 1 h. According to the Mislow's observations,[7] isomerization of **4a** and **4b** in refluxing methanol was appreciably slower (26% isomerization after 5 h). A considerably higher diastereoselectivity was obtained in the reaction of **4b** with the thiophile,

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